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Schizophrenia and Other Psychotic Disorders (J Csernansky, Section Editor)

Targeting the Immune System With Pharmacotherapy in Schizophrenia

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Opinion statement

The clinical manifestations of increased cytokine activity in individuals with schizophrenia have 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 that 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 antiinflammatory 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 antiinflammatory 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 antiimmune 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-1β, in serum [2•, 3]. Gene expression profiling of circulating peripheral blood mononuclear cells (PBMCs) also demonstrates increased messenger RNA (mRNA) expression of these cytokines [4–6]. Additionally, there is evidence that cell signaling pathways critical in inflammation, NF-κB and Janus kinase/signal transducers and activators of transcription (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 inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2), as well as decreased antioxidant status [9–11].

In additional to reports of peripheral inflammation, studies in postmortem 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 postmortem 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 18 kD 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 antiinflammatory drugs (NSAIDS), antibody immunotherapy, tetracycline antibiotics, antirheumatic drugs, neurosteroids, antioxidants, and statins, on the other hand, are not mainstay treatments in schizophrenia but have gone

through varying degrees of preclinical 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

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 proinflammatory cytokines (IL-1β and IL-6 and TGF-β) and increases in antiinflammatory 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 antiinflammatory 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 6 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-1β 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].

NSAIDS

NSAIDS work by inhibiting the activity of 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].

Aspirin

Aspirin is a commonly used non-steroidal antiinflammatory 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 mg 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 Positive and Negative Syndrome Scale (PANSS) scores but no improvement on the remaining PANSS scales or cognitive measures [43].

COX-2 inhibitors

Celecoxib, a selective COX-2 inhibitor that is able to penetrate the CNS, has been trialed in doses of 400 mg 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 0.96 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].

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 five 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-1β antibody, and natalizumab, an anti-α4-integrin antibody, are currently in preparation [48•]. These trials will focus on participants who have elevated C-reactive protein (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 the off-target effects seen with many less specific immune modulatory drugs.

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 proinflammatory cytokines, such as IL-1β, 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 postmortem 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 that 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].

Antirheumatic drugs

Antirheumatic 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 2 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 antiinflammatory effects of methotrexate appear 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].

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 antiinflammatory effects [62–64]. For example, treatment of human monocyte-derived macrophages with ALLO resulted in a reduction of IL-1β, 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].

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.

N-Acetylcysteine

N-Acetylcysteine is an antioxidant precursor that has antiinflammatory 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*-acetylcsysteine 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].

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 eicosapentaenoic acid (EPA) and docosahexaenoic acid (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-κB 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 peroxisome proliferator-activated receptor gamma (PPARγ), which we have shown to be more highly expressed in immune cells from individuals with schizophrenia [5]. PPARγ has antiinflammatory properties and has been shown decrease production of pro-inflammatory cytokines in vitro [77, 79, 80].

One meta-analysis that included seven 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 was 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.

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, 40 mg 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, 20 mg 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 40 mg/day simvastatin in 250 participants with schizophrenia for a period of 12 months [88].

Future directions

Obesity is a prevalent co-morbidity in schizophrenia, which is at least partly a side effect of antipsychotic mediation use and associated with elevated immunoreactivity. PPARγ is highly expressed in adipose and immune tissue and improves metabolic control in addition to having antiinflammatory activity [89]. PPARγ, therefore, represents a small molecule target that could serve an antiinflammatory, antioxidant, and proenergetic role [10]. There are small molecule ligands for these nuclear receptors with well-studied epigenetic effects [90]. Thiazolidinediones, such as rosiglitazone and pioglitazone, are potent agonists of PPARγ, 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 PPARγ 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-κB 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-κB 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 postmortem 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 limits the antibody-induced damage.

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Compliance with Ethical Standards

Conflict of Interest

Jennifer K. Melbourne declares that she has no conflict of interest. Benjamin Feiner declares that he has no conflict of interest. Cherise Rosen declares that she has no conflict of interest. Rajiv P. Sharma declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

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).

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Hinze-Selch D, Pollmächer T. In vitro cytokine secretion in individuals with schizophrenia: results, confounding factors, and implications for further research. Brain Behav Immun. 2001;15:282–318.
2.• Goldsmith DR, Rapaport MH, Miller BJ (2016) A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 1–14 The most up to date meta-analysis of peripheral cytokine activity in schizophrenia and related psychiatric illnesses.
3. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr Res. 2014;155:101–8.
4. Song X-Q, Lv L-X, Li W-Q, Hao Y-H, Zhao J-P. The interaction of nuclear factor-kappa B and cytokines is

associated with schizophrenia. Biol Psychiatry. 2009;65:481–8.
5. Chase KA, Rosen C, Gin H, Bjorkquist O, Feiner B, Marvin R, Conrin S, Sharma RP. Metabolic and inflammatory genes in schizophrenia. Psychiatry Res. 2015;225:208–11.
6. Chase KA, Cone JJ, Rosen C, Sharma RP. The value of interleukin 6 as a peripheral diagnostic marker in schizophrenia. BMC Psychiatry. 2016;16:152.
7. García-Bueno B, Bioque M, Mac-Dowell KS, et al. Pro-/anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. Schizophr Bull. 2014;40:376–87.
8. Sharma RP, Rosen C, Melbourne JK, Feiner B, Chase KA. Activated phosphorylated STAT1 levels as a biologically relevant immune signal in schizophrenia. Neuroimmunomodulation. 2016; doi:10.1159/000450581.
9. Cabrera B, Bioque M, Penadés R, González-Pinto A., Parellada M, Bobes J, Lobo A, García-Bueno B, Leza JC, Bernardo M (2016) Cognition and psychopathology in first-episode psychosis: are they related to inflammation? Psychol Med 1–12
10. Leza JC, Bueno B, Bioque M, Arango C, Parellada M, Do K, O'Donnell P, Bernardo M. Inflammation in schizophrenia: a question of balance. Neurosci Biobehav Rev. 2015;55:612–26.
11. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. Biol Psychiatry. 2013;74:400–9.
12. Hess JL, Tylee DS, Barve R, et al. Transcriptome-wide mega-analyses reveal joint dysregulation of immunologic genes and transcription regulators in brain and blood in schizophrenia. Schizophr Res. 2016;176:114–24.
13. Volk DW, Chitrapu A, Edelson JR, Roman KM, Moroco AE, Lewis DA. Molecular mechanisms and timing of cortical immune activation in schizophrenia. Am J Psychiatry. 2015;172:1112–21.
14. Fillman SG, Cloonan N, Miller LC, Weickert CS. Markers of inflammation in the prefrontal cortex of individuals with schizophrenia. Mol Psychiatry. 2013;18:133.
15.•• Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP (2016) Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry 1009–1026

Extensive review that covers both positive and negative findings of CNS inflammatory markers and gial cell alterations in schizophrenia.

16. Bloomfield PS, Selvaraj S, Veronese M, et al. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [11C]PBR28 PET brain imaging study. Am J Psychiatry. 2016;173:44–52.
17. Hafizi S, Tseng H-H, Rao N, et al (2016) Imaging microglial activation in untreated first-episode psychosis: a PET study with [(18)F]FEPPA. Am J Psychiatry appiajp201616020171
18. Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun. 2011;25:181–213.
19. Khandaker GM, Dantzer R. Is there a role for immune-to-brain communication in schizophrenia? Psychopharmacology. 2015; doi:10.1007/s00213-015-3975-1.
20. Felger JC, Treadway MT. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology. 2016;42:1–88.
21. Frydecka D, Misiak B, Pawlak-Adamska E, Karabon L, Tomkiewicz A, Sedlaczek P, Kiejna A, Beszłej JA. Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur Arch Psychiatry Clin Neurosci. 2015;265:449–59.
22. Martínez-Cengotitabengoa M, Mac-Dowell KS, Leza JC, Micó JA, Fernandez M, Echevarría E, Sanjuan J, Elorza J, González-Pinto A. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. Schizophr Res. 2012;137:66–72.
23. Bulzacka E, Boyer L, Schürhoff F, et al (2016) Chronic peripheral inflammation is associated with cognitive impairment in schizophrenia: eesults from the multicentric FACE-SZ dataset. Schizophr Bull 42:sbw029
24. Horváth S, Mirnics K. Immune system disturbances in schizophrenia. Biol Psychiatry. 2014;75:316–23.
25. Chen M-L, Wu S, Tsai T-C, Wang L-K, Tsai F-M. Regulation of macrophage immune responses by antipsychotic drugs. Immunopharmacol Immunotoxicol. 2013;35:573–80.
26. Chen M-L, Tsai T-C, Wang L-K, Lin Y-Y, Tsai Y-M, Lee M-C, Tsai F-M. Clozapine inhibits Th1 cell differentiation and causes the suppression of IFN-γ production in peripheral blood mononuclear cells. Immunopharmacol Immunotoxicol. 2012;34:686–94.
27. Debnath M. Adaptive immunity in schizophrenia: functional implications of T cells in the etiology, course and treatment. J NeuroImmune Pharmacol. 2015;10:610–9.
28. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70:663–71.
29. Røge R, Møller BK, Andersen CR, Correll CU, Nielsen J. Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr Res. 2012;140:204–13.
30. Witte L De, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS, Bahn S (2014) Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. Schizophr Res 154:23–29
31. Song X, Fan X, Li X, Zhang W, Gao J, Zhao J, Harrington A, Ziedonis D, Lv L. Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first-episode schizophrenia. Psychopharmacology. 2014;231:319–25.

32. Kéri S, Szabó C, Kelemen O. Antipsychotics influence toll-like receptor (TLR) expression and its relationship with cognitive functions in schizophrenia. Brain Behav Immun. 2016:1–9.
33. Chen ML, Tsai TC, Lin YY, Tsai YM, Wang LK, Lee MC, Tsai FM. Antipsychotic drugs suppress the AKT/NF-κB pathway and regulate the differentiation of T-cell subsets. Immunol Lett. 2011;140:81–91.
34. Cotel M-C, Lenartowicz EM, Natesan S, Modo MM, Cooper JD, Williams SCR, Kapur S, Vernon AC. Microglial activation in the rat brain following chronic antipsychotic treatment at clinically relevant doses. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2015;25:2098–107.
35. Zhu F, Zheng Y, Ding YQ, Liu Y, Zhang X, Wu R, Guo X, Zhao J. Minocycline and risperidone prevent microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of lipopolysaccharide in rats. PLoS One. 2014; doi:10.1371/journal.pone.0093966.
36. Bian Q, Kato T, Monji A, Hashioka S, Mizoguchi Y, Horikawa H, Kanba S. The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-γ. Prog Neuro-Psychopharmacology Biol Psychiatry. 2008;32:42–8.
37. Wang H, Liu S, Tian Y, Wu X, He Y, Li C, Namaka M, Kong J, Li H, Xiao L. Quetiapine inhibits microglial activation by neutralizing abnormal STIM1-mediated intercellular calcium homeostasis and promotes myelin repair in a cuprizone-induced mouse model of demyelination. Front Cell Neurosci. 2015;9:1–11.
38. Kato T, Mizoguchi Y, Monji A, Horikawa H, Suzuki SO, Seki Y, Iwaki T, Hashioka S, Kanba S. Inhibitory effects of aripiprazole on interferon-γ-induced microglial activation via intracellular Ca2+ regulation in vitro. J Neurochem. 2008;106:815–25.
39. Dodd S, Maes M, Anderson G, Dean OM, Moylan S, Berk M. Progress in neuro-psychopharmacology & biological psychiatry putative neuroprotective agents in neuropsychiatric disorders. Prog Neuro-Psychopharmacol Biol Psychiatry. 2013;42:135–45.
40. Berk M, Dean O, Drexhage H, et al. Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. BMC Med. 2013;11:74.
41. Fond G, Hamdani N, Kapczinski F, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. Acta Psychiatr Scand. 2014;129:163–79.
42. Sommer IE, Van Westrhenen R, Begemann MJH, De Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull. 2014;40:181–91.
43. Laan W, Grobbee D, Selten J-P, Heijnen C, Kahn R, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010;71:520–7.
44.• Marini S, De Berardis D, Orsolini L, et al. Celecoxib adjunctive treatment to risperidone in schizophrenia: a review of randomized clinical add-on trials. Eur Neuropsychopharmacol. 2016;26:S534–5.

Provides an overview of trials with adjunct celecoxib in schizophrenia

45. Baheti T, Nischal A, Nischal A, Khattri S, Arya A, Tripathi A, Pant KK. A study to evaluate the effect of celecoxib as add-on to olanzapine therapy in schizophrenia. Schizophr Res. 2013;147:201–2.
46. Chan AC, Carter PJ. Therapeutic antibodies for autoimmunity and inflammation. Nat Rev Immunol. 2010;10:301–16.
47. Miller BJ, Dias JK, Lemos HP, Buckley PF. An open-label, pilot trial of adjunctive tocilizumab in schizophrenia. J Clin Psychiatry. 2016;77:275–6.
48.• Miller BJ, Buckley PF. Monoclonal antibody immunotherapy in psychiatric disorders. The Lancet Psychiatry. 2017;4:13–5.

Provides a rationale for the use of antibody immunotherapy in schizophrenia and outlines trials in preparation

49. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression. JAMA Psychiatry. 2013;70:31.
50. Miller BJ, Buckley PF. The case for adjunctive monoclonal antibody immunotherapy in schizophrenia. Psychiatr Clin North Am. 2016;39:187–98.
51. Watkins CC, Andrews SR. Clinical studies of neuroinflammatory mechanisms in schizophrenia. Schizophr Res. 2015; doi:10.1016/j.schres.2015.07.018.
52. Fekadu A, Mesfin M, Medhin G, et al. Adjuvant therapy with minocycline for schizophrenia (the MINOS trial): study protocol for a double-blind randomized placebo-controlled trial. Trials. 2013;14:1–10.
53. Inta D, Lang UE, Borgwardt S, Meyer-Lindenberg A, Gass P (2016) Microglia activation and schizophrenia: lessons from the effects of minocycline on postnatal neurogenesis, neuronal survival and synaptic pruning. Schizophr Bull sbw088
54. Oya K, Kishi T, Iwata N (2014) Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials. 483–491
55.• Xiang Y, Zheng W, Wang S, Yang X, Cai D, Ng CH, Ungvari GS, Kelly DL, Xu W, Xiang Y. Adjunctive minocycline for schizophrenia: a meta-analysis of randomized controlled trials. Eur Neuropsychopharmacol. 2017;27:8–18.

Most recent meta-analysis regarding the use of minocycline in schizophrenia

56. Chaudhry IB, Husain N, ur Rahman R, et al (2015) A randomised double-blind placebo-controlled 12-week feasibility trial of methotrexate added to treatment as usual in early schizophrenia: study protocol for a randomised controlled trial. Trials 16:9
57. Chan ESL, Cronstein BN. Methotrexate—how does it really work? Nat Rev Rheumatol. 2010;6:175–8.

58. Levine J, Gutman J, Feraro R, Levy P, Kimhi R, Leykin I, Deckmann M, Handzel Z, Shinitzky M. Side effect profile of azathioprine in the treatment of chronic schizophrenic patients. Neuropsychobiology. 1997;36:172–6.
59. Barnholt KE, Kota RS, Aung HH, Rutledge JC. Adenosine blocks IFN-γ-induced phosphorylation of STAT1 on serine 727 to reduce macrophage activation. J Immunol. 2009;183:6767–77.
60. Zhang Z, Zhao P, Li A, Lv X, Gao Y, Sun H, Ding Y, Liu J. Effects of methotrexate on plasma cytokines and cardiac remodeling and function in postmyocarditis rats. Mediat Inflamm. 2009; doi:10.1155/2009/389720.
61. Boison D, Singer P, Shen HY, Feldon J, Yee BK. Adenosine hypothesis of schizophrenia—opportunities for pharmacotherapy. Neuropharmacology. 2012;62:1527–43.
62. Ritsner MS. Pregnenolone, dehydroepiandrosterone, and schizophrenia: alterations and clinical trials. CNS Neurosci Ther. 2010;16:32–44.
63. Vuksan-Ćusa B, Šagud M, Radoš I. The role of dehydroepiandrosterone (DHEA) in schizophrenia. Psychiatr Danub. 2016;28:30–3.
64. Marx CE, Lee J, Subramaniam M, et al. Proof-of-concept randomized controlled trial of pregnenolone in schizophrenia. Psychopharmacology. 2014;231:3647–62.
65. Noorbakhsh F, Baker GB, Power C. Allopregnanolone and neuroinflammation: a focus on multiple sclerosis. Front Cell Neurosci. 2014;8:134.
66. Ritsner M, Maayan R, Gibel A, Weizman A. Differences in blood pregnenolone and dehydroepiandrosterone levels between schizophrenia patients and healthy subjects. Eur Neuropsychopharmacol. 2007;17:358–65.
67. Marx CE, Keefe RSE, Buchanan RW, et al. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. Neuropsychopharmacology. 2009;34:1885–903.
68. Savitz A (2010) Multi-year continuation study of pregnenolone in patients with schizophrenia. Neurosteroids as Nov. Ther. Schizophr. other CNS Disord. Soc. Biol. Psychiatry Annu. New Orleans, LA
69. Kreinin A, Bawakny N, Ritsner M (2014) Adjunctive pregnenolone ameliorates the cognitive deficits in recent-onset schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. Clin Schizophr Relat Psychoses 1–31
70. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuro-Psychopharmacology Biol Psychiatry. 2011;35:676–92.
71. Lanté F, Meunier J, Guiramand J, De Ferreira MCJ, Cambonie G, Aimar R, Cohen-Solal C, Maurice T, Vignes M, Barbanel G. Late N-acetylcysteine treatment prevents the deficits induced in the offspring of dams exposed to an immune stress during gestation. Hippocampus. 2008;18:602–9.
72. Farokhnia M, Azarkolah A, Adinehfar F, et al. N-Acetyl cysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. Clin Neuropharmacol. 2013;36:185–92.
73. Berk M, Copolov D, Dean O, et al. N-Acetyl cysteine as a glutathione precursor for schizophrenia-a double-blind, randomized, placebo-controlled trial. Biol Psychiatry. 2008;64:361–8.
74. Rossell SL, Francis PS, Galletly C, et al. N-Acetyl cysteine (NAC) in schizophrenia resistant to clozapine: a double blind randomised placebo controlled trial targeting negative symptoms. BMC Psychiatry. 2016;16:320.
75. Fusar-poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia. J Clin Psychopharmacol. 2012;32:179–85.
76. Calder PCP. Mechanisms of action of (n-3) fatty acids. J Nutr. 2012;142:592S–9S.
77. Calder PC. Long-chain fatty acids and inflammation. Proc Nutr Soc. 2012;71:284–9.
78. Novak TE, Babcock TA, Jho DH, Helton WS, Espat NJ. NF-kappa B inhibition by omega-3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. Am J Physiol Cell Mol Physiol. 2003;284:L84–9.
79. Kong W, Yen J-H, Vassiliou E, Adhikary S, Toscano MG, Ganea D. Docosahexaenoic acid prevents dendritic cell maturation and in vitro and in vivo expression of the IL-12 cytokine family. Lipids Heal Dis. 2010;9:12.
80. Zapata-Gonzalez F, Rueda F, Petriz J, Domingo P, Villarroya F, Diaz-Delfin J, de Madariaga M a, Domingo JC (2008) Human dendritic cell activities are modulated by the omega-3 fatty acid, docosahexaenoic acid, mainly through PPAR :RXR heterodimers: comparison with other polyunsaturated fatty acids. J Leukoc Biol 84:1172–1182
81.• Bozzatello P, Brignolo E, De Grandi E, Bellino S. Supplementation with omega-3 fatty acids in psychiatric disorders: a review of literature data. J Clin Med. 2016;5:1–26.
Reviews clinical data investigating the use of adjunct omega-3 PUFAs in schizophrenia and other psychiatric disorders
82. Amminger GP. Long-chain n-3 fatty acids for indicated prevention of psychotic disorders. Arch Gen Psychiatry. 2010;67:146–54.
83. Markulev C, Mcgorry PD, Nelson B, et al. NEURAPRO-E study protocol: a multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. Early Interv Psychiatry. 2015; doi:10.1111/eip.12260.
84. Jougasaki M, Ichiki T, Takenoshita Y, Setoguchi M. Statins suppress interleukin-6-induced monocyte chemo-attractant protein-1 by inhibiting Janus kinase/signal transducers and activators of transcription 1 (JAK-STAT1) pathways in human vascular endothelial cells. Br J Pharmacol. 2010;159:1294–303.

85. Gómez-García A, Martínez Torres G, Ortega-Pierres LE, Rodríguez-Ayala E, Alvarez-Aguilar C. Rosuvastatin and metformin decrease inflammation and oxidative stress in patients with hypertension and dyslipidemia. Rev española Cardiol. 2007;60:1242–9.
86. Vincenzi B, Stock S, Borba CPC, et al. A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: effect on inflammation, psychopathology, cognition and lipid metabolism. Schizophr Res. 2014;159:395–403.
87. Ghanizadeh A, Rezaee Z, Dehbozorgi S, Berk M, Akhondzadeh S. Lovastatin for the adjunctive treatment of schizophrenia: a preliminary randomized double-blind placebo-controlled trial. Psychiatry Res. 2014;219:431–5.
88. Begemann MJH, Schutte MJL, Slot MIE, Doorduin J, Bakker PR, van Haren NEM, Sommer IEC. Simvastatin augmentation for recent-onset psychotic disorder: a study protocol. BBA Clin. 2015;4:52–8.
89. Sharma AM, Staels B. Review: peroxisome proliferator-activated receptor γ and adipose tissue—understanding obesity-related changes in regulation of lipid and glucose metabolism. J Clin Endocrinol Metab. 2007;92:386–95.
90. Chase K, Sharma RP. Epigenetic developmental programs and adipogenesis: implications for psychotropic induced obesity. Epigenetics. 2013;8:1133–40.
91. Henderson DC, Fan X, Sharma B, Copeland PM, Borba CP, Boxill R, Freudenreich O, Cather C, Eden Evins A, Goff DC. A double-blind, placebo-controlled trial of rosiglitazone for clozapine-induced glucose metabolism impairment in patients with schizophrenia. Acta Psychiatr Scand. 2009;119:457–65.
92. Smith RC, Jin H, Li C, Bark N, Shekhar A, Dwivedi S, Mortiere C, Lohr J, Hu Q, Davis JM. Effects of pioglitazone on metabolic abnormalities, psychopathology, and cognitive function in schizophrenic patients treated with antipsychotic medication: a randomized double-blind study. Schizophr Res. 2013;143:18–24.
93. Stocker DJ, Taylor AJ, Langley RW, Jezior MR, Vigersky RA. A randomized trial of the effects of rosiglitazone and metformin on inflammation and subclinical atherosclerosis in patients with type 2 diabetes. Am Heart J. 2007; doi:10.1016/j.ahj.2006.11.005.
94. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK–STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs. 2017;77:521–46.
95. Boyle DL, Soma K, Hodge J, et al. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. Ann Rheum Dis. 2015;74:1311–6.
96. Miller BJ, Goldsmith DR. Towards an immunophenotype of schizophrenia: progress, potential mechanisms, and future directions. Neuropsychopharmacology. 2016;42:1–19.