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A REVIEW OF ANTI-INFLAMMATORY AGENTS FOR SYMPTOMS OF SCHIZOPHRENIA

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Abstract

Schizophrenia is a chronic debilitating mental disorder that affects about 1% of the U.S population. The pathophysiology and etiology remain unknown, thus new treatment targets have been challenging and few novel treatments with new mechanisms of action have come to market in the past few decades. Increasing attention has been paid to the role of inflammation in schizophrenia and new data suggests that decreasing inflammation and inflammatory biomarkers may play some role in schizophrenia treatment. This review summarizes the clinical trial literature regarding medications that possess anti-inflammatory properties that have been tested for schizophrenia symptoms and covers such medications as nonsteroidal anti-inflammatory agents, such as the cyclooxygenase-2 (COX-2) inhibitors and aspirin, omega-3 fatty acids, neurosteroids and minocycline. Overall, there is accumulating evidence, albeit mostly adjunctive treatments, that agents working on inflammatory pathways have some benefits in people with schizophrenia. In the next few years the field will begin to see data on many treatments with anti-inflammatory properties that are currently under study. Hopefully advancements in understanding inflammation and effective treatments having anti-inflammatory properties may help revolutionize our understanding and provide new targets for prevention and treatment in schizophrenia.

Keywords

inflammation; schizophrenia; aspirin; cytokines; minocycline; omega 3 fatty acids

Introduction

Schizophrenia is a chronic debilitating mental disorder that affects about 1% of the U.S population. Onset is typically in adolescence or early adulthood, and rarely in childhood (Shi et al., 2009). The causes of this disorder are still unknown and as such most of the treatments have been focused on eliminating symptoms of the disease through blockade of the dopamine system (Howes et al., 2012). Some recent attention, however, has been paid to the role of infection and inflammation in schizophrenia psychopathology.

The first findings around this hypothesis showed prenatal infections with bacterial or viral agents during pregnancy were associated with an increased risk of schizophrenia in the offspring during adulthood (Fan et al., 2007). In a separate review by Brown and Derkits (Brown and Derkits, 2010), they discussed and critically evaluated the common mechanisms by which in utero exposure to infection alters neurodevelopment, potentially increasing susceptibility to schizophrenia. There is also evidence relating subclinical chronic

inflammation and schizophrenia in individuals, usually in their adulthood, who have already developed the illness (Fan et al., 2007). Furthermore, other supporting immune challenge data shows that a dysfunctional immune response is evident in schizophrenia, and may play a pivotal role in the pathophysiology of this illness. In humans, an increased maternal level of the pro-inflammatory cytokine interleukin-8 (IL-8) during pregnancy is associated with an increased risk for schizophrenia in offspring. The increased risk is present regardless of the reason for increased IL-8 (Brown et al., 2004).

Also, there are systematic quantitative reviews and meta-analysis on abnormal cytokines in people with schizophrenia relative to controls (Potvin et al., 2008; Miller et al., 2011). A meta-analysis of 62 studies with 2298 people with schizophrenia and 1858 healthy volunteers was done to verify the cytokine imbalances in schizophrenia (Potvin et al., 2008). Investigators found that in vivo IL-1RA, soluble IL-2 receptor (sIL-2R), and IL-6 were increased and there was a decrease in in vitro IL-2. In another meta-analysis of 40 studies (Miller et al., 2011), the effect sizes for comparison to controls, first episode patients, and acutely relapsed patients were similar, suggesting that abnormal cytokine levels in schizophrenia are not a result of antipsychotic treatment. IL-1B, IL-6, and transforming growth factor-beta (TGF-B) were significantly increased in first episode and acutely relapsed patients and were state biomarkers. In contrast, IL-12, IFN-gamma, TNF-alpha, and sIL-2R were trait markers. At this time the exact mechanism of immune changes leading to schizophrenia is unclear. There are several competing hypotheses for immune alterations. One hypothesis describes activated microglial cells in the central nervous system releasing proinflammatory cytokines leading to neuronal changes (neurogenesis and degradation) which contribute to the pathophysiology of schizophrenia (Monji et al., 2009). Another theory posits abnormalities of CNS metabolism arise in schizophrenia due to genetically modulated inflammatory reactions damaging the microvascular system of the brain in reaction to environmental stimuli (Hanson and Gottesman, 2005). Lastly, an imbalance of TH1 and TH2 immune response with a viral etiology shift towards TH2 in people with schizophrenia has been proposed (Schwarz et al., 2001).

In addition, researchers found significant association with several markers spanning the major histocompatibility complex (MHC) region on chromosome 6p21.3-22.1 (Stefansson et al., 2008). These findings show the MHC region is consistent with an immune component and schizophrenia risk, implicated with perturbation of pathways involved in brain development, memory and cognition (Stefansson et al., 2008). Autoimmune disease and increasing numbers of infections appear to be a risk factor for developing schizophrenia which is consistent with an aberrant immunological response as a contributing factor to the pathophysiology of schizophrenia (Benros et al., 2011). Thus, emerging evidence in schizophrenia may link inflammation to the etiopathophysiology of this debilitating disorder.

On a related note, epidemiological and clinical evidence has emerged during the past decade linking inflammation to the development of insulin resistance and metabolic disturbances (Shoelson et al., 2007), which are common in the schizophrenic population (Fan et al., 2007). Furthermore, it has been argued that dysfunctional fatty acid metabolism could be involved in the etiology of schizophrenia, based on the findings of reduced omega-3 poly unsaturated fatty acids (PUFAs) in individuals deemed to be ultra high risk for psychotic disorders (Amminger et al., 2010). This is due to their altering effect on membrane fluidity and receptor responses following their incorporation into the cell. Omega-3 PUFAs are also thought to interact with the dopaminergic and serotonergic systems, which have been associated with the pathophysiology of schizophrenia. Furthermore, the omega-3 PUFA, eicosapentaenoic acid (EPA), may increase glutathione in the temporal lobes of first-episode psychotic patients. Glutathione protects neurons from excitotoxicity and oxidative stress.

Several studies have shown that glutathione levels may be low in schizophrenia patients (Raffa et al., 2011). These suggest that omega-3 PUFAs may have neuroprotective or anti-inflammatory properties.

In addition to the evidence presented, many recent trials have supported the hypothesis of the role of inflammation and nutritional deficiencies in the pathogenesis of schizophrenia. This paper will review the published clinical trial data involving medications thought to act in part through anti-inflammatory mechanisms and to have schizophrenia symptomatology as the primary focus. Studies performed using anti-inflammatory agents for the treatment of weight and metabolic complications are not presented here.

Non-Steroidal Anti-inflammatory Agents

CycloOxygenase 2 (COX-2) Inhibitors

Cyclo-oxygenase (COX) is an enzyme responsible for the formation of important mediators of inflammation including prostaglandins, which help promote the inflammatory process. COX is involved in the production of pain and fever, supporting the blood clotting function of platelets, and protects the stomach lining from damaging effect of acids. Prostaglandins are produced by the cyclo-oxygenase of which there are two variants, COX-1 and COX-2. They both function in the promotion of inflammation, pain, and fever, but only COX-1 produces prostaglandins that support blood clotting and protection of the stomach lining. COX-2 has been found to be involved in important aspects of the central nervous system such as synaptic activity, long-term potentiation, long-term depression, memory consolidation, and neurovascular coupling during functional hyperemia (Aid and Bosetti, 2011). COX-2 inhibitors are selective for COX-2 and help in reducing pain and inflammation while reducing the risk of stomach lining damage and not affecting platelet function. The main mechanism of action of COX-2 inhibitors is inhibiting the conversion of arachadonic acid into active prostanoids such as prostaglandin E2, prostaglandin D2, prostaglandin I2 and others (Aid and Bosetti, 2011).

Müller et al. (Muller et al., 2010) published a 6-week, randomized double blind, placebo-controlled study of celecoxib (Celebrex), a COX-2 inhibitor. Psychiatric symptoms in this trial were measured using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) scale. Forty-nine patients with a first episode of schizophrenia were included in this trial. They were randomly treated with amisulpride (200-1000mg) plus celecoxib (400 mg) or amisulpride (200-1000 mg) plus placebo. A significantly better outcome in both positive and negative symptoms was observed in the group treated with adjunct celecoxib compared to the placebo group (PANSS negative: $p=0.03$; PANSS global; $p=0.05$ and PANSS total: $p=0.02$). In addition, the adjunct celecoxib group also showed a significant improvement on the CGI Improvement scale ($p<0.001$). Overall, a significantly superior therapeutic effect was observed with celecoxib group, showing a first time improvement in negative symptoms with celecoxib treatment in schizophrenia patients. Müller et al also published a smaller double blind trial of celecoxib vs. placebo as an adjunct to risperidone in a 5-week study with 50 subjects (Muller et al., 2002). In parallel, serum levels of serum tumor necrosis factor (sTNF)-R1 and serum interleukin (IL)-2R, and the percentages of CD3 (+)-, CD4 (+)-, and CD19 (+) lymphocytes were estimated. They found both groups (placebo and celecoxib) showed significant improvement in symptoms. However, the celecoxib add-on therapy group showed a significant group effect in the PANSS total scale. Moreover, the fact that treatment with an immunomodulatory drug shows beneficial effects on the symptomatology of schizophrenia indicates immune dysfunction in schizophrenia is not just an unrelated association, but is related to the underlying pathophysiology of the disorder (Muller et al., 2004).

Akhondzadeh et al. (Akhondzadeh et al., 2007) published a similar experiment with celecoxib to assess its efficacy as an adjuvant agent in the treatment of chronic schizophrenia. The 60 participants were randomly given risperidone 6mg/day plus celecoxib 400mg/day or risperidone 6mg/day plus placebo in an 11-month, double blind study. The authors showed a significantly superior improvement in positive symptoms; general psychopathology symptoms as well as total PANSS score for the combination risperidone and celecoxib over risperidone alone. Thus, suggesting that celecoxib may be an effective adjuvant agent in the management of people with chronic schizophrenia and that anti-inflammatory therapies should be further investigated. It should be noted that there is one other double blind study published by Rapaport (Rapaport et al., 2005) where celecoxib showed no effect. In this study, 38 symptomatic outpatient schizophrenia subjects on a stable dose of a second generation antipsychotic medication for at least three months were randomized to receive 8 weeks of double blind placebo or celecoxib (400 mg/day) augmentation. Measures of psychopathology, functional disability, and extrapyramidal side effects were performed throughout the study. The treatment cohorts did not differ on any of the clinical outcome measures. The authors concluded that celecoxib augmentation of continuously ill outpatient subjects with schizophrenia did not improve clinical symptoms or measures of disability. The Rapaport study is the only study not showing an effect. This could be due to multiple factors including a smaller sample size compared to the other studies, focusing the study on treatment refractory schizophrenia, and differing doses of antipsychotics.

Aspirin

Acetylsalicylic acid (aspirin) is a salicylate drug often used as an analgesic, an antipyretic, and an anti-inflammatory medication. Aspirin is part of the non-steroidal anti-inflammatory drugs, but differs significantly from them in the mechanism of action. Aspirin, unlike other NSAIDs, inhibits the enzyme cyclooxygenase in an irreversible manner. This effect is more pronounced on the COX-1 variant than the COX-2 variant of the enzyme, thus causing the anti-platelet effect of aspirin to last for days.

Laan et al. (Laan et al., 2010) published a study conducted between May 2004 and August 2007 that investigated the efficacy of adjuvant treatment with aspirin or placebo (1000 mg/day) in schizophrenia spectrum disorder. The researchers conducted a randomized double blind, placebo-controlled study with seventy antipsychotic-treated inpatients and outpatients. During the follow-up, results showed greater improvement in the aspirin group than the placebo group on the PANSS positive score, with treatment efficacy on the PANSS total score substantially larger in participants with the more abnormalities and elevations in inflammatory cytokines ($p=0.02$). No substantial side effects were recorded due to the high dosage of aspirin. Thus, adjunct aspirin may improve symptoms of schizophrenia spectrum disorder but is most effective in those with more altered immune function.

Omega-3 Fatty Acids

Peet et al (Peet and Stokes, 2005) investigated the role of omega-3 fatty acids in the treatment of psychotic disorders by publishing a review of several clinical trials, in which they concluded that there is increasing evidence that omega-3 PUFA might be important to mental health. Biochemical studies have shown low levels of omega-3 PUFA in red blood cells of people with either major depressive disorder or schizophrenia (Peet and Stokes, 2005). Omega-3 Fatty Acids are thought to have some effects on inflammation by modulation of the amount and types of eicosanoids made, and other effects are elicited by eicosanoid-independent mechanisms, including actions upon intracellular signaling pathways, transcription factor activity and gene expression (Simopoulos, 2002). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two main omega-3 fatty

acids in fish oil, have an important role in the central nervous system (CNS). DHA is a major structural component of neuronal membranes, which is important for cognitive and behavioral functions. EPA on the other hand has important physiological functions such as proper growth, development and functioning of the brain (Peet and Stokes, 2005). EPA and DHA are thought to exert their anti-inflammatory effect through mediators called resolvins and protectins. Resolvins are biosynthesized from EPA and DHA and decrease inflammation by binding to G-protein coupled receptors on leukocytes and blocking production of proinflammatory mediators. Resolvins also stop migration of leukocytes and reduce cytokine expression by microglial cells. Protectins are synthesized exclusively from DHA via a separate pathway from resolvins. Protectins decrease inflammation by stopping leukocyte infiltration and reducing cytokine production by glial cells (Serhan, 2008).

The first double-blind placebo controlled trial compared EPA and DHA, in 45 people with schizophrenia on stable antipsychotic medications, and who were considered to still be symptomatic (Peet et al., 2001). In this study subjects were treated with EPA (2g/day), DHA (2g/day) or placebo for 3 months. EPA showed statistically superior improvement to both DHA and placebo on the total PANSS, as compared to DHA or placebo ($p=0.04$). These results prompted a second placebo-controlled trial of EPA as a sole treatment for schizophrenia in new or relapsed patients. Patients were allocated at random to be treated double blind with capsules containing either 2 g/day of EPA or an identical appearing matching corn oil placebo for 8 weeks. By the end of the study all 12 placebo, but only 8 out of 14 patients on EPA, were taking antipsychotic drugs. Only baseline EPA emerged as a significant predictor of improvement in clinical scores ($t=2.84$, $p=0.02$, adjusted $R^2=0.44$). From these results, Peet et al (Peet et al., 2001) concluded EPA may represent a new approach to the treatment of schizophrenia and requires investigation by large-scale placebo-controlled trials.

Amminger et al (Amminger et al., 2010) conducted a randomized, double blind, placebo-controlled trial in people at high risk for schizophrenia. This trial was designed to determine if omega-3 PUFAs reduce the rate of progression to first-episode psychotic disorder in adolescents and young adults ages 13 to 25 years with subthreshold psychosis. This was based on findings of reduced long chain omega-3 PUFAs in individuals with schizophrenia. This trial involved 81 participants of which sixty-six completed the intervention. There was a 12-week intervention period of 1.2g/d omega-3 PUFA or placebo followed by a 40-week monitoring period; with a total study period of 12 months. The results indicated significantly reduced positive symptoms ($p=0.01$), negative symptoms ($p=0.02$) and general symptoms ($p=0.01$) in the omega-3 PUFA group compared with placebo. The most notable finding was the decreased rate of conversion at 12-month follow-up to a DSM-IV schizophrenia diagnosis (4.9%) compared to the placebo group (27.5%). They concluded that long chain omega-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and effective strategy for indicated prevention in young people with subthreshold psychotic states. Emsley et al (Emsley et al., 2002) also did a double blind, randomized, placebo controlled trial in a 12-week pilot with ethyl EPA as supplemental treatment. The forty-six patients pilot showed significantly greater reduction of Positive and Negative Syndrome Scale total scores in the E-EPA group than the placebo group.

Lastly, Yao et al. (Yao et al., 2004) examined whether supplementation with EPA modified serotonin (5-HT) amplified Adenosine Diphosphate (ADP)-induced platelet in people with schizophrenia. Previous trials showed 5-HT implicated in the pathophysiology of schizophrenia and in the mechanism of some antipsychotic agents. In this open-label design (Yao et al., 2004) ethyl-EPA (2 gram daily) was given for 6 months supplementally to ongoing antipsychotic treatment. This involved 12 people with chronic schizophrenia. The platelet levels and red blood cell (RBC) membrane fatty acids were monitored at baseline

for the first, third and sixth months. The EPA levels were elevated more than five-fold after 3 months supplementation in the RBC membranes of all participants. There was also inhibition of ADP-induced platelet aggregation and enhancement of 5-HT by EPA supplementation. The researchers concluded that EPA might be mediating its therapeutic effects in schizophrenia by modulation of the 5-HT receptor complex.

Despite these positive findings there have been a few studies that have found no effect. Fenton et al (Fenton et al., 2001) did a double blind, placebo controlled study to determine if augmentation of neuroleptics 3g/day of ethyl EPA improves symptoms and cognition in patients with schizophrenia and schizophrenia disorder. Eighty-seven patients meeting criteria for schizophrenia or schizoaffective disorder were randomly assigned to receive either 3 g/day of ethyl EPA (N=43) or placebo (N=44) in a 16-week study. Assessments were performed at baseline and at weeks 1, 2, 4, 8, 12, and 16; a cognitive battery was administered at baseline and at week 16. No differences were found between groups in positive or negative symptoms, mood, cognition, or global impression ratings. Results were similar for the intention-to-treat (N=87) and completed (N=75) groups.

However, overall the effects of omega-3 fatty acids appear promising for schizophrenia treatment. A recent Cochrane Review suggests that antipsychotic doses can be reduced in schizophrenia patients who are allocated omega-3 supplementation (Joy et al., 2006). Currently several large clinical trials are being conducted to determine the mechanism and the role omega-3 PUFAs may play in the treatment of schizophrenia.

Other Medications Having Some Anti-Inflammatory Properties

Neurosteroids- Pregnenolone

Neurosteroids perform a variety of actions that impact critical brain functions such as modulation of inhibitory GABAergic and excitatory glutamatergic neurotransmitter systems (Wu et al., 1991), myelination (Koenig et al., 1995), reduction of apoptosis (Charalampopoulos et al., 2004), and reduction of inflammatory responses (He et al., 2004). Pregnenolone and its metabolite pregnenolone sulfate, belong to the group of neurosteroids found in high concentrations in certain areas in the brain which positively modulate excitatory glutamatergic NMDA receptors (Javitt, 2004).

Pregnenolone administration results in elevations in downstream neurosteroids, such as allopregnanolone, a molecule with neuroprotective effects that also increases neurogenesis, decreases apoptosis and inflammation (thus its downstream anti-inflammatory function), modulates the hypothalamic-pituitary-adrenal axis, and markedly increases GABA (A) receptor responses (Marx et al., 2011). Pregnenolone and its sulfate ester are under investigation for their potential to improve cognitive and memory functioning.

Emerging preclinical and clinical evidence suggests pregnenolone may be a promising novel therapeutic candidate in schizophrenia. Evidence consistent with a therapeutic role for pregnenolone in schizophrenia includes neurosteroid changes following administration of certain antipsychotics in rodent models. For example, clozapine elevates pregnenolone levels in rat hippocampus, and these increases may potentially contribute to its superior antipsychotic efficacy (Marx et al., 2006). Also, pregnenolone levels appear to be altered in postmortem brain tissue from patients with schizophrenia compared to control subjects (Marx et al., 2011), which suggest neurosteroid changes may play a role in the neurobiology of this disorder and/or its treatment. In a proof-of-concept 10-week, randomized placebo controlled trial, treatment with pregnenolone significantly decreased negative symptoms in people with schizophrenia or schizoaffective disorder (N=21) and elevations in pregnenolone and allopregnanolone post-treatment with this intervention were correlated

with cognitive improvements (Marx et al., 2009). Another pilot randomized placebo controlled 7 week trial (N=35) found significant improvement in negative symptoms, verbal memory, and attention following treatment with adjunctive pregnenolone, in addition to enduring effects in a small subset of study participants, who received long-term pregnenolone treatment (Marx et al., 2009). A third pilot double-blind, randomized, placebo controlled clinical trial reported significantly decreased positive symptoms and extrapyramidal side effects following adjunctive pregnenolone in people with schizophrenia, in addition to increased attention and working memory performance (Ritsner et al., 2010). This study included 44 participants with schizophrenia and lasted for 8 weeks. Future efforts in larger cohorts will be required to investigate pregnenolone as a possible therapeutic candidate in schizophrenia, but early efforts are promising and merit further investigation.

Minocycline

Minocycline is a synthetic second-generation tetracycline that exerts anti-inflammatory and antimicrobial effects while having a distinct neuroprotective profile (Yrjanheikki et al., 1998). It has excellent brain tissue penetration (Klein and Cunha, 1995); is well tolerated and almost completely absorbed when taken orally (MacDougall, 2011). Recent findings in animal models and human case reports suggest its potential for the treatment of schizophrenia. This is linked to the effect of minocycline on the glutamatergic system, through inhibition of nitric oxide synthase and the dopaminergic system. Its anti-inflammatory actions are possibly mediated by inhibiting the activation and proliferation of microglia, through the inhibition of cytokine production and reduction of cyclooxygenase2 expression and prostaglandin E2 production (Yrjanheikki et al., 1998; Lai and Todd, 2006). Minocycline is postulated to exert its anti-inflammatory effects by inhibiting IFN-gamma induced protein kinase C α /B β II which regulates the expression of inflammatory genes on the major histocompatibility complex class II (Nikodemova et al., 2007). Minocycline also decreases inflammation by downregulation of the activity of microglia and decreasing TNF- α levels produced by T cells which affect the ability of T cells to bind to microglia (Giuliani et al., 2005).

In an open label study, researchers used minocycline as adjunctive therapy for schizophrenia. Twenty-two participants were given 100 mg/day of minocycline for the first week and 150 mg/day for weeks 2 through 4. The results were assessed using the PANSS positive and negative scale. Before the trial, the participants had a mean PANSS positive symptom subscale score of 35.7 ± 7.0 , negative symptoms subscale score of 32.6 ± 9.7 , and general psychopathology subscale score of 56.3 ± 16.0 . After the 4-week minocycline adjunct therapy, participants showed statistically significant and robust clinical improvements, with a 40.4% reduction at 4 weeks (mean score, 14.5 ± 5.0), and this reduction was maintained at the 4-week follow-up (mean score, 13.8 ± 4.4). The PANSS negative symptoms subscale score was reduced to 44.0% at 4 weeks (mean score, 14.4 ± 5.3), and this reduction was maintained at the 4-week follow-up (mean score, 14.1 ± 4.9). The PANSS general psychopathology subscale score was reduced to 52.1% at 4 weeks (mean score, 29.3 ± 10.7), and this reduction was maintained at the 4-week follow-up (mean score, 25.6 ± 9.4) (Miyakawa, 2008). Levkovitz et al (Levkovitz et al., 2010) published a 6-month double blind, randomized, placebo-controlled trial, which involved seventy early phase people with schizophrenia. They found minocycline was well tolerated with few adverse events. It showed a beneficial effect on negative symptoms and general outcome (evident in SANS and CGI). A similar pattern was found for cognitive functioning, mainly in executive functions (working memory, cognitive shifting, and cognitive planning). Recently Chaudhry et al (Chaudhry et al., 2012) found significant improvements relative to placebo in negative symptoms in a one year two country study. Additionally, subjects in Brazil significantly improved in positive symptoms relative to placebo as well. Currently our

group is examining adjunct minocycline to clozapine in a double blind randomized placebo controlled study (NCT#01433055). We have recently published a case series (N=2) reporting that minocycline may be effective as an adjunct to clozapine treatment (Kelly et al., 2011).

Discussion

Overall, there is accumulating evidence, albeit mostly adjunctive treatments, that agents working on inflammatory pathways have been modestly effective for symptoms in people with schizophrenia. This accumulating evidence has led to a rapidly growing interest in this area. It remains unknown, however, if inflammatory mediators relate to the pathophysiology of the disorder or are secondary effects of the illness presentation. Furthermore, the association of metabolic dysregulation and environmental factors such as smoking and stress need to be elucidated. Agents such as 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitors (statins) and other medications may have anti-inflammatory properties but have only been studied to date on the primary outcome of metabolic abnormalities. Statins exert an anti-inflammatory effect, but the precise mechanism of action is unclear. These agents too may have effects on neuroinflammation. Therefore, in the next few years the field will begin to see data on multiple treatment modalities as several agents are currently under study that affect inflammatory pathways such as salicylate an inhibitor of NF- κ B which is a transcription factor for inflammatory mediators (Goldfine et al., 2008) (NCT01182727), omega 3 fatty acids, minocycline (NCT01433055), acetylsalicylic acid (NCT01320982), pravastatin (NCT1082588), and dextromethorphan which is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist and protects dopamine neurons against inflammation mediated damage (Li et al., 2005) (NCT01189006), for example. Hopefully advancements in understanding inflammation and treatments having anti-inflammatory properties found to be effective will revolutionize our understanding and targets for new treatments and prevention in schizophrenia.

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