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REVIEW ARTICLE

Pharmacological management of neurocognitive impairment in schizophrenia: A narrative review

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Abstract

Background: Cognitive impairment are among the core features of schizophrenia, experienced by up to 75% of patients. Available treatment options for schizophrenia including dopamine antagonists and traditional antipsychotic medications have not been shown to confer significant benefits on cognitive deficits. Contrary to the focus on management of positive symptoms in schizophrenia, cognitive abilities are main predictor of independent living skills, functional abilities, employment, engagement in relapse prevention, and patients' subjective sense of well-being and quality of life. This review aims to provide a summary of recent literature on pharmacological options for the treatment of cognitive deficits in schizophrenia.

Methods: We conducted a literature search of studies from 2011 to 2021 across four electronic databases including PubMed, PsycInfo, MEDLINE, and Embase. Human studies using a pharmacological treatment for cognitive impairment in schizophrenia were included.

Results: Fifty-eight eligible publications, representing 11 pharmacological classes, were included in this review. Major limitations involved small sample size, methodological limitations as well as heterogeneity of participants and outcome measures.

Conclusions: Overall evidence remains inconclusive for any pharmacological classes studied for the treatment of cognitive deficits in schizophrenia. Methodological limitations in a majority of the studies rendered their findings preliminary. We further discuss possible explanations for these findings that could guide future research.

KEYWORDS
cognition, cognitive dysfunction, neuropharmacology, psychopharmacology, schizophrenia

1 | INTRODUCTION

Cognitive impairment is known to be a core feature of schizophrenia spectrum disorder and experienced by up to 75% of patients with schizophrenia.[1,2] This can vary in severity, from mild deficits to marked impairment, with the most evidence suggesting that cognition is moderately to severely impaired in people with schizophrenia compared with healthy controls. Estimates include reaching 2 SD below healthy controls.[1] Evidence suggests that cognitive impairment occurs prior to diagnosis of schizophrenia or the development of positive or negative symptoms. Neurocognitive deficit is the biggest predictor of functional ability[3] such as occupation and social function.[4]

Contrary to psychiatry's focus on management of positive symptoms, patients' subjective sense of quality of life is more related to control of negative symptoms, depression, and cognitive impairment. Furthermore, the impact of cognitive impairment on QoL can be objectively measured with validated tools (e.g., Heinrich's QoL scale). Reductions in quality of life are associated with degree of cognitive impairment.[5] Cognitive impairment and cognitive functioning are associated with many outcomes including quality of life, independent living skills, functional abilities, relapse prevention, and employment,[1] and for many patients, these are important factors in subjective sense of well-being and QoL.

Given the prevalence of neurocognitive deficits, the association with functional impacts and patient well-being, and the little improvement conventional treatment of antipsychotic medication has on improvement of these symptoms, this presents an area of significance in understanding and treatment and warranting further investigation. There is a dearth of literature that summarizes the effects of augmenting agents for cognitive impairment in schizophrenia. We present a narrative review of various classes of augmenting medication and the impact on cognitive deficits in schizophrenia.

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. Studies included were from 2010 onward considering the prior articles were all captured in Goff's review article.[6] The final search was conducted on June 17, 2021, across four electronic databases including PubMed, PsychINFO, MEDLINE, and Embase. Considering subject headings are different in each database, our searches used the appropriate terms that covered all these variations, as relevant to each database. Search terms included "cognitive dysfunction," "cognitive deficit," "cognitive impairment," "schizophrenia," "drug therapy," and "pharmacotherapy." Eligible articles were also searched to identify additional relevant studies. In addition, a subsequent search for meta-analyses or systematic reviews for each drug or compound studied was completed during manuscript preparation to summarize the most recent evidence up to 2023.

2.2 | Study selection

For completeness, we included all randomized clinical trials (RCTs), open trials, and case series. All relevant studies which reported on any pharmacotherapeutic agent for the treatment of cognitive deficits in schizophrenia were included. We excluded review articles, posters, preprints, and investigational agents in the early phases of development. Antipsychotic medications (i.e., dopamine antagonists) were also excluded from this review considering the interplay between cognitive deficits and antipsychotic medications are extensively reviewed and considered out of the scope of this paper.

2.3 | Data extraction and outcome measures

A data extraction table was developed by the authors for each agent (Table S1). It was pilot tested on eight randomly selected studies and refined accordingly. The following data were extracted from each study: author/year/country of publication, study design, duration of the study, patient population, number/setting, medication/dose, cognitive measures, cognitive results, side effects, and other findings. We summarized the findings on a range of outcome measures as reported by the studies including impact of treatment on various domains of cognition among patients with schizophrenia.

3 | RESULTS

The results section of this paper will include overarching classes of medications reviewed, data from articles identified for individual agents in those classes, pharmacological mechanism of action, the number of articles reviewed, and summary statements from recent meta-analyses or systematic reviews that were identified. In addition, the common indications of the agents along with those in clinical use versus experimental use is provided.

3.1 | Nicotinic agents (7 articles)

Nicotinic receptors are responsible for a wide variety of brain processes, including cognitive functions in the areas of learning, attention, and memory.[7] Specific subtypes such as α-7 receptors have been shown to be impaired in the brains of patients with schizophrenia.[8] Nicotinic agonists act upon postganglionic nicotinic receptors, at neuroeffector junctions in the peripheral nervous system and on nicotinic receptors in the central nervous system. Agonists bind and activate nicotinic cholinergic receptors and are suggested as having

important therapeutic implications for disorders with cognitive dysfunction such as schizophrenia and Alzheimer's dementia. Nicotinic agents reviewed included nicotine replacement, varenicline, tropisetron (alpha-7 subunit-containing nicotinic acetylcholine receptors) as well as encenicline. Three full-text articles on varenicline, three on tropisetron, and one on encenicline were located that matched study criteria.

3.1.1 | Nicotine replacement (2 articles)

Studies that examined the cognition enhancing of nicotine primarily used a transdermal patch or chewing gum on participants with schizophrenia and without schizophrenia, including smokers and non-smokers in each group. The randomized controlled trial conducted by Hahn et al. in 2013[9] used the Spatial Attentional Resource Allocation Task (SARAT) and the Singleton Detection Task in examining patients smoking ad libitum and using transdermal nicotine patch (14 mg/24 h) or a placebo patch. It was found that attention task performance was improved by transdermal nicotine vs. placebo with intermediate performance by ad libitum smoking. Furthermore, a trial by Hahn et al. in 2019[10] showed nicotine replacement did not potentiate any training benefits of cognitive rehabilitation programs for schizophrenia. Self-reported ability to concentrate changed with nicotine status in healthy controls but not in those with schizophrenia. These overall study findings suggest that subjective or objective attentional benefits are unlikely the primary driving force of tobacco consumption in SCZ.

3.1.2 | Varenicline (3 articles)

As partial agonist and blocker of alpha-4-beta-2 nicotinic acetylcholine receptor subtype, this medicine blocks the effects of nicotine on the brain and is used as a common smoking cessation agent in clinical practice. Through partial agonism, varenicline reduces dopaminergic activation by nicotine stimulation of the mesolimbic dopamine system associated with nicotine addiction.[11] Overall, the results surrounding varenicline on cognition in schizophrenia is mixed and a meta-analysis conducted in 2020 by Tanzer et al.[12] concluded that it was not a useful agent for improving multiple domains of cognition including attention, executive function, or processing speed in schizophrenia. Furthermore, they suggested that a trial of at least 2500 patients would be needed to possibly show significant findings, which is significantly greater than any previous trial.

A randomized cross-over human laboratory study on varenicline was published by Kozak and George[13] in 2017 which included 15 non-smokers with schizophrenia (SZ), 15 non-psychiatric non-smokers, 14 SZ tobacco smokers, and 14 non-psychiatric smokers who received between 0 and 2 mg of varenicline per day (29 patients with schizophrenia, with 29 controls) divided into smokers or non-smokers. Visuospatial working memory (VSWM) and cognitive processing therapy were used to measure the cognition of subjects where it was concluded that there were complex effects of smoking and diagnostic status on verbal learning and working memory, independent of varenicline dose. Notably, non-smoker patients with schizophrenia performed worse than all groups across VSWM and verbal memory, regardless of varenicline dose. In 2016, Smith et al.[14] published a double-blind randomized parallel-group design study on varenicline which enlisted 87 total patients (all smokers). Doses ranged between 0 and 2 mg of varenicline per day and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used in analysis of subjects. Results showed that varenicline was not a cognitive enhancer in this study and did not worsen any psychiatric symptoms, with some weak improvement noted on certain measures of depression. Some subjects experienced side effects during the study which included nausea and vomiting. An 8-week trial on varenicline conducted by Shim et al.[15] in 2012 on 120 clinically stable patients with schizophrenia employed the Digital Symbol Substitution Test (DSST) and Wisconsin Card Sorting Test (WCST) as well as Cognitive Performance Test (CPT) to measure cognition. Varenicline improved cognition compared with the placebo on the DSST and WCST. In smokers, CPT hit reaction time and Stroop interference were reduced for varenicline vs. placebo (no treatment difference was observed in non-smokers). In the primary analysis of neurocognitive differences at Week 8, no varenicline-placebo differences were significant.

3.1.3 | Tropisetron (2 articles)

A serotonin 5HT3 receptor antagonist that is primarily used in the prevention of chemotherapy-induced nausea and vomiting in clinical practice and is a alpha-7 nicotinic acetylcholine receptor partial agonist.[16]

A doubled-blind, placebo-controlled RCT by Shiina et al.[17] in 2010 on tropisetron involved 40 patients with chronic schizophrenia who had taken risperidone (2–6 mg/day). Patients were randomly assigned to a fixed titration of tropisetron (10 mg/day) or placebo. Cognitive measures analyzed auditory sensory gating P50 deficits and employed the Quality-of-Life Scale (QLS), as well as the Cambridge Neuropsychological Test Automated Battery (CANTAB) and Positive And Negative Syndrome Scale (PANSS). Administration of tropisetron but not placebo significantly improved auditory sensory gating P50 deficits in non-smoking patients with schizophrenia. The drug was overall well tolerated. One patient in the tropisetron group dropped out of the trial due to chest pain. Three in the placebo group dropped out due to influenza, worsening of illness, and extrapyramidal symptoms. The scores on the rapid visual information processing task of CANTAB were significantly improved by tropisetron while PANSS scores were not changed. QLS scores in all patients but not non-smoking patients were significantly improved by the tropisetron trial.

A 1-day trial conducted by Xia et al. in 2020[18] on tropisetron improved both cognitive and P50 inhibition deficits in the 40 schizophrenic non-smoking patients studied.

3.1.4 | Encenicline (1 article)

Encenicline (1 article) was a study drug undergoing clinical trials for the treatment of cognitive impairment in Alzheimer's disease and schizophrenia, as a selective partial agonist of the alpha-7 nicotinic acetylcholine receptor, but failed to meet the study endpoints in 2016 and has been discontinued by the Federal Drug Administration (FDA) in the United States.[19]

A phase 2 double-blinded, randomized, placebo-controlled, parallel design, multinational study conducted by Keefe et al. in 2015.[20] Three hundred nineteen randomized patients were enlisted in the study: 317 included in safety population, and 307 included in intent-to-treat population. All were schizophrenic patients on chronic stable atypical antipsychotics. The drug was administered 0.27 or 0.9 mg daily or placebo (over the 12-week study period). Cognitive measures used included the Overall Cognition Index (OCI), MATRICS, the Schizophrenia Cognition Rating Scale (SCoRS), and PANSS. Encenicline was well tolerated and demonstrated clinically meaningful improvement in cognition and function in patients with schizophrenia. Most significant effects were observed in the 0.9 mg group. Improvement trends were seen in both the MCCB and PANSS scores at 0.27 and 0.9 mg with a more beneficial effect observed at 0.9 mg.

The major studies on varenicline can be confounded by inclusion of the smoking characteristic in some patients making it difficult to differentiate whether improvement in cognition could be seen in the administration of varenicline alone. Varenicline did not appear to be a cognitive enhancer in one major study, which included smokers only.[14] Information on tropisetron was limited but showed some promise in improvement of cognitive features; a major limitation was no improvement in cognition seen in non-smoking schizophrenic patients. Studies assessing encenicline while limited showed cognitive benefits primarily at the 0.9 mg dose range. The presence of smoking was not discussed in the study and could also serve as a factor influencing cognition.

3.2 | Dopaminergic agents

Dopamine agonists bind to dopamine receptors and activate cellular signaling pathways. Dopaminergic agents researched included pergolide, tolcapone, l-dopa, and bromocriptine. No full-text articles meeting the criteria were compiled; a poster abstract was also excluded. Given the lack of information meeting the study criteria, conclusions on potential for use in treating cognitive deficits in schizophrenia cannot be adequately drawn.

3.3 | Psychostimulants

Stimulants help to increase neurotransmitters in the synaptic cleft through various mechanisms including dopamine, norepinephrine, and serotonin. They may also increase agonistic activity at catecholamine or serotonin receptors.[21]

Stimulants researched included all amphetamine and methylphenidate-based medications. No full-text articles meeting the criteria were compiled, and all poster abstracts were eliminated from the assessment. Given the lack of information meeting the study criteria, conclusions on potential for use in treating cognitive deficits in schizophrenia cannot be adequately drawn. A systematic review and exploratory meta-analysis of by Solmi et al.[22] looking at psychostimulants and atomoxetine in patients with schizophrenia or schizoaffective disorder suggested that atomoxetine and amphetamines may improve cognitive symptoms, and methylphenidate should be avoided in this group, as the use consistently worsened symptoms or predicting relapse.

3.4 | Glutamatergic medications (7 articles)

Glutamate is the major excitatory neurotransmitter in the central nervous system. Indirect evidence from animal models, post-mortem studies, and pharmacological studies have linked glutamatergic dysfunction to cognitive impairments in schizophrenia.[23] However, given the heterogeneity of schizophrenia and the fact that glutamatergic neurons are ubiquitous in the brain, direct evidence regarding the precise nature of the glutamate system in schizophrenia is still incomplete and insufficient.[24] Our search identified seven studies involving the use of glutamatergic drugs to treat cognitive dysfunction in patients with schizophrenia, with six demonstrating positive results. These include three RCTs and one open-label extension study on memantine, two RCTs on benzoate, and one RCT on D-cycloserine. These studies primarily investigated the changes in cognition of either monotherapy or adjunctive therapy when compared to placebo, with treatment duration ranging from 8 to 52 weeks. Participants were otherwise healthy adults diagnosed with schizophrenia including both inpatients and outpatients. Cognition was measured in native language using analogs of tests from the MCCB (MATRICS Consensus Cognitive Battery), BACS (Brief Assessment of Cognition Scale), and CANTAB.

3.4.1 | Memantine (4 articles)

Memantine (4 articles) is an antagonist of the NMDA receptor subtype of the glutamate receptor, that have broad roles in cognitive processes and other brain functions, typically prescribed to stabilize cognitive and functional decline in the setting of Alzheimer's dementia.[25]

Glutamate excess is hypothesized to lead to increased excitability of the brain and be associated with neurotoxic effects. This medication has been explored as a possible neuroprotective agent for the treatment of schizophrenia.[26] Due to its low affinity, non-competitive nature, and rapid off-rate kinetics, memantine differs from NMDA-R blockers such as ketamine, which are known to induce symptoms of psychosis.[27]

In a 2016 study by Veerman et al.,[28] memantine augmentation in 52 patients with clozapine-refractory schizophrenia showed significant improvements in verbal and visual memory as assessed by CANTAB, as well as decreased negative symptoms as assessed by PANSS (Positive and Negative Syndrome Scale). In the following 1-year extension study,[26] the favorable cognitive effects of adjunctive memantine (20 mg/day) on memory were sustained in 40 patients with clozapine-refractory schizophrenia. Interestingly, further improvement of negative, positive, and overall symptoms was observed without serious adverse effects. Similarly, in a proof-of-concept study with 24 patients with schizophrenia, adjunctive memantine (10 mg twice daily) on top of stable risperidone showed significantly higher performance in attention intensity, problem-solving, verbal learning, flexibility, and immediate memory when compared to the placebo group.[27] Another study that investigated add-on treatment of memantine (20 mg/day) in 40 patients on a stable antipsychotic regimen saw all subscale scores of the BACS increase significantly in the memantine group only.[29] These studies are in line with recent discussions postulating that memantine as a NMDA receptor modulator may have neuroprotective properties to improve long-term outcome and cognition in patients with schizophrenia. However, it is important to note that major limitations were present in the above studies. Most did not control for differences in baseline treatment regimen and had small sample sizes ($n = 24–52$). This is in keeping with a meta-analysis and systematic review by Kishi et al.[30] looking at the anti-dementia drugs (which included memantine) for cognitive impairment in schizophrenia, which suggested that although these medications may offer some improvement in some measures of cognition, they are influenced by small study effects and bias and when looking at composite cognitive test scores, they were not superior to placebo.

3.4.2 | Sodium benzoate (2 articles)

Decreased function of the NMDA receptor has an important role in the pathophysiology of schizophrenia and mechanisms to increase NMDA has been studied for potential improvements in cognition. Sodium benzoate is a D-amino acid oxidase (DAAO) inhibitor that enhances NMDA function by blocking the metabolism of D-amino acids.[31]

In a 2013 study by Lane et al.,[32] add-on sodium benzoate (1 g/day) was compared with placebo in 52 patients with chronic schizophrenia. They reported overall improvement of neurocognition, specifically in processing speed and visual learning/memory as assessed by the MCCB, as well as a 21% reduction in PANSS total score. A different study by Lin et al.[33] that included 49 patients compared sarcosine (2 g/day) alone, sodium benzoate (1 g/day) plus sarcosine (2 g/day), and placebo, and saw the greatest improvement in cognition and global functioning in the sodium benzoate group using the MCCB. They also observed additional improvements of both positive and negative symptoms in the sodium benzoate group. Both studies suggest benzoate adjunctive therapy as a novel approach for improving neurocognition and symptom severity in patients with schizophrenia. Seetharam et al.[34] showed in their meta-analysis that add-on sodium benzoate in the treatment of schizophrenia did not offer any significant improvement in cognition, QoL nor overall functioning.

3.4.3 | D-cycloserine (1 article)

D-cycloserine (1 article) is a partial agonist at the glycine site of the glutamatergic NMDA receptor and most used as antibiotic therapy in tuberculosis. It has been increasingly studied for its possible therapeutic benefit in neuropsychiatric disorders.[35]

To test its potential as a neuroprotective drug for schizophrenia, Takiguchi et al.[36] compared D-cycloserine (50 mg/day) and placebo in 41 patients with schizophrenia and saw no improvement in cognitive function or positive or negative symptoms. Moreover, the study suggested that treatment response to D-cycloserine is influenced by heterogeneity derived from differences in white matter integrity and age of onset.

In summary, among the glutamatergic agents, there are a few small-scale studies of memantine with positive results on cognition. However, these studies suffer limitations and larger scale studies are required before conclusion could be drawn.

3.5 | Noradrenergic medications

Noradrenaline is an important neuromodulator in normal cognition, and it has been suggested that disruption of noradrenergic function could be associated with cognitive deficits in neuropsychiatric illnesses.[37] Despite this, noradrenergic agents as a potential treatment for cognitive deficits in schizophrenia have been largely unsuccessful in previous trials.

3.5.1 | Guanfacine (1 article)

Guanfacine (1 article) is a selective alpha-2 A-adrenergic receptor agonist, originally used to manage hypertension, now most used in the management of ADHD as an adjunctive or second-line agent to psychostimulants.

Our search identified one RCT by McClure et al.[38] that examined the triple interaction of guanfacine, with computerized cognitive remediation and social skills training on cognitive and functional outcomes. Specifically, 28 patients with schizotypal personality disorder received either guanfacine (2 mg/day) or placebo while undergoing computer-based cognitive enhancement exercises and manualized social skills training modified from cognitive enhancement therapy. Those in the guanfacine group demonstrated significantly greater improvements in reasoning, problem-solving, functional skills, and social cognition.

These results suggest that guanfacine may augment the results of cognitive remediation and social skills training, perhaps due to its hypothesized effect of enhancing attentional ability.

3.6 | Serotonergic medications (8 articles)

In recent years, new drugs targeting serotonin (5-HT) receptors in the brain have been intensively investigated as potential targets for different symptom domains of schizophrenia. Our search identified eight articles describing the use of serotonergic agents for the treatment of cognitive deficits in patients with schizophrenia: two RCTs on ondansetron, two RCTs on fluvoxamine, one open-label study on vortioxetine, one RCT on buspirone, one RCT on citalopram, and one RCT on avisetron. Each study used a different battery of tests to measure of cognition and duration of treatment arm ranged from 6 to 24 weeks.

3.6.1 | Ondansetron (2 articles)

Ondansetron (2 articles) is a 5-HT3 receptor antagonist, commonly used as an anti-emetic agent of chemotherapy-induced and radiation-induced nausea and vomiting. Evidence suggests that 5 HT3 receptors are implicated in the pathogenesis of schizophrenia. Ondansetron has seen modest success in recent trials as a treatment for cognitive impairments in patients with chronic schizophrenia.[39]

5-HT3 receptors have increased density in the human prefrontal cortex, nucleus accumbens, hippocampal formation, and amygdala, which are areas heavily involved in emotion, cognition, depression, and anxiety.[39] Therefore, the rationale is that modulation of this system can ameliorate cognitive symptoms seen in schizophrenia. Our search includes one positive study and one negative study of ondansetron. A recent study with 85 participants from Kulkarni et al. in 2018 suggests adjunctive ondansetron (8 mg/day) provides significant improvement in the cognitive subscale of PANSS and appears to be well tolerated with no adverse effects. Conversely, a 2010 study by Mohammadi et al.[39] that included 30 patients failed to show significant differences between adjunctive ondansetron (8 mg/day) compared with placebo, which were both in addition to risperidone (4–5 mg/day). There was no improvement in cognitive deficits at endpoint except for some components of visual memory. A meta-analysis by Zheng et al.[40] shows that data around adjunctive ondansetron on cognition, assessed by different measures, have shown conflictual results and should be further assessed through large, prospective, RCTs.

3.6.2 | Fluvoxamine (2 articles)

Fluvoxamine (2 articles) is a selective serotonin reuptake inhibitor (SSRI), commonly used in the treatment of anxiety and depressive disorders, which inhibits reuptake of serotonin through a variety of mechanisms which ultimately leads to increased serotonin in the synaptic cleft and increased activity post-synaptically, and also has high sigma-1 receptor agonism.[41]

Fluvoxamine has also been studied as a potential agent for addressing cognitive deficits in patients with schizophrenia, with variable results. In a 2018 trial by Haji Seyed Javadi et al.[42] with 68 participants, risperidone augmentation with fluvoxamine (50 mg/day titrated to 100 mg/day) was shown to significantly improve Wechsler Memory Scale scores when compared to risperidone alone. Interestingly, several subdomains in the SANS (Scale for the Assessment of Negative Symptoms) also showed significant improvement in the intervention group only, such as poverty of speech, attention deficit, and curbing of interests. However, these results contrast with an older study in 2012 by Niitsu et al.[43] with 44 patients that suggests add-on fluvoxamine (50 mg/day titrated to 150 mg/day) has no major impact on cognitive impairments or clinical symptoms in patients with schizophrenia.

3.6.3 | Vortioxetine (1 article)

Vortioxetine (1 article) is a serotonergic antidepressant with multimodal activity. It acts as both a serotonin receptor agonist and antagonist while also having reuptake inhibition properties.

Our search includes one positive study on Bruno et al.[44] demonstrated in a pilot study with 20 patients that vortioxetine (10 mg/day starting dose, titrated to 20 mg/day) significantly improved performances on Verbal Fluency Test and Stroop Task, which correlates to an improvement in attentional resistance to competing stimuli and word generation within a given category, respectively. Additionally, positive symptoms, total average symptoms, and depressive symptoms were all significantly improved by the end of the trial, with no adverse side effects reported.

3.6.4 | Buspirone (1 article)

Buspirone (1 article) is an anxiolytic drug, that has strong, partial agonist for the serotonin 5-HT1A receptors, weak affinity for serotonin 5HT2 receptors and acts as a weak antagonist on dopamine D2 autoreceptors.[45]

Our search identified one positive study on Buspirone by Wang et al.[46] It includes 196 patients and demonstrated that co-treatment of buspirone with atypical antipsychotics outperformed atypical antipsychotics alone in improvements in logical reasoning, generalization, visual discrimination/memory/comprehension, and spatial coordination in patients with schizophrenia, supporting the notion that cognitive dysfunction in schizophrenia may be alleviated through 5-HT1A stimulation. A recent meta-analysis in this area suggested that buspirone can improve attention and processing speed in patients with schizophrenia.[47]

3.6.5 | Citalopram (1 article)

Citalopram (1 article) works similarly to other SSRIs, such as fluvoxamine. Using our search criteria, we identified one RCT on citalopram. In this 12-week study of 198 patients with schizophrenia, it was found that there were no significant differences between citalopram (20 mg/day) and placebo in changes in cognition.[48] To assess patients' cognition, a test battery was used which included the MMSE, Digit Span Distractibility Test, Letter and Category Fluency, Trail-Making Test, CPT, Digit-Symbol-Coding, Symbol Search, and Letter-Number Sequencing.

3.6.6 | Avisetron

Avisetron is a new selective 5-HT6R antagonist, currently an investigational agent not currently approved for use in clinical practice, that is being studied as a novel therapy for schizophrenia.

Our search identified a 6-week study by Morozova et al.[49] comparing Avisetron (4 mg starting dose, titrated to 8 mg) and placebo, which included 80 patients with schizophrenia. BACS and CPT were used for endpoint assessment. This was a negative study, with no between-group differences observed at any stage of the study.

In summary, of the very few studies which have explored the impact of serotonergic agents on cognitive deficits in schizophrenia, there is one positive pilot study of vortioxetine and one positive study for buspirone. The remaining studies did not demonstrate significant improvement in cognitive deficits with serotonergic agents. This is consistent with a meta-analysis of antidepressant medications more broadly, including those with additional targets to serotonin, which found that there was a statistically significant but clinically negligible effect of antidepressant agents on executive function and cognitive composite score, compared with placebo.[50]

3.7 | Wakefulness promoting agents

3.7.1 | Modafinil/armodafinil (3 articles)

Modafinil/armodafinil (3 articles) are wakefulness-promoting drugs which act predominantly as inhibitors of the dopamine transporter or dopamine reuptake pump which indirectly activates the release of orexin neuropeptides which stimulate wakefulness[41] which are the major cognitive enhancing mechanisms, although there are other including effects on glutamate and histamine. Armodafinil is the R enantiomer of Modafinil.

Modafinil has been suggested to have positive effect in cognitive improvement studies. Three double-blind, randomized, placebo-controlled clinical trials[51-53] with a total of 128 cases were identified. Across all studies, Modafinil was generally well tolerated, with two reports of increased difficulty of sleeping[51] and one report of increased blood pressure.[53] All trials administered 200 mg per day of Modafinil. One study[51] reported a significant cognitive improvement in the working memory, spatial working memory, and strategy use of FES patients.[51] Another trial reported a trend toward working memory improvement and significant improvement in the visual learning of early schizophrenia patients.[52] These results also noted that healthy volunteers were significantly more responsive to Modafinil on visual learning measures than schizophrenia patients.[52] Combination of Modafinil and cognitive training did not lead to significant cognitive improvements in chronic schizophrenia patients.[53]

A single double-blind, randomized, placebo-controlled, proof-of-concept study with 60 stable schizophrenia cases was reviewed.[54] Administered doses (50 mg, 100 mg, or 200 mg per day) were generally well tolerated; however, cases of folliculitis, hostility, restlessness, and sleep-related side effects were reported. The trial reported no significant improvements in cognitive measures, and a reduction in PANSS score without worsening of positive symptoms in the 200 mg treatment group.[54]

Reviewed clinical trials in this category suggest that modafinil may be a promising agent for preventing deterioration and/or improving memory and learning cognitive domains, particularly in early schizophrenia. However, future studies needed to replicate these results as well as to demonstrate tolerability and safety.

3.8 | Cholinergic/muscarinic agents

3.8.1 | Galantamine (2 articles) and donepezil (1 article)

Galantamine (2 articles) and donepezil (1 article) are acetylcholinesterase inhibitor medication, that enhances cholinergic function in the brain through different mechanisms, commonly used in the setting of Alzheimer's dementia. These include inhibiting the enzyme responsible for degradation of acetylcholine, and potentiating activity at nicotinic receptors.[55] As discussed above, evidence suggests that individuals with schizophrenia have changes in nicotinic receptor activity and consistent with other acetylcholinesterase inhibitors, this class has been shown to increase frontal cortical dopamine levels.

Two papers looking at the use of galantamine in schizophrenia were included, a clinical trial and a position paper were identified.[56,57] Data on the use of galantamine to improve deficits in cognitive impairment in schizophrenia have been mixed.

A single randomized, double-blind, placebo-controlled trial administering donepezil was identified.[58] Donepezil was administered at 5 mg per day to 52 schizophrenia patients with no reported side effects. The 12-week trial identified significant improvements in working memory, verbal memory, and processing speed.[58]

As mentioned above in the section on memantine, a meta-analysis and systematic review by Kishi et al.[30] looking at the anti-dementia drugs (which included acetylcholinesterase inhibitors) for cognitive impairment in schizophrenia, and suggested that although these medications may offer some improvement in some domains of cognition, they are influenced by small study effects and bias, and when looking at composite cognitive test scores, they were not superior to placebo.

3.9 | Anti-inflammatory and related agents (8 articles)

Various anti-inflammatory and related agents are being investigated as the treatment for schizophrenia as a proinflammatory response is hypothesized to play a role in the development of schizophrenia. Six double-blind, randomized, placebo-controlled clinical trials[59-64] and two open-label trials[65,66] were identified.

3.9.1 | Minocycline (3 articles)

Minocycline (3 articles) is an anti-bacterial agent from the class of tetracyclines, that exerts anti-inflammatory activity through a variety of mechanisms and is commonly used to treat several bacterial infections of the respiratory tract or skin, among other areas.

Three clinical trials administered minocycline at a maximum dose of 200 mg per day to a total of 203 early and chronic schizophrenia patients.[60,61,63] Several adverse side effects reported, including weight gain,[60,61] indigestion, pigmentation, suicide attempt, and weight gain.[61] Studies reported improvement in attention domain,[60] visuospatial memory, executive functioning,[61] and verbal fluency.[63]

3.9.2 | Tocilizumab (2 articles)

Tocilizumab (2 articles) is an interleukin-6 (IL-6) receptor inhibitor, is a biologic medication approved for the treatment of rheumatologic conditions such as rheumatoid arthritis and giant cell arteritis.

In two reviewed clinical trials, tocilizumab was administered at 4 mg/kg[65] and 8 mg/kg[64] to a total of 41 schizophrenia patients. Tocilizumab was generally well tolerated with several mild adverse effects reported.[64] While one clinical trial reported no significant cognitive effects,[64] the other study reported improvement in digit symbol and global cognition.[65]

3.9.3 | Pregnenolone (1 article)

Pregnenolone (1 article) is the precursor to gonadal steroid hormones and the adrenal corticosteroids, which also exhibits anti-inflammatory actions.

Similarly, a single eight-week trial administering pregnenolone at 50 mg per day to 60 patients reported no adverse side effects and improvements in visual attention.[62]

3.9.4 | Cilostazol (1 article)

Cilostazol (1 article) is classified as an antiplatelet agent but is also shown to exhibit anti-inflammatory effects.

A single 8-week open-label pilot trial administering 50 mg per day of cilostazol to six stable chronic schizophrenia patients was identified.[66] No adverse side effects were reported. Results indicated a mixture of cognitive improvement and worsening.[66]

3.9.5 | Salsalate (1 article)

Salsalate (1 article) is a nonsteroidal anti-inflammatory agent.

A single, 12-week clinical trial administering combination anti-inflammatory therapy (Salsalate 4 g per day, omega-3 FA and Fluvastatin 40 mg per day) to 39 schizophrenia patients was reviewed. No significant cognitive changes were observed over the course of the study, and three cases of tinnitus as an adverse effect were reported.[59]

Overall, some anti-inflammatory and related agents appear to have positive effects on cognitive functioning in schizophrenia patients the results of these studies remain conflictual.

3.10 | Hormone-modulating drugs

There are two potential hormone-modulating treatments for cognitive decline in schizophrenia: raloxifene and oxytocin. Pregnenolone is included above under anti-inflammatory agents.

3.10.1 | Raloxifene (7 articles)

The significant sex difference that is seen in schizophrenia between males and females and the later median age of onset in females compared with males, has been suggested to be accounted for by estrogen levels. As a result, the potential beneficial effect of estrogen has been studied with the use of selective estrogen receptor modulator (SERM) as an augmentative agent.[67] SERM effects on the body depend on their variable tissue-dependent interaction with an estrogen receptor, acting either as an agonist or antagonist.

Raloxifene is one of these agents and has been studied in multiple randomized-control trials ($n = 5$) with varying results depending on the patient population. Two RCTs showed significant cognitive improvement with raloxifene in both postmenopausal women[68] and middle-aged men and women.[69] Specifically, raloxifene improved memory, attention, processing speed, and executive functioning. Recently, the authors of the first study attempted to reproduce their results, and over a longer period of 24 weeks instead of 12 weeks, but were unsuccessful.[69] Compared with the first study, the women in the Huerta-Ramos study of 2020[69] were more symptomatic, rated their schizophrenia as more severe and were on higher dosages of antipsychotics. In line with these findings, additional studies[70,71] found no significant improvement in cognition for postmenopausal women with severe refractive schizophrenia, as did a meta-analysis of raloxifene augmentation in men and women showing no significant

effects on cognitive functioning.[72] Therefore, raloxifene may have limited effectiveness in more severe cases of schizophrenia.

3.10.2 | Oxytocin (8 articles)

Oxytocin (8 articles) is commonly known as a key regulator of reproduction and childbirth and has a role in social bonding, behavior, and cognition. As a result, it has been studied for a possible role in the expression of schizophrenia.

The data around the impact of oxytocin on cognition have been conflictual, and it may lead to further improvement on certain domains of cognition than others, such as social cognition. In one study, intranasal oxytocin was shown to improve theory of mind.[73] Oxytocin was also seen to improve a patient's ability to perceive emotions evaluated with the TASIT.[74-76] Improvement in other cognitive domains with oxytocin has been less convincing; outcomes on MCCB and MSCEIT (emotional intelligence) were not significantly improved,[77] and one study showed beneficial effect of oxytocin on verbal learning but not on working memory,[78] while another showed beneficial results with one dose of oxytocin on Digit Span, evaluating working memory.[79] Overall, intranasal oxytocin is well tolerated by patients, with no reported side effects in all studies.

3.11 | Other agents (Insulin [1 article], exenatide—GLP-1 agonist [1 article], agomelatine [1 article], and rosiglitazone [1 article])

Other studies have been done on hormone-modulating drugs for the treatment of cognitive deficits in schizophrenia. Randomized controlled trials of rosiglitazone[80] an antidiabetic drug in the thiazolidinedione class, agomelatine[81] a novel and atypical antidepressant agent that acts as a melatonin receptor (MT_1 and MT_2) agonist and serotonergic ($5HT_{2C}$) antagonist and intranasal insulin[82] and exenatide[83] did not demonstrate significant cognitive improvement.

Overall, despite some initial positive results, the overall effect of hormone-modulating agents on cognitive deficits in schizophrenia does not appear promising.

3.12 | Supplements

Dietary supplementations, which are easy to use and relatively accessible compared with other medications, have received growing interest among researchers in the treatment of psychiatric disorders. Furthermore, patients are increasingly using supplements to manage symptoms of illness across medicine and frequently ask their physicians for guidance on these agents and the evidence behind them. Below are a few supplements targeting specific markers that may be involved in cognitive impairments such as oxidative stress, cytokines, and inflammation in the brain.[84,85]

3.12.1 | Bergamot (1 article)

Bergamot (1 article) is a citrus fruit native to Southern Italy.

Bergamot has recently been tested to help with cognitive deficit in schizophrenia. The research was based on prior evidence that flavonoids, phenolic structures found in bergamot, may have neuroprotective effects in the brain against neurodegenerative diseases.[86,87]

In an Italian 8-week open-label pilot study, researchers used Bergamot polyphenolic fraction (BPN) on 20 adults with schizophrenia.[88] Results showed significant improvement in some areas of cognition. They noted significance in the Wisconsin Card Sorting Test (WCST) preservative errors and semantic fluency test while WCST categories, phonemic fluency, and Stroop Color-Word Test also showed optimistic results.

3.12.2 | Omega-3 fatty acids (2 articles)

Omega-3 fatty acids (2 articles) are among essential nutrients and have been linked to having effects on suppressing inflammation, regulating neurogenesis, and protecting against oxidative stress in the brain.[89]

Studies on omega-3 fatty acids and cognitive deficits in schizophrenia were previously summarized in the Goff review which found that it had unconvincing effects on cognitive improvements; however, a more recent trial showed more promising results.[6]

An RCT involving 80 schizophrenia patients with olanzapine-induced metabolic syndrome was done over a 12-week period using omega-3 (2400 mg of fish oil combined with 720 mg of long-chain omega-3 fatty acid).[90] Results showed enhanced delayed memory factor in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at the end of the 12-week study as well as enhanced brain-derived neurotropic factor and reduced inflammation factors for the omega-3 group.

3.12.3 | N-acetyl cysteine (NAC) (1 article)

N-acetyl cysteine (NAC) (1 article) is a form of the amino acid cysteine, which acts as a precursor to the powerful antioxidant glutathione.

Similarly to omega-3, a recent study found the effects of NAC on schizophrenia-induced cognitive deficits differed from the Goff review which again was determined to have unconvincing effects.[6] Adjunctive NAC (1200 mg) were used in a 12-week RCT invoking 84 participants with stable chronic schizophrenia.[91] The results showed improvement in areas of cognition such as attention, short-term memory, working memory, executive functioning, and speed of processing after the 12-week trial. Furthermore, patients given NAC had improved in both positive and negative PANSS subscale.

3.12.4 | Other supplements

Other notable supplements included Curcumin, or curry extract and Coenzyme Q10. Curcumin, which targets epigenetic dysregulation inhibiting histone deacetylase (HDAC), has shown early signs of improved cognition in a 2018 letter to the editor open-label parallel-group randomized study.[92]

In summary, supplements such as bergamot and curcumin have each had one or two preliminary positive study in the treatment of cognitive deficits in schizophrenia. Omega-3 and NAC have shown more promising results since the Goff review. However, none of these studies had a follow-up period, to assess whether the noted improvement persist over time. Coenzyme Q10 results were unconvincing. Future studies are needed to assess replicability of these findings, as well as applicability in clinical setting.

3.13 | Miscellaneous

3.13.1 | Sodium nitroprusside (SNP) (1 article)

Sodium nitroprusside (SNP) (1 article) exerts its vasodilator actions through breaking down to nitric oxide in circulation.

SNP has shown varying results in its effects on cognition in schizophrenia. In a 6-week RCT, SNP was given to 42 patients with schizophrenia and found no significant effect of SNP over placebo on cognitive functions.[93] However, a 2015 pilot study demonstrated significant change in executive function in their trial involving 18 participants.[94] In a 2017 letter to the editor, the authors of the latter pilot study stipulated that differences in patient demographics such as duration of disease, ethnicity, and lifestyle may lead to such disparities among trials.[94] Thus, larger scale studies using more homogeneous samples are required to assess whether SNP can demonstrate replicable positive effects on cognitive deficiencies in schizophrenia.

3.13.2 | Cannabidiol (CBD) (1 article)

Cannabidiol (CBD) (1 article) is one of the over 100 phytocannabinoids identified in Cannabis sativa, and constitutes up to 40% of the plant's extract, being the second most abundant component. CBD antagonizes the action of CB_1 and CB_2 receptor agonists, and is suggested to act as an inverse agonist of these receptors.[95]

Pre-clinical studies demonstrated protective effects of cannabidiol (CBD) against cognitive deficits brought upon by acute use of THC in mice; however, studies on its effect against cognitive impairments seen in schizophrenia are still limited.[96]

A 2018 study measured the effects of CBD (300 mg twice daily) over a 6-week period to 36 patients with treated schizophrenia.[97] Cognition was evaluated using the MCCB. Results showed no significant differences between the CBD and placebo. Other studies such as Hallack et al. 2010[98] and McGuire et al. 2017[99] showed similarly negative results using doses as high as 600 mg and 1000 mg respectively.

Both SNP and CBD demonstrated negative results in treating cognitive impairments seen in schizophrenia; however, this may in part be due to the sample demographics. For SNP, the patients used in the negative study had significantly longer illness duration than in the studies showing more positive results.[13-15] CBD does not seem very promising given the multiple trials using a fairly wide dose range all showing limited results.[97-99]

3.13.3 | Roflumilast (1 article)

Roflumilast (1 article) is a long-acting PDE-4 inhibitor that prevents the hydrolysis of cyclic adenosine monophosphate (cAMP) in inflammatory cells. This results in elevated cAMP levels which has anti-inflammatory effects through various mechanisms. It is primarily used in the treatment of COPD due to its anti-inflammatory properties in the lungs,[100] but has been suggested to improve cognition secondary to preventing the breakdown of cAMP.

A 2021 RCT compared a previously published RCT with results of a healthy control taken from another study. In this cross-over RCT, 10 patients with schizophrenia received consecutive 8-day treatments of 100 μg followed by 250 μg of roflumilast with a 14-day washout period between treatments and results suggested a dose-dependent effect on attention and cognitive flexibility.[101] Roflumilast has also been shown to improve verbal memory in schizophrenia.[102]

With preliminary positive results, larger scale studies are required to replicate these findings.[101,102]

3.13.4 | Valacyclovir (1 article)

Valacyclovir (1 article) is an antiviral medication that has been in medical use since 1995 for the treatment of herpes simplex virus (HSV) and varicella zoster virus (VZV). Its effect on cognitive impairments of schizophrenia has been studied as it was found that HSV infection may lead to negative effects on cognition, and more so in patients with schizophrenia.[103]

In a 24-patient RCT, HSV1-seropositive subjects with schizophrenia/schizoaffective disorder were given 1.5 g twice daily of oral valacyclovir. Cognition was measured using the Penn Computerized Neurocognitive Battery with results showing improved cognition among the treated individuals.[24] Although positive results were observed in the valacyclovir trials, the drug remains limited to those suffering from HSV and is not likely to apply to the general population.[104]

4 | DISCUSSION

This review aimed to explore pharmacological augmentation agents for the treatment of cognitive deficits in schizophrenia. Many of the agents listed in this review have approval for use in conditions other

than cognitive deficits in schizophrenia and are used off-label. While the review showed a few preliminary positive studies in different classes, the overall evidence remains conflictual and inconclusive for any pharmacological classes studied for the treatment of cognitive deficits in schizophrenia. To the best of our knowledge, to date there are no approved agents in this area.

Our review of the studies conducted in the past 11 years yielded similar results to the review by Goff et al.[6] despite a decade of research and advances in various areas of psychopharmacology. There are several potential explanations for the unsuccessful search for psychopharmacological treatment of cognitive deficits in schizophrenia, namely heterogeneity of the illness, heterogeneity of the cognitive deficits, challenges in recruitment, and confounding effects of various medications.

From the methodology perspective, conducting clinical trials in schizophrenia has several ongoing challenges.[105,106] Schizophrenia is a heterogeneous illness, and therefore inclusion of participants under a heterogeneous diagnostic umbrella may contribute to low-yield results which are difficult to replicate, in many schizophrenia-related trials.

Furthermore, the cognitive deficit profile could also be heterogeneous among patients with schizophrenia. Up to 75% of patients with schizophrenia have some degree of cognitive impairment in various domains of memory, attention, motor skills, executive function, and intelligence.[107] None of the studies in this review, considered inclusion of participants based on their baseline cognitive deficit profile. Furthermore, many studies face recruitment and retention challenges in schizophrenia trials, and therefore, considering a wider inclusion criterion to ensure enough recruitment, such approach may add to the heterogeneity of the participants, and inconclusiveness of the results. Lastly, the confounding effects of medications on cognitive functioning is another barrier in this area.

To overcome the above-mentioned challenges, potential solutions may include for future studies to consider inclusion criteria that is narrowed down to a homogenous group of patients with schizophrenia with a similar cognitive profile at baseline. Furthermore, consideration of antipsychotic medications as well as stage of illness (early on vs chronic) into inclusion criteria, may also improve the homogeneity of the sample. Even though cognitive deficits in schizophrenia are generally stable over time, it is possible that the stage of illness have an impact on response to treatment with cognitive enhancing agents, considering the potential impact of duration of exposure to various psychotropics as well as duration of untreated psychosis[108] on underlying neurobiological pathways.

Another potential strategy to bypass a number of confounding factors (such as medications, duration of illness, and psychosocial factors) is to assess the pharmacological interventions on unaffected first-degree relatives of patients with schizophrenia, who also is shown to exhibit cognitive deficits.[109]

Nonetheless, noting the inconclusive results of studies over several decades raises the question as whether the pathology underlying cognitive deficits in schizophrenia is reversible? And if so, perhaps we need to shift our intervention strategies, to improve adaptive functioning.

AUTHOR CONTRIBUTIONS

Naista Zhand provided overall supervision of the article, design, search, writing the manuscript, and revising it. Kyle Arsenault-Mehta compiled all the results of the search from the small working groups, authored portions of the manuscript, and revised supplementary table and manuscript. Mario Hochman-Bérard, Alexander Johnson, Dar'ya Semenova, Bea Nguyen, and Jessie Willis each contributed to the literature search, reading abstract, and extracting data from different medication classes. Natalia Mouravska and Ridha Joober assisted in revision of the final manuscript.

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The authors declare no conflict of interest.

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