

## Review Article

# Celecoxib Adjunctive Treatment to Antipsychotics in Schizophrenia: A Review of Randomized Clinical Add-On Trials

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Schizophrenia is a severe, chronic and debilitating mental disorder. Past literature has reported various hypotheses about the psychopathology of schizophrenia. Recently, a growing literature has been trying to explain the role of inflammation in the etiopathogenesis of schizophrenia. In the past, numerous immune modulation and anti-inflammatory treatment options have been proposed for schizophrenia, but sometimes the results were inconsistent. Electronic search was carried out in November 2015. PubMed and Scopus databases have been used to find studies to introduce in this review. Only randomized-placebo-controlled add-on trials were taken into account. In this way, six articles were obtained for the discussion. Celecoxib showed beneficial effects mostly in early stages of schizophrenia. In chronic schizophrenia, the data are controversial, possibly in part for methodological reasons.

## 1. Introduction

Schizophrenia is a severe, chronic, and debilitating mental disorder [1]. The adult prevalence is approximately 1%, but schizophrenics constitute close to 10% of the permanently disabled population [2].

Past literature has reported various hypotheses about the psychopathology of the schizophrenia. The dopamine hypothesis has tried to explain positive, negative, and cognitive symptoms of the schizophrenia suggesting different alterations of the dopamine activity in different brain regions [3–5]. The glutamate hypothesis suggested that phencyclidine and ketamine block of the N-methyl-D-aspartate receptor

induced positive, negative, and cognitive symptoms [6–12]. The cytokine alterations in schizophrenics are consistent with the glutamate hypothesis of schizophrenia [13–17]. In fact, proinflammatory cytokines may influence dopaminergic and glutamatergic pathways and cognitive processes that are implicated in schizophrenia. Recently, alterations in the central gamma-aminobutyric acid and in the cholinergic systems have been proposed to be relevant for cognitive functions in schizophrenia [18–20].

A growing literature has been trying to explain the role of the inflammation in the pathophysiology of the schizophrenia. Emerging literature suggest that infectious exposures (e.g., influenza, genital reproductive infections,

*Toxoplasma gondii*, and herpes simplex virus type 2) during the prenatal period may contribute to the etiopathogenesis of the schizophrenia [21–26]. Interesting data comes from animal studies of the maternal immune activation model of the schizophrenia. In animals, cytokines generated during the pregnancy may cross the placenta and blood-brain barrier and contribute to the oxidative stress [27–29].

A recent meta-analysis [30] has highlighted higher proinflammatory cytokines (IL-6, TNF-alpha, TGF-beta, and IFN-gamma) in acutely relapsed inpatients and in first-episode psychosis compared to controls. On the other hand, anti-inflammatory cytokine IL-10 levels were lower only in acutely relapsed patients with respect to controls.

The inflammatory hypothesis of the schizophrenia psychopathology has been supported by peripheral and central inflammatory signs in schizophrenic patients. Elevated proinflammatory factors, such as prostaglandin E2 (PGE2), C-reactive protein (CRP), interleukin- (IL-) 1beta, IL-6, IL-8, and tumor necrosis factor- (TNF-) alpha, have been reported in serum/plasma levels (for recent reviews, see [31–33]).

Established correlations are that proinflammatory cytokines impair negative symptoms of schizophrenia [34, 35], deficiency in sustained attention [36], and psychomotor retardation [37]. Some authors have highlighted a positive correlation between the severity of cognitive deficit and increased levels of inflammatory markers in schizophrenic patients [38–40]. Proinflammatory cytokines have a role in altering the synthesis and the release of dopamine and noradrenalin [41–43]. This activity may play a role in the emergence of positive symptoms, but the studies have not found a significant correlation between positive symptoms and enhanced proinflammatory cytokines levels [44–46].

There are some evidences that antipsychotics may induce immune-modulatory effects [47–49]. Long-term treatment with antipsychotics exerts concomitant augmentation of anti-inflammatory cytokines (sIL-1RA, sIL-2R, and IL-10) [50–55] and a reduction of proinflammatory ones (IL-1beta, IL-6, sIL-6R, and TNF-alpha) [56–59]. Interestingly, second-generation antipsychotics may be more efficacious than first generations in enhancing anti-inflammatory cytokines (reviewed in [60, 61]). Moreover, some authors have reported that, in drug resistant schizophrenia patients, immune abnormalities cannot be normalized [62].

Past literatures have reported decreases in volume of the central nervous system in schizophrenia, already during the first episode, especially in schizophrenics with a poor outcome [63, 64]. Moreover, some authors have showed a relationship between brain volume, IL-1, and IL-6 [65, 66]. Numerous imaging studies have reported microglia activation and alteration in astrocytes population in the brains of recent onset and chronic schizophrenics, supporting the neuroinflammation hypothesis [67–69]. Some small post-mortem studies have indicated an increased immunoreactive microglia in schizophrenic patients [70–72].

The tryptophan metabolism has been hypothesized to have a role in the etiopathogenesis of the schizophrenia. In fact, increased levels of kynurenic acid have been found in particular brain regions of schizophrenics [73–75]. Moreover

antipsychotic treatments have an impact on kynurenic acid levels in humans and rats [76].

In the past, numerous immune modulation and anti-inflammatory treatment options have been proposed for schizophrenia, but sometimes the results were inconsistent. Between the immune modulation options, authors proposed omega-3 fatty acids [77–81], erythropoietin [82, 83], tetracycline antibiotic [84], minocycline [85–89], azithromycin [90], and valacyclovir [91]. Between the anti-inflammatory options, some trials were conducted with acetylsalicylic acid [92, 93], neurosteroids, and pregnenolone [94–96]. Recently, N-acetyl-cysteine add-on to anti-inflammatory agents has been tried [97, 98]. Emerging and promising adjunctive treatments for schizophrenia are represented by hormones (e.g., estrogen and oxytocin) [99–101], glutamatergic (e.g., glycine and d-serine) [102, 103], and nicotinic compounds (e.g., varenicline and galantamine) [104, 105] and cannabidiol [106] (for an extensive review, see [107]).

## 2. Materials and Methods

Electronic search was carried out in November 2015. PubMed and Scopus databases have been used to find studies to introduce in this review. Keywords used in the search process were represented by “celecoxib add-on to antipsychotics”, “celecoxib adjunctive treatment to antipsychotics”, “celecoxib treatment for schizophrenia”, and “celecoxib treatment for schizophrenics”. Moreover, also studies found by hand search have been obtained to be included in this paper. Only randomized-placebo-controlled add-on trials were taken into account. In this way, six articles were obtained for the discussion.

## 3. Discussion

In literature only six randomized-placebo-controlled celecoxib add-on to antipsychotics trials are present [108–113] (see Table 1).

There are two variants of cyclooxygenase (COX) enzyme: COX-1 and COX-2. Celecoxib is a selective inhibitor of COX-2. Both variants function in the promotion of inflammation, pain, and fever, but only COX-2 plays an important role in the central nervous system [115]. Contrary to COX-1 inhibitors which could cause psychotic symptoms and cognitive dysfunctions, the therapeutic effect of celecoxib in schizophrenia is represented by the COX-2 inhibitor-mediated decrease of kynurenic levels [116].

Effects of celecoxib have been studied in add-on to risperidone, to olanzapine in one study, and to amisulpride in another. Only one study used constant doses of antipsychotics [110], the others used flexible doses. In each trial, 400 mg/day of celecoxib was administered. Durations of trials were different between studies, except for two. Even if the subjects enrolled in the studies were all schizophrenics, some differences have to be highlighted. In fact, two studies enrolled first manifestation schizophrenics [111, 113], whilst the others recruited continuously ill or chronic in active phase patients.

TABLE 1: Celecoxib randomized clinical add-on trials.

Authors	Study design	Participants	Treatment duration	Celecoxib doses	Antipsychotics	Major findings
Müller et al. 2002 [108]	Double-blind, randomized, placebo-controlled, add-on	N = 50 Schizophrenics Duration of illness not specified (mean 5.9 years)	5 weeks	400 mg/day	Risperidone (flexible dose)	Significant advantage of the COX-2 inhibitor
Rappart and Müller 2004 [109]	Double-blind, randomized, placebo-controlled, add-on	N = 270 Schizophrenics Duration of illness ≤10 years	11 weeks	400 mg/day	Risperidone (flexible dose)	No advantage on the COX-2 inhibitor
Rapaport et al. 2005 [110]	Double-blind, randomized, placebo-controlled, add-on	N = 38 Schizophrenics Continuously ill (mean 20 years)	8 weeks	400 mg/day	Risperidone or olanzapine (constant dose)	No advantage on the COX-2 inhibitor
Zhang et al. 2006 [111]	Double-blind, randomized, placebo-controlled, add-on	N = 40 First manifestation schizophrenia	12 weeks	400 mg/day	Risperidone (flexible dose)	Significant advantage of the COX-2 inhibitor
Akhondzadeh et al. 2007 [112]	Double-blind, randomized, placebo-controlled, add-on	N = 60 Active phase of chronic schizophrenia	8 weeks	400 mg/day	Risperidone (flexible dose)	Significant advantage of the COX-2 inhibitor
Müller et al. 2010 [113]	Double-blind, randomized, placebo-controlled, add-on	N = 49 First manifestation schizophrenia	6 weeks	400 mg/day	Amisulpride (flexible dose)	Significant advantage of the COX-2 inhibitor

Adapted from [114].

Four studies showed at least partial benefit in the celecoxib add-on treatment to antipsychotics groups based on the Positive and Negative Syndrome Scale (PANSS) [117] or Clinical Global Impressions scale (CGI) [118]. Even if two studies were conducted in particular patient populations (Chinese first manifestation and Iranian chronic schizophrenics) [111, 112], the adjunctive celecoxib treatment reported similar benefits than other populations.

Since previous trials had been performed with risperidone, Müller et al. [113] decided to add celecoxib to amisulpride. A significantly better outcome in both positive and negative symptoms was observed in the group treated with adjunctive celecoxib compared to the placebo group. For the first time, a pronounced effect by celecoxib on schizophrenic negative symptoms was demonstrated [113], even if the particular effect of amisulpride on these symptoms is well known [119].

Two studies have not shown any therapeutic effect [109, 110], maybe due to the patient selection (refractory schizophrenia) and the different antipsychotics utilized (risperidone and olanzapine) and the duration of the trials. In fact, in animal studies observed that the effects of celecoxib on cytokines and behavioural symptoms depend on the time

of administration of celecoxib [120]. Moreover, since first episodes of schizophrenia are easier to treat than recurrent manifestation [121], these negative reports may have been due to chronic conditions.

A recent and useful meta-analysis [122] has investigated five randomized clinical trials reporting data on 264 patients in treatment with Non-Steroid Anti-Inflammatory Drugs (NSAID) augmentation to antipsychotics in schizophrenia. The authors calculated the effect of NSAIDs on symptom severity measured with the Positive and Negative Syndrome Scale (PANSS) [117]. Likewise to our review, NSAID adjunctive treatment to antipsychotics showed a moderate beneficial effect on total symptom severity as well as on positive symptoms in schizophrenia and a small effect on negative symptoms in schizophrenia.

Very recently, Baheti et al. [123] have conducted an open-labeled, prospective, 6-week controlled trial to evaluate the effect of celecoxib as add-on to olanzapine therapy in acute exacerbation schizophrenics. Beneficial effects in positive, negative, and general psychopathology and total scores on PANSS have been reported, maybe for the short-term period of the trial and for the use of ICD-10 criteria for the diagnosis of schizophrenia.

Side effects were not significantly different between groups. Two trials used biperiden and lorazepam to treat extrapyramidal and anxiety side effects [108, 112]. Drop-out rates were different between trials. Even if the number of patients who dropped out from the trial was low, data are contrasting (major in celecoxib group [108], major in placebo group [112, 113]). Other studies have not reported drop-out rates [109–111].

Since inflammation has been correlated with the development of insulin resistance and metabolic disturbances [124], which are frequent in schizophrenics increased also by the antipsychotics [31], the use of anti-inflammatory agents may be very useful in future treatments.

In recent years, innovative therapies for autoimmune diseases have provided futuristic candidate agents for the cytokine based treatment of the schizophrenia. These treatment are based on antibodies or antibody components against cytokines or cytokine receptors [125–127].

#### 4. Conclusions

A growing literature has been trying to explain the role of the inflammatory process in the pathophysiology of the schizophrenia. In the past, numerous studies have proposed anti-inflammatory treatment for schizophrenics, but sometimes results were inconsistent. Recently some trials have studied the effects of celecoxib add-on to risperidone, to olanzapine, and to amisulpride. Celecoxib showed beneficial effects mostly in early stages of the schizophrenia. In chronic schizophrenics the data are controversial, possibly in part for methodological reasons. In the authors' opinion, future research should investigate celecoxib alone in the treatment of schizophrenia symptoms to better evaluate the schizophrenia inflammatory hypothesis and the real effect of the COX-2 inhibitor.

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#### Competing Interests

The authors declare that they have no competing interests.

#### References

- [1] J. van Os and S. Kapur, "Schizophrenia," *The Lancet*, vol. 374, no. 9690, pp. 635–645, 2009.
- [2] S. J. H. Ebisch, A. Salone, F. Ferri et al., "Out of touch with reality? Social perception in first-episode schizophrenia," *Social Cognitive and Affective Neuroscience*, vol. 8, no. 4, pp. 394–403, 2013.
- [3] H. Y. Meltzer and S. M. Stahl, "The dopamine hypothesis of schizophrenia: a review," *Schizophrenia Bulletin*, vol. 2, no. 1, pp. 19–76, 1976.
- [4] D. R. Weinberger, "Implications of normal brain development for the pathogenesis of schizophrenia," *Archives of General Psychiatry*, vol. 44, no. 7, pp. 660–669, 1987.
- [5] K. L. Davis, R. S. Kahn, G. Ko, and M. Davidson, "Dopamine in schizophrenia: a review and reconceptualization," *American Journal of Psychiatry*, vol. 148, no. 11, pp. 1474–1486, 1991.
- [6] E. D. Luby, J. S. Gottlieb, B. D. Cohen, G. Rosenbaum, and E. F. Domino, "Model psychoses and schizophrenia," *American Journal of Psychiatry*, vol. 119, no. 1, pp. 61–67, 1962.
- [7] D. C. Javitt and S. R. Zukin, "Recent advances in the phenylcyclidine model of schizophrenia," *The American Journal of Psychiatry*, vol. 148, no. 10, pp. 1301–1308, 1991.
- [8] J. H. Krystal, L. P. Karper, J. P. Seibyl et al., "Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses," *Archives of General Psychiatry*, vol. 51, no. 3, pp. 199–214, 1994.
- [9] C. M. Adler, A. K. Malhotra, I. Elman et al., "Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia," *The American Journal of Psychiatry*, vol. 156, no. 10, pp. 1646–1649, 1999.
- [10] A. C. Lahti, M. A. Weiler, T. Michaelidis, A. Parwani, and C. A. Tamminga, "Effects of ketamine in normal and schizophrenic volunteers," *Neuropsychopharmacology*, vol. 25, no. 4, pp. 455–467, 2001.
- [11] A. K. Malhotra, D. A. Pinals, C. M. Adler et al., "Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics," *Neuropsychopharmacology*, vol. 17, no. 3, pp. 141–150, 1997.
- [12] J. T. Kantrowitz and D. C. Javitt, "N-methyl-D-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia?" *Brain Research Bulletin*, vol. 83, no. 3–4, pp. 108–121, 2010.
- [13] M. M. Behrens, S. S. Ali, and L. L. Dugan, "Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia," *The Journal of Neuroscience*, vol. 28, no. 51, pp. 13957–13966, 2008.
- [14] V. Tancredi, M. D'Antuono, C. Cafè et al., "The inhibitory effects of interleukin-6 on synaptic plasticity in the rat hippocampus are associated with an inhibition of mitogen-activated protein kinase ERK," *Journal of Neurochemistry*, vol. 75, no. 2, pp. 634–643, 2000.
- [15] D. Balschun, W. Wetzel, A. Del Rey et al., "Interleukin-6: a cytokine to forget," *The FASEB Journal*, vol. 18, no. 14, pp. 1788–1790, 2004.
- [16] D. Braida, P. Sacerdote, A. E. Panerai et al., "Cognitive function in young and adult IL (interleukin)-6 deficient mice," *Behavioural Brain Research*, vol. 153, no. 2, pp. 423–429, 2004.
- [17] C. J. Heyser, E. Masliah, A. Samimi, I. L. Campbell, and L. H. Gold, "Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 4, pp. 1500–1505, 1997.
- [18] F. M. Benes and S. Berretta, "GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder," *Neuropsychopharmacology*, vol. 25, no. 1, pp. 1–27, 2001.
- [19] D. A. Lewis and B. Moghaddam, "Cognitive dysfunction in schizophrenia: convergence of  $\gamma$ -aminobutyric acid and glutamate alterations," *Archives of Neurology*, vol. 63, no. 10, pp. 1372–1376, 2006.



- [20] L. F. Martin and R. Freedman, "Schizophrenia and the  $\alpha 7$  nicotinic acetylcholine receptor," *International Review of Neurobiology*, vol. 78, pp. 225–246, 2007.
- [21] A. S. Brown, M. D. Begg, S. Gravenstein et al., "Serologic evidence of prenatal influenza in the etiology of schizophrenia," *Archives of General Psychiatry*, vol. 61, no. 8, pp. 774–780, 2004.
- [22] P. B. Mortensen, B. Nørgaard-Pedersen, B. L. Waltoft et al., "Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth," *Biological Psychiatry*, vol. 61, no. 5, pp. 688–693, 2007.
- [23] A. S. Brown, C. A. Schaefer, C. P. Quesenberry Jr., L. Liu, V. P. Babulas, and E. S. Susser, "Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring," *The American Journal of Psychiatry*, vol. 162, no. 4, pp. 767–773, 2005.
- [24] V. Babulas, P. Factor-Litvak, R. Goetz, C. A. Schaefer, and A. S. Brown, "Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia," *The American Journal of Psychiatry*, vol. 163, no. 5, pp. 927–929, 2006.
- [25] S. L. Buka, M. T. Tsuang, E. F. Torrey, M. A. Klebanoff, D. Bernstein, and R. H. Yolken, "Maternal infections and subsequent psychosis among offspring," *Archives of General Psychiatry*, vol. 58, no. 11, pp. 1032–1037, 2001.
- [26] S. L. Buka, T. D. Cannon, E. F. Torrey, and R. H. Yolken, "Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring," *Biological Psychiatry*, vol. 63, no. 8, pp. 809–815, 2008.
- [27] C.-Y. Chen, Y.-L. Huang, and T.-H. Lin, "Association between oxidative stress and cytokine production in nickel-treated rats," *Archives of Biochemistry and Biophysics*, vol. 356, no. 2, pp. 127–132, 1998.
- [28] L. Yan, R. K. Ohls, C. Rosa, M. Shah, D. S. Richards, and R. D. Christensen, "Maternal and umbilical serum concentrations of granulocyte colony-stimulating factor and its messenger RNA during clinical chorioamnionitis," *Obstetrics and Gynecology*, vol. 86, no. 3, pp. 428–432, 1995.
- [29] W. A. Banks, A. J. Kastin, and E. G. Gutierrez, "Penetration of interleukin-6 across the murine blood-brain barrier," *Neuroscience Letters*, vol. 179, no. 1–2, pp. 53–56, 1994.
- [30] B. J. Miller, P. Buckley, W. Seabolt, A. Mellor, and B. Kirkpatrick, "Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects," *Biological Psychiatry*, vol. 70, no. 7, pp. 663–671, 2011.
- [31] X. Fan, D. C. Goff, and D. C. Henderson, "Inflammation and schizophrenia," *Expert Review of Neurotherapeutics*, vol. 7, no. 7, pp. 789–796, 2007.
- [32] S. Potvin, E. Stip, A. A. Sepehry, A. Gendron, R. Bah, and E. Kouassi, "Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review," *Biological Psychiatry*, vol. 63, no. 8, pp. 801–808, 2008.
- [33] R. C. Drexhage, E. M. Knijff, R. C. Padmos et al., "The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder," *Expert Review of Neurotherapeutics*, vol. 10, no. 1, pp. 59–76, 2010.
- [34] H.-J. Möller, "Clinical evaluation of negative symptoms in schizophrenia," *European Psychiatry*, vol. 22, no. 6, pp. 380–386, 2007.
- [35] R. Tandon, H. A. Nasrallah, and M. S. Keshavan, "Schizophrenia, 'just the facts' 4. Clinical features and conceptualization," *Schizophrenia Research*, vol. 110, no. 1–3, pp. 1–23, 2009.
- [36] J. M. Holden, J. E. Meyers-Manor, J. B. Overmier, E. Gahtan, W. Sweeney, and H. Miller, "Lipopolysaccharide-induced immune activation impairs attention but has little effect on short-term working memory," *Behavioural Brain Research*, vol. 194, no. 2, pp. 138–145, 2008.
- [37] L. Brydon, N. A. Harrison, C. Walker, A. Steptoe, and H. D. Critchley, "Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans," *Biological Psychiatry*, vol. 63, no. 11, pp. 1022–1029, 2008.
- [38] F. Dickerson, C. Stallings, A. Origoni, J. Boronow, and R. Yolken, "C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia," *Schizophrenia Research*, vol. 93, no. 1–3, pp. 261–265, 2007.
- [39] A. Pedersen, M. Diedrich, F. Kaestner et al., "Memory impairment correlates with increased S100B serum concentrations in patients with chronic schizophrenia," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 32, no. 8, pp. 1789–1792, 2008.
- [40] L. Liu, F. Jia, G. Yuan et al., "Tyrosine hydroxylase, interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  are overexpressed in peripheral blood mononuclear cells from schizophrenia patients as determined by semi-quantitative analysis," *Psychiatry Research*, vol. 176, no. 1, pp. 1–7, 2010.
- [41] S. Zalcman, J. M. Green-Johnson, L. Murray et al., "Cytokine-specific central monoamine alterations induced by interleukin-1, -2 and -6," *Brain Research*, vol. 643, no. 1–2, pp. 40–49, 1994.
- [42] S. Hayley, P. Wall, and H. Anisman, "Sensitization to the neuroendocrine, central monoamine and behavioural effects of murine tumor necrosis factor- $\alpha$ : peripheral and central mechanisms," *European Journal of Neuroscience*, vol. 15, no. 6, pp. 1061–1076, 2002.
- [43] A. J. Dunn, "Effects of cytokines and infections on brain neurochemistry," *Clinical Neuroscience Research*, vol. 6, no. 1–2, pp. 52–68, 2006.
- [44] Y.-K. Kim, L. Kim, and M.-S. Lee, "Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics," *Schizophrenia Research*, vol. 44, no. 3, pp. 165–175, 2000.
- [45] X. Y. Zhang, D. F. Zhou, L. Y. Cao, G. Y. Wu, and Y. C. Shen, "Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics," *Neuropsychopharmacology*, vol. 30, no. 8, pp. 1532–1538, 2005.
- [46] X. Y. Zhang, D. F. Zhou, L. Y. Qi et al., "Superoxide dismutase and cytokines in chronic patients with schizophrenia: association with psychopathology and response to antipsychotics," *Psychopharmacology*, vol. 204, no. 1, pp. 177–184, 2009.
- [47] M. Ozek, K. Toreci, I. Akkok, and Z. Guvener, "Influence of therapy on antibody-formation," *Psychopharmacologia*, vol. 21, pp. 401–412, 1971.
- [48] M. J. Schwarz, M. Riedel, M. Ackenheil, and N. Müller, "Decreased levels of soluble intercellular adhesion molecule-1 (sICAM-1) in unmedicated and medicated schizophrenic patients," *Biological Psychiatry*, vol. 47, no. 1, pp. 29–33, 2000.
- [49] I. Wilke, V. Arolt, M. Rothermundt, C. Weitzsch, M. Hornberg, and H. Kirchner, "Investigations of cytokine production in whole blood cultures of paranoid and residual schizophrenic patients," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 246, no. 5, pp. 279–284, 1996.
- [50] M. Maes, E. Bosmans, R. Ranjan et al., "Lower plasma CCL16, a natural anti-inflammatory protein, and increased plasma interleukin-1 receptor antagonist in schizophrenia: effects of

- antipsychotic drugs," *Schizophrenia Research*, vol. 21, no. 1, pp. 39–50, 1996.
- [51] M. Maes, E. Bosmans, G. Kenis, R. De Jong, R. S. Smith, and H. Y. Meltzer, "In vivo immunomodulatory effects of clozapine in schizophrenia," *Schizophrenia Research*, vol. 26, no. 2-3, pp. 221–225, 1997.
- [52] N. Müller, M. Empl, M. Riedel, M. Schwarz, and M. Ackenheil, "Neuroleptic treatment increases soluble IL-2 receptors and decreases soluble IL-6 receptors in schizophrenia," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 247, no. 6, pp. 308–313, 1997.
- [53] C. Song, A.-H. Lin, G. Kenis, E. Bosmans, and M. Maes, "Immunosuppressive effects of clozapine and haloperidol: enhanced production of the interleukin-1 receptor antagonist," *Schizophrenia Research*, vol. 42, no. 2, pp. 157–164, 2000.
- [54] C. L. Cazzullo, E. Sacchetti, A. Galluzzo et al., "Cytokine profiles in schizophrenic patients treated with risperidone: a 3-month follow-up study," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 26, no. 1, pp. 33–39, 2002.
- [55] P. Sirota, M. Meiman, R. Herschko, and H. Bessler, "Effect of neuroleptic administration on serum levels of soluble IL-2 receptor-alpha and IL-1 receptor antagonist in schizophrenic patients," *Psychiatry Research*, vol. 134, no. 2, pp. 151–159, 2005.
- [56] X.-Q. Song, L.-X. Lv, W.-Q. Li, Y.-H. Hao, and J.-P. Zhao, "The interaction of nuclear factor-kappa B and cytokines is associated with schizophrenia," *Biological Psychiatry*, vol. 65, no. 6, pp. 481–488, 2009.
- [57] H. Sugino, T. Futamura, Y. Mitsumoto, K. Maeda, and Y. Marunaka, "Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharide-treated mice," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 33, no. 2, pp. 303–307, 2009.
- [58] Y.-K. Kim, A.-M. Myint, R. Verkerk, S. Scharpe, H. Steinbusch, and B. Leonard, "Cytokine changes and tryptophan metabolites in medication-naïve and medication-free schizophrenic patients," *Neuropsychobiology*, vol. 59, no. 2, pp. 123–129, 2009.
- [59] N. Müller, P. Dobmeier, M. Empl, M. Riedel, M. Schwarz, and M. Ackenheil, "Soluble IL-6 receptors in the serum and cerebrospinal fluid of paranoid schizophrenic patients," *European Psychiatry*, vol. 12, no. 6, pp. 294–299, 1997.
- [60] T. Pollmächer, M. Haack, A. Schuldt, T. Kraus, and D. Hinze-Selch, "Effects of antipsychotic drugs on cytokine networks," *Journal of Psychiatric Research*, vol. 34, no. 6, pp. 369–382, 2000.
- [61] Ł. Drzyzga, E. Obuchowicz, A. Marcinowska, and Z. S. Herman, "Cytokines in schizophrenia and the effects of antipsychotic drugs," *Brain, Behavior, and Immunity*, vol. 20, no. 6, pp. 532–545, 2006.
- [62] A. Lin, G. Kenis, S. Bignotti et al., "The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6," *Schizophrenia Research*, vol. 32, no. 1, pp. 9–15, 1998.
- [63] N. Gogtay, A. Lu, A. D. Leow et al., "Three-dimensional brain growth abnormalities in childhood-onset schizophrenia visualized by using tensor-based morphometry," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 41, pp. 15979–15984, 2008.
- [64] R. G. Steen, C. Mull, R. McClure, R. M. Hamer, and J. A. Lieberman, "Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies," *The British Journal of Psychiatry*, vol. 188, pp. 510–518, 2006.
- [65] E. M. Meisenzahl, D. Rujescu, A. Kirner et al., "Association of an interleukin-1 $\beta$  genetic polymorphism with altered brain structure in patients with schizophrenia," *The American Journal of Psychiatry*, vol. 158, no. 8, pp. 1316–1319, 2001.
- [66] D. L. Garver, R. L. Tamas, and J. A. Holcomb, "Elevated interleukin-6 in the cerebrospinal fluid of a previously delinquent schizophrenia subtype," *Neuropsychopharmacology*, vol. 28, no. 8, pp. 1515–1520, 2003.
- [67] J. Doorduyn, E. F. J. de Vries, A. T. M. Willemsen, J. C. De Groot, R. A. Dierckx, and H. C. Klein, "Neuroinflammation in schizophrenia-related psychosis: a PET study," *Journal of Nuclear Medicine*, vol. 50, no. 11, pp. 1801–1807, 2009.
- [68] B. N. van Berckel, M. G. Bossong, R. Boellaard et al., "Microglia activation in recent-onset schizophrenia: a quantitative (R)-[<sup>11</sup>C]PK11195 positron emission tomography study," *Biological Psychiatry*, vol. 64, no. 9, pp. 820–822, 2008.
- [69] A. Takano, R. Arakawa, H. Ito et al., "Peripheral benzodiazepine receptors in patients with chronic schizophrenia: a PET study with [<sup>11</sup>C]DAA1106," *International Journal of Neuropsychopharmacology*, vol. 13, no. 7, pp. 943–950, 2010.
- [70] T. A. Bayer, R. Buslei, L. Havas, and P. Falkai, "Evidence for activation of microglia in patients with psychiatric illnesses," *Neuroscience Letters*, vol. 271, no. 2, pp. 126–128, 1999.
- [71] K. Radewicz, L. J. Garey, S. M. Gentleman, and R. Reynolds, "Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics," *Journal of Neuropathology and Experimental Neurology*, vol. 59, no. 2, pp. 137–150, 2000.
- [72] J. Steiner, C. Mawrin, A. Ziegeler et al., "Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization," *Acta Neuropathologica*, vol. 112, no. 3, pp. 305–316, 2006.
- [73] S. Erhardt, K. Blennow, C. Nordin, E. Skogh, L. H. Lindström, and G. Engberg, "Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia," *Neuroscience Letters*, vol. 313, no. 1-2, pp. 96–98, 2001.
- [74] K. R. Linderholm, E. Skogh, S. K. Olsson et al., "Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia," *Schizophrenia Bulletin*, vol. 38, no. 3, pp. 426–432, 2012.
- [75] R. Schwarcz, A. Rassoulpour, H.-Q. Wu, D. Medoff, C. A. Tamminga, and R. C. Roberts, "Increased cortical kynurenate content in schizophrenia," *Biological Psychiatry*, vol. 50, no. 7, pp. 521–530, 2001.
- [76] G. Ceresoli-Borroni, A. Rassoulpour, H.-Q. Wu, P. Guidetti, and R. Schwarcz, "Chronic neuroleptic treatment reduces endogenous kynurenic acid levels in rat brain," *Journal of Neural Transmission*, vol. 113, no. 10, pp. 1355–1365, 2006.
- [77] G. P. Amminger, M. R. Schäfer, K. Papageorgiou et al., "Long-chain  $\omega$ -3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial," *Archives of General Psychiatry*, vol. 67, no. 2, pp. 146–154, 2010.
- [78] B. M. Ross, J. Seguin, and L. E. Sieswerda, "Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid?" *Lipids in Health and Disease*, vol. 6, no. 1, article 21, pp. 1–19, 2007.
- [79] M. Peet, J. Brind, C. N. Ramchand, S. Shah, and G. K. Vankar, "Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia," *Schizophrenia Research*, vol. 49, no. 3, pp. 243–251, 2001.
- [80] J. K. Yao, S. Magan, A. F. Sonel, J. A. Gurklis, R. Sanders, and R. D. Reddy, "Effects of omega-3 fatty acid on platelet serotonin

- responsivity in patients with schizophrenia,” *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 71, no. 3, pp. 171–176, 2004.
- [81] W. S. Fenton, F. Dickerson, J. Boronow, J. R. Hibbeln, and M. Knable, “A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia,” *The American Journal of Psychiatry*, vol. 158, no. 12, pp. 2071–2074, 2001.
- [82] H. Ehrenreich, D. Hinze-Selch, S. Stawicki et al., “Improvement of cognitive functions in chronic schizophrenic patients by recombinant human erythropoietin,” *Molecular Psychiatry*, vol. 12, no. 2, pp. 206–220, 2007.
- [83] T. Wüstenberg, M. Begemann, C. Bartels et al., “Recombinant human erythropoietin delays loss of gray matter in chronic schizophrenia,” *Molecular Psychiatry*, vol. 16, no. 1, pp. 26–36, 2011.
- [84] C. Chaves, C. R. Marque, I. B. Chaudhry et al., “Short-term improvement by minocycline added to olanzapine antipsychotic treatment in paranoid schizophrenia,” *Schizophrenia Bulletin*, vol. 35, pp. 354–355, 2009.
- [85] N. Ahuja and B. T. Carroll, “Possible anti-catatonic effects of minocycline in patients with schizophrenia,” *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 31, no. 4, pp. 968–969, 2007.
- [86] T. Miyaoka, “Clinical potential of minocycline for schizophrenia,” *CNS and Neurological Disorders—Drug Targets*, vol. 7, no. 4, pp. 376–381, 2008.
- [87] Y. Levkovitz, S. Mendlovich, S. Riwkes et al., “A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia,” *Journal of Clinical Psychiatry*, vol. 71, no. 2, pp. 138–149, 2010.
- [88] I. B. Chaudhry, J. Hallak, N. Husain et al., “Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment,” *Journal of Psychopharmacology*, vol. 26, no. 9, pp. 1185–1193, 2012.
- [89] D. L. Kelly, G. Vyas, C. M. Richardson et al., “Adjunct minocycline to clozapine treated patients with persistent schizophrenia symptoms,” *Schizophrenia Research*, vol. 133, no. 1–3, pp. 257–258, 2011.
- [90] F. B. Dickerson, C. R. Stallings, J. J. Boronow, A. E. Origoni, and R. H. Yolken, “A double-blind trial of adjunctive azithromycin in individuals with schizophrenia who are seropositive for *Toxoplasma gondii*,” *Schizophrenia Research*, vol. 112, no. 1–3, pp. 198–199, 2009.
- [91] F. B. Dickerson, C. R. Stallings, J. J. Boronow, A. E. Origoni, A. Sullens, and R. H. Yolken, “Double blind trial of adjunctive valacyclovir in individuals with schizophrenia who are seropositive for cytomegalovirus,” *Schizophrenia Research*, vol. 107, no. 2–3, pp. 147–149, 2009.
- [92] W. Laan, D. E. Grobbee, J.-P. Selten, C. J. Heijnen, R. S. Kahn, and H. Burger, “Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial,” *Journal of Clinical Psychiatry*, vol. 71, no. 5, pp. 520–527, 2010.
- [93] M. Weiser, S. Burshtein, L. Fodoreanu et al., “A randomized trial administering aspirin, minocycline or pramipexole vs placebo as add-on to antipsychotics in patients with schizophrenia or schizoaffective disorder,” *Neuropsychopharmacology*, vol. 28, pp. 314–446, 2012.
- [94] C. E. Marx, R. S. E. Keefe, R. W. Buchanan et al., “Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia,” *Neuropsychopharmacology*, vol. 34, no. 8, pp. 1885–1903, 2009.
- [95] C. E. Marx, D. W. Bradford, R. M. Hamer et al., “Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence,” *Neuroscience*, vol. 191, pp. 78–90, 2011.
- [96] M. S. Ritsner, A. Gibel, T. Shleifer et al., “Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial,” *Journal of Clinical Psychiatry*, vol. 71, no. 10, pp. 1351–1362, 2010.
- [97] S. Lavoie, M. M. Murray, P. Deppen et al., “Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients,” *Neuropsychopharmacology*, vol. 33, no. 9, pp. 2187–2199, 2008.
- [98] M. Bulut, H. A. Savas, A. Altindag, O. Virit, and A. Dalkilic, “Beneficial effects of N-acetylcysteine in treatment resistant schizophrenia,” *The World Journal of Biological Psychiatry*, vol. 10, no. 4, pp. 626–628, 2009.
- [99] E. Ghafari, M. Fararouie, H. G. Shirazi, A. Farhangfar, F. Ghaderi, and A. Mohammadi, “Combination of estrogen and antipsychotics in the treatment of women with chronic schizophrenia: a double-blind, randomized, placebo-controlled clinical trial,” *Clinical Schizophrenia and Related Psychoses*, vol. 6, no. 4, pp. 172–176, 2013.
- [100] J. Kulkarni, E. Gavrilidis, W. Wang et al., “Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age,” *Molecular Psychiatry*, vol. 20, no. 6, pp. 695–702, 2015.
- [101] C. M. Gibson, D. L. Penn, K. L. Smedley, J. Leserman, T. Elliott, and C. A. Pedersen, “A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia,” *Schizophrenia Research*, vol. 156, no. 2–3, pp. 261–265, 2014.
- [102] U. Heresco-Levy, D. C. Javitt, M. Ermilov, C. Mordel, G. Silipo, and M. Lichtenstein, “Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia,” *Archives of General Psychiatry*, vol. 56, no. 1, pp. 29–36, 1999.
- [103] J. T. Kantrowitz, A. K. Malhotra, B. Cornblatt et al., “High dose D-serine in the treatment of schizophrenia,” *Schizophrenia Research*, vol. 121, no. 1–3, pp. 125–130, 2010.
- [104] G. N. Pachas, C. Cather, S. I. Pratt et al., “Varenicline for smoking cessation in schizophrenia: safety and effectiveness in a 12-week open-label trial,” *Journal of Dual Diagnosis*, vol. 8, no. 2, pp. 117–125, 2012.
- [105] M. H. Schubert, K. A. Young, and P. B. Hicks, “Galantamine improves cognition in schizophrenic patients stabilized on risperidone,” *Biological Psychiatry*, vol. 60, no. 6, pp. 530–533, 2006.
- [106] F. M. Leweke, T. M. Odorfer, and J. M. Bumb, “Medical needs in the treatment of psychotic disorders,” *Handbook of Experimental Pharmacology*, vol. 212, pp. 165–185, 2012.
- [107] J. M. Bumb, F. Enning, and F. M. Leweke, “Drug repurposing and emerging adjunctive treatments for schizophrenia,” *Expert Opinion on Pharmacotherapy*, vol. 16, no. 7, pp. 1049–1067, 2015.
- [108] N. Müller, M. Riedel, C. Scheppach et al., “Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia,” *American Journal of Psychiatry*, vol. 159, no. 6, pp. 1029–1034, 2002.
- [109] F. Rappart and N. Müller, “Celecoxib add-on therapy does not have beneficial antipsychotic effects over risperidone alone in



- schizophrenia," *Neuropsychopharmacology*, vol. 29, no. 1, p. 222, 2004.
- [110] M. H. Rapaport, K. K. Delrahim, C. J. Bresee, R. E. Maddux, O. Ahmadpour, and D. Dolnak, "Celecoxib augmentation of continuously ill patients with schizophrenia," *Biological Psychiatry*, vol. 57, no. 12, pp. 1594–1596, 2005.
- [111] Y. Zhang, D. Chun Chen, Y. Long Tan, and D. F. Zhou, "A double-blind, placebo-controlled trial of celecoxib added to risperidone in first-episode and drug-naive patients with schizophrenia," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 256, no. 2, p. 50, 2006.
- [112] S. Akhondzadeh, M. Tabatabaee, H. Amini, S. A. Ahmadi Abhari, S. H. Abbasi, and B. Behnam, "Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial," *Schizophrenia Research*, vol. 90, no. 1–3, pp. 179–185, 2007.
- [113] N. Müller, D. Krause, S. Dehning et al., "Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment," *Schizophrenia Research*, vol. 121, no. 1–3, pp. 118–124, 2010.
- [114] N. Müller, A. M. Myint, D. Krause, E. Weidinger, and K. J. Schwarz, "Anti-inflammatory treatment in schizophrenia," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 42, pp. 146–153, 2013.
- [115] S. Aid and F. Bosetti, "Targeting cyclooxygenases-1 and -2 in neuroinflammation: therapeutic implications," *Biochimie*, vol. 93, no. 1, pp. 46–51, 2011.
- [116] L. Schwieler, S. Erhardt, C. Erhardt, and G. Engberg, "Prostaglandin-mediated control of rat brain kynurenic acid synthesis—opposite actions by COX-1 and COX-2 isoforms," *Journal of Neural Transmission*, vol. 112, no. 7, pp. 863–872, 2005.
- [117] S. R. Kay, A. Fiszbein, and L. A. Opler, "The positive and negative syndrome scale (PANSS) for schizophrenia," *Schizophrenia Bulletin*, vol. 13, no. 2, pp. 261–276, 1987.
- [118] W. Guy, "Clinical global impressions," in *ECDEU Assessment Manual for Psychopharmacology, Revised (DHEW Publ No ADM 76-338)*, pp. 218–222, National Institute of Mental Health, Rockville, Md, USA, 1976.
- [119] H.-J. Möller, "Amisulpride: efficacy in the management of chronic patients with predominant negative symptoms of schizophrenia," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 251, no. 5, pp. 217–224, 2001.
- [120] P. Casolini, A. Catalani, A. R. Zuena, and L. Angelucci, "Inhibition of COX-2 reduces the age-dependent increase of hippocampal inflammatory markers, corticosterone secretion, and behavioral impairments in the rat," *Journal of Neuroscience Research*, vol. 68, no. 3, pp. 337–343, 2002.
- [121] J. A. Lieberman, J. M. Alvir, A. Koreen et al., "Psychobiologic correlates of treatment response in schizophrenia," *Neuropsychopharmacology*, vol. 14, no. 3, pp. 13–21, 1996.
- [122] I. E. Sommer, L. De Witte, M. Begemann, and R. S. Kahn, "Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis," *Journal of Clinical Psychiatry*, vol. 73, no. 4, pp. 414–419, 2012.
- [123] T. Baheti, A. Nischal, A. Nischal et al., "A study to evaluate the effect of celecoxib as add-on to olanzapine therapy in schizophrenia," *Schizophrenia Research*, vol. 147, no. 1, pp. 201–202, 2013.
- [124] S. E. Shoelson, L. Herrero, and A. Naaz, "Obesity, inflammation, and insulin resistance," *Gastroenterology*, vol. 132, no. 6, pp. 2169–2180, 2007.
- [125] J. S. Smolen, D. Aletaha, M. Koeller, M. H. Weisman, and P. Emery, "New therapies for treatment of rheumatoid arthritis," *The Lancet*, vol. 370, no. 9602, pp. 1861–1874, 2007.
- [126] E. H. S. Choy and G. S. Panayi, "Cytokine pathways and joint inflammation in rheumatoid arthritis," *The New England Journal of Medicine*, vol. 344, no. 12, pp. 907–916, 2001.
- [127] C. L. Raison, R. E. Rutherford, B. J. Woolwine et al., "A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers," *JAMA Psychiatry*, vol. 70, no. 1, pp. 31–41, 2013.





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