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Beyond anti-psychotics: the perspective of treating negative and cognitive symptoms with a combination of anti-dementia drugs

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Summary

Schizophrenia is a severe psychiatric disorder characterised by a broad spectrum of symptoms, including psychotic, negative and cognitive symptoms. Despite advances in antipsychotic treatment, current therapies do not fully alleviate negative and cognitive symptoms, making it difficult for patients to function adequately in society. Recent research suggests that combining anti-dementia drugs, specifically galantamine and memantine, with standard neuroleptic treatment may offer a novel approach to improving these symptoms. This paper explores the mechanisms of action of galantamine and memantine, their potential synergistic effects and their impact on key pathways implicated in schizophrenia, such as the cholinergic, glutamatergic and kynurenine pathways. The combination of these drugs shows promise in enhancing cognitive functions and reducing negative symptoms, potentially leading to better overall outcomes for patients with schizophrenia. However, further clinical trials are needed to validate these findings and optimise treatment protocols.

Key words: schizophrenia, cognitive impairment, memantine, galantamine, negative symptoms

Introduction

Schizophrenia is one of the most severe and challenging to treat disorder in psychiatry. Current therapy is based on more recent generations of anti-psychotics, which, despite their good efficacy in controlling psychotic symptoms, still leave a clear gap in the areas of negative and cognitive symptoms. Unsurprisingly, patients with schizophrenia are rarely able to resume work or return to full functioning in society [1]. Schizophrenia remains a disease that, in terms of the degree of cognitive impairment, is almost as bad as Alzheimer's or Parkinson's disease [2]. Additionally, as this

is a disease in which multiple pathophysiological pathways have been identified, the idea of single-agent treatment seems to be insufficient [3]. Due to the multidimensionality of the disorder, the approach of using a single, overly selective drug may lead to a situation in which discoveries regarding the neurobiology of schizophrenia are not implemented in clinical trials [4]. This concept is clearly exemplified by the infamous queen of anti-psychotics – clozapine. Its non-selectivity responsible for side effects may theoretically reflect a broader spectrum of action, thus increasing its chances of therapeutic success [5]. This is consistent with the heterogeneity of the clinical manifestations and causes of schizophrenia in patients, in whom the underlying cause of the disease is associated with various possible mechanisms [6]. A similar approach has been postulated by a growing number of specialists [7], pointing to the need to revise the treatment of cognitive symptoms.

The answer to this problem may lie in adding at least two drugs to antipsychotic treatment, instead of one for cognitive improvement, which would potentiate their effect on each other. Ultimately, such drugs should not have difficult-to-predict interactions with the primary treatment of schizophrenia and also be pharmacokinetically and dynamically predictable. These conditions may be met by combining galantamine with memantine, which together respond to at least several pathways [8]. Both of them are approved by the US Food and Drug Administration (FDA) for the treatment of Alzheimer's disease: in this case, galantamine 24 mg and memantine 28 mg daily are typically prescribed [9]. Moreover, memantine is a substance that has shown promising results in treating cognitive dysfunction in patients with schizophrenia [10], and its interaction with galantamine could potentiate the effect.

1. Mechanisms of action

Galantamine, in addition to its acetylcholinesterase inhibition, differs from the rest of the compounds in its group in its additional affinity for the α7-nicotinic receptor on cholinergic receptors, with which it binds as an allosteric modulator. These actions lead to an increase in cholinergic neurotransmission [11]. In addition, due to its weaker AChEI inhibition, its effect on nicotinic receptor desensitization is lesser compared to the rest of the group [12]. Through this mechanism it increases the release of glutamate, which, paradoxically, does not reduce but improves the effect of memantine. Memantine blocks the excessive tonic activity of the N-methyl-D-aspartate (NMDA) receptor by increasing the volitional ceiling required to stimulate the receptor, while galantamine, through the release of glutamine, improves the plasticity of synapses and enhances the post-synaptic NMDA action potential, which ultimately leads to better and still safe glutamatergic conduction than in the situation of using only one of the preparations. In addition, galantamine via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) potentiates the neuroprotective effects of memantine [4]. On top of that combining these preparations can normalize the level of metabolites of the kynurenine pathway and promote brain-derived neurotrophic factor (BDNF) synthesis (Figure 1).

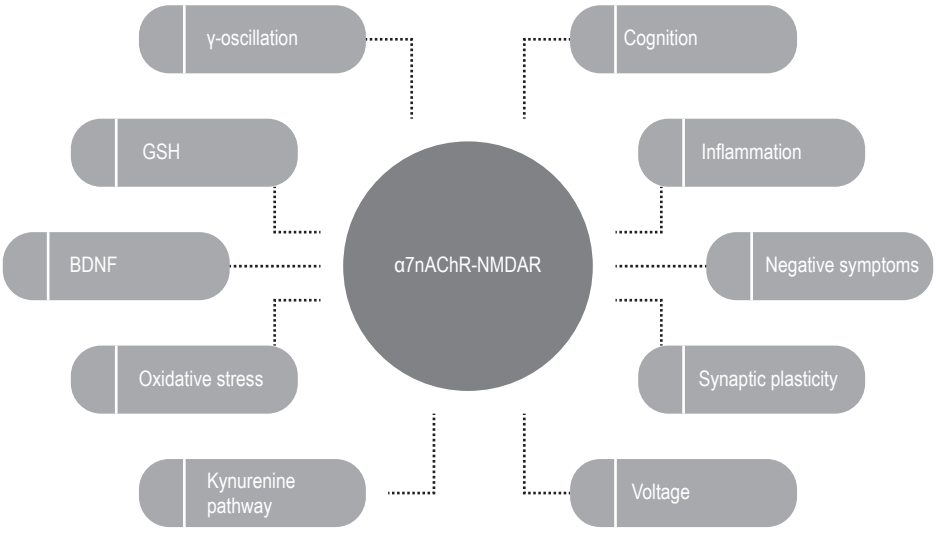


Figure 1. **Selected factors influenced by α7-nAChR-NMDAR combination.**

Abbreviations: glutathione (GSH), brain-derived neurotrophic factor (BDNF), gamma-oscillation (y – oscillation).

1.1. Voltage

NMDA receptor activation, with depolarized membrane potentials and an increase in intracellular Mg2+, might prevent nAChr activation. Both NMDA and a-bgT-sensitive nAChrs are highly dependent on Ca2+, so their controlled combined activation could help avoid intracellular Ca ion overload. Especially since memantine is inserted into the NMDAR channel in a voltage-dependent manner, not only through the open channel mechanism but also through the plasma membrane [13].

1.2. Oxidative stress

Galantamine shows antioxidant activity, as first described in an in vitro study [14]. Antioxidant effects have also been shown in preclinical studies with memantine [15]. In addition, glutathione (GSH) is synthesized by glutamate-cysteine ligase and glutathione synthase from cysteine, which is transported by the cysteine/glutathione antiport system (Sxc), which may be important in the treatment of diseases associated with glutathione depletion, such as schizophrenia [16]. Therapeutically relevant concentrations of memantine on thalamocortical glutamatergic transmission are primarily due to activation of Sxc [17].

1.3. Inflammation

While staying with oxidative stress, consider its association with inflammation, both of which can be treated as biomarkers of schizophrenia [18]. It is recognized that low baseline GSH levels in erythrocytes predispose to psychosis. Moreover, it is also believed that the redox, glutamatergic/NMDA and neuroimmune receptor systems may be key points in schizophrenia. Therefore, it seems that the combination of galantamine and memantine could work well in this regard as well, due to its N-acetylcysteine-like effects. The anti-inflammatory effect on the hippocampus of galantamine has been demonstrated, and similar evidence can also be provided for memantine [19].

1.4. Gamma oscillations

Variable oscillatory gamma-receptor activity is an important pathological mechanism in schizophrenia, for positive, negative as well as cognitive symptoms [20]. Abnormal activity in the γ-band is observed in patients with schizophrenia and animal models of the disease, and has been suggested to underlie psychosis and cognitive and perceptual deficits [21]. It has been suggested that high-frequency oscillations may be a translational biomarker of the disease [22]. NMDA receptors control the timing and synchronization of long-range GABA interneurons [23], and these are responsible for the primary generation of high-frequency oscillations and their local synchronization. Activation of α7nACh receptors enhances hippocampal oscillations [24], moreover, α7nAChRs are also expressed at pre – and postsynaptic sites of GABAergic interneurons, where they control inhibitory transmission. Thus, in addition to direct depolarization of interneurons, another important function of α7nAChRs is the regulation of synaptic transmission and plasticity [25]. A combination of memantine and galantamine significantly increased oscillations in rodent hippocampus [26].

1.5. BDNF

There are many arguments supporting the role of BDNF as a biomarker associated with cognitive functions in schizophrenia [27]. BDNF appears to be involved in numerous neuronal processes related to schizophrenia, as confirmed in animal models, although the data still require verification [28]. However, it has been shown that BDNF acts through various intracellular signaling pathways triggered by the activation of tyrosine kinase receptor B (TrkB), which enhances synaptic plasticity [29]. In studies, memantine reversed memory impairments and significantly increased the mRNA levels of BDNF and TrkB in both the prefrontal cortex and hippocampus of stress-exposed rats [30]. Additionally, galantamine increased the phosphorylation of TrkA and TrkB in the mouse hippocampus [31]. Finally, the interaction between α7nACh and NMDA receptors can synergistically enhance BDNF levels and induce synaptic plasticity and long-term potentiation [32].

1.6. Kynurenine pathway (KP)

The KP that metabolizes tryptophan leads to the formation of neuroactive metabolites in the central nervous system [33]. One of the products of its further metabolism is kynurenic acid (KYNA), which is an antagonist of the α7-nicotinic receptor [34], as well as the NMDA receptor [35]. A growing number of studies indicate that this metabolite is involved in the pathogenesis of schizophrenia [33, 36]. It has been suggested that schizophrenia is associated with a combination of reduced phasic dopamine responses to relevant stimuli and increased spontaneous dopamine release. Reduced phasic responses to relevant stimuli help explain negative symptoms [37].

Blockade of kynurenine aminotransferase II was associated with decreased dopamine discharge activity in the ventral tegmental area [36]. The important role of KYNA is also indicated by the fact that KYNA levels modulate the levels of neurotransmitters such as glutamate, dopamine, acetylcholine, and GABA [39, 40].

2. Galantamine-memantine combination in schizophrenia

The use of galantamine and memantine may be a valuable component of schizophrenia treatment, especially given the safety which is observed in treating Alzheimer's disease. The most common side effects of galantamine are parasympathetic effects such as nausea, vomiting and diarrhea, and for memantine, dizziness, headache, constipation, drowsiness, and high blood pressure [41]. These drugs are safe and well tolerated, but interactions with other medications should also be considered and their safety profile should be assessed from this perspective.

Table 1. **Metanalysis of RCTs regarding memantine and galantamine**

Meta-Analyses of RCTs in Schizophrenia	Positive symptoms	Cognitive symptoms	Negative symptoms
Koola, 2018 [4]; Koola et al., 2020 [42] Galantamine: 6 studies (*N* = 226)	*ES* = 0.076 *P* = 0.6	*ES* = 0.269 *P* <0.001	*ES* = 0.107 *P* = 0.5
Zheng et al., 2019 [10] Memantine: 9 studies (*N* = 512)	*ES* = 0.32 *P* = 0.05	*ES* = 1.07 *P* <0.0001	*ES* = 0.71 *P* = 0.0003

ES – effect size

There is still a lack of studies analyzing the combined treatment with memantine and galantamine in schizophrenia. However, studies evaluating the effectiveness of these drugs separately may provide some insights (Table 1).

In a meta-analysis of six randomized controlled trials (RCTs) (*N* = 226) assessing the efficacy of galantamine as an adjunct to antipsychotic treatment in patients with schizophrenia, a significant improvement in cognitive function was observed compared to placebo (*ES* = 0.269). Cognitive performance was measured using neuropsychological tests or tasks specific to each study. According to the meta-analysis, the effect size (*ES*) was not significant for positive symptoms (*ES* = 0.076) and negative symptoms (*ES* = 0.107). However, this study was limited by the small sample size and the num-

ber of studies included in the analysis. Another limitation was that only the overall cognitive score was analyzed [42].

In contrast, a meta-analysis of nine RCTs (N = 512) utilizing memantine as an adjunct to antipsychotic treatment in patients with schizophrenia demonstrated a significant effect on cognitive impairments (ES = 1.07) and negative symptoms (ES = 0.71), with the smallest impact on positive symptoms (ES = 0.32). However, the superiority of memantine as an adjunct treatment for improving negative symptoms was observed in only one RCT that extended beyond sixteen weeks of treatment with a combination of memantine and risperidone [43]. No significant improvement was noted in studies lasting 6–12 weeks, suggesting that memantine's therapeutic effect may require a treatment duration exceeding 12 weeks [44]. The limitations of this meta-analysis include varying doses of memantine used across the studies (ranging from 5 to 20 mg/day), as well as the concurrent use of different antipsychotic, mood-stabilizing and antidepressant medications, which makes it difficult to clearly assess the efficacy of memantine [10].

3. Conclusions and future directions

Current results suggest that using a combination of galantamine and memantine may offer benefits, particularly in terms of improving cognitive functions and reducing negative symptoms of schizophrenia. However, there is currently limited data available, so further research to assess whether such a combination is clinically beneficial seems justified. In Poland, conducting clinical trials and using the drug off-label is challenging due to the availability of galantamine only in injection form. Efforts are needed to make the drug available in tablet form.

In summary, a comprehensive therapeutic approach that addresses multiple pathophysiological mechanisms of schizophrenia appears to be a promising direction in psychiatry, improving the quality of life for patients. The combination of galantamine and memantine, due to its synergistic effects, could be a valuable component in the treatment of schizophrenia.

Aleksandra Julia Oracz and Stefan Modzelewski declare equal contribution to this work.

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