Anti-inflammatory Strategies for Schizophrenia: A Review of Evidence for Therapeutic Applications and Drug Repurposing

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Schizophrenia is a debilitating psychiatric disorder with a substantial socioeconomic and humanistic burden. Currently available treatment strategies mostly rely on antipsychotic drugs, which block dopaminergic effects in the mesolimbic pathway of the brain. Although antipsychotic drugs help relieve psychotic symptoms, a definitive cure for schizophrenia has yet to be achieved. Recent advances in neuroinflammation research suggest that proinflammatory processes in the brain could cause alterations in neurobehavioral development and increase vulnerability to schizophrenia. With a growing need for novel strategies in the treatment of schizophrenia, it would be meaningful to review the current evidence supporting the therapeutic potential of anti-inflammatory strategies. This review details the key findings of clinical trials that investigate the efficacy of anti-inflammatory agents as adjuvants to antipsychotic treatment. We further discuss the possibilities of repurposing anti-inflammatory agents and developing novel strategies for the treatment of schizophrenia.

KEY WORDS: Schizophrenia; Inflammation; Anti-inflammatory agents; Drug repositioning.

INTRODUCTION

Schizophrenia is a debilitating psychiatric disorder with a substantial socioeconomic and humanistic burden not only on the affected individuals but also on the caregivers [1,2]. Since the proposal of the dopamine hypothesis, aberrations in the central dopaminergic system have been considered as a core pathophysiological mechanism of schizophrenia [3,4]. Currently used antipsychotic drugs (APDs), which reduce mesolimbic dopamine transmission by blocking postsynaptic D2 receptors, influence the clinical remission of psychotic symptoms in patients with schizophrenia [5]. However, the effect is modest and there is still a long way to go before a definitive cure for schizophrenia is achieved. Moreover, the long-term administration of APDs causes considerable side effects, including extrapyramidal symptoms, metabolic dysregula-

tions, and tardive dyskinesia [6,7]. Accordingly, there has been an increasing need for the development of novel therapeutic strategies to treat schizophrenia.

On the basis of the existing evidence that inflammation is fundamentally involved in the development and progression of schizophrenia, we aimed to review the up-to-date evidence supporting the therapeutic potential of anti-inflammatory agents in patients with schizophrenia. Recent clinical trials of anti-inflammatory agents as an adjuvant to antipsychotic drugs have shown some positive results, suggesting that the regulation of inflammatory processes may be therapeutically beneficial. This review provides meaningful insights into repurposing anti-inflammatory agents and developing novel strategies for the treatment of schizophrenia.

IMMUNE DYSREGULATION IN THE PATHOGENESIS OF SCHIZOPHRENIA

A body of epidemiological studies suggests that maternal immune activation (MIA) induced by prenatal infection is closely associated with an increased risk for developing schizophrenia in offspring [8,9]. Preclinical

studies using non-human MIA models have provided yet more compelling evidence that MIA increases vulnerability to schizophrenia by causing acute and long-lasting alterations in fetal neurobehavioral development [10,11]. Deficits in prepulse inhibition and latent inhibition, the well-known behavioral phenotypes in animal models of schizophrenia [12], have been consistently observed in rodent offspring of MIA mothers [13-16]. Moreover, morphological and neurochemical alterations in the central nervous system (CNS) that confer susceptibility to schizophrenia have been shown at early and late postnatal ages in response to prenatal MIA [17-21].

The detrimental effects of MIA on the fetal brain are considered to be mediated by the elevated release of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, in the fetal environment [22-24]. Increased expression of pro-inflammatory cytokines is reportedly found in the fetal brain of rats following maternal administration of endotoxins, such as lipopolysaccharide and polyinosinic:polycytidylic acid (poly I:C) [25-28]. In particular, IL-6 has been suggested as a critical mediator of neuroinflammation that alters the fetal neurodevelopmental process and causes structural and functional deficits in the brain [29,30].

In accordance with the findings from animal studies, elevated pro-inflammatory cytokines during pregnancy were found to be associated with an increased risk for schizophrenia [31-33]. Patients with schizophrenia with a history of prenatal exposure to infection showed impaired neurocognitive performance [34-36] and structural abnormalities in the brain [37,38]. Thus, immune dysregulation may fundamentally contribute to the pathogenesis of schizophrenia, even before the onset of full-blown psychosis.

INFLAMMATORY MECHANISMS IN THE SCHIZOPHRENIC BRAIN

Recent studies revealed that pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, were increased in the peripheral blood of patients with schizophrenia during acute psychotic exacerbations, suggesting that immunological alterations may affect the clinical status after the onset of illness [39,40]. Cytokines are also released from microglia, the innate immune cells residing in the CNS, in response to injury, infection, and stressful life events [41]. The inflammatory reactions in the CNS can be conditioned to certain stimuli and promoted by a 'priming' or kindling mechanism of the immune system, particularly via perinatal activation of microglia [42-45]. The release of pro-inflammatory cytokines from primed microglia is exaggerated by conditioned stimuli, for example, prior infections and environmental stress [46,47]. This process confers intrinsic susceptibility to external stressors during adolescence, leading to brain damages to stress-sensitive regions, including the prefrontal cortex and hippocampus [48]. Previous animal studies showed that administration of IL-6 to mice produced sensitization to neurobiological insults by amphetamine [49,50] or ketamine [51], suggesting an intertwined interaction of pro-inflammatory cytokines with the dopaminergic and glutaminergic neurotransmitter systems.

Activated microglia themselves also play a critical role in inflammation-induced brain damage by shifting kynurenine metabolism toward the production of quinolinic acid (QA), which causes oxidative stress and excitatory neurotoxicity [52-54]. The high concentration of QA was found to disrupt the neurodevelopmental process and cause cognitive and behavioral alterations relevant to schizophrenia in animal studies [55,56]. Although it remains to be further elucidated how kynurenine metabolites are implicated in schizophrenia, sustained microglial activation may cause further neurodegeneration and deterioration of illness [41,57]. The involvement of activated microglia is supported by previous studies that showed an increased density of microglia in postmortem brain analysis of patients with chronic schizophrenia [58,59]. *In vivo* neuroimaging studies using positron emission tomography also provided supportive evidence for the presence of activated microglia in the gray matter of patients with schizophrenia [60,61] and individuals at ultra-high risk for psychosis [62].

Taken together, the possible roles of immune-activated microglia and inflammation throughout the disease course of schizophrenia indicates that developing anti-inflammatory strategies would be a promising avenue to optimize the treatment for schizophrenia (Fig. 1) [63]. Next, we review preclinical and clinical studies that investigate the efficacy of anti-inflammatory agents as an adjunct to antipsychotic medications.
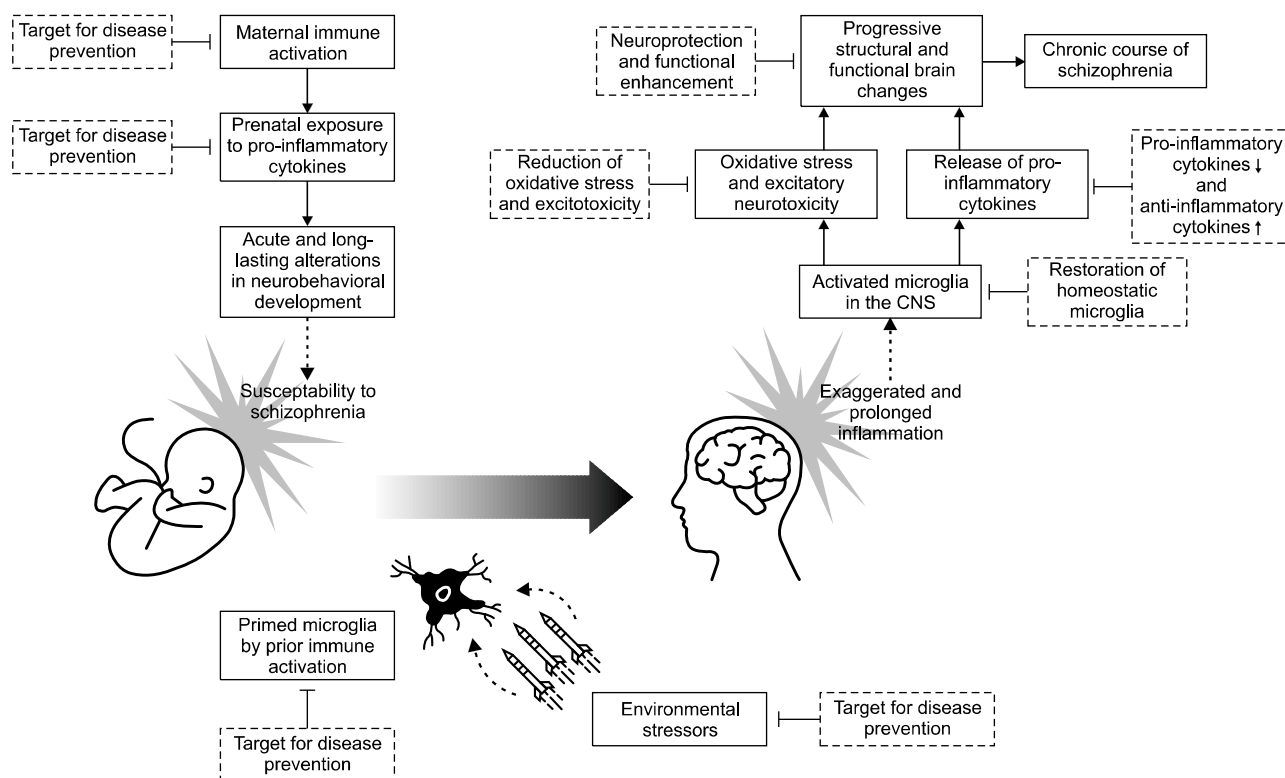
Fig. 1. The role of inflammation and the immune system in schizophrenia and potential targets for the treatment of schizophrenia. Currently used anti-inflammatory drugs, such as aspirin and celecoxib, inhibit the cyclooxygenase pathway of inflammation at the systemic level. Several drugs, originally indicated for the treatment of medical diseases, appear promising for the treatment of schizophrenia owing to their anti-inflammatory property (e.g., minocycline, statins). In addition, omega-3 fatty acids and neurosteroids can reduce oxidative stress and enhance neuronal repair. Davunetide, derived from the activity-dependent neuroprotective protein, promotes neuronal stability and repair. Biological agents, including monoclonal antibodies, target specific pro-inflammatory cytokines and modulate the inflammatory process. Recently, the immune modulatory property of mesenchymal stem cells has received much attention for potential therapeutic application in psychiatry. Mesenchymal stem cells have an ability to change the functional phenotype of microglia from an activated to an anti-inflammatory state. Although future investigation will be required to establish effective and safe treatment strategies, these anti-inflammatory agents may be applied before the onset of schizophrenia.

PRECLINICAL STUDIES OF THE THERAPEUTIC EFFECTS OF ANTI-INFLAMMATORY AGENTS ON SCHIZOPHRENIA

Preclinical studies have provided evidence for a potential therapeutic role of anti-inflammatory agents in the treatment of schizophrenia; however, the reliability of behavioral alterations induced by psychomimetic drugs in animal models is limited compared with psychotic symptoms manifested in humans. El-Sayed El-Sisi *et al.* [64] showed a significant therapeutic effect of celecoxib, a well-known anti-inflammatory agent that selectively inhibits cyclooxygenase (COX)-2, using the amphetamine-induced model in rats [64]. Combined administration of celecoxib with risperidone reversed behavioral impairments induced by amphetamine and reduced

TNF-α levels in the rat brain. Brenhouse and Andersen [65] revealed that prophylactic COX-2 inhibition prevented the loss of parvalbumin (PV), a calcium-binding protein expressed in a specific type of γ-aminobutyric acid (GABA)-ergic cells [66], in male rats with early-life stress exposure. Given that impaired functioning of PV-expressing GABAergic neurons is closely associated with the pathogenesis of schizophrenia [67,68], previous results may imply that the suppression of neuro-inflammation has the potential to restore neuronal alterations relevant to schizophrenia.

LITERATURE SELECTION CRITERIA FOR CLINICAL TRIALS

We selected eligible articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) statement [69]. The systematic search was conducted until August 2019 using electronic databases (EBSCO Discovery Service, MEDLINE Complete, and PubMed). The following terms were used to identify relevant studies: (aspirin or celecoxib or n-acetylcysteine or minocycline or statin or omega-3 or davunetide or erythropoietin or pregnenolone or estrogen or selective estrogen receptor modulators [SERMs] or raloxifene or biologics or interferon or mesenchymal stem cell or monoclonal antibody) and (schizophrenia or psychosis or antipsychotics). In the next step, we manually searched for additional relevant articles.

We defined our literature selection criteria as follows: (1) randomized controlled trials (RCTs), case-controlled studies, pilot studies, and meta-analyses comprising patients with schizophrenia spectrum disorders; (2) studies including administration of anti-inflammatory drugs with antipsychotics to patients; (3) if the total number of clinical trials regarding certain drugs was above five, we selected the corresponding meta-analyses instead; (4) for meta-analyses, we selected those that included as many studies or as much information as possible; and (5) written in English. Seventeen studies were finally included in this review (Fig. 2).

CLINICAL EVIDENCE FOR THE THERAPEUTIC EFFECTS OF ANTI-INFLAMMATORY AGENTS ON SCHIZOPHRENIA

Table 1 summarizes the results of clinical trials that have investigated the therapeutic effects of anti-inflammatory agents used as adjuvants to antipsychotic treatment in patients with schizophrenia. The current findings of those trials suggest that adjuvant anti-inflammatory strategies may be beneficial by relieving clinical symptoms in patients with schizophrenia. Drug repurposing, which is the application of existing therapeutics for a novel disease indication [70], is a promising approach to overcome limitations of current antipsychotic medications targeting dopaminergic pathways.

Aspirin

Aspirin is one of the most commonly used anti-inflammatory drugs that inhibits the COX enzymes. Laan *et al.* [71] conducted a randomized, double-blind, placebo-controlled study to determine the efficacy of aspirin adjuvant therapy. Patients were administered aspirin (1,000 mg/day) or a placebo as adjuvant therapy to antipsychotics for 3 months. The adjuvant therapy significantly reduced the positive subscale and total scores of the Positive and Negative Syndrome Scale (PANSS) but did not improve cognition. A recent aspirin study con-

Records identified through database searching (n = 15,039)

Additional records identified through other sources (n = 1)

Records after duplicates removed (n = 7,393)

Records screened (n = 2,083)

Records excluded (n = 1,738)

Full-text articles assessed for eligibility (n = 345)

Full-text articles excluded (n = 328)
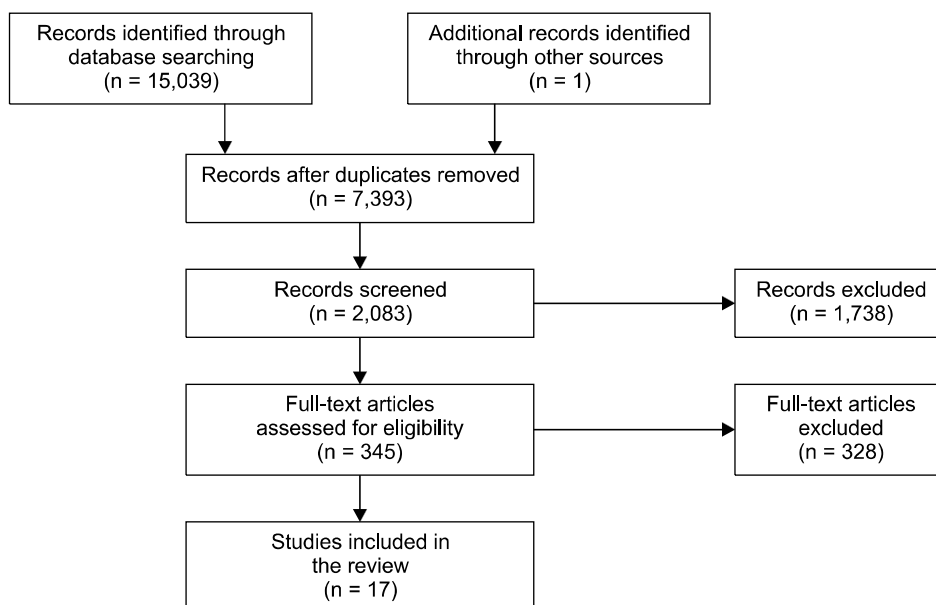
Studies included in the review (n = 17)

Fig. 2. Flowchart of the literature selection procedure.

Table 1. Clinical trials using anti-inflammatory agents combined with antipsychotic treatment and their therapeutic effects on clinical symptoms in patients with schizophrenia

Author	Number	Dosing and duration	Results
Aspirin (ASP)			
Attari *et al.* [72]	60 SSD: 20 ASP (325 mg) + APD; 20 ASP (500 mg) + APD; 20 PL + APD	ASP 325 or 500 mg/day; 6 weeks	- The positive, negative, and general psychopathology scores of the PANSS were more reduced in the aspirin groups than in the placebo group. - Omeprazole (20 mg/day) was given to all patients to reduce gastrointestinal complications. - There were no significant side effects.
Laan *et al.* [71]	70 SCZ: 33 ASP + APD; 37 PL + APD	ASP 1,000 mg/day; 3 months	- The total PANSS scores were improved. - Pantoprazole (40 mg/day) was given to all patients for gastric protection. - There were no significant side effects.
Celecoxib (CEL)			
Akhondzadeh *et al.* [74]	60 SCZ: 30 CEL + RIS; 30 PL + RIS	CEL 400 mg/day; RIS 6 mg/day; 8 weeks	- The treatment significantly reduced the PANSS positive and total scores. - No significant benefit for negative symptoms. - There were no significant side effects.
Müller *et al.* [73]	50 SCZ: 25 CEL + RIS; 25 PL + RIS	CEL 400 mg/day; RIS 2−6 mg/day; 5 weeks	- None of the positive and negative symptom scores of the PANSS showed significant improvement. - The total PANSS scores were reduced. - The cognitive items 'difficulty in abstract thinking' and 'conceptual disorganization' were improved. - There were no significant side effects in the treatment group.
Müller *et al.* [76]	50 SCZ: 25 CEL + AMI; 25 PL + AMI	CEL 400 mg/day; AMI 200−1,000 mg/day; 6 weeks	- The negative symptom scores of the PANSS were reduced. - There were no significant side effects.
Rapaport *et al.* [75]	35 SCZ: 18 CEL + APD; 17 PL + APD	CEL 400 mg/day; 8 weeks	- The treatment cohorts did not differ on any of the clinical outcome measures. - There were no significant side effects.
***N*-acetylcysteine (NAC)**			
Berk *et al.* [85]	140 SCZ: 69 NAC + APD; 71 PL + APD	NAC 2 g/day; 24 weeks	- The total, negative, and general psychopathology scores of PANSS were reduced. - Positive symptoms were not significantly improved. - The CGI-severity, CGI-improvement scores were improved. - There were no significant side effects.
Farokhnia *et al.* [81]	42 SCZ: 21 NAC + RIS; 21 PL + RIS	NAC 2 g/day; RIS 6 mg/day; 8 weeks	- The negative symptom scores of the PANSS were significantly improved. - There were no significant side effects.
Minocycline (MIN)			
Xiang *et al.* [87]	548 SSD: 286 MIN + APD; 262 PL + APD	MIN 171.9 ± 31.2 mg/day; 18.5 ± 13.4 weeks	- 8 trials - The total, positive, negative, and general psychopathology scores of the PANSS and BPRS were improved. - There was no significant improvement in cognitive function. - No significant differences in adverse events were found between the adjuvant therapy group and the placebo group.
Statins (STAs)			
Shen *et al.* [97]	339 SCZ: 169 STA + APD; 170 PL + APD	Pravastatin 40 mg/day; lovastatin 20 mg/day; simvastatin 40 mg/day; atorvastatin 20 mg/day; 6 weeks−6 months	- 6 trials - The positive and negative symptom scores of the PANSS were decreased. - There was a correlation with simvastatin adjunctive therapy and the reduction in negative symptoms.

Table 1. Continued

Author	Number	Dosing and duration	Results
Other agents			
Cho et al. [101]	816 SSD	EPA; DHA; EPA + DHA + oleic acid; 4−26 weeks	- 20 trials - The total, positive, and negative symptom scores of the PANSS were not significantly reduced. - Cognitive function was not significantly improved.
	264 SSD: 135 PRG + APD; 129 PL + APD	PRG 0.03−0.5 g/day; 8 weeks	- 5 trials - The total PANSS scores were decreased, but positive and negative symptoms were not significantly improved in 4 trials. - Cognitive function was significantly improved.
	492 SSD	ESR 0.2−2 mg/day; 2−8 weeks	- 8 trials - The total, positive, and negative symptom scores of the PANSS were decreased.
	583 SSD: 297 SERMs + APD; 286 PL + APD	Raloxifene 60 or 120 mg/day; 6−24 weeks	- 9 trials - The total and positive symptom scores of the PANSS were decreased.
Ehrenreich et al. [105]	39 SCZ: 20 EPO + APD; 19 PL + APD	EPO 40,000 IU/week for 3 months; 2 years	- Cognitive function was improved. - There were no benefits for the PANSS and social functioning. - There were no significant side effects.
Javitt et al. [102]	63 SCZ: 20 DAV (5 mg) + APD; 21 DAV (30 mg) + APD; 22 PL + APD	DAV 5 or 30 mg/day; 12 weeks	- There were no significant benefits for cognitive function measured using the MCCB and SCoRS. - The UPSA-measured everyday functioning was improved. - There were no significant side effects.

SSD, schizophrenia spectrum disorders; APD, antipsychotic drugs; PL, placebo; PANSS, positive and negative syndrome scale; SCZ, schizophrenia; RIS, risperidone; AMI, amisulpride; CGI, clinical global impression scale; BPRS, brief psychiatric rating scales; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PRG, pregnenolone; ESR, estrogens; SERM, selective estrogen receptor modulators; EPO, erythropoietin; DAV, davunetide; MCCB, matrics consensus cognitive battery; SCoRS, schizophrenia cognition rating scale; UPSA, ucsd performance-based skills assessment.

ducted by Attari et al. [72] showed significant improvement in positive, negative, and general psychopathology of patients with schizophrenia who received lower doses of aspirin (325 or 500 mg) daily for 6 weeks. Since regular use of aspirin increases the risk of gastrointestinal bleeding in a dose-dependent manner, more research is needed to determine appropriate doses that minimize side effects for anti-inflammatory treatment strategies in schizophrenia.

Celecoxib

Celecoxib, a well-known selective COX-2 inhibitor, also has been suggested to have antipsychotic potential, although the findings remain controversial. Several clinical trials were conducted to assess the efficacy of celecoxib adjuvant therapy. Müller et al. [73] gave celecoxib (400 mg/day) to patients with schizophrenia for 5 weeks and reported a significant improvement in the total PANSS score along with an improvement in cognition, contrarily to the results of the aspirin study by Laan et al. [71] In a similar trial, Akhondzadeh et al. [74] reported that celecoxib (400 mg/day) combined with risperidone (6 mg/day) administered to patients with chronic schizo-

phrenia for 8 weeks was superior to risperidone alone on the positive subscale and total scores of the PANSS. In contrast, Rapaport et al. [75] reported that the outcomes of celecoxib (400 mg/day) with antipsychotics for 8 weeks did not differ from the outcomes of placebo with antipsychotics for continuously symptomatic patients with schizophrenia. Recently, Müller et al. [76] conducted celecoxib (400 mg/day) adjuvant treatment with amisulpride (200−1,000 mg/day) for early-stage patients with schizophrenia. This study showed a significant improvement of the negative subscale scores of the PANSS, but no significant effects on the other PANSS subscale scores.

N-acetylcysteine

N-acetylcysteine (NAC) has both an anti-inflammatory property, which leads to the reduction of proinflammatory cytokines [77,78], and a well-known antioxidant property. Several studies have demonstrated that NAC regulated impaired glutamate and dopamine neurotransmission [79,80]. Farokhnia et al. [81] administered NAC (2 g/day) adjuvant treatment with risperidone (6 mg/day) to patients with chronic schizophrenia for 8

weeks. In this study, the total PANSS scores and negative subscale scores decreased significantly, but there were no significant differences in the positive subscale scores.

Other properties can also be helpful in alleviating schizophrenia symptoms. NAC is a direct precursor of glutathione, which protects cells against the effects of reactive oxygen species [82]. Decreased glutathione levels in the brain lead to hypofunction of N-methyl-D-aspartate (NMDA) receptors, suggesting that glutathione dysregulation contributes to the development of clinical symptoms of schizophrenia [83]. NAC administration can increase glutathione levels, which are decreased in schizophrenia, and potentiate the NMDA receptor response to glutamate [84]. Berk *et al.* [85] conducted a trial to investigate the potential of NAC to increase brain glutathione levels that are decreased in schizophrenia. In this trial, the total, negative, and general scores of the PANSS were significantly improved in the NAC group, but not positive scores. Further studies are required to understand the therapeutic role of NAC in the treatment of schizophrenia.

Minocycline

Minocycline is a tetracycline antibiotic. The effects of minocycline on schizophrenia are considered to be due to anti-inflammatory, neuroprotective properties, and inhibition of cytochrome P450 enzymes that metabolize antipsychotics such as clozapine [86]. Several studies on adjunctive minocycline for schizophrenia have been conducted. A meta-analysis [87] of 8 RCTs showed this therapy was superior to placebo. The PANSS and Brief Psychiatric Rating Scale scores of total, positive, negative, and general symptoms were improved, but there was no significant improvement of cognitive function. Although there were some adverse drug reactions like weight gain and dizziness in the individual studies, the meta-analysis found no significant differences between the minocycline group and the placebo group.

Statins

Statins are cholesterol-lowering agents that act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. Several studies suggested that statins have anti-inflammatory properties, with lowering proinflammatory markers such as IL-1β, IL-6, TNF-α, and C-reactive protein (CRP) levels [88-91]. Animal research showed that simvastatin promoted hyperlocomotion and alleviated anxi-

ety-like behavior by up-regulation of NMDA receptors [92]. In addition, simvastatin also could alleviate cognitive function and had antipsychotic-like effects by modulating muscarinic receptors M1/4, central dopamine receptors D1/2, and the serotonin transporter [93-96]. A meta-analysis [97] of statin adjunctive therapy for schizophrenia showed statins improved the positive and negative symptom scores of the PANSS in 6 RCTs comprising 339 patients. Especially, only in the simvastatin group (40 mg/day), there was a correlation between statin adjunctive therapy and the reduction in negative symptoms.

Omega-3 fatty acids

The effects of omega-3 fatty acids on psychiatric disorders have also been examined widely. The typical properties of omega-3 fatty acids are anti-oxidation, anti-inflammation, and neuroprotection [98,99]. They are also essential for many biological activities including neurotransmission associated with psychiatric disorders [100]. However, Cho *et al.* [101] reported that there was no significant benefit of omega-3 adjunctive schizophrenia therapy in the 20 trials from 2001 to 2017 investigating the effects of omega-3. From a duration of 4 to 26 weeks, 816 schizophrenia spectrum patients participated and were administered placebo or eicosapentaenoic acid (EPA) in 11 trials, docosahexaenoic acid (DHA) in 1 trial and a mixture of EPA, DHA, and oleic acid in 6 trials. However, there were no significant improvements in the total, positive, and negative PANSS scores of patients or in their cognitive function.

Other agents

Several trials have been conducted to investigate the repurposing potential of various agents with neuroprotective properties. Javitt *et al.* [102] conducted a trial with 22 schizophrenia patients using davunetide, an eight-amino acid peptide derived from activity-dependent neuroprotective protein [103]. However, davunetide showed no benefit for schizophrenia. Erythropoietin (EPO) is widely used for treating anemia. Several studies reported neuroprotective effects of EPO, such as anti-apoptotic, anti-oxidative, and neurotrophic properties [104]. Ehrenreich *et al.* [105] conducted a trial with patients with chronic schizophrenia presenting with a cognitive deficit. They reported that weekly administration of 40,000 IU recombinant human EPO for 3 months was effective for

Table 2. Clinical trials using biological agents combined with antipsychotic treatment and their therapeutic effects on clinical symptoms in patients with schizophrenia

Author	Number	Dosing and duration	Results
Interferon-γ-1b (IFN-γ-1b)			
Grüber et al. [115]	2 SCZ	INF-γ-1b 1.5 ml/week; 4 weeks	- The total PANSS scores were decreased.
Monoclonal antibody			
Girgis et al. [117]	36 SCZ: 19 TOC + APD; 17 PL + APD	TOC 8 mg/kg, 3 infusions per month (as necessarily dose decreased for tolerability); 12 weeks	- The negative symptom scores of the PANSS were significantly improved. - No significant changes in behavioral outcomes
Miller et al. [116]	6 SCZ	TOC 4 mg/kg, 2 infusions (0, 4 weeks); 8 weeks	- No significant changes were observed. - Verbal fluency performance was improved.
Weickert et al. [118]	27 SCZ + SZA: CNK + APD; PL + APD (The number of patients in each group is not presented)	CNK 150 mg, 1 infusion; APD; 8 weeks	- The severity of positive symptoms was improved. - A positive correlation between the high-sensitive CRP levels and positive symptom scores of the PANSS was shown.

SCZ, schizophrenia; APD, antipsychotic drugs; PANSS, positive and negative syndrome scale; TOC, tocilizumab; PL, placebo; SZA, schizoaffective disorder; CNK, canakinumab; CRP, c-reactive protein.

cognitive deficits, but there were no beneficial effects on the PANSS scores and social functioning.

Pregnenolone, which acts as a neurosteroid, modulates synaptic function, such as NMDA and GABA functions [106] and also may promote neuroprotection by repairing myelin [107]. Cho et al. [101] reported that in 4 trials conducted from 2009 to 2014, total scores of the PANSS showed greater improvement in pregnenolone adjunction groups than control groups, but positive and negative scores did not. Estrogens are also considered as neuroprotective steroids. They exert anti-inflammatory properties by reducing proinflammatory cytokines and oxidative stress [108]. Estrogens also modulate many neurotransmitter mechanisms in the brain, thus estrogens can be associated with psychiatric disorders [109,110]. Cho et al. [101] assessed 8 trials since 2001 on estrogen adjunctive therapy and reported that the total, positive, and negative scores of the PANSS were reduced. Furthermore, SERMs such as raloxifene reduce proinflammatory cytokines of glial cells, such as IL-6 and interferon (IFN)-γ [111]. Cho et al. [101] reported that in 9 trials investigating raloxifene adjunctive therapy, raloxifene significantly decreased the total and positive scores of the PANSS.

In summary, several therapeutic trials using anti-inflammatory agents as adjuvants to antipsychotic drugs in treating schizophrenia have shown promising results. Altogether, Cho et al. [101] comprehensively analyzed 62 trials comprising 2,914 patients that investigated the use of the 10 medicines mentioned above (aspirin, celecoxib, NAC, minocycline, omega-3 fatty acids, davunetide, EPO, pregnenolone, estrogens, and SERMs) as adjuvant therapy. Their meta-analysis showed decrease in overall scores of the PANSS and improvement in general functioning by all of the medicines and cognition improvement in the minocycline and pregnenolone trials. Cho et al. [101] also showed no significant differences in side effects between the adjuvant therapy and control groups. Likewise, Shen et al. [97] comprehensively showed beneficial effects of statins on positive and negative symptoms in 6 trials. Considering the mixed and negative results of other trials, further studies to determine effective and safe strategies for the adjunctive use of anti-inflammatory agents in patients with schizophrenia are warranted.

CLINICAL EVIDENCE FOR THE THERAPEUTIC EFFECTS OF BIOLOGICAL AGENTS MODULATING INFLAMMATORY PROCESSES ON SCHIZOPHRENIA

The results of clinical trials on the use of biological agents in the treatment of schizophrenia are summarized in Table 2. As neuroinflammation is considered to be involved in the pathophysiology of schizophrenia, anti-in-

flammatory treatment strategies along with immune-modulating trials have been conducted. The main mechanism of conventional anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs is the inhibition of the COX pathway of inflammation at the systematic level [112]. Alternatively, biological agents designed to target specific physiological processes could be more useful to modulate neuroinflammation involved in the pathophysiology of schizophrenia.

Interferon-γ-1b

The pro-inflammatory cytokine IFN-γ plays a pivotal role in modulating immune and inflammatory responses [113]. Based on previous findings of the reduced type 1 and increased type 2 immunity in patients with schizophrenia [114], Grüber *et al.* [115] administered recombinant human IFN-γ-1b as an adjuvant to antipsychotic treatment to two patients with treatment-resistant schizophrenia. The effect of IFN-γ-1b on stimulating the type 1 immune response showed preliminary but encouraging results in reducing clinical symptoms of schizophrenia. After approximately 1.5 months of treatment with IFN-γ-1b of 1.5 ml/week, the total PANSS score of both patients had decreased. Although no significant adverse events were noted in this study, IFN-γ treatment requires careful monitoring of side effects such as unwanted immune reactions.

Monoclonal antibodies

In the last few years, monoclonal antibodies have been used for treatment in a variety of diseases. With the pathophysiology of psychiatric disorders now becoming clearer, treatments using monoclonal antibodies that target specific cytokines have also been tried, including for schizophrenia. Some recent studies showed that antipsychotic therapies with monoclonal antibodies targeting cytokines related to neuroinflammation were effective strategies for schizophrenia.

Tocilizumab, which is usually used to treat rheumatoid arthritis, prevents inflammation by inhibiting IL-6 receptor. IL-6 may be related to hippocampal volume loss and cognitive deficits [116]. Miller *et al.* [116] conducted a small-sized pilot study of tocilizumab adjuvant therapy for schizophrenia. Two infusions of 4 mg/kg tocilizumab were administered for 8 weeks, but there were no significant changes observed and no adverse effects.

However, in a recent, larger-size RCT [117], the negative symptom scores of the PANSS were significantly decreased. In this study, higher doses (8 mg/kg, which was decreased as necessary for tolerability) were administered than in previous studies. However, adverse events were developed in the tocilizumab group, such as nausea, fatigue, neutrophil count decrease, and elevation in liver function test.

Canakinumab, an IL-1β blocking drug, was also used as an adjunct to antipsychotics for 8 weeks in a clinical study of patients with chronic schizophrenia [118]. In this study, only one infusion (150 mg) was administered to patients, and substantial decreases in the positive subscale scores of the PANSS and the high-sensitivity CRP levels were observed. No adverse events were reported.

Clinical trials are still ongoing, with some of them investigating the use in schizophrenia of monoclonal antibody therapies whose effects have been demonstrated in other neuropsychiatric disorders. Natalizumab is a multiple sclerosis drug that regulates neuroinflammation by inhibiting α4-integrin. A randomized controlled trial investigating the response to natalizumab in first psychotic episode patients is being conducted (NCT03093064). Fingolimod is another drug treating multiple sclerosis that is also being investigated in patients with schizophrenia (NCT01779700). Although not a monoclonal antibody, this drug is an immunomodulator acting on sphingosine-1-phosphate receptor. Similarly, Siltuximab, an anti-IL-6 chimeric monoclonal antibody used for Castleman disease, is currently being investigated for treating schizophrenia (NCT02796859).

Mesenchymal stem cells

In addition to their capacity for tissue regeneration, mesenchymal stem cells (MSCs) have an immune-modulating effect by producing anti-inflammatory cytokines, such as PGE-2, IL-10, and TGF-β [119,120]. MSCs migrate to injury sites, where they inhibit inflammation and activate restorative mechanisms [121-125].

Many recent studies have investigated the potential therapeutic effects of MSCs in brain disorders, particularly neurodegenerative diseases [126,127]. An inflammatory environment and immune deregulation are also considered to lead to the development of autism, which possesses many characteristics similar to schizophrenia. Ichim *et al.* [128] proposed mesenchymal stem cell ther-

apy for autism, and research that is yet to be published gives an early indication that the use of MSCs in neurological disorders could be effective. In schizophrenia, mesenchymal stem cell therapy also has huge potential; many groups are now investigating this therapy to better understand the pathophysiology of schizophrenia, regardless of the therapy's outcome.

In summary, similarly to anti-inflammatory chemical agents, several biological agents have recently been investigated for adjuvant schizophrenia therapy. While the research field remains in its infancy, the results of several trials have shown the effects of adjunction of these drugs, especially monoclonal antibodies. Moreover, the effects of mesenchymal stem cells on neurological disorders and their immune-modulating properties suggest that MSCs could be effective in adjunctive schizophrenia therapy.

DISCUSSION

Various antipsychotics are being developed and several trials have been conducted to treat schizophrenia spectrum disorders. However, schizophrenia patients are currently only being treated with antipsychotics. The findings described in this review are encouraging, as they suggest that anti-inflammatory drugs may relieve psychotic symptoms and treat cognitive deficits. Moreover, the fact that the drugs used as adjuvant therapies in trials produced no notable adverse effects supports their application in the clinic. Because biological agents can inhibit specific cytokines, they also hold the promise to be effective in treating resistant, clinically well-defined patients. With the promising results recently presented by clinical trials using biological agents for neuropsychiatric disorders, successful drug repurposing and target finding for schizophrenia will likely increase.

However, as of now, there are still some limitations to the clinical application of anti-inflammatory drugs and adjuvant therapies. Due to small sample sizes in previous studies and a lack of data, more and larger studies are needed to establish anti-inflammatory adjunctive therapy as an effective method for schizophrenia. Adequate dosages of adjunctive drugs are also yet to be determined. To this end, studies about not only the effects of anti-inflammatory adjunctive drugs, but also the interactions between adjunctive drugs and antipsychotics should be conducted. Moreover, adjuvant drugs can interact with antipsychotics and induce unexpected adverse effects that need to be monitored. Finally, cost is an important limiting factor for the potential application of biological agents as adjunctive therapy in the future.

In conclusion, although there are several limiting factors, many clinical trials have presented promising results highlighting the therapeutic potential of anti-inflammatory approaches to alleviate symptoms of schizophrenia. These efforts not only pave the way for the development of effective treatments for schizophrenia but also provide valuable insights into the etiology of a complex disorder.

■ **Author Contributions**

Conceptualization: Jonghee Hong, Minji Bang. Data review, interpretation, and manuscript preparation: Jonghee Hong, Minji Bang. Writing—original draft: Jonghee Hong. Writing—review & editing: Jonghee Hong, Minji Bang. Funding: Minji Bang. Supervision: Minji Bang.

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