The effect of antipsychotic drugs on nonspecific inflammation markers in the first episode of schizophrenia

Efekat antipsihotika na nespecifične markere inflamacije u prvoj epizodi shizofrenije

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Abstract

Background/Aim. Immune system disorder, including inflammation, takes a significant place when considering still unclear etiology of schizophrenia. The aim of this study was to determine the blood levels of nonspecific inflammation markers in the first episode of schizophrenia and their relation to the therapy response. Methods. In this study we determined the blood levels of nonspecific inflammation markers: white blood cells count (WBC), C-reactive protein (CRP), erythrocytes sedimentation rate (ESR) and the elements of differential white blood cell counts (or the leukocyte formula): granulocytes (Gra), lymphocytes (Lym) and monocytes (Mon), in the first episode of schizophrenia, in 78 patients hospitalized at the Clinic for Psychiatric Disorders “Dr Laza Lazarević” in Belgrade. The levels were measured at admission to the clinic, as well as after 4 weeks of antipsychotic treatment. The Positive and negative syndrome scale for schizophrenia (PANSS) was applied to measure the severity of psychopathology and response to the treatment. Results. During the first episode of schizophrenia, before initiation of antipsychotic treatment, the frequency of abnormal values was high (≥ 25% of the patients) for the following non-specific inflammation markers: WBC, CRP, ESR and Gra, in the leukocyte formula, but dropped after 4 weeks of antipsychotic treatment at the level of high statistical significance for WBC and Gra (p < 0.001). The ESR remained unchanged in as many as 50% of the patients even after 4-week antipsychotic treatment, at the level of statistical significance in the non-responders compared to the responders (p = 0.045). Conclusion. The obtained results indicate that in the first episode of schizophrenia the blood levels of non-specific inflammation markers (WBC, CRP, ESR and Gra from the leukocyte formula) were high in the subpopulation of patients with the tendency towards normalization of inflammation parameters after a 4-week antipsychotic treatment.

Key words: schizophrenia; antipsychotic agents; inflammation mediators; sensitivity and specificity; predictive value of tests.

Apstrakt

Uvod/Cilj. U razmatranju još uvk nepoznate etiologije shizofrenije, disfunkcija imunskog sistema koja uključuje i inflamaciju zauzima značajno mesto. Cilj našeg rada bio je da se odrede koncentracije nespecifičnih markera zapaljenja u krvi, u prvoj epizodi shizofrenije i njihova povezanost sa terapijskim odgovorom na antipsihotike. Metode. U radu smo određivali koncentracije nespecifičnih markera zapaljenja u krvi: leukocita (WBC), C-reaktivnog proteina (CRP), sedimentacije eritrocita (SE) i elemenata leukocitarne formule: granulocita (Gra), limfocita (Lym) i monocita (Mon), i to u prvoj epizodi šizofrenije, kod 78 hospitalizovanih bolesnika u Klinici za psihiatrijske bolesti „Dr Laza Lazarević“ u Beogradu. Njihove koncentracije određivali smo pri prijemu i četiri sedmice nakon antipsihotičke terapije. Težinu psihopatologije i farmakoterapijski odgovor pratili smo pri menom Skale pozitivnih i negativnih sindroma shizofrenije (Positive and negative syndrome scale for schizophrenia – PANSS). Rezultati. U prvoj epizodi shizofrenije, pre uvođenja antipsihotika, postojala je visoka učestalost abnor malnih laboratorijskih vrednosti (≥ 25% bolesnika) sledećih ne...
specifičnih markera inflamacije: WBC, CRP i SE, kao i Gra u leucocitarnoj formuli, ali i smanjenje svih njih nakon četiri sedmice antipsihotičke terapije, na nivou visoke statističke značajnosti za WBC i Gra (p < 0.001). Sedimentacija eritrocita ostala je povećana kod čak 50% bolesnika i nakon 4-sedmješnjeg antipsihotičkog lečenja, na nivou statističke značajnosti kod onih koji nisu reagovali na terapiju u odnosu na one koji jesu (p = 0.045).

Zaključak. Dohiđeni rezultati pokazuju da u prvoj epizodi shizofrenije kod subpopulacije bolesnika postoje povećane vrednosti nespecifičnih markera inflamacije u krvi (WBC, CRP, SE i Gra iz leucocitarne formule), sa tendencijom njihove normalizacije nakon četiri sedmice antipsihotičkog tretmana.

Ključne reči: shizofrenija; antipsihotici; zapaljenje, medijatori; osjetljivost i specifičnost; testovi, prognostička vrednost.

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Introduction

Schizophrenia is a heterogeneous disorder with still unclear etiology that affects about 1% of the world population. Numerous theories have been considering the possible causes of this devastating disease.

Recent researches related to neuroinflammation in schizophrenia give an increasing importance to prolonged microglial activation, when pro-inflammatory cytokines and free radicals lead to apoptosis of cortical neurons and oligodendrocytes as well as changes of the synaptic organization in the brain.

Increased serum concentrations of various cytokines and their soluble receptors, as well as interleukin-6 (IL-6), soluble interleukin-6 receptor (sIL-6R), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-4 (IL-4), and tumor necrosis factor-alpha (TNF-α) were observed in schizophrenic patients.

The effect of antipsychotics in terms of reduction and normalization of various proinflammatory immune parameters is an important factor which contributes to the clinical efficacy in the treatment of psychotic symptoms.

Inflammation in schizophrenia is also associated with the increased production of prostaglandin E2, and the increased expression of cyclooxygenase-2 (COX-2), of which the inhibitors can have a significant role in the treatment of schizophrenia, particularly in the early stage of the disease.

There is growing evidence of significant effects of pro- and anti-inflammatory cytokines in the tryptophan/kynurenine metabolism when the increased production of kynurenine acid leads to glutamatergic hypofunction and consequent dopaminergic dysfunction in schizophrenia. In the subpopulation of psychotic patients there is a high degree of comorbidity with chronic inflammatory and autoimmune disorders, which suggests a common immune disorder background.

The proteins and immunoglobulins of the acute phase are nonspecific markers of the immune system changes. Their levels may be affected by a variety of conditions, infection, inflammation and stress. As isolated parameters they cannot be directly linked to the development of schizophrenic psychoses but can be used as an additional parameter in explaining the role of specific immune subsystems.

The aim of our study was to establish the blood levels of nonspecific inflammation markers [white blood cells (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] and the elements of the leukocyte formula] in patients with the first episode of schizophrenia, who up to then did not take antipsychotics (drug naïve), as well as the effect of antipsychotic treatment after four weeks of treatment in correlation with clinical treatment response by implementing the Positive and negative syndrome scale for schizophrenia (PANSS).

Methods

The study included 78 patients hospitalized at the Clinic of Psychiatric Disorders “Dr. Laza Lazarevic” in Belgrade, during a 6-month period. At admission to the Clinic all subjects met the criteria of the International Classification of Diseases, 10th revision, for the first episode of schizophrenia (F 20). The patients signed the consent to participate in the study abiding by the principles of Good Clinical Practice and prior approval of the Ethics Committee of the Clinic. The study protocol was in compliance with the Declaration of Helsinki.

The inclusion criteria were the age between 18 and 45 years, both genders, and that the patients had not previously received antipsychotic drugs (drug naïve).

The exclusion criteria were comorbidity with inflammatory, neurodegenerative, malignant diseases, congestive heart disease and infectious diseases, as well as patients who were identified as alcohol or psychoactive substance abusers.

The patients were divided into 3 groups depending on the applied antipsychotic therapy, the group I of patients treated with first-generation antipsychotics (FGAs), a total of 38 patients; the group II of 22 patients treated with second-generation antipsychotics (SGAs), and the group III of 18 patients treated with combined antipsychotic therapy (antipsychotic combination of the first and second generation antipsychotics).

The protocol procedures implied three planned visits. The following activities were conducted at admission: clinical psychiatric exploration that included a structured clinical interview in order to evaluate the diagnosis of schizophrenia according to the criteria of the International statistical classification of diseases and related health problems, 10th revision (ICD-10); application of the PANSS for the assessment and clinical monitoring of the disease course and pharmacotherapeutic response; as well as the physical examination including measuring of vital parameters (heart rate, arterial blood pressure, respiratory rate per minute, body temperature); venous blood sampling after a 12-hour overnight fast, between 8 and 8.30 a.m., prior to antipsychotic therapy (leukocytes, lymphocytes, monocytes, granulocytes, ESP, CRP).

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The attending psychiatrist prescribed antipsychotic treatment for the patients, pursuant to the Good Clinical Practice Guidelines.

The applied drug dosages were as follows: haloperidol – from 2 to 15 mg/pd (approximately 12.7 mg/pd at admission, average 8.8 g/day at dismissal), risperidone – from 2 to 6 mg/day (approximately 3.6 mg/day); olanzapine – from 2 to 20 mg/day (approximately 8.3 mg/day), and clozapine – from 25 to 125 mg/day (approximately 67.3 mg/day).

The patients were hospitalized during the entire treatment. All study procedures from the first visit (day 0), except for the already completed questionnaires, were also conducted after 30 days of hospital treatment, as well as at the final third visit. The second visit, two weeks after admission included clinical exploration.

The laboratory hematologic tests were carried out using a hematology analyzer ABX MICROS 60-OT (UK).

The primary obtained data were analyzed by the descriptive statistical methods and the application of the regression model. As for the descriptive statistical methods, the central tendency measures (arithmetic mean and median), the variability measures (standard deviation and variation interval) and the data structures expressed in percentages were applied. The methods for testing the difference of numerical data (scores on the PANSS scales, hematological and biochemical variables) included t-test and one-way analysis of variance. When conditions for the application of parametric statistical methods were not met we applied the Mann-Whitney test and the Kruskal-Wallis test. For testing the differences of categorical data (gender, education, marital status, treatment, and categorically transformed numeric data) Pearson’s χ²-test and Fisher's exact probability test were applied. The repeated measurements of continuous numeric data were analyzed using the repeated measures analysis of variance, and when appropriate conditions were not met, we applied the Wilcoxon test. Statistical hypotheses were tested at the level of significance of 0.05.

**Results**

This study included 45 (57.7%) female, and 33 (42.3%) male patients out of a total of 78.

The socio-demographic characteristics indicate that in relation to gender, there was a statistically significant difference between males and females with regard to education ($p = 0.002$) and employment ($p = 0.028$) (Table 1).

| Socio-demographic characteristics of the study participants |
|--------------------------------------------------------------|
| Characteristics                                              | Male (n = 33) | Female (n = 45) | $p$     |
| Age (years), n (%)                                          |              |                |        |
| 16–30                                                       | 16 (49)      | 13 (29)        | 0.192  |
| 18–30                                                       | 9 (27)       | 19 (42)        |        |
| 31–40                                                       | 8 (24)       | 13 (29)        |        |
| ≥ 41                                                        |              |                |        |
| Married, n (%)                                              | 4 (12)       | 10 (22)        | 0.251  |
| Education, n (%)                                            |              |                | 0.002**|
| Elementary school                                           | 3 (9)        | 7 (16)         |        |
| High school                                                 | 26 (79)      | 18 (40)        |        |
| University                                                  | 4 (12)       | 20 (44)        |        |
| Employment, n (%)                                           | 5 (15)       | 17 (38)        | 0.028* |
| Heredity, n (%)                                             | 11 (33)      | 14 (31)        | 0.835  |
| Method of hospitalisation, n (%)                            |              |                | 0.085  |
| voluntary                                                   | 18 (55)      | 33 (73)        |        |
| forced                                                      | 15 (45)      | 12 (27)        |        |
| Cigarette smoking, n (%)                                    | 15 (45)      | 19 (42)        | 0.776  |
| DUP, n (%)                                                  |              |                |        |
| up to 30 days                                               | 7 (21)       | 13 (29)        | 0.443  |
| 2–6 months                                                  | 8 (24)       | 14 (31)        |        |
| > 6 months                                                  | 18 (55)      | 18 (40)        |        |

* $p < 0.05$; ** $p < 0.01$; DUP – duration of untreated psychosis.

Figure 1 shows the percentage of abnormal laboratory values of nonspecific inflammation markers (WBC, Gra, Lym, Mon, ESR, CRP), at admission and after a 4-week antipsychotic treatment. In our study, abnormal values were defined as those higher than the reference range.

![Fig. 1 – The percentage of patients with abnormal laboratory values of nonspecific inflammation markers at admission and after 4 weeks of antipsychotic treatment.](image)

**Note:** abnormal is defined as levels of values higher than the reference range: white blood cells (WBC) – 3.5–10 $\times 10^9$/L; granulocytes – 43.0–76.0%; lymphocytes – 17.0–78.0%; monocytes – 4.3–10.0%; erythrocyte sedimentation rate – 2–12 mm/h; C-reactive protein – 0–5 ng/L.

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With regard to the observed values of PANSS scores (total and subscales: positive, negative and general psychopathology) and nonspecific markers of inflammation at the admission and after four weeks antipsychotic treatment, there was no statistical significance only when ESR and C-reactive protein were concerned ($p = 0.970$ and $p = 0.359$, respectively) (Table 2).

The responders had statistically less values at the PANSS total score and subscales compared to the non-responders after 4 weeks of antipsychotic treatment ($p < 0.001$), while there were no statistically significant differences in the therapy response among the antipsychotic therapy groups ($p = 0.215$) (Table 3).

The differences between the therapy responders and non-responders in relation to the nonspecific inflammation markers at admission and after 4 weeks of antipsychotic therapy showed a statistical significance with regard to ESR ($p = 0.045$) (Table 4).

### Table 2

| Parameters                              | Baseline ($\bar{x} \pm SD$) | Control visit ($\bar{x} \pm SD$) | $p$  |
|----------------------------------------|-------------------------------|-----------------------------------|------|
| PANSS positive subscore                | 25.4 $\pm$ 5.7                | 12.2 $\pm$ 5.7                    | $< 0.001^{**}$ |
| PANSS negative subscore                | 21.8 $\pm$ 5.8                | 12.9 $\pm$ 6.3                    | $< 0.001^{**}$ |
| PANSS general psychopathology         | 52.9 $\pm$ 6.5                | 29.9 $\pm$ 11.5                   | $< 0.001^{**}$ |
| PANSS total score                      | 100.1 $\pm$ 13.0              | 55.0 $\pm$ 21.8                   | $< 0.001^{**}$ |
| WBC ($\times 10^9$/L)                  | 9.1 $\pm$ 3.1                 | 7.8 $\pm$ 5.4                     | $< 0.001^{**}$ |
| Granulocytes (%)                       | 72.3 $\pm$ 11.0               | 65.9 $\pm$ 9.1                    | $< 0.001^{**}$ |
| Lymphocytes (%)                        | 22.5 $\pm$ 8.9                | 27.9 $\pm$ 7.7                    | $< 0.001^{**}$ |
| Monocytes (%)                          | 5.2 $\pm$ 2.9                 | 6.7 $\pm$ 4.4                     | 0.001* |
| ESR (mm/h)                             | 18.1 $\pm$ 16.2               | 17.9 $\pm$ 17.1                   | 0.970 |
| C-reactive protein (ng/L)              | 7.8 $\pm$ 20.9                | 3.7 $\pm$ 2.1                     | 0.359 |

*p < 0.01; **p < 0.001; WBC – white blood cells; ESR– erythrocyte sedimentation rate.

### Table 3

| Characteristics                          | Responders (n = 36) | Non-responders (n = 42) | $p$  |
|-----------------------------------------|---------------------|-------------------------|------|
| Antipsychotic therapy, n (%)            |                     |                         |      |
| first generation antipsychotics         | 14 (38)             | 24 (57)                 | 0.215|
| second generation antipsychotics        | 11 (31)             | 11 (26)                 |      |
| antipsychotic combination               | 11 (31)             | 7 (17)                  |      |
| Scores at baseline, $\bar{x} \pm SD$   |                     |                         |      |
| PANSS positive subscore                 | 26.1 $\pm$ 5.3      | 24.8 $\pm$ 6.0          | 0.460|
| PANSS negative subscore                 | 22.8 $\pm$ 4.9      | 20.9 $\pm$ 6.4          | 0.119|
| PANSS general psychopathology          | 53.4 $\pm$ 4.8      | 52.5 $\pm$ 7.7          | 0.845|
| PANSS total score                       | 102.3 $\pm$ 10.8    | 98.2 $\pm$ 15.5         | 0.405|
| Scores at week 4, $\bar{x} \pm SD$     |                     |                         |      |
| PANSS positive subscore                 | 8.6 $\pm$ 2.1       | 15.3 $\pm$ 6.1          | $< 0.001^{*}$ |
| PANSS negative subscore                 | 8.7 $\pm$ 3.0       | 16.4 $\pm$ 6.3          | $< 0.001^{*}$ |
| PANSS general psychopathology          | 21.0 $\pm$ 4.9      | 37.6 $\pm$ 10.0         | $< 0.001^{*}$ |
| PANSS total score                       | 38.4 $\pm$ 7.8      | 69.2 $\pm$ 19.7         | $< 0.001^{*}$ |

*p < 0.001; Antipsychotic combination – combination of the first and second generation antipsychotics.

### Table 4

| Characteristics                          | Responders (n = 36) | Non-responders (n = 42) | $p$  |
|-----------------------------------------|---------------------|-------------------------|------|
| Values at baseline, $\bar{x} \pm SD$   |                     |                         |      |
| WBC ($\times 10^9$/L)                   | 9.5 $\pm$ 3.6       | 8.7 $\pm$ 2.5           | 0.584|
| Granulocytes (%)                        | 71.5 $\pm$ 11.4     | 72.8 $\pm$ 10.6         | 0.690|
| Lymphocytes (%)                         | 23.1 $\pm$ 9.5      | 22.0 $\pm$ 8.3          | 0.902|
| Monocytes (%)                           | 5.4 $\pm$ 2.9       | 5.1 $\pm$ 2.9           | 0.627|
| ESR (mm/h)                              | 15.8 $\pm$ 15.4     | 20.0 $\pm$ 16.4         | 0.193|
| C-reactive protein (ng/L)               | 9.6 $\pm$ 27.9      | 5.8 $\pm$ 10.6          | 0.518|
| Values at week 4, $\bar{x} \pm SD$     |                     |                         |      |
| WBC ($\times 10^9$/L)                   | 8.8 $\pm$ 7.6       | 6.9 $\pm$ 1.7           | 0.186|
| Granulocytes (%)                        | 67.0 $\pm$ 10.2     | 64.8 $\pm$ 7.9          | 0.355|
| Lymphocytes (%)                         | 27.0 $\pm$ 8.8      | 28.6 $\pm$ 6.6          | 0.387|
| Monocytes (%)                           | 6.0 $\pm$ 2.2       | 7.4 $\pm$ 5.6           | 0.216|
| ESR (mm/h)                              | 15.1 $\pm$ 15.6     | 20.8 $\pm$ 18.1         | 0.045*|
| C-reactive protein (ng/L)               | 3.5 $\pm$ 2.2       | 7.3 $\pm$ 20.3          | 0.161|

*p < 0.05 ; WBC – white blood cells; ESR – erythrocyte sedimentation rate.
The combination of the first and second generation antipsychotics had weaker influence on nonspecific inflammation markers comparing to the first generation antipsychotics and second generation antipsychotics after a 4-week treatment, showing a statistical significance with regard to the value of WBC and lymphocytes, but no statistical significant changes in the blood concentrations of granulocytes and monocytes (Table 5).

Discussion

In treatment of the first psychotic episode, the clinician’s attention should be drawn to both the psychological and somatic symptoms as well as the laboratory parameters. Careful evaluation is especially important in the purpose of excluding many potential somatic and neurological causes of psychosis.

Research data indicate that the disorders of various body systems in schizophrenia (inflammation and immune processes, metabolic disorders, fatty acids metabolism, plasma antioxidants) do not have to be of secondary character, but may be an inherent part of schizophrenic disease itself. Studies on antipsychotic-naive patients with first-episode psychosis find that inflammation is present already at this stage. Some of these abnormalities resolve after the initiation of treatment, suggesting that they are state markers of acute psychosis, but other abnormalities persist. For this reason continuous monitoring of laboratory parameters is imposed as necessary already at the very beginning of the treatment, in order to clearly distinguish those abnormalities that are direct consequences of the disease itself from the disorders due to antipsychotic therapy. Prompted by many years of our clinical experience in work with psychotic patients and the numerous studies supporting the hypothesis that inflammation is involved in the etiopathogenesis of psychotic disorders, we came to the idea to do our study.

Having defined the blood levels of nonspecific inflammation markers (WBC with leukocyte formula, CRP, ESR) in patients with the first episode of schizophrenia before ini-

| Antipsychotics | Baseline (± SD) | Control (± SD) | p |
|----------------|-----------------|----------------|---|
| **First generation antipsychotics** | | | |
| WBC (x 10⁹/L) | 9.1 ± 2.9 | 7.3 ± 2.1 | 0.001*** |
| Granulocytes (%) | 71.4 ± 11.6 | 66.8 ± 8.9 | 0.007** |
| Lymphocytes (%) | 23.8 ± 9.9 | 27.1 ± 7.4 | 0.029* |
| Monocytes (%) | 4.9 ± 2.3 | 6.0 ± 2.4 | 0.008** |
| ESR (mm/h) | 19.3 ± 17.6 | 20.0 ± 18.2 | 0.579 |
| C-reactive protein (ng/L) | 6.7 ± 12.6 | 4.0 ± 2.5 | 0.872 |
| **Second generation antipsychotics** | | | |
| WBC (x 10⁹/L) | 9.2 ± 3.3 | 8.7 ± 9.5 | 0.005** |
| Granulocytes (%) | 72.9 ± 10.0 | 63.2 ± 8.4 | 0.001*** |
| Lymphocytes (%) | 21.2 ± 8.0 | 29.6 ± 7.4 | 0.001** |
| Monocytes (%) | 5.2 ± 2.8 | 8.8 ± 7.0 | 0.002** |
| ESR (mm/h) | 20.2 ± 18.5 | 15.5 ± 16.9 | 0.133 |
| C-Reactive protein (ng/L) | 13.8 ± 35.1 | 3.5 ± 2.1 | 0.089 |
| **Antipsychotic combination** | | | |
| WBC (x 10⁹/L) | 9.0 ± 3.2 | 7.5 ± 2.1 | 0.050* |
| Granulocytes (%) | 73.6 ± 11.7 | 67.2 ± 10.0 | 0.065 |
| Lymphocytes (%) | 20.5 ± 8.0 | 27.2 ± 8.7 | 0.025* |
| Monocytes (%) | 5.8 ± 4.1 | 5.5 ± 2.1 | 0.943 |
| ESR (mm/h) | 12.9 ± 6.8 | 16.1 ± 14.8 | 0.437 |
| C-reactive protein (ng/L) | 3.1 ± 2.4 | 3.4 ± 1.5 | 0.636 |

* p < 0.05; ** p < 0.01; *** p < 0.001; WBC – white blood cells; ESR – erythrocyte sedimentation rate; Antipsychotic combination – combination of the first and second generation antipsychotics.
ments, which can be found in the background of metabo-
lation between blood pressure and intensity of inflammatory
have everyday clinic significance by highlighting the correla-
increased erythrocyte sedimentation which might potentially
also a strong correlation between systolic and diastolic and
omental obesity, is reported to be significantly associated
maintained increased in 20% of the patients after four weeks of
of antipsychotic treatment. In our study, however, monocyto
did not have the lymphocyte counts within the reference
nerythocyte sedimentation rate is used as an indirect
measure of the concentration of acute phase proteins. One
study revealed ESR increase in 17% of the patients with acu-
treatment response to antipsychotics. Observing the nonspe-
cific inflammation markers in correlation to the therapy res-
ponsibility, the results of our study show that there were 36 re-
ponders, or 46% patients, and 42 non-responders or 54% pa-
tients. They are in compliance with data from the literature
hich indicate that 40–50% patients have no optimum
therapy response to antipsychotics. Observing the nonspe-
cific inflammation markers in correlation to the therapy re-
ponse by implementing the PANSS scale, our results show
that only the erythrocyte sedimentation values were
statistically significantly higher in the non-responders com-
pared to the responders.

Several studies have investigated the effects of
antipsychotics on inflammation. Given the association
between inflammation and schizophrenia, antipsychotics
would be expected to have an anti-inflammatory effect.
However, the anti-inflammatory effects of antipsychotics
vary based on whether the antipsychotic is typical or
atypical. To date, there have been conflicting reports re-
garding the effects of antipsychotics on cytokine levels, and
no antipsychotic has been shown to have consistent anti-
inflammatory action

The literature has largely ignored possible direct (not
explained by metabolic syndrome) effects of antipsychotics
on CRP and other inflammatory markers. According to
the results of our study, after 4 weeks of antipsychotic trea-
tment there was a decrease of blood levels of non-specific
inflammation markers (WBC, Gra, ESR, CRP), but the dif-
ferent antipsychotic therapy groups had different effects on

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certain non-specific inflammation markers. Variable blood levels of nonspecific inflammation markers after antipsychotic treatment could possibly explain their still undefined mechanism of action in schizophrenia.

Lately, several trials have been conducted investigating the potential of anti-inflammatory agents to improve symptoms of schizophrenia.\textsuperscript{17,15} With regard to their usage and efficacy in adjunctive antipsychotic therapy in schizophrenia, the literature in this field is fraught with significant heterogeneity, including contradictory findings. Some of them claim that the results of aspirin addition to antipsychotic treatment seem promising, provided information on the efficacy on symptom severity\textsuperscript{17}, while the results of the other studies indicate that adjunctive nonsteroidal anti-inflammatory drugs (NSAIDs) for schizophrenia may not benefit patients treated with first-line antipsychotics judged by the PANSS total score change. However, due to a limited database, further controlled studies are needed, especially in first-episode patients.\textsuperscript{38}

The limitations of our study relate to the relatively short follow-up period and assessment of a limited number of nonspecific inflammation markers, as well as the lack of personal experience related to the anti-inflammatory therapy application in the purpose of antipsychotic therapy augmentation.

Conclusion

The results of our study show that there is a subpopulation of patients in first-episode schizophrenia with increased values of nonspecific inflammation markers (WBC, CRP, ESR), tending to their normalization after 4-weeks of antipsychotic treatment.

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