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Potential Role of Antipsychotic-Galantamine-Memantine Combination in the Treatment of Positive, Cognitive, and Negative Symptoms of Schizophrenia

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Keywords

Schizophrenia · Cognition · Negative symptoms · Galantamine · Memantine · Randomized controlled trials · Efficacy signal · Methodological issues · Kynurenine

Abstract

Schizophrenia is, in part, a cognitive illness. There are no approved medications for cognitive impairments associated with schizophrenia (CIAS) and primary negative symptoms. Cholinergic and glutamatergic systems, alpha-7 nicotinic acetylcholine (α-7nACh) and *N*-methyl-D-aspartate (NMDA) receptors, kynurenic acid (KYNA), and mismatch negativity have been implicated in the pathophysiology of CIAS and negative symptoms. Galantamine is an acetylcholinesterase inhibitor that is also a positive allosteric modulator at the α4β2 and α7nACh receptors. Memantine is a noncompetitive NMDA receptor antagonist. Galantamine and memantine alone and in combination were effective for cognition in animals and people with Alzheimer's disease. The objective of this article is to critically dissect the published randomized controlled trials with galantamine and memantine for CIAS to highlight the efficacy signal. These studies may have failed to detect a clinically meaningful efficacy signal due to limitations, methodological issues, and possible medication nonadherence. There is evidence from a small open-label study that the galantamine-memantine combination may be effective for CIAS with kynurenine pathway metabolites as biomarkers to detect the severity of cognitive impairments. Given that there are no available treatments for cognitive impairments and primary negative symptoms in schizophrenia, testing of this "five-pronged strategy" (quintuple hypotheses: dopamine, nicotinic-cholinergic, glutamatergic/NMDA, GABA, and KYNA) is a "low-risk high-gain" approach that could be a major breakthrough in the field. The galantamine-memantine combination has the potential to treat positive, cognitive, and negative symptoms, and targeting the quintuple hypotheses concurrently may lead to a major scientific advancement – from antipsychotic treatment to antischizophrenia treatment.

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Introduction

Schizophrenia is, in part, a cognitive illness [1]. Cognitive impairments associated with schizophrenia (CIAS) are core features of schizophrenia. CIAS is the best predictor of functional outcome [2]. Unfortunately, there are no approved medications for CIAS. Cholinergic [3, 4] and glutamatergic systems [5, 6], alpha-7 nicotinic acetylcholine (α7nACh) receptors [7], and *N*-methyl-D-aspartate (NMDA) receptors [8] have been strongly implicated in the pathophysiology of CIAS. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project, designed to facilitate the development of new drugs for the treatment of cognitive impairments in people with schizophrenia, identified three drug mechanisms of particular interest: dopaminergic, nicotinic-cholinergic, and glutamatergic [9].

Galantamine is an acetylcholinesterase inhibitor that also acts as an allosteric modulator at the α4β2 and α7nACh receptors [10]. Memantine is a noncompetitive NMDA receptor antagonist [11] that attenuates the neurotoxic tonic overstimulation of NMDA receptors by glutamate [12]. Through the presynaptic α7nACh receptor, galantamine increases glutamate release [13–15]. The synergistic actions of the α7nACh and NMDA receptors and cholinergic and glutamatergic systems were demonstrated in pyramidal neurons of the auditory cortex in rats. The authors argued that this synergistic action led to synaptic plasticity in the sensory neocortex [13]. Memantine decreases the tonic NMDA current, and galantamine enhances the action potential mediated by a postsynaptic NMDA current, which results in an increased signal transmission [16, 17]. Therefore, a greater signal-to-noise ratio occurs with the galantamine-memantine combination than with memantine alone [16, 17]. Galantamine improves the α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate (AMPA)-mediated signaling, which could be neuroprotective and may improve memory coding [16, 17]. The synergistic action of NMDA and AMPA receptors is well documented [18]. Galantamine may augment the noise suppression of memantine's glutamatergic action. Galantamine potentiates glutamatergic neurotransmission mediated by AMPA and NMDA receptors [19]. Memantine modulates Kir6.2 activity (Kir6.2 is a major subunit of the ATP-sensitive K^+ channels and functions in synaptic plasticity). It has been argued that the Kir6.2 channel is a novel therapeutic target to enhance cognition in people with Alzheimer's disease (AD) [20]. This mechanism of action may be relevant in schizophrenia as well. Galantamine [21] and memantine [22, 23] have increased brain-derived neurotrophic factor (BDNF). Finally, galantamine [24–26] and memantine [27] have antioxidant activity.

The α7nACh receptor enhanced NMDA cognitive circuits in the dorsolateral prefrontal cortex (dlPFC) in monkeys. α7nACh receptor stimulation is essential for the excitation of NMDA receptor-mediated attention and working memory circuits [28]. Stimulation of the nicotinic α4β2 receptor enhanced attention and working memory-related firing of dlPFC in monkeys [29]. The combination of galantamine and memantine improved the attentional set-shifting task and novel object recognition task in rodents compared to vehicle-treated rats; the combination was more effective than either medication alone because of the synergistic role of the α7nACh and NMDA receptors [30]. In older rabbits, the galantamine-memantine combination had a superior effect on cognition compared to the donepezil-memantine combination [31]; memantine was common in both combinations, thus this finding suggests a synergistic role of the α7nACh and NMDA receptors. The galantamine-memantine combination produced synergistic neuroprotection in a transient global cerebral ischemia model in gerbils [32]. Several other preclinical studies have shown that cognition was significantly [33, 34] and synergistically [35, 36] improved with the galantamine-memantine combination than with either medication alone.

In a 2-year randomized controlled trial (RCT) with 232 elderly subjects with cognitive impairments, in AD prodrome ($n = 39$) a combination of galantamine and memantine significantly improved cognitive scores compared to galantamine alone; cognitive decline occurred after discontinuation of galantamine [37]. In AD patients, the galantamine-memantine combination ($n = 53$) significantly improved cognition compared to donepezil-memantine ($n = 61$) [38]. Given the overlap in pathophysiology, these findings in animals and in patients with AD may be translated to patients with schizophrenia [39, 40].

In a meta-analysis of 6 RCTs in schizophrenia ($n = 226$), galantamine significantly improved cognition (effect size = 0.233; $p < 0.001$) compared to placebo [41]. In a meta-analysis of 8 RCTs in schizophrenia ($n = 448$), memantine improved cognition (mean difference [MD] = 3.07, $p < 0.0001$), negative symptoms (standardized MD [SMD] = 0.96, $p = 0.006$), and psychosis (SMD = 0.46, $p = 0.07$) compared to placebo [42]. In another meta-analysis of 8 RCTs ($n = 452$) in schizophrenia, memantine improved cognition compared to placebo, with a weighted MD of 3.09 ($p < 0.00001$) [43]. Improvements in negative symptoms, which are associated with functioning [44, 45],

have also been shown with memantine. However, these findings should be taken with caution, as negative symptoms were measured with the Scale for the Assessment of Negative Symptoms (SANS), the Positive and Negative Syndrome Scale (PANSS), and the Brief Psychiatric Rating Scale (BPRS), which do not differentiate primary versus secondary negative symptoms, instead of the Schedule for the Deficit Syndrome [46], which does differentiate these symptoms.

The objective of this article is to critically dissect [47, 48] all of the published studies conducted with galantamine and memantine for CIAS and to highlight the efficacy signal. A perception remains in the field that galantamine and memantine were found to be ineffective in schizophrenia, yet there are many reasons why this combination is worth trying if the studies are well designed. This article sheds light on the possibility that these RCTs failed to detect a clinically meaningful efficacy signal due to limitations, methodological issues, and possible medication nonadherence [49]. This objective coincides with the new National Institutes of Health policy on how to address scientific premise to enhance reproducibility through rigor and transparency [50, 51].

Methods

PubMed and Google Scholar were searched using the keywords schizophrenia, cognition, galantamine, memantine, and guidelines. RCTs published to date as of this writing were included. Twelve RCTs published in English (7 on galantamine and 5 on memantine) were identified and are summarized in Table 1. Five other RCTs on memantine did not assess cognition [52–56] and are not included in Table 1.

Limitations of the FDA-NIMH-MATRICS Guidelines

Although the US Food and Drug Administration National Institute of Mental Health MATRICS (FDA-NIMH-MATRICS) provide comprehensive guidelines on how to conduct clinical trials for cognitive enhancement in schizophrenia [57, 58], several issues have not been addressed. For example, the age criterion for a proof-of-concept study is not mentioned in the guidelines. Hence, the upper age limit in RCTs has been inconsistent and has ranged from 50 to 70 years. Also, the guidelines do not provide an adequate duration for a proof-of-concept study. Two-thirds of the studies with galantamine and memantine identified in this article had a duration ≥12 weeks. Among the 4 studies [59–62] with a duration <12 weeks, only one was associated with an efficacy signal [59]. Among 118 RCTs on CIAS, a large majority had a duration ≤8 weeks [63]. These findings shed light on the importance of adequate study duration to detect an efficacy signal. Additionally, the updated guidelines [58] recommend the inclusion of participants taking up to two antipsychotics. This recommendation is nonspecific with no limitation on the maximum dose allowed. With this criterion, a participant taking haloperidol 60 mg and risperidone 16 mg could be enrolled in a study, and these high doses may interfere with signal detection [64]. Administration of chlorpromazine-equivalent doses ≥1,000 mg/day, which is suggestive of treatment resistance [65], lowers the likelihood of detecting a signal on cognition [66]. Furthermore, the guidelines suggest adding any two antipsychotics if there are no pharmacokinetic or pharmacodynamic considerations but provide no specific examples of which two antipsychotics should not be combined. The only concern, although not mentioned in the guidelines, may be combining thioridazine with other antipsychotics because of the possibility of QTc prolongation; however, participants taking thioridazine should be excluded because of the drug's significant anticholinergic activity (AA). The guidelines only mention excluding participants taking clozapine and a high dose of olanzapine, which is not defined. It should be noted that thioridazine has more AA than olanzapine [67]. Finally, FDA-NIMH-MATRICS provide no guidelines on the electroconvulsive therapy (ECT) criterion. Among all the studies in Table 1, only one excluded those who received ECT in the past 2 weeks [68]. Ideally, subjects should be excluded from a study if they received ECT in the past 6 months so that they have time to recover from the associated cognitive impairments [69].

Lack of Adherence to the FDA-NIMH-MATRICS Guidelines

On the basis of the limitations and methodological issues of the studies presented in Table 1, it is clear that the FDA-NIMH-MATRICS guidelines were not stringently followed. However, several of the studies were in progress before the guidelines were published. The inclusion and exclusion criteria became less stringent in the second version of the guidelines, in part, because of the recruitment challenge, and revisions were made to address feasibility issues, while still maintaining methodological rigor. A few specific issues are addressed below.

Table 1. Randomized controlled trials of galantamine and memantine in schizophrenia

First author [Ref.], year and country where study was conducted	Mean Age, years (range)/sample size (drug, placebo)[a]/ duration, weeks/ cognitive assessment	Significant efficacy signal in cognition	Limitations and methodological issues
Galantamine 24 mg			
Schubert [59], 2006, USA	48.3 (26–55)/ 8, 6/8/ RBANS	–Delayed memory and attention (increase in RBANS total score = 12.1)	–Small sample size –24 mg only for 4 weeks –SUD only within 30 days excluded; recommended guideline is last 6 months –Excluded use of any anticholinergic or psychotropic medications; this is too nonspecific –Jadad score: 3
Lee [86], 2007 (galantamine 16 mg), Korea	39.5 (range unavailable)/ 12, 12/12/standard neuro-psychological battery	–Visual learning (Rey Complex Figure Test score 5.7–6.4)	–Small sample size –16 mg only for 6 weeks –Inpatients with an average BPRS score of 55 with an average CPZ dose equivalence of 1,280 mg in those who received galantamine –Only those with MMSE scores 18–24 were included –Dose of anticholinergics not defined –SUD not excluded –Jadad score: 1
Buchanan [89], 2008, USA	49.9 (18–60)/ 35, 38/12/ 8-test neuropsychological battery	–Processing speed (digit symbol score: 5.8–6.7) –Verbal learning: 7.1–7.8	–24 mg only for 4 weeks –Out of 42 patients on galantamine (35 completed the study), 32 were outpatients and 10 were inpatients; out of 44 on placebo (38 completed the study), 31 were outpatients and 13 were inpatients; acutely sick patients in the inpatient setting are not the ideal target population for a proof-of-concept cognition enhancement study –Only those with RBANS total score ≤90 were included; this may have excluded the cognitive enhancement among those with scores 91–99 –BPRS total and positive symptoms scores were not defined in the inclusion criteria –Those on a low dose of typical antipsychotic were included; low dose was not defined –Those with anticholinergic treatment were excluded; other anticholinergic medications were not excluded –Jadad score: 4
Dyer [60], 2008 (galantamine 32 mg),USA	44.3 (18–60)/9, 9/8/ neuropsychological tests	–Several cognitive measures worsened on galantamine	–Small sample size –Clozapine was included –32 mg has an antagonistic action –PANSS total and positive symptoms scores were not defined in the inclusion criteria –Those on anticholinergic medication were excluded; however, details were not given –Jadad score: 4
Lindenmayer [70], 2011, USA	41.9 (18–70)/7, 9/26/ computerized test battery (Cogtest)	–Worsening of social cognition on galantamine	–Small sample size –Including participants up to age 70 years may have obscured to detect a signal –Inclusion of PANSS scores 5–7 may have attenuated to detect a signal –No mention about SAS and CDSS in the criteria[b] –Dose of anticholinergics and details regarding the use were not clearly documented –Medications with significant anticholinergic activity were not excluded –PEAT may not be the ideal test to measure social cognition; MCCB uses MSCEIT, which was not a part of MCCB when this study was done –Jadad score: 4

Table 1 (continued)

First author [Ref.], year and country where study was conducted	Mean Age, years (range)/sample size (drug, placebo)[a]/ duration, weeks/ cognitive assessment	Significant efficacy signal in cognition	Limitations and methodological issues
Deutsch [72], 2013, USA	54.4 (18–70)/ 15, 19/16/ MCCB	–Verbal learning (13.0–13.9 in spatial span) –Significant improvement in the scale of functioning	–Including participants up to age 70 years may have obscured to detect a signal –Only those who had a score of at least 4 (moderate) on at least one of the following five PANSS negative symptom items were included: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation –Excluded those with the PANSS positive symptom score for conceptual disorganization, hallucinations, suspiciousness, and delusions that exceeded 18; no cutoff score provided for each item; this could have potentially led to participants with a score of 6–7 being enrolled, which is not ideal for a proof-of-concept study –Anticholinergic medications were not excluded SUD excluded within three months of enrollment (guidelines recommend 6 months) –Jadad score: 4
Buchanan et al. [62], 2017, USA	45.8 (18–65)/ 18, 17/6/ MCCB	–None –The 3-arm (galantamine, oxytocin, and placebo) study was designed to tease apart whether negative symptoms and CIAS have overlapped or if independent pathophysiology is present	–Small sample size –Received galantamine 24 mg only for 4 weeks –Including participants up to 65 years may have attenuated signal detection –Including inpatients (although they fulfilled the inclusion/exclusion criteria) made the target population heterogeneous –SANS total score ≥20 or alogia global score ≥3 may have hindered signal detection; mean total score of 36.6; however, the FDA-NIMH-MATRICS guidelines do not recommend using negative symptoms in the inclusion/ exclusion criteria –BPRS positive symptoms total score ≤16 was included; there was no maximum limit on an individual item score; participants with scores 5–7 may have been included, which likely affected signal detection; however, the mean score was only 1.8 in the galantamine group –Only SAS score ≤10 and those with BPRS anxiety/depression factor score ≤14 were included; SAS score ≤6 and CDSS score ≤10 are recommended by the FDA-NIMH-MATRICS guidelines; including those with SAS scores 7–10 may have affected signal detection –Clozapine was the second most commonly used antipsychotic; the significant anticholinergic activity may have interfered in efficacy signal detection. –Exclusion criterion: female subjects may not be taking olanzapine at doses higher than 30 mg; male subjects may not be taking olanzapine at doses higher than 40 mg; the package insert recommends a maximum of 20 mg daily; including participants taking >20 mg may have affected signal detection; also, there is no rationale for dose differences for men and women –There is no mention about anticholinergics and other medications with anticholinergic activity in the inclusion/exclusion criteria –Jadad score: 5
Memantine 20 mg			
Lieberman [61], 2009, USA	40.9 (18–65)/61, 56/8/ BACS	–None –Focus of the study was on persistent residual psychopathology and not on cognition	–Participants up to age 65 years may have attenuated a signal detection in BACS –Received memantine 20 mg only for 6 weeks –Only included participants with BPRS total score ≥26 and score ≥4 on at least one of the BPRS psychosis factor items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content –Did not exclude anticholinergic medications –Jadad score: 3

Table 1 (continued)

First author [Ref.], year and country where study was conducted	Mean Age, years (range)/sample size (drug, placebo)[a]/ duration, weeks/ cognitive assessment	Significant efficacy signal in cognition	Limitations and methodological issues
de Lucena [87], 2009, Brazil	34.7 (18–65)/ 10, 11/12/ MMSE	–MMSE scores increased from 22.3 to 28.2, effect size (ES) = 1.32 and $p = 0.005$ –Focus of the study was on negative symptoms and not on cognition –Improvement in CIAS despite having high scores on BPRS positive and negative symptoms	–Significant improvement in cognition despite including age up to 65 years –Small sample size –Received memantine 20 mg only for 9 weeks –SAS score 6.4±3.4 may have attenuated with the signal detection; FDA-NIMH-MATRICS guidelines recommend including participants' SAS score ≤6 –MMSE is not a valid instrument for measuring cognitive impairments associated with schizophrenia (CIAS) –Jadad score: 3
Lee [85], 2012, Korea	44.3 (18–50)/ 15, 11/12/ standard neuropsycho-logical battery	–Digit Symbol Substitution Test: 23.5–29.5, $p = 0.06$	–Small sample size –Received memantine 20 mg only for 9 weeks –Only those with MMSE scores 18–24 were included –Enrolling only inpatients with a daily CPZ equivalent dose of 1,262 mg may have obscured to detect a signal –Acutely sick patients in the inpatient setting are not the ideal target population for a proof-of-concept cognition enhancement study –Dose of anticholinergics not defined; with such a high CPZ dose equivalence with only typical antipsychotics prescribed, patients are also likely to be prescribed high doses of anticholinergics as well, which may have hindered with the signal detection –Jadad score: 4
Veerman [88], 2016, Netherlands[c]	42.4 (18–60)/ 23, 21/12/ CANTAB	–Verbal (ES = 0.5) and visual (ES = 0.3) learning	–Small sample size –Crossover study design with carry-over effects –Six inpatients were included –SUD was not excluded –Anticholinergics and medications with anticholinergic activity were not excluded –No mention of SAS and CDSS in the inclusion/exclusion criteria –CANTAB assessed six domains in MCCB (reasoning and problem solving were not assessed) –Practice effects of CANTAB are unknown; however, the study had memantine and placebo arms –Jadad score: 5
Mazinani [68], 2017, Iran	44.8 (18–55)/ 18, 18/12/ MMSE	–MMSE score increased from 26.3 to 28.2	–Small sample size –Inpatients not in an acute phase were enrolled –PANSS positive symptoms scores were not clearly defined in the inclusion criteria –No mention of SAS, CDSS, or anticholinergic medications in the inclusion/ exclusion criteria –Excluded those who received ECT in the past 2 weeks; ideally, patients who received ECT in the past six months should be excluded to recover from amnesia –MMSE is not a valid instrument for measuring cognition in schizophrenia –Jadad score: 5

BACS, Brief Assessment of Cognition in Schizophrenia; BPRS, Brief Psychiatric Rating Scale; CANTAB, Cambridge Neuropsychological Test Automated Battery; CDSS, Calgary Depression Scale for Schizophrenia; CIAS, cognitive impairments associated with schizophrenia; CPZ, chlorpromazine; ECT, electro-convulsive therapy; MCCB, MATRICS Consensus Cognitive Battery; MMSE, Mini-Mental State Examination; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS, Positive and Negative Syndrome Scale; PEAT, Penn Emotional acuity Test; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; SANS, Scale for the Assessment of Negative Symptoms; SAS, Simpson-Angus Scale; SUD, substance use disorder. [a] Completed the study; not intent-to-treat sample [167]. [b] Several authors did not mention some information/variables/criteria in their papers. It is unclear whether they did include those information/variables/criteria in their study and did not mention it in the article or did not include them at all in their study. [c] An open-label 1-year extension study ($n = 24$) had sustained effect on verbal and visual learning [168]. The Jadad score is a 7-item scale to assess the methodological quality of RCTs. Scores range from 0 to 5; higher scores indicate superior quality. Ease of use and brevity are advantages. A score of 5 does not rule out other limitations of the study.

Substance Use Disorder

Among all the studies in Table 1, only 2 conducted a urine drug screen (UDS) at baseline to exclude people with substance use disorder (SUD) [61, 70]; one study conducted a salivary drug screen [60]. A negative UDS at baseline is recommended as an inclusion criterion in the latest FDA-NIMH-MATRICS guidelines for proof-of-concept studies for cognitive enhancement in schizophrenia. Historical evidence is not sufficient to rule out SUD. The UDS does not assess alcohol use disorder. A UDS dip test is available and easy to complete; however, some studies may not have conducted the test due to monetary constraints. Another reason for not including the UDS is that the first FDA-NIMH-MATRICS guidelines did not mention SUD. However, inclusion of participants with SUD is likely to interfere with signal detection [58, 71]. The second version of the guidelines recommends that the project investigator use clinical judgment to decide whether to include a participant who tests positive on a UDS at the end of the study, as it may affect the sample size. The second version also uses the term "illicit." In one study, those with a history of illicit drug use in the past 6 months were excluded [68]. However, the term illicit is misleading because alcohol is licit, thus it is unclear whether those with alcohol use disorder in the last 6 months were excluded, which is a requirement.

Rating Scales

Of 12 studies, only 2 [62, 72] used the MATRICS Consensus Cognitive Battery (MCCB [73]). It is unclear how cognitive rating scales used in the other studies would translate to changes in the MCCB. The MCCB also has limitations – important cognitive measures such as sensory gating, mismatch negativity (MMN) [74, 75], and cortical oscillatory response dynamics/gamma oscillations [76] are not captured by the scale.

Most of the studies in Table 1 used the BPRS [77] or 4-item PANSS [78] to measure psychoses. In the BPRS positive symptoms, it is redundant to use the item suspiciousness. Suspiciousness is captured in the unusual thought content item; thus, capturing the data twice may lead to a falsely increased score, and the participant may not fulfill the criteria for enrollment in the study. Hallucination is captured and documented as a composite score; it is not scored in all of the five sensory modalities. The same analogy can be made for delusion as well. The FDA-NIMH-MATRICS guidelines recommend using only three items to measure psychoses. The BPRS 3-item (hallucinatory behavior, unusual thought content, conceptual disorganization), which captures all of the psychoses items, has been used successfully [79, 80].

Only one study in Table 1 conducted a measurement of functional capacity [62]. The FDA-NIMH-MATRICS guidelines recommend using UCSD Performance-Based Skills Assessment (UPSA)-2 [81]. None of the studies in Table 1 used Calgary Depression Scale for Schizophrenia (CDSS [82]) scores ≤10 as an inclusion criterion, which is recommended by the guidelines. Also, no studies excluded medications that have significant AA [67] that can affect signal detection [83, 84].

Miscellaneous Issues

Of the 12 studies, only one had an adequate sample size [61], and it was a multicenter study. It is important to note that single-site studies are limited by small sample size because of the recruitment and retention challenge. Rather than adjusting the inclusion and exclusion criteria to enhance recruitment [49], a multicenter or multinational (n = 319; [80]) study with an adequate sample size and stringent criteria may provide clinically valid results. As shown in Table 1, it is difficult to draw a firm conclusion from a failed study with a small sample size and several limitations and methodological issues. Studies often report the intent-to-treat (ITT) sample as the final sample size. Ideally, those who completed the study should be reported as the final sample size. There is a large discrepancy between the ITT sample size and the number who completed the study. In one study [70], the ITT sample was 32, and only 16 completed the study; n = 32 is reported as the final sample size, which is misleading. The last-observation-carried-forward results may not be as valid as those in participants who completed the study [48].

Four studies enrolled only participants with schizophrenia [68, 85–87]. Two studies excluded those with schizoaffective disorder, bipolar type [59–60], and one study excluded those with schizoaffective disorder [88]. The rationale for these exclusions was not described. The FDA-NIMH-MATRICS guidelines recommend including schizophrenia and schizoaffective disorder.

Of the 12 studies, only 2 documented adherence [62, 89]. However, both studies used a weekly pill count and medication review to check for adherence, which is not a foolproof method [90], and only participants who received 75% or more of their assigned study medication were included in the analysis [62, 89]. Efficacy signal detection may be enhanced in future RCTs if all of these issues are addressed.

Issues for Future Studies

For an ideal proof-of-concept cognition enhancement study, the age criterion would be 18–40 years (clinicaltrials.gov NCT02008773; this is a multicenter study). However, for a proof-of-concept study, considering the recruitment challenge and for feasibility reasons, 18–55 years would be acceptable (ClinicalTrials.gov Identifier: NCT02234752). For example, in a phase 2 study with encenicline for CIAS [80], 18–55 years was used as the age criterion. For phase 3 studies, 18–64 years may be used. To ensure consistency and interpretation of results between studies, these arbitrary age ranges would be ideal. Also, to detect an efficacy signal, the duration of the study should be at least 12 weeks [80]. Keep in mind that several weeks are needed for titration of medications to reach the maximum dose. If 12 weeks is not feasible due to monetary reasons, a 4- to 12-week study may be conducted [91]. A limit of chlorpromazine 1,000 mg/day equivalence may be used. Also, the maximum dose of an antipsychotic allowed should be no more than what is recommended in the package insert; none of the studies in Table 1 mentioned this. Medications with significant AA (>15 pmol/mL) such as amitriptyline, atropine, clozapine, dicyclomine, doxepin, L-hyoscyamine, thioridazine, and tolterodine [67] should be excluded in phase 2 treatment studies for CIAS. It may be a good idea to exclude participants if they are on two or more of the following: chlorpromazine, diphenhydramine, nortriptyline, olanzapine, oxybutynin, and paroxetine (AA values of 5–15 pmol/mL [67]). It may be worthwhile to conduct a gamma-glutamyl transferase test to capture alcohol use disorder; nail and hair analyses are not feasible. ECT within 6 months as an exclusion criterion may be added.

Kynurenine Pathway

Kynurenic acid (KYNA) is an antagonist of the NMDA [92, 93] and α7nACh receptors [94]. There is mounting evidence regarding the role of the kynurenine pathway (KP) in schizophrenia [95, 96] and CIAS [97]. The KYNA hypothesis in schizophrenia is well documented [98, 99]. The galantamine-memantine combination may be effective for CIAS with KYNA as a biomarker to detect the severity of cognitive impairments and monitor progress (target engagement) with treatment [100, 101]. There is also evidence from a small open-label study that this combination may be effective for CIAS with concurrent improvement in KP metabolite concentrations [102]. In that study, reduction of KYNA concentration was seen in all participants [102]. Decreased concentration of KYNA may be important not only for cognition but also for psychosis because increased KYNA concentration may be associated with psychosis [103–105]. Furthermore, inhibition of kynurenine aminotransferase II was associated with a marked reduction in dopamine firing activity in the ventral tegmental area [106]. KP modulations may be potential targets of novel antipsychotics [107]. Finally, KYNA levels bidirectionally modulate levels of neurotransmitters such as glutamate, dopamine, acetylcholine, and GABA [97, 108–114].

Negative Symptoms

Thirty-six patients with AD who did not respond to treatment with donepezil were switched to galantamine and followed for 24 weeks. Apathy and executive functioning improved significantly [115]. Thirty-one participants with schizophrenia received 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-A), which is a partial α7 nicotinic agonist. Those who received DMXB-A 150 mg twice daily had significant improvement in SANS total, anhedonia, and alogia scores (significant improvement in attention/vigilance and working memory) compared to those who received DMXB-A 75 mg twice daily or placebo [116]. In an RCT of galantamine in schizophrenia ($n = 86$), galantamine significantly improved alogia compared to placebo [89], which is not surprising since galantamine has been shown to improve primary progressive aphasia in frontotemporal dementia [117]. Galantamine administration had a beneficial effect on chronic poststroke aphasia in 45 patients [118]. Nicotinic action consistently improves alogia, which is an intriguing finding. In an RCT in schizophrenia ($n = 185$), an α7 nicotinic receptor agonist significantly improved executive functioning and the SANS total score compared to placebo [119]. In another RCT of encenicline (an α7 nicotinic partial agonist) in schizophrenia, negative symptoms significantly improved ($d = 0.33$) with encenicline 0.9 mg ($n = 105$) compared to 105 on placebo [80]. Finally, in another RCT in schizophrenia ($n = 215$), an α7 nicotinic agonist significantly improved total negative symptoms compared to placebo [120].

Memantine treatment reversed anhedonia in stressed rats [121]. Memantine was administered to neonatal rats with early maternal deprivation; social interaction was significantly enhanced in adult rats [122]. In an RCT with 28 chronic poststroke patients, memantine was effective for aphasia [123]. In a 52-year-old man with schizophre-

Table 2. Meta-analysis of RCTs with galantamine and memantine in schizophrenia: efficacy signal

Studies	Positive symptoms	Cognitive symptoms	Negative symptoms
Koola et al. [41], Galantamine 6 studies (n = 226)	Effect size Hedges' g = –0.076 (improved) not significant	Effect size Hedges' g = 0.233, p < 0.001 5 studies: effect size = 0.269	Effect size Hedges' g = –0.107 (improved) not significant
Kishi et al. [42], 2017 Memantine 8 studies (n = 448)	SMD = 0.46, p = 0.07	MD = 3.07, p < 0.0001	SMD = 0.96, p = 0.006
Zheng et al. [43], 2018 Memantine 8 studies (n = 452)	SMD = 0.12 not significant	Weighted MD = 3.09, p < 0.00001	SMD = 0.63, p = 0.009

MD, mean difference; SMD, standardized mean difference. If we combine the meta-analysis findings of galantamine and memantine (let alone synergy), we are likely to get a clinically significant efficacy signal with an effect size of at least 0.8 for positive, cognitive, and negative symptoms.

nia, memantine 20 mg daily for 2 months decreased SANS scores from 96 to 70 (avolition-apathy: −8, anhedonia-asociality: −7, affective flattening: −7, alogia: −1, and attention: −3) in 4 months [124]. Participants with deficit schizophrenia (n = 40) showed increased IgA responses to KP metabolites such as xanthurenic acid, picolinic acid, and quinolinic acid and relatively lowered IgA responses to KYNA and anthranilic acid compared to healthy controls (n = 40) and 40 subjects with nondeficit schizophrenia [125]. In a meta-analysis of 8 RCTs (n = 448) in schizophrenia [42], memantine significantly improved negative symptoms compared to placebo (SMD = 0.96, p = 0.006).

Eugen Bleuler's four As include affect, autism, ambivalence, and associations. Both galantamine (or medications acting at the nicotinic receptor) and memantine consistently improve affect, autism, and ambivalence, which is termed negative symptoms in the current literature. In a 6-week open-label study in schizophrenia with the galantamine-memantine combination, the SANS total score improved from 5 to 0 in one participant [102]. This finding is suggestive of primary negative symptoms because the BPRS psychosis, CDSS, and Simpson-Angus Scale scores were 4, 0, and 0 (all minimum scores), respectively. Medications that act at the NMDA receptor have been suggested as potential treatments for both negative symptoms and CIAS [126]. Therefore, use of the galantamine-memantine combination to treat negative symptoms is an additional benefit. Finally, to treat negative symptoms in schizophrenia, medications that target the glutamatergic system and α7nACh receptors are hypothesized to yield positive results [127–129].

Mismatch Negativity

MMN is a neurophysiological response elicited by a sequence of repetitive standard stimuli that is interrupted infrequently by a physically different oddball stimulus. MMN functioning [130] occurs via interaction of NMDA [131] and α7nACh receptors [132–134]. In addition, smaller MMN amplitude was significantly associated with lower GABA and glutamate (measured by magnetic resonance spectroscopy) level in 45 people with schizophrenia compared to 53 healthy controls [135]. MMN deficits are tied to poor functional outcome [136, 137], as recently confirmed in a study of 1,415 subjects with schizophrenia. In this study, early auditory processing event-related potential (MMN, P300, and reorienting negativity) predicted cognition (β = 0.37, p < 0.001), while cognition itself directly predicted negative symptoms (β = −0.16, p < 0.001) and indirectly predicted functional outcome [138]. Furthermore, MMN is highly predictive of response to auditory cognitive remediation [139]. MMN was found to be a sensitive and predictive biomarker of perceptual learning during auditory cognitive training in 28 individuals with schizophrenia [140]. MMN was enhanced in 13 healthy subjects with memantine 30 mg (Cohen's d = 0.87; [141]), in rodents with memantine 10 mg/kg [142], and in 41 people with schizophrenia with memantine 20 mg [75]. No studies have been conducted with galantamine on MMN. However, an RCT of encenicline in schizophrenia showed a dose-dependent increase in MMN [143]. Interactive effects of the α7nACh and NMDA receptors on MMN are well documented [144–146]. MMN is not only a cognitive bio-

marker but also a biomarker for negative symptoms in schizophrenia [147]. The pharmacology of cognition as a panacea for neuropsychiatric diseases was recently published [148]. This is important because neuropsychological tests were unable to distinguish CIAS versus cognitive impairments after traumatic brain injury [149]. MMN could be a potential biomarker with the galantamine-memantine combination in the treatment and prevention of schizophrenia [150, 151].

Summary and Future Directions

In the meta-analysis described previously, positive symptoms in schizophrenia improved at a trend level ($p = 0.07$) with memantine compared to placebo [42]. NMDA receptor dysfunction and dysregulation have been proposed as the final common pathway of positive, cognitive, and negative symptoms in schizophrenia [152]. Use of the positive allosteric modulator of α7nAChR to target positive, cognitive, and negative symptoms in schizophrenia is well documented [153–157]. Therefore, the galantamine-memantine combination has the potential to treat positive, cognitive, and negative symptoms of schizophrenia as shown in Table 2. The major pathophysiological mechanisms of cognitive and negative symptoms, KYNA, MMN, and BDNF [158, 159] are NMDA and nicotinic receptors. Although there is a diversity of biomarkers focused on CIAS, BDNF has accumulated the vast majority of evidence [160]. The galantamine-memantine combination has the potential to target both receptors concurrently, which is a paradigm shift in the treatment of schizophrenia since historically only one receptor (NMDA or nicotinic with partial treatment response) has been targeted at a time. Given that there are no available treatments for CIAS and negative symptoms, testing of quintuple hypotheses (dopamine, nicotinic-cholinergic, glutamatergic/NMDA, GABA, and KYNA) is a "low-risk high-gain" approach that could significantly advance our field. Multitarget drug discovery may play a role in the treatment of complex diseases [161] including, but not limited to, schizophrenia [100, 162].

The field should focus on all of the studies that showed an efficacy signal from one medication despite having methodological issues. Adequately powered, at least 12-week, well-designed RCTs (proof-of-concept study: galantamine-memantine combination versus galantamine-placebo or memantine-placebo) using galantamine 24 mg daily and memantine 28 mg daily to enhance efficacy [163], and stringently following the FDA-NIMH-MATRICS guidelines with this combination may significantly enhance cognition. In medicine, combination treatment is the rule rather than the exception. Psychiatry has lagged behind other specialties with regard to obtaining approval for combination treatments. If results of future RCTs are positive, "repurposing" of these already approved medications could lead to rapid clinical implementation.

Imbalance in one system (neurotransmitter/receptor/pathway) affects the entire system [164]. Hence, a reversal of anomalous activity in one system, or any combinations thereof, may have beneficial effects on the entire system [49]. After all, at the end of the day, schizophrenia is dementia praecox, weakening of volition [165], and Bleuler's 4 As. The field may be able to move beyond antipsychotic treatment towards "antischizophrenia" treatment [166] via the quintuple hypotheses strategy.

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