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Word
Efficacy of Spironolactone as an Adjunctive Therapy to Risperidone to Improve Symptoms of Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled, Clinical Trial

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Abstract

Objective: Spironolactone (C24H32O4S), a potent mineralocorticoid receptor (MR) inhibitor, is a potassium-sparing diuretic that is traditionally used to treat fluid build-up in the body or for its anti-androgenic properties. This study is a double-blind, placebo-controlled, randomized clinical trial assessing the beneficial effects of spironolactone in addition to risperidone in improving negative symptoms of schizophrenia.

Method: 40 patients with chronic schizophrenia, aged 18–60 years, were assigned to two groups: risperidone + spironolactone or risperidone + placebo. Risperidone was administered to both the spironolactone and placebo groups with a dose up to 6 mg/day throughout the trial. Spironolactone (C24H32O4S) was ordered 100 mg/day for the full 8-week course of the study. Patients were rated on the Positive and Negative Syndrome Scale (PANSS) at four time points: baseline, weeks two, four, and eight. The PANSS negative subscale score was the main objective.

Results: PANSS negative, positive, and total scores showed significantly greater improvements in the spironolactone relative to the placebo group from baseline to the trial endpoint (P (Cohen’s d): 0.004 (0.96), 0.007 (0.90), and 0.042 (0.66), respectively). Similarly, ANOVA also presented significant time × treatment interaction effect for spironolactone on PANSS negative (F = 9.04; np² = 0.19; df = 1.38; P = 0.002), positive (F = 3.43; np² = 0.08; df = 2.72; P = 0.023), and total (F = 3.94; np² = 0.09; df = 2.05; P = 0.022) scores. However, spironolactone did not cause significant decrease in the general psychiatric pathology score of PANSS.

Conclusion: Our findings suggest the efficacy and safety of spironolactone as an adjunctive therapy to risperidone in improving the symptoms of schizophrenia.

Key words: Controlled Clinical Trial; Hypothalamo-Hypophyseal System; Schizophrenia; Spironolactone
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Materials and Methods

Study design
This was a double-blind, placebo-controlled, randomized clinical trial conducted on in-patients with schizophrenia at Roozbeh Hospital (Tehran University of Medical Sciences (TUMS), Tehran, Iran) and Imam Ali Hospital (Alborz University of Medical Sciences, Karaj, Iran) from November 2019 to July 2020. Prior to the study, written informed consent was obtained from patients and their legal guardian to enter the study. They were informed that at any time during the study and without the need to provide any reason and without any disruption in receiving routine services related to their disease, they could withdraw from the study. Patients were randomly divided into two parallel spironolactone and placebo groups and were assessed after the first week and then at weeks two, four and eight. The trial was conducted in agreement with the ethical principles mandated in the Declaration of Helsinki and its later amendments (13). Also, the ethics committee and institutional review board of TUMS approved the protocol for this study (IR.TUMS.VCR.REC.1398.540). This study is registered at the Iranian Registry of Clinical Trials (IRCT20090117001556N120).

Participants
Patients with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, which ranged in age from 18 to 60 years and met the inclusion criteria and had a minimum of 2 years of disease duration (defined as chronic schizophrenia) were studied (14). An experienced psychiatrist evaluated the diagnostic status and severity of the disease among patients (according to the Structured Clinical Interview for Diagnosis in conjunction with Statistical Manual-5 Clinical Version; SCID-5-CV). The other inclusion criteria were a total score of at least 60 on PANSS accompanied by a score of ≥ 19 on the negative subscale. The exclusion criteria of the study were as follows: 1) a score of ≥ 14 on the 17-item Hamilton Depression Rating Scale (HDRS) and/or a score of ≥ 4 on the PANSS depression item, 2) concurrent alcohol/substance dependence or positive history of dependence during the six months previous to start of this study, 3) intelligence quotient less than 70, 4) other mental disorders, 5) severe medical problem, 6) pregnancy/lactation, 7) female of childbearing age without sufficient contraception, 8) electroconvulsive therapy in the last six months, 9) drug- or insulin-dependent diabetes, 10) hepatitis, 11) CHF, 12) neuroleptic use within the last seven days, and 13) long acting neuroleptic use within the last 30 days.

Interventions
Risperidone was ordered for both the spironolactone and the placebo groups. The starting daily dose of risperidone and its increasing weekly dose was 2 mg, which was increased to a maximum of 6 mg daily according to the clinical response. Spironolactone...
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(C24H32O4S) dosage was 100 mg per day for the eight-week duration of the study. No other medication was allowed in this study.

**Outcomes and Tools**

PANSS was the assessment tool in this study. PANSS is comprised of 30 items categorized to three subscales evaluating negative (7 items), positive (7 items), and general psychopathological symptoms (16 items) (15). This rating scale is used in Farsi with acceptable reliability (Cronbach's alpha: 0.77) and validity (16, 17). Subjects were rated with PANSS at the baseline session and at weeks two, four, and eight. The raters were experienced clinicians with an inter-reliability of 90% on PANSS. The PANSS negative score was the main objective of the trial, while positive, general psychopathological and total scores of PANSS comprised the secondary outcome measures.

**Side Effects**

Side effects were assessed by a clinician or checked by family during the study. Participants were educated to report any unexpected medication side effects through a 24-hour hotline. Moreover, open-ended questions about medication side effects were also asked at each visit by an experienced psychiatrist. Adverse events checklist was used to record the adverse events (18). The ESRS was also utilized to record extrapyramidal symptoms (19).

**Sample Size**

We considered a three-score variation in PANSS negative subscale score with a SD of three assumed for sample size calculation. The total sample size of the trial was 40 patients while assuming a power of 80%, a two-sided significance level of 5%, and a 20% drop out rate.

**Randomization and Blinding**

Patients were randomly divided into two equally distributed groups consisting of spironolactone and placebo. The allocation and randomization were carried out using block randomization by the PI, who was not engaged in diagnosis and follow-up. The allocations were retained in confidential opaque envelopes and were exposed at the end of the trial. Randomizations, allocations, drug administration, scoring, data entry, and statistics were conducted by separate individuals.

**Statistical Methods**

Categorical variables are demonstrated as frequency (percentage) and continuous variables are displayed as mean (standard deviation). Student t-test (two-tailed) was used to compare mean change in PANSS scores from baseline to the study endpoint between spironolactone and placebo groups and Cohen’s d effect sizes were reported (20). The categorical variables, including the nominal and ordinal demographic features and number of adverse events, and the Chi-square test or Fisher’s exact test was used to compare the frequency between the two study groups. The general linear model (GLM) repeated-measures analysis was applied to investigate time, treatment, and time × treatment effects for PANSS between the two groups, considering the study groups (spironolactone or placebo) as the between-subject factor and the study outcomes at baseline and follow-up sessions as the within-subject variable (time). Effect sizes were reported as partial eta squared (ηp2) (21). P-value of < 0.05 was designated as statistically significant.

**Results**

**Participants and Baseline/Clinical Characteristics**

Among 85 subjects with schizophrenia who were screened for the inclusion and exclusion criteria, 46 subjects were enrolled and randomly allocated to two groups of risperidone + spironolactone or risperidone + placebo in a 1:1 ratio (Figure 1). Six subjects (three in each trial group) were excluded before week two due to consent withdrawal. Eventually, 40 patients with schizophrenia ended the eight-week course of the trial. The baseline characteristics of the patients are presented in Table 1. The participants in spironolactone and placebo groups were comparable based on age, sex, disease duration, education, marital status, occupation, smoking, substance abuse, and admission history. Moreover, there was no significant difference between the two study groups based on baseline PANSS scores (Table 1).

**Outcomes**

PANSS scores of spironolactone and placebo groups at the beginning of the study and three follow-up visits are shown in Table 2. Moreover, the results of GLM repeated-measure analysis for all study outcomes are detailed in Table 3. Patients in both the spironolactone and the placebo group demonstrated remarkable improvements in all PANSS scores from the starting point to the end of study (effect of time: P < 0.001 for all study outcomes), indicating therapeutic effect of risperidone in both groups.

**PANSS**

**PANSS negative subscale score**

Results from the independent t-test demonstrated remarkably greater decline in PANSS negative subscale scores in the spironolactone group relative to the placebo group from baseline to all follow-up visits (t = 2.14, df = 38, P = 0.039 (Cohen’s d = 0.67) for week two; t = 3.38, df = 38, P = 0.002 (Cohen’s d = 1.07), for week four; and t = 3.08, df = 38, P = 0.004 (Cohen’s d = 0.96), for week eight) (Table 2 and Figure 2a). Accordingly, GLM repeated-measures analysis found significant time × treatment effect for spironolactone on the PANSS negative subscale score (F = 9.04; ηp2 = 0.19; df = 1.38; P = 0.002) (Table 3).

**PANSS positive subscale score**

From screening to week four and eight, the PANSS positive subscale score showed significantly greater decrease in the spironolactone group compared to the placebo group (t = 2.18, df = 38, P = 0.035 (Cohen’s d = 0.69) for week four and t = 2.86, df = 38, P = 0.007
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(Cohen’s d = 0.90) for week eight (Table 2 and Figure 2b). However, no remarkable between-group difference was found in mean PANSS positive subscale change score from baseline to week two (t = 1.48, df = 38, P = 0.146). Moreover, significant time × treatment interaction effect was observed for spironolactone on the PANSS positive score (F = 3.43; ηp2 = 0.08; df = 2.72; P = 0.023) (Table 3).

PANSS general psychopathology subscale score
In contrast to positive and negative subscale scores of PANSS, we found no significant between-group difference in mean PANSS general psychopathology subscale change score from baseline to any post-baseline visits (t = 0.18, df = 38, P = 0.986 for week two; t = 0.64, df = 38, P = 0.526 for week four; and t = 0.58, df = 38, P = 0.562 for week eight) (Table 2 and Figure 2c). In agreement, no significant time × treatment interaction effect was found for spironolactone on PANSS general psychopathology subscale score (F = 0.308; ηp2 = 0.008; df = 2.28; P = 0.764) (Table 3).

PANSS total score
As depicted in Figure 2d, from the baseline to week four and eight, PANSS total score exhibited significantly superior improvement in the spironolactone group relative to the placebo group (t = 2.91, df = 38, P = 0.006 (Cohen’s d = 0.92) for week four and t = 2.10, df = 38, P = 0.042 (Cohen’s d = 0.66) for week eight) (Table 2). There was no remarkable difference between the two groups in PANSS total change score from the start of the study to week two (t = 1.12, df = 38, P = 0.269). Moreover, GLM ANOVA demonstrated significant time × treatment interaction effect for spironolactone on the PANSS total score (F = 3.94; ηp2 = 0.09; df = 2.05; P = 0.022) (Table 3).

Clinical Complications and Side Effects
There were no severe side effects, and no one was excluded for this reason. Seven adverse events were identified. Stomach pain (15%), nausea (15%), dizziness (15%), and dry mouth (15%) were the most prevalent adverse events observed in the spironolactone group, and stomach pain (20%) and nausea (20%) were the most common complaints in the placebo group. However, no significant difference was found in the frequency of side effects between the two groups (Table 4). Moreover, no significant between-group difference was found with respect to extrapyramidal symptoms.

Table 1. Comparison of Two Groups of Participants in Terms of Demographic Features Using Independent t-Test

|                         | Spironolactone arm (n = 20) | Placebo arm (n = 20) | P-value  |
|-------------------------|----------------------------|---------------------|----------|
| Age [years; mean (SD)]  | 38.00 (9.25)               | 40.00 (8.46)        | 0.480a   |
| Sex [n (%)]             |                            |                     | 0.999b   |
| • Male                  | 12 (60%)                   | 11 (55%)            |          |
| • Female                | 8 (40%)                    | 9 (45%)             |          |
| Disease duration [years; mean (SD)] | 9.25 (4.05) | 9.60 (3.69) | 0.777a |
| Education               |                            |                     | 0.794b   |
| • Illiterate            | 4 (20%)                    | 4 (20%)             |          |
| • Primary school        | 9 (45%)                    | 10 (50%)            |          |
| • Diploma               | 4 (20%)                    | 4 (20%)             |          |
| • Bachelor’s            | 1 (5%)                     | 2 (10%)             |          |
| • Master’s              | 1 (5%)                     | 0 (0%)              |          |
| • Doctorate             | 1 (5%)                     | 0 (0%)              |          |
| Marital status          |                            |                     | 0.319b   |
| • Single                | 12 (60%)                   | 8 (40%)             |          |
| • Married               | 3 (15%)                    | 7 (35%)             |          |
| • Widow                 | 0 (0%)                     | 1 (5%)              |          |
| • Divorce               | 5 (25%)                    | 4 (20%)             |          |
| Occupation              |                            |                     | 0.298b   |
| • Unemployed            | 7 (35%)                    | 9 (45%)             |          |
| • Housewife             | 6 (30%)                    | 3 (15%)             |          |
| • Worker                | 3 (15%)                    | 5 (25%)             |          |
| • Employee              | 2 (10%)                    | 0 (0%)              |          |
| • Businessman           | 2 (10%)                    | 1 (5%)              |          |
Table 2. Comparison of Positive and Negative Syndrome Scale (PANSS) between Two Groups Participating in the Study Based on Cohen’s d

|                          | Spironolactone arm (n = 20) | Placebo arm (n = 20) | P-value (Cohen’s d) |
|--------------------------|-----------------------------|----------------------|---------------------|
| **PANSS negative subscale score** |                             |                      |                     |
| Baseline                 | 24.95 (5.39)                | 25.45 (5.58)         | 0.775               |
| Week 2                   | 17.80 (3.42)                | 20.60 (4.29)         | 0.028 (0.72)        |
| Week 4                   | 13.85 (2.27)                | 19.05 (3.85)         | <0.001 (1.64)       |
| Week 8                   | 11.50 (2.92)                | 16.90 (3.64)         | <0.001 (1.63)       |
| Change score from baseline to Week 2 | 7.15 (3.74)                | 4.85 (3.01)          | 0.039 (0.67)        |
| Change score from baseline to Week 4 | 11.10 (5.06)                | 6.40 (3.58)          | 0.002 (1.07)        |
| Change score from baseline to Week 8 | 13.45 (5.42)                | 8.55 (4.74)          | 0.004 (0.96)        |
| Baseline                 | 34.00 (4.89)                | 35.60 (2.68)         | 0.210               |
| Week 2                   | 28.35 (4.71)                | 31.75 (3.17)         | 0.011 (0.84)        |
| Week 4                   | 23.10 (4.17)                | 27.70 (3.68)         | 0.001 (1.16)        |
| Week 8                   | 20.20 (3.01)                | 25.45 (4.18)         | <0.001 (1.44)       |
| **PANSS positive subscale score** |                             |                      |                     |
| Baseline                 | 42.95 (6.65)                | 40.90 (9.65)         | 0.439               |
| Week 2                   | 32.40 (7.50)                | 30.40 (9.19)         | 0.455               |
| Week 4                   | 25.70 (7.84)                | 25.45 (7.02)         | 0.916               |
| Week 8                   | 20.95 (8.55)                | 21.25 (11.65)        | 0.927               |
| Change score from baseline to Week 2 | 5.65 (4.38)                | 3.85 (3.19)          | 0.146               |
| Change score from baseline to Week 4 | 10.90 (5.07)                | 7.90 (3.46)          | 0.035 (0.69)        |
| Change score from baseline to Week 8 | 13.80 (4.21)                | 10.15 (3.84)         | 0.007 (0.90)        |
| **PANSS general psychopathology subscale score** |                             |                      |                     |
| Baseline                 | 101.90 (8.16)               | 101.95 (10.91)       | 0.997               |
| Week 2                   | 101.90 (8.16)               | 101.95 (10.91)       | <0.001 (1.28)       |
| Week 4                   | 78.55 (8.55)                | 82.75 (10.30)        | 0.169               |
| Week 8                   | 62.65 (6.43)                | 72.25 (8.42)         | <0.001 (1.28)       |
| Change score from baseline to Week 2 | 10.55 (9.40)                | 10.50 (8.03)         | 0.986               |
| Change score from baseline to Week 4 | 17.25 (8.00)                | 15.45 (9.69)         | 0.526               |
| Change score from baseline to Week 8 | 22.00 (10.38)               | 19.65 (14.67)        | 0.562               |
| **PANSS total score**    |                             |                      |                     |
| Baseline                 | 101.90 (8.16)               | 101.95 (10.91)       | 0.997               |
| Week 2                   | 101.90 (8.16)               | 101.95 (10.91)       | <0.001 (1.28)       |
| Week 4                   | 78.55 (8.55)                | 82.75 (10.30)        | 0.169               |
| Week 8                   | 62.65 (6.43)                | 72.25 (8.42)         | <0.001 (1.28)       |
| Change score from baseline to Week 2 | 23.35 (12.77)               | 19.20 (10.52)        | 0.269               |
| Change score from baseline to Week 4 | 39.25 (10.03)               | 29.70 (10.66)        | 0.006 (0.92)        |
| Change score from baseline to Week 8 | 47.50 (13.37)               | 38.35 (14.06)        | 0.042 (0.66)        |

P-value of < 0.05 was designated statistically significant; Data are shown as mean (standard deviation).
Table 3. General Linear Model Repeated-Measures Analysis Information Related to Positive and Negative Syndrome Scale about Study Participants

| Factors                              | Time | Treatment | Time × Treatment |
|--------------------------------------|------|-----------|------------------|
|                                      | F    | η²        | F                | η²   | F       | η²   |
| PANSS negative subscale              | 153.40*** | 0.80 | 9.95**         | 0.20 | 9.04** | 0.19 |
| PANSS positive subscale              | 149.16*** | 0.79 | 14.44**        | 0.27** | 3.43' | 0.08 |
| PANSS general psychopathology subscale | 68.69*** | 0.64 | 0.025         | 0.007 | 0.308 | 0.008 |
| Baseline PANSS total score           | 268.97*** | 0.87 | 7.09'        | 0.15 | 3.94' | 0.09 |

*** P-value < 0.001, ** P-value < 0.01, * P-value < 0.05

Table 4. Frequency of Adverse Events in the Study Population

| Side effect       | Spironolactone group (n = 20) | Placebo group (n = 20) | P-values |
|-------------------|-------------------------------|------------------------|----------|
| Drowsiness, n (%) | 2 (10%)                       | 3 (15%)                | 1.000    |
| Stomach Pain, n (%) | 3 (15%)                  | 4 (20%)                | 1.000    |
| Nausea, n (%)     | 3 (15%)                       | 4 (20%)                | 1.000    |
| Vomiting, n (%)   | 2 (10%)                       | 3 (15%)                | 1.000    |
| Headache, n (%)   | 2 (10%)                       | 3 (15%)                | 1.000    |
| Dizziness, n (%)  | 3 (15%)                       | 3 (15%)                | 1.000    |
| Dry Mouth, n (%)  | 3 (15%)                       | 3 (15%)                | 1.000    |

P-value of < 0.05 was designated statistically significant.
* Fisher's exact test was applied for comparison of all adverse events.

Figure 1. CONSORT Flow Diagram for Study Participants
Figure 2. Comparison of PANSS Subscale Scores [Mean (Standard Error)] between the Spironolactone and Placebo Groups. a) PANSS Negative Subscale Score. b) PANSS Positive Subscale Score. c) PANSS General Psychopathology Subscale Score. d) PANSS Total Score

Discussion
This investigation was the first RCT assessing the beneficial effects of spironolactone as an adjunct to risperidone in improving negative symptoms of schizophrenia. In this regard, PANSS negative scores were determined as the primary outcome measures, and PANSS positive, general psychopathology, and total scores were considered as the secondary outcome measures. We demonstrated that adjuvant pharmacotherapy with spironolactone leads to remarkable reductions in all PANSS subscale scores (including negative, positive, and total scores) except for the general psychopathology subscale. In addition, there was no difference between the two groups in terms of frequency of side effects. Thus, our study suggests spironolactone as a potential beneficial adjunct pharmacotherapy to diminish negative symptoms in patients with schizophrenia. However, our findings need to be verified by larger controlled studies. Of note, it should be mentioned that both the spironolactone and the placebo groups had significant improvements in all PANSS subscale scores over the course of the trial, confirming the therapeutic effect of risperidone in ameliorating cognitive, negative, and positive symptoms of schizophrenia. However, the effect sizes for improvements in our study (both for risperidone plus spironolactone and risperidone plus placebo) were larger than previous typical trials of risperidone (22). The beneficial effects of spironolactone on schizophrenia’s negative symptoms might be due to several underlying mechanisms that are involved in
pathophysiology of schizophrenia. In this context, both NRG1, a membrane-bound ligand, and its receptor (ERBB4) were reported to be potential risk genes for schizophrenia (23). Furthermore, studies have shown an increased expression of NRG1 in post-mortem brain samples of schizophrenia patients, further supporting involvement of the NRG1-ERBB4 signaling pathway in pathogenesis of schizophrenia (24, 25). In agreement, studies on murine models overexpressing NRG1 have demonstrated schizophrenia-like behaviors such as reduced social interaction, increased hyperactivity, and cognitive impairments (26-29). Of note, it was exhibited that reversion of NRG1-overexpression led to improvement of schizophrenia-like behaviors (30) and was accompanied by re-establishing normal glutamatergic synaptic functioning (30, 31). Based on this evidence, a preclinical study used a drug repurposing strategy to find agents that can improve schizophrenia-like behaviors in an Nrg1 transgenic mouse model (12). Using a cell-based assay, NIH-NCC compound library of drugs for chemical modulators that induce alterations in activity of NRG1-ERBB4 signaling were screened, and spironolactone, an MR antagonist, was identified as an inhibitor of ERBB4 activity. They further demonstrated that spironolactone decreased phosphorylation levels of ERBB4 and enhanced inhibitory neurotransmission both in vitro and in vivo. Finally, chronic treatment of Nrg1 transgenic mice with spironolactone led to improvements in both positive symptoms and working memory (12).

Spironolactone is a potent inhibitor of MR, one of the main receptors for glucocorticoids. Over the past decade, a robust bulk of evidence has substantiated the role of HPAA in schizophrenia and other psychoses (32, 33). In this regard, studies demonstrated that cortisol and adrenocorticotropic hormones, markers of HPAA activity, are elevated in patients with non-medicated and first-episode schizophrenia (34-36). Conventional antipsychotics are typically associated with decreased levels of cortisol, especially in drug responders (33). Studies have also shown that psychosis is associated with down-regulated levels of glucocorticoid receptors, indicating impaired negative feedback on HPAA (33). Consistently, cortisol levels were positively related to severity of symptoms in psychotic patients (37). This evidence suggests that inhibition of HPAA activity by spironolactone may be the main reason for the beneficial effects of spironolactone on adverse symptoms in our trial. In this trial, no difference was observed in the frequency and severity of adverse events between spironolactone and placebo groups.

**Limitation**

One of the limitations of this trial was a relatively small population. Moreover, the eight-week course of the trial might not show the long-term beneficial efficacy and adverse events of spironolactone. Thus, our findings need to be verified by multi-centered long-term trials. In addition, this mineralocorticoid may increase blood pressure (BP) and we did not measure BP. The results of our trial are restricted to adjunctive therapy with spironolactone, and no conclusion could be drawn regarding spironolactone monotherapy from this study. More importantly, since the study was conducted in participants having both positive and negative symptoms during acute phase of psychosis, one might ask whether only those schizophrenia negative symptoms that were secondary to positive symptoms were decreased or spironolactone improved both primary and secondary negative symptoms. We tried to control for the confounding effects of positive symptoms using the following: a) both trial groups had comparable positive symptoms at the start of the trial, b) we excluded patients with depression and extrapyramidal symptoms, c) we assessed correlation between any decline in negative and positive symptoms and found no significant correlation, demonstrating that effect of spironolactone on negative symptoms was independent of positive symptoms, and d) finally, after eight weeks of treatment (when the positive and secondary negative symptoms were suppressed), patients receiving spironolactone had better negative symptoms, confirming beneficial spironolactone effect on primary negative symptoms of schizophrenia. Nevertheless, the adjuvant nature of our study may have also accentuated generalizability of our results since optimal treatment of negative symptoms, both primary and secondary, is vital because they are correlated with poor outcome and long-term disability. Identification of the most appropriate dose of spironolactone and understanding the main target of spironolactone through functional neuroimaging can be effective in this regard.

**Conclusion**

In summary, negative symptoms of schizophrenia do not respond optimally to current antipsychotics, thus, necessitating presentation of new therapeutic approaches. Preclinical evidence suggests that spironolactone can ameliorate schizophrenic-like behavior. In the present RCT, we assessed the therapeutic effects of adjunctive treatment with spironolactone on negative symptoms of schizophrenia. We demonstrated that adding spironolactone to risperidone leads to significant reduction in PANSS negative, positive and total scores.

**Acknowledgment**

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**Conflict of Interest**

None.
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