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Research article

Escitalopram augmentation improves negative symptoms of treatment resistant schizophrenia patients – A randomized controlled trial

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ABSTRACT

Serum interleukin (IL)-6 levels in schizophrenia correlate with the severity of negative symptoms. This study aimed to explore the potential immune mechanism of SSRI augmentation in the management of patients with treatment-resistant schizophrenia, assessing changes in IL-6 and CRP amounts. This was a randomized double-blind, placebo-controlled, 8-week study of escitalopram augmentation in 62 schizophrenic patients treated in 2016–2017 at the Shandong Mental Health Center. Twenty-nine healthy controls were also included. Patients received add-on escitalopram or placebo for 8 weeks. Serum IL-6 and CRP were measured at baseline and 8 weeks. The primary outcome was the Positive and Negative Syndrome Scale (PANSS). After 8 weeks of treatment, reductions in total PANSS, negative subscore, and affective subscore were more important in escitalopram treated patients than in the placebo group (all $P < 0.05$). Escitalopram significantly decreased CRP and IL-6 levels (both $P < 0.05$). At baseline, IL-6's effects on negative and cognitive symptoms represented 16.2% and 20.1%, respectively; at week 8, these effects were 22.7% and 20.8% on negative and cognitive symptoms, respectively. CRP had no impact on any PANSS score. Overall, escitalopram augmentation may be a useful addition for schizophrenic patients with persistent negative symptoms. Changes in IL-6 may be associated with negative and cognitive symptoms.

1. Introduction

Selective serotonin reuptake inhibitor (SSRI) augmentation is useful in the treatment of schizophrenic patients with persistent and refractory negative symptoms, although current findings are inconclusive [1]. Combination of SSRIs and antipsychotics may improve negative symptoms of schizophrenia unresponsive to antipsychotics alone [2–4]. At least two SSRIs (fluvoxamine and fluoxetine) improve primary negative symptoms in patients with chronic schizophrenic administered first-generation antipsychotics. Jockers-Scherübl also suggested that paroxetine is efficient in the treatment of negative symptoms in chronic schizophrenia [5]. Meanwhile, SSRIs and other antidepressants provide no global support for improving negative symptoms with SSRI augmentation therapy in schizophrenia [6,7]. Nevertheless, the known mechanisms of action of these drugs cannot explain the synergistic effects [8]. Several hypotheses were proposed, including the release of dopamine and 5-HT in brain regions, and changes in γ-aminobutyric acid (GABAA) receptor (GABBAR) and related signaling systems [8,9]. Indeed, increased dopamine release after administration of SSRI-antipsychotics is considered to be controlled by specific serotonergic receptors and tyrosine hydroxylase [10]. We hypothesized that the effects of these drugs could also be due, at least in part, to changes in immune factors such as cytokines. Interleukin (IL)-6, an important cytokine in the central nervous system (CNS), is altered in psychiatric disorders [9,11–13]. Studies support that high serum levels of IL-6 in schizophrenic patients correlate with symptom severity [11,12,14]. Depending on the microenvironment of the CNS, IL-6 can exert a neuroprotective effect [15] but can also impair neurogenesis, playing a pivotal role in microglial activity and inflammatory responses [16,17]. C-reactive protein (CRP) is a reliable marker of systemic inflammation [18]. Iancu et al. [19] reported that escitalopram is effective for treating negative symptoms in chronic schizophrenia, but a recent study [20] supports the opposite. Meanwhile, Kaminska et al. [18] and Rogoz et al. [21] support that co-administration of risperidone and escitalopram may be used to treat negative and positive symptoms of schizophrenia.

We hypothesized that escitalopram has potential anti-inflammatory effects, which could relate to symptom improvement in resistant schizophrenia. Therefore, this study aimed to explore the potential immune mechanism of SSRI augmentation for treatment-resistant schizophrenia and negative symptoms and assess changes in IL-6 and CRP levels, also evaluating associations of IL-6 levels with clinical symptoms. Finally, we explored the evidence for the synergistic effects of escitalopram on negative symptoms in treatment-resistant schizophrenia.

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2. Materials and methods

2.1. Study design

This randomized double-blind, placebo-controlled, 8-week study of escitalopram augmentation in patients with treatment-resistant schizophrenia treated between August 1st, 2016 and March 1st, 2017 at the Shandong Mental Health Center, was approved by the ethics committee of the Shandong Mental Health Center (#2016R14) (Chinese Clinical Trials registry (#ChiCTR-INR-17011986)).

2.2. Subjects

Ninety-one participants were recruited, including 29 healthy controls and 62 unrelated patients with treatment-resistant schizophrenia and persistent negative symptoms. The 62 patients were randomly administered escitalopram (treatment group) or placebo (placebo group) for 8 weeks.

Inclusion criteria for schizophrenic patients were: 1) treatment-resistant schizophrenia diagnosed according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, ICD-10 Diagnostic criteria [22]. 2) 18–60 years of age; 3) disease course ≥5 years; 4) positive and negative syndrome scale (PANSS) negative symptoms (N1, blunted affect; N2, emotional withdrawal; N3, poor rapport; N4, passive/apathetic social withdrawal; N5, difficulty in abstract thinking; N6, lack of spontaneity and flow of conversation; and N7, stereotyped thinking) score ≥4 in at least three items or ≥5 in at least two items; 5) PANSS positive symptoms [23] (hallucination; delusion behavior; exaggeration; suspicion; stereotyped thinking; health concern; unusual thought content; and sense of lack of self-control) score ≥4 in at least three items or ≥5 in at least two items; 6) hospitalization for > 6 months and stable symptoms; 7) combination antipsychotics (olanzapine + risperidone or risperidone + aripiprazole) or single antipsychotics (olanzapine or risperidone); 8) more than three types of drugs previously used; 9) drug side effects not obvious; 10) no recent MECT, TMS, or psychotherapy; 11) no substance abuse or alcohol addiction; 12) no disease of any other major organ; 13) signed informed consent.

Exclusion criteria for the patients were: 1) single use of antipsychotic drugs; 2) serious side reactions; 3) other psychiatric comorbidity; 4) substance or alcohol abuse or dependence; 5) acute infection or autoimmune diseases; 6) history of neurological disease or head trauma; 7) pregnancy or breast-feeding in females; 8) complications with any other serious mental illness.

Exclusion criteria for healthy controls were: 1) current psychiatric problem; 2) neurological disorder; 3) a family history of schizophrenia; or 4) chronic or acute physical illness (infection, autoimmune disease, allergic diseases, etc.).

2.3. Sample size calculation

According to previous studies [18,19], the PANSS score was used to calculate the sample size as: "$n = 2\sigma^2(\alpha, \beta)/(\mu1-\mu2)^2$ ", where σ(SD) = 11.9, μ1(PANSS Total) = 91, μ2(Quasi reduction PANSS Total) = 81. When α = 0.05 and β = 0.1, n = 30. Therefore, 31 patients were recruited per group.

2.4. Randomization

Under double-blind conditions 62 patients with treatment-resistant schizophrenia were randomized to add-on treatment with escitalopram (Escitalopram −Lexapro; 10 mg/pill; Xian-Janssen Pharmaceutical Ltd; drug registration number: H20150163; batch number: J20150119) at up to 20 mg/day for 8 weeks. The dose was escalated by 5 mg/d for the first 3 days, 10 mg/d for day 4 to week 4, and 20 mg/d for weeks 5–8. The placebo was identical in shape, size, and color.

2.5. Clinical measurements

The clinical state was assessed by psychiatrists using the PANSS [23]. Positive symptoms, negative symptoms, and general psychopathology were assessed using a 7-point scale ranging from score 1 (no symptom) to 7 (extreme symptom). Then, the scores were analyzed in five dimensions [23]: positive symptoms (P1, hallucination; P3, hallucinatory behavior; N6, lack of spontaneity and flow of conversation; G9, unusual thought content); negative symptoms (P5, exaggeration; N1, blunted affect; N2, emotional withdrawal; N3, poor rapport; N4, passive/apathetic social withdrawal; N6, lack of spontaneity and flow of conversation; G7, slow motion; G13, volitional disorder; G16, active avoidance); cognitive symptoms (P2, associative looseness; N5, difficulty in abstract thinking; N7, stereotyped thinking; G5, packing and posturing; G10, disorientation; G11, attention disorder; G15, preoccupation); aggressive symptoms (G1, pay attention to physical health; G2, anxiety; G3, guilt; G4, nervous; G6, depression; G12, lack of judgment); and affective symptoms (N4, passive/apathetic social withdrawal; P7, hostility; G8, uncooperative; G14, blunted affect). The PANSS was administered by a clinical psychiatrist who was blind to grouping.

2.6. Serum IL-6 and CRP levels

Fasting blood was drawn by venipuncture between 7:00 AM and 9:00 AM following an overnight fast at baseline and week 8, centrifuged at 2000 rpm for 15 min, and stored at −70 °C. Serum IL-6 and CRP levels were measured by chemiluminescence immunoassay using commercially available kits.

2.7. Safety and tolerability

To achieve maximal efficacy and avoid side effects as much as possible, slow titration was used. The overall treatment compliance was calculated based on drug dispensing records (date and drug amounts). Side effects were recorded at each visit covering a large range of complaints.

2.8. Statistical analysis

SPSS 18.0 (SPSS, USA) was used for data analysis. Continuous data were tested for normal distribution by the Kolmogorov-Smirnov test. Normally distributed parameters were presented as mean ± standard deviation, and analyzed by ANOVA with the LSD post hoc test. Non-normally distributed data were presented as median (range) and analyzed by the Kruskal-Wallis test. Categorical variables were presented as frequency and analyzed using the Chi-square test or Fisher exact test. Correlation regression analysis was used to assess associations ($0.2 < r < 0.4$, low correlation; $0.4 < r < 0.6$, moderate correlation; $0.6 < r$, high correlation). Linear regression analysis was used to test the involvement of inflammatory markers (IL-6 and CRP) on PANSS score changes after 8 weeks ($10\% < R^2 < 20\%$, moderate impact; $R^2 > 20\%$, high impact). Two-sided $P < 0.05$ was considered statistically significant. Clinical efficacy was evaluated after eight weeks of treatment based on the PANSS score, CRP amounts and IL-6 levels. The differences in each dimension of the PANSS between the two groups were analyzed by *t*-test, with $p < 0.001$ indicating statistical significance.

3. Results

3.1. Subjects

Fig. S1 depicts the study flowchart. Of the 62 patients, four were excluded due to side effects after 2 weeks (two patients each had emesis and dry mouth, respectively), and four others were discharged before