Published in final edited form as:

Curr Treat Options Psychiatry. 2017 June ; 4(2): 139–151. doi:10.1007/s40501-017-0114-0.

Targeting the Immune System with Pharmacotherapy in Schizophrenia

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Keywords

schizophrenia; immune; drugs; cytokines; antipsychotics; anti-inflammatory

OPINION STATEMENT

The clinical manifestations of increased cytokine activity in individuals with schizophrenia has not been clearly delineated, thus planning pharmacological interventions remains an entirely empirical endeavor. Although there are many preliminary findings regarding the use of adjunct pharmacotherapeutic strategies targeting the immune system, in most instances clearly efficacious results require further validation. Antipsychotics remain the most effective pharmacological treatment approach in schizophrenia, and evidence suggests they impact cytokine and immune cellular physiology in the patient, though this requires improved mechanistic understanding. Omega-3 polyunsaturated fatty acids (PUFAs) and statins may be a beneficial supplement in the situation where a patient with metabolic syndrome is a candidate for dietary modifications and/or control of LDL-cholesterol. Such an approach would require adjusting the diet and pharmacology towards a profile that could have anti-inflammatory effects, especially considering that adiposity is a source of increased inflammatory activity. Another strategy would be the addition of the neurosteroid pregnenolone, which appears to be well tolerated. Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed for other clinical conditions, thus their use in schizophrenia could be easily implemented, however, their efficacy is unclear and side effects require careful monitoring. The use of tetracycline antibiotics such as minocycline or

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Conflict of Interest

None of the authors declare any conflicts of interest.

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

anti-immune drugs such as azathioprine or methotrexate should be left to an academic research group, where the outcome and molecular signatures can be monitored in a controlled manner. Ultimately the benefit/risk ratio of each of these adjunct treatments should be considered on a case-by-case basis. Finally, lifestyle changes such as improved sleep, reduced smoking, and weight reduction strategies, all factors which are associated with increased inflammation, should not be overlooked when working towards an improved functional outcome.

INTRODUCTION

The literature indicating that schizophrenia is associated with elevated levels of proinflammatory cytokines dates back over 30 years [1], and meta-analyses conducted within the last few years are generally in agreement that schizophrenia is characterized by increased expression of proinflammatory cytokines, such as IL-6, TNF- α and IL-1 β , in serum [2, 3]. Gene expression profiling of circulating peripheral blood mononuclear cells (PBMCs) also demonstrates increased mRNA expression of these cytokines [4–6]. Additionally, there is evidence that cell signaling pathways critical in inflammation, NF- κ B and JAK-STAT1, are activated to a greater degree in PBMCs from some individuals with schizophrenia compared to controls [4, 7, 8]. Excess inflammation can be accompanied by oxidative and nitrosative stress, and there is evidence in schizophrenia of increased markers such as iNOS, COX-2 and PGE₂, as well as decreased antioxidant status [9–11].

In addition to reports of peripheral inflammation, studies in post-mortem brain tissue from individuals with schizophrenia also repeatedly demonstrate increased expression of proinflammatory cytokines and other genes involved in the immune response [12–14]. Additionally, both post-mortem and *in-vivo* imaging studies have reported increased markers of activated microglia, the cells responsible for secreting the majority of these inflammatory cytokines in the central nervous system (CNS), though findings are somewhat mixed [15]. For example, a recent *in-vivo* imaging study using positron emission tomography reported increased expression of the 18kD translocator protein (TSPO), a marker of activated microglia, in participants with schizophrenia as well as those at ultra-high risk of psychosis [16], whereas another recent study did not find a diagnostic difference [17].

It is known that there is constant bidirectional communication between peripheral central immune cells, including microglia and astrocytes [18, 19], and there are a number of hypotheses that outline how altered peripheral and central immune activity may interact with neuronal function to impact illness development and progression in schizophrenia. These include effects on mesolimbic dopamine signaling, and therefore reward and motivation [20], and altered tryptophan/kynurenine metabolism, which may impact glutamatergic transmission [19]. While the exact nature of this interaction is not yet well understood, peripheral markers of inflammation and oxidative/nitrosative stress have been demonstrated to associate with positive symptomatology [6] as well as cognitive deficits in schizophrenia [9, 21–23].

For the purpose of this review, we outline pharmacotherapeutic strategies that have been used to target the immune system in schizophrenia. In the case of commonly used

antipsychotics, immune modulation is not generally considered to be the primary mechanism of action, yet may contribute to some of the efficacy of these drugs in the treatment of schizophrenia [24]. Non-steroidal anti-inflammatory drugs (NSAIDs), antibody immunotherapy, tetracycline antibiotics, anti-rheumatic drugs, neurosteroids, antioxidants and statins, on the other hand, are not mainstay treatments in schizophrenia but have gone through varying degrees of pre-clinical and clinical investigation with the hope that they may serve as adjunct therapeutic agents that target altered immune activity to more effectively treat symptoms.

TREATMENTS

A) Antipsychotics

Antipsychotics can impact the expression of genes that code for cytokines, chemokines, pattern recognition receptors (PRRs) and cytokine receptors, as well as the distribution and/or differentiation of immune cell populations including monocytes, T cells and B cells [25–27]. In the clinical subject, antipsychotic treatment is associated with changes in cytokine levels. For example, in a meta-analysis of antipsychotic treated clinical subjects, suppression of pro-inflammatory cytokines (IL-1 β and IL-6 and TGF- β) and increases in anti-inflammatory cytokines have been reported following treatment [28].

However, the effects of antipsychotics on the function of immune cells and expression of immune molecules appear to vary depending on the properties of each medication. Treatment with clozapine appears to increase serum cytokine levels although overall findings are mixed [29]. Olanzapine and risperidone both reduced serum expression of the anti-inflammatory cytokines IL-1RA and IL-10, but did not affect the expression of seven other cytokines measured [30]. A study which measured cytokine levels each month for six months of treatment in antipsychotic naïve participants found an increased baseline level of IL-1 β , IL-6 and TNF- α [31]. Following treatment with risperidone, there was an initial decrease in IL-1 β and IL-6 which normalized by the sixth month, whereas TNF- α levels continued to increase over the study period.

In addition to examining the effect of antipsychotics on cytokine expression, which may indicate activation of innate or adaptive immunity, antipsychotic actions on innate immunity have been investigated by measuring effects on TLR-4 [32]. TLR-4 is an important PRR that responds to immune stimuli, such as the bacterial endotoxin lipopolysaccharide (LPS), initiating an inflammatory response. Risperidone and olanzapine were shown to normalize the expression of TLR-4 on monocytes, serving to control an initial step in the activation of the innate immune system. Modulation of adaptive immunity, on the other hand, is partly reflected by antipsychotic effects on T-cells. Clozapine and risperidone inhibited production of INF- γ by CD4+ T-cells and Th1 differentiation [26], while haloperidol was shown to inhibit Th2 differentiation [33].

Opposing effects of antipsychotics on microglial activation have been reported. In animal studies, chronic treatment with haloperidol and olanzapine induced a reactive microglial state in multiple brain regions [34]. Others report reduced microglial activation following treatment with risperidone [35], ziprasidone, quetiapine [36, 37] and aripiprazole [38].

Additional effects on oxidative stress and release of nitric oxide by paliperidone, quetiapine and ziprasidone, on both *in-vivo* as well as *in-vitro* models has been reported [39].

B) NSAIDS

NSAIDS work by inhibiting the activity of cyclooxygenase (COX) enzymes responsible for the production of prostaglandins. COX-1 is constitutively expressed in most tissues and elevated activity is implicated in inflammatory disorders [40]. COX-2, on the other hand, is not detected in most tissues unless induced by ambient inflammatory stimuli, however it is constitutively expressed in the central nervous system [10]. In the CNS, COX-2 is thought to play a role in synaptic activity, particularly glutamate transmission, as well as cytokine metabolism [41].

i. Aspirin—Aspirin is a commonly used non-steroidal anti-inflammatory drug that is significantly more effective at inhibiting COX-1 compared to COX-2 [41]. It has been shown to decrease production of proinflammatory cytokines and blunt the response of the innate immune system to inflammatory stimuli, leading to decreased oxidative and nitrosative stress [40]. A meta-analysis evaluated findings from two trials of adjunct treatment with aspirin at a dose of 1000 mgs per day, and it was found to have a beneficial effect in schizophrenia with a mean effect size of 0.3 [42]. In the Laan et al trial, participants in the group that received aspirin demonstrated significant improvement in positive PANSS scores, but no improvement on the remaining PANSS scales or cognitive measures [43].

ii. COX-2 inhibitors—Celecoxib, a selective COX-2 inhibitor that is able to penetrate the CNS, has been trialed in doses of 400mgs per day as an adjunct to antipsychotic therapy in schizophrenia [41, 42]. In one meta-analysis the effect size for improvement of positive symptoms was 0.15 and not significant [42]. However, in an independent meta-analysis which combined results from celecoxib and aspirin into a NSAID category, the effect size of 0.43 was significant [41]. Evidence of a potential benefit of celecoxib appears stronger when considering trials of use early in illness onset, as observed by two trials with a participant sample of first episode treatment naïve patients [44]. These findings are outlined in a recent review by Marini et al [44]. Finally, in an open label study, participants with schizophrenia, most of whom had a short duration of illness (average. 96 years), demonstrated improvement in all domains of the PANSS with adjunct celecoxib treatment [45].

However, both of these NSAIDS have potentially serious side effects. The high doses of aspirin used required gastric protection with pantoprazole [43]. Celecoxib has a ‘black box warning’ for cardiovascular and gastrointestinal risk and patients on celecoxib require monitoring for liver enzymes [41].

C) Antibody Immunotherapy

It is possible to directly target inflammatory molecules using antibody immunotherapy. Monoclonal antibodies directed against cytokines, cytokine receptors and other immune effectors are successfully utilized in a number of immune system disorders such as rheumatoid arthritis and inflammatory bowel disease [46]. However, the use of these treatments in schizophrenia is only recently being investigated. A small clinical trial with 5

stable outpatients with schizophrenia reported a positive effect of adjunct treatment with the anti-IL-6 receptor antibody, tocilizumab, on cognitive symptoms as measured by the Brief Assessment of Cognition in Schizophrenia (BACS), but with no overall change in PANSS scores [47]. Trials to test the effects of adjunct treatment with siltuximab, a direct anti-IL-6 antibody, canakinumab, an anti-IL-1 β antibody, and natalizumab, an anti- α 4-integrin antibody, are currently in preparation [48]. These trials will focus on participants who have elevated CRP, a marker of systemic immune activation. The anti-TNF- α antibody, infliximab, has not yet been trialed for schizophrenia, but showed some promise for treating depression in participants with high markers of inflammation [49].

The side effects of immune suppression are an obvious concern when considering the therapeutic potential of these drugs [50]. However, one clear advantage of antibody-mediated therapies is the lack of the off-target effects seen with many less specific immune modulatory drugs.

D) Tetracycline antibiotics

Microglia are CNS resident immune cells that are capable of releasing high levels of proinflammatory cytokines and contributing to oxidative and nitrosative stress when acutely or chronically activated [51]. As such, these cells are a critical therapeutic target in disorders with a neuroinflammatory component. Minocycline is a broad spectrum tetracycline antibiotic that easily crosses the blood brain barrier [52] and inhibits microglial activation, decreasing the production of several pro-inflammatory cytokines, such as IL-1 β , IL-6, TNF- α , and IFN- γ , as well as reducing COX-2 expression, PGE2 synthesis and iNOS mRNA expression [41, 52, 53].

Based on post-mortem and *in-vivo* evidence of microglial activation in individuals with schizophrenia, minocycline has been trialed as an adjunct treatment to antipsychotics. There have been multiple meta-analyses conducted to examine the role of minocycline supplementation. One meta-analysis consisting of four studies in a total of 348 schizophrenia patients reported there was no significant effect of minocycline supplementation to antipsychotics [42]. However, a subsequent meta-analysis of four trials including 330 participants with schizophrenia that used adjunct treatment with minocycline ranging from 8 weeks to 12 months reported that minocycline was superior to placebo for PANSS total scores, specifically negative and general subscales, but not the positive subscale [54]. Additionally, minocycline was reported to improve cognitive symptomatology in some of the studies, but cognitive measures were not included in the analysis. A more recent meta-analysis with eight trials including a total of 548 participants with schizophrenia, found that minocycline was superior to placebo for PANSS total and all subscales, including the positive subscale, but was not superior to placebo when analyzed based on tests of cognitive function [55].

Although these trials reported no serious side effects compared to placebo [55], it is critical to keep in mind the potential activation of autoimmune disorders such as lupus, thyroiditis, and hepatitis with minocycline administration [42].

E) Anti-rheumatic drugs

Anti-rheumatic drugs such as methotrexate and azathioprine are used to treat a number of immune system disorders including rheumatoid arthritis, inflammatory bowel disease, psoriasis and lupus [56, 57]. An early trial that studied azathioprine in schizophrenia reported that two of the 11 participants demonstrated a significant improvement in symptomatology [58]. To date there are no published data on the efficacy of methotrexate in schizophrenia; however, a study protocol has been registered and described [56]. The anti-inflammatory effects of methotrexate appear to be at least partly mediated via an increase in adenosine [57]. Adenosine inhibits macrophage activation, and treatment with methotrexate has resulted in decreased levels of TNF- α and IL-6 *in-vivo* [57, 59, 60]. The outcome of the methotrexate trial will be particularly interesting given the immunomodulatory properties of the drug as well as the adenosine hypothesis of schizophrenia, which lends further theoretical support to its therapeutic potential [61].

F) Neurosteroids

Pregnenolone, and its downstream metabolites, such as allopregnenolone (ALLO) and dehydropiandrosterone (DHEA), have multiple roles in normal neuronal function as well as neuroprotective and anti-inflammatory effects [62–64]. For example, treatment of human monocyte-derived macrophages with ALLO resulted in a reduction of IL-1 β , TNF- α , and IDO expression after PMA treatment [65]. Similarly, in animal studies ALLO prevented against central and peripheral inflammation in models of traumatic brain injury and multiple sclerosis. Furthermore, it has been reported that serum levels of pregnenolone are decreased in schizophrenia [66].

To date, five trials have been conducted to determine the efficacy of adjunct pregnenolone treatment in schizophrenia [62, 64, 67–69]. Doses ranged from 30 to 500 mg over the course of 8 weeks. Two of the studies report improved scores on the PANSS negative subscales [67, 68], and one trial showed improvements in positive symptomatology that appeared to be dose dependent [62]. Further, many of the trials reported improvements in multiple neurocognitive measures [62, 68, 69]. However, the most recent trial did not find a significant improvement in cognitive symptomatology, though improved overall functional capacity was reported [64]. Pregnenolone is generally well tolerated [67].

G) Antioxidants

Based on findings of increased oxidative and nitrosative stress and decreased antioxidant status in individuals with schizophrenia [11], a number of antioxidant treatments have been trialed.

a. N-acetylcysteine—N-acetylcysteine is an antioxidant precursor that has anti-inflammatory activity and neuroprotective effects [42, 70]. In rodent studies, N-acetylcysteine was shown to inhibit the effects of inflammatory stimuli such as LPS [71]. Two trials of N-acetylcysteine at a dose of 2 g per day were conducted in a total of 182 patients for a duration of 6 [72] and 24 [73] weeks in acutely ill patients. In both studies there was a significantly superior response of N-acetylcysteine to placebo and improvements in PANSS total and negative scores, but not PANSS positive scores. Another

study protocol has been recently published which aims to determine the effects of adjunct treatment with N-acetylcysteine specifically for participants with clozapine-resistant schizophrenia [74].

b. Polyunsaturated fatty acids—Polyunsaturated fatty acids (PUFAs) are important for brain development, membrane fluidity and integrity, and the proper functioning of membrane bound neurotransmitter receptors [75]. A typical western diet delivers a 10 to 1 ratio, and even up to a 30 to 1 ratio, of omega-6 PUFAs to omega-3 PUFAs [76]. Treatment with omega-3 PUFAs, such as EPA and DHA, is thought to be therapeutic because EPA and DHA replace and reduce the amount of omega-6 PUFAs, which include arachidonic acid, in cell membranes over a period of months leading to decreased synthesis of proinflammatory prostaglandins by COX enzymes [77]. Omega-3 PUFAs have also been shown to decrease cellular activation commonly associated with innate immunoreactivity by inhibiting NF- κ B activity [78]. This leads to decreased production of a number of proinflammatory cytokines, as well as COX-2 and iNOS, in monocytes, macrophages and microglia [77]. PUFAs are also endogenous ligands for the nuclear receptor PPAR γ , which we have shown to be more highly expressed in immune cells from individuals with schizophrenia [5]. PPAR γ has anti-inflammatory properties and has been shown decrease production of proinflammatory cytokines *in-vitro* [77, 79, 80].

One meta-analysis that included 7 trials focused on adjunct treatment with EPA in schizophrenia, and did not find a statistically significant effect of treatment [75]. Additionally, a recent review that outlined the findings of 11 trials using adjunct omega-3 PUFAs in schizophrenia concluded that the results regarding overall efficacy still remain unclear [81]. Doses ranged from 1 to 4 g per day and mean length of study was 14 weeks with the exception of one trial that lasted 2 years. There were a mix of positive and negative findings regarding treatment with omega-3 PUFAs in both chronic schizophrenia and first episode psychosis. Interestingly, one study with participants at ultra-high risk of psychosis found decreased transition to a psychotic disorder following treatment with omega-3 PUFAs [82]. A study protocol to further investigate the preventative efficacy of omega-3 PUFAs over the course of 6 months has been published [83].

It is possible that the lack of efficacy of adjunct treatment at chronic stages of illness is due to dietary and metabolic disturbances that may be caused by antipsychotics and lifestyle changes, particularly diet, which can easily reverse any attempts to increase the ratio of omega-3 to omega-6 PUFAs.

H) Statins

Statins are typically implicated in the treatment of cardiovascular disease due to their lipid-lowering actions [39]. However, statins also exhibit an inhibitory effect on cellular mediators of inflammation, which has encouraged their use in treating immune diseases. For example, treatment with fluvastatin, simvastatin, and atorvastatin was shown to block the inflammatory effects of IL-6 *in-vitro*, resulting in decreased intracellular signaling and inhibition of monocyte chemotaxis [84]. In a clinical trial of rosuvastatin in participants with hypertension and dyslipidemia, there were reductions in serum levels of proinflammatory

cytokines and markers of oxidative stress [85]. However, it should be noted that effects on immune parameters seem to differ based on the statin used.

There are two recent trials of adjunct treatment with statins in participants with schizophrenia. In one trial with 56 total participants, 40mg per day for 12 weeks of adjunct pravastatin resulted in a decrease in cholesterol, but not CRP, IL-6, or TNF- α [86]. Additionally, there was no effect on PANSS scores or neurocognitive measures at 12 weeks, though there was an initial decrease in PANSS positive scores at 6 weeks that was not maintained. In the second trial with 36 total participants, 20mg per day of adjunct lovastatin for 8.5 weeks did not lead to any significant improvement in PANSS measures compared to placebo [87]. There is a third trial currently underway which plans to determine the effects of adjunct treatment with 40mg/day simvastatin in 250 participants with schizophrenia for a period of 12 month [88].

I) Future directions

Obesity is a prevalent co-morbidity in schizophrenia, which is at least partly a side effect of antipsychotic medication use and associated with elevated immunoreactivity. PPAR γ is highly expressed in adipose and immune tissue and improves metabolic control in addition to having anti-inflammatory activity [89]. PPAR γ , therefore, represents a small molecule target that could serve an anti-inflammatory, anti-oxidant and pro-energetic role [10]. There are small molecule ligands for these nuclear receptors with well-studied epigenetics effects [90]. Thiazolidinediones, such as rosiglitazone and pioglitazone, are potent agonists of PPAR γ , and trials in schizophrenia have found improvements in metabolism [91, 92]. Rosiglitazone has been shown to decrease CRP levels in participants with type 2 diabetes [93], but effects on immune parameters have not yet been investigated in schizophrenia. We have reported increased levels of PPAR γ in peripheral blood cells from medicated schizophrenia patients, which could suggest a homeostatic regulation to balance an inflammatory milieu [5].

Another strategy is to target intracellular immune cell signaling pathways characteristic of activated immune cells. Both the JAK-STAT1 and NF- κ B pathways, which demonstrate elevated activity in schizophrenia, require defined activity by catalytic enzymes such as kinases [4, 7, 8]. JAK inhibitors, such as tofacitinib and ruxolitinib have shown efficacy in clinical trials for a number of immune disorders, and tofacitinib has been approved for use in rheumatoid arthritis [94]. Treatment with tofacitinib led to reduced levels of activated STAT1 in affected peripheral tissue [95].

CONCLUSION

Both data regarding immune activity in schizophrenia as well as response to immunomodulatory pharmacotherapy highlight the need to consider individual differences in baseline inflammatory markers as well as illness stage and severity of clinical symptoms [96]. Stratifying the sample based on immune activity using available biomarkers, such as CRP, is already being implemented in some trials. There is also a need for longitudinal studies in individuals with schizophrenia to determine the nature by which immune activity changes with symptom activity, clinical metrics and treatment. It may be that there is only a

subset of individuals with schizophrenia who have altered immune activity that will respond to these interventions.

While there are clearly peripheral and central immune alterations in schizophrenia, the field would benefit from a better understanding of the contribution of specific cell types and phenotypes, allowing for new theory-driven therapeutic targets. In the periphery, for example, CD14⁺ monocytes are key players in innate immune activation through crosstalk between JAK-STAT and NF- κ B pathways. In the CNS, the nature of glial alterations and neuroinflammatory activity remains to be characterized. Findings are conflicting likely due to heterogeneous phenotypes of glial cells, the markers/ligands selected for post-mortem studies and PET imaging, and small heterogeneous samples of participants [15]. As knowledge improves, more appropriate immune-related targets, and biological measures of treatment efficacy will likely emerge.

Another challenge is to disentangle the immunomodulatory effects of many of the pharmacotherapies discussed with other non-immune effects [50, 72]. There is also a need to separate bona-fide autoimmune disorders due to autoantibodies against CNS proteins, such as anti-NMDA receptor antibodies, from non-autoimmune causes of symptoms associated with schizophrenia. Identifying these types of protein targets could support the use of small molecule pharmacology that limit the antibody induced damage.

Acknowledgments

This work was supported in part by PHS grant (NIH) R01MH094358 (R.P.S.).

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