Research Article

Naltrexone Augmentation of Risperidone in Treatment of Schizophrenia Symptoms: a Randomized Placebo-Controlled Study

Faezeh Tatari[1], Jalal Shakeri[1], Vahid Farnia[1]*, Amirhossein Hashemian[2], Mohsen Rezaei[3] and Nasrin Abdoli[1]

[1]*Department of Psychiatry, Kermanshah University of Medical Sciences, Iran*
[2]*Department of Health Services, Kermanshah University of Medical Sciences, Iran*
[3]*Student research center, Kermanshah University of Medical Sciences, Iran*

Abstract

Objectives: To investigate the hypothesis that naltrexone augmentation of antipsychotics may show beneficial effects on symptoms of schizophrenia.

Method: Sixty nine participants were randomized to two groups for a 12-weeks trial. Positive and negative symptoms of schizophrenia were assessed with the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS). Subjects received naltrexone100 mg or placebo augmented to risperidone in a double-blind method. All participants were under treatment of risperidone 4mg as a primary antipsychotic treatment.

Results: Patients in both treatment groups showed a reduction in their overall mean SAPS & SANS score at all measurement points compared with baseline scores, but there was significant difference between the 2 groups (p<0.05). Mean SANS score decreased 8.20 and 4.23 in Naltrexone and placebo group respectively after trial course (p<0.05). SAPS score decreased 7.67 and 4.63 in Naltrexone and placebo group respectively after trial course (p<0.05).

Discussion: In this study the augmentation of naltrexone to risperidone showed a significant reduction of schizophrenia symptoms according to SAPS & SANS scores. Further studies to evaluate the efficacy of Naltrexone augmentation to atypical antipsychotic are warranted.

OBJECTIVES

Numerous studies suggest that opiate antagonists may have antipsychotic properties and use of these medications have benefit in controlling psychotic symptoms [1-3]. Few studies reported the hypotheses indicating the role of endogenous opioids in the pathophysiology of schizophrenia. These studies suggested that the naturally occurring endorphins and opiate receptors in the brain may play a role in some of the symptomatology of schizophrenia [4,5] .

One hypothesis suggests that increased endorphin activity contributes to some of the psychotic symptoms seen in schizophrenia and possibly mania [6]. Nevertheless the pathway which the endogenous opiate system contributes to schizophrenia has been difficult to interpret because micro opiate agonists have been reported to both reduce and exacerbate symptoms [7,8].

Naloxone, a medication limited by poor oral bioavailability and short plasma half-life with other routes of administration, was the first opiate antagonist studied as an augmentation strategy for antipsychotic treatment. Promising initial findings suggested potentiation of antipsychotic drug action were not replicated in subsequent trials [9,10]. Naltrexone and nalmefene, two opiate antagonists with better bioavailability when administered orally and with longer plasma half-lives, reported to have controversial results in clinical trials of schizophrenia. Although both of these compounds are antagonists at the micro, delta, and kappa opiate

receptor subtypes, they have the highest affinity for the micro receptor.

Early studies attempting to use naltrexone to treat schizophrenia suggested that it was ineffective as sole treatment and not clearly better than placebo as an adjunct [11,12]. Also [13] conducted a trial which patients were randomized to receive either placebo or naltrexone 200 mg/day for three weeks in addition to their antipsychotic. The study failed to indicate a clinical benefit when naltrexone was added to the antipsychotic regimen. In contrast one four weeks randomized clinical trial reported that patients whom received naltrexone 100 mg/day in addition to their antipsychotic showed more improvement in their negative symptoms of schizophrenia [14]. They concluded that augmentation of antipsychotic was effective in treating negative symptoms of schizophrenia.

In contrast, using a crossover design in 11 patients, [1] found that nalmefene, at a mean dosage of 79 mg/day for an average of 37 days, reduced positive, but not negative, symptoms. In these studies, opiate antagonists were well tolerated by patients with schizophrenia. Almost all of the previous mentioned studies had small sample size and/or short period treatment trial to assess the efficacy of opioid antagonists in treatment of schizophrenia symptoms.

We hypothesized that opioid antagonists augmentation of the antipsychotic may show positive effects on symptoms of schizophrenia. We designed a 12-week double-blind randomized controlled trial assessing the efficacy of naltrexone augmentation to the antipsychotic for the treatment of positive and negative symptoms of schizophrenia.

METHODS

Participants

Written and signed informed consent which was approved by the local ethics committee was obtained from the participants. Participation in the study was voluntary and confidential. No remuneration was provided for participation. The study was registered with the Iranian Clinical Trials Registry (IRCT201110093010N4; www.irct.ir) and was conducted between February 2011 and September 2012. The participants who met criteria for schizophrenia according diagnostic and statistical manual of mental disorders, 4th edition, totally revised (DSM-IV-TR) with the help of a psychiatrist were recruited through admitting in Farabi Mental Hospital.

Eligible participants were patients who fulfilled DSM-IV criteria for schizophrenia, were 18–55 years, and in good physical health as determined by medical history, electrocardiogram, and vital signs. Psychiatric exclusion criteria included unstable psychotic symptoms or serious current psychiatric symptoms (suicidal or homicidal ideation), co-morbid symptoms of psychiatric disorders, including mood disorders, anxiety disorders, personality disorders, and other psychotic disorders. Medical problems that would contraindicate the use of naltrexone, including liver function tests over three times the normal level, using any substance other than nicotine especially opioids, also

were in our exclusion criteria. Additional exclusions were current treatment with stimulants, and, in the case of women, pregnancy, breast feeding, and unwillingness to use an adequate method of birth control.

Treatments

Patients who met all inclusion criteria were enrolled in the study and randomly assigned to naltrexone100 mg or placebo once daily at bedtime. All patients were under treatment with risperidone 4mg daily during trial. Assignment to treatment groups was determined by a computer-generated random sequence. Patient numbers were assigned at the first visit, and they were randomly allocated to double-blind treatment at the second visit. During the study neither the patients nor the psychiatrist (responsible for making diagnoses) knew about the type of medication administered in each groups. Patients were under inpatient treatment for first four weeks and then followed as outpatient treatment during trial.

Assessments

108 subjects with schizophrenia were evaluated for inclusion. After providing written informed consent, subjects completed an intake assessment, which included a physical examination, laboratory assessments, and an interview with a psychiatrist. Laboratory screening tests included complete cell blood count, fasting blood sugar, electrolytes, urine opium test, liver function test, and renal function test. Electrocardiography was also performed. Following completion of these baseline assessments, 69 subjects were randomized to two groups for a 12-week trial. Finally 60 participants (33 males and 27 females) who completed the study were analyzed. (Figure 1) Positive and negative symptoms of schizophrenia were assessed with the Scale for Assessment of Negative Symptoms (SANS) [15] and the Scale for Assessment of Positive Symptoms (SAPS) [16] and were administered by the research staff at the baseline and end of the trial course. The SANS is a rating scale to measure negative symptoms in schizophrenia and is split into 5 domains, and within each domain separate symptoms are rated include affective flattening, poverty of speech, apathy, anhedonia and inattention consists of 30 items each scored from 0 (absent) to 5 (severe). The scale is closely linked to the SAPS which is a rating scale to measure positive symptoms in schizophrenia. SAPS is split into 4 domains include hallucinations, delusions, bizarre behavior and thought disorder, and within each domain separate symptoms are rated from 0 (absent) to 5 (severe). Side effects were evaluated by the research staff using interview and physical exam during treatment course.

Data analysis

Statistical analyses were executed using SPSS-16 software. The primary outcomes of interest were changes in the SANS and SAPS scores between baseline and completion of the trial. In order to assess treatment response, overall mean scores on the two scales were compared between these two time points using paired sample t-tests. Mean differences between the two groups were compared using independent sample t-tests. Results were considered significant if the P-value was less than 0.05.
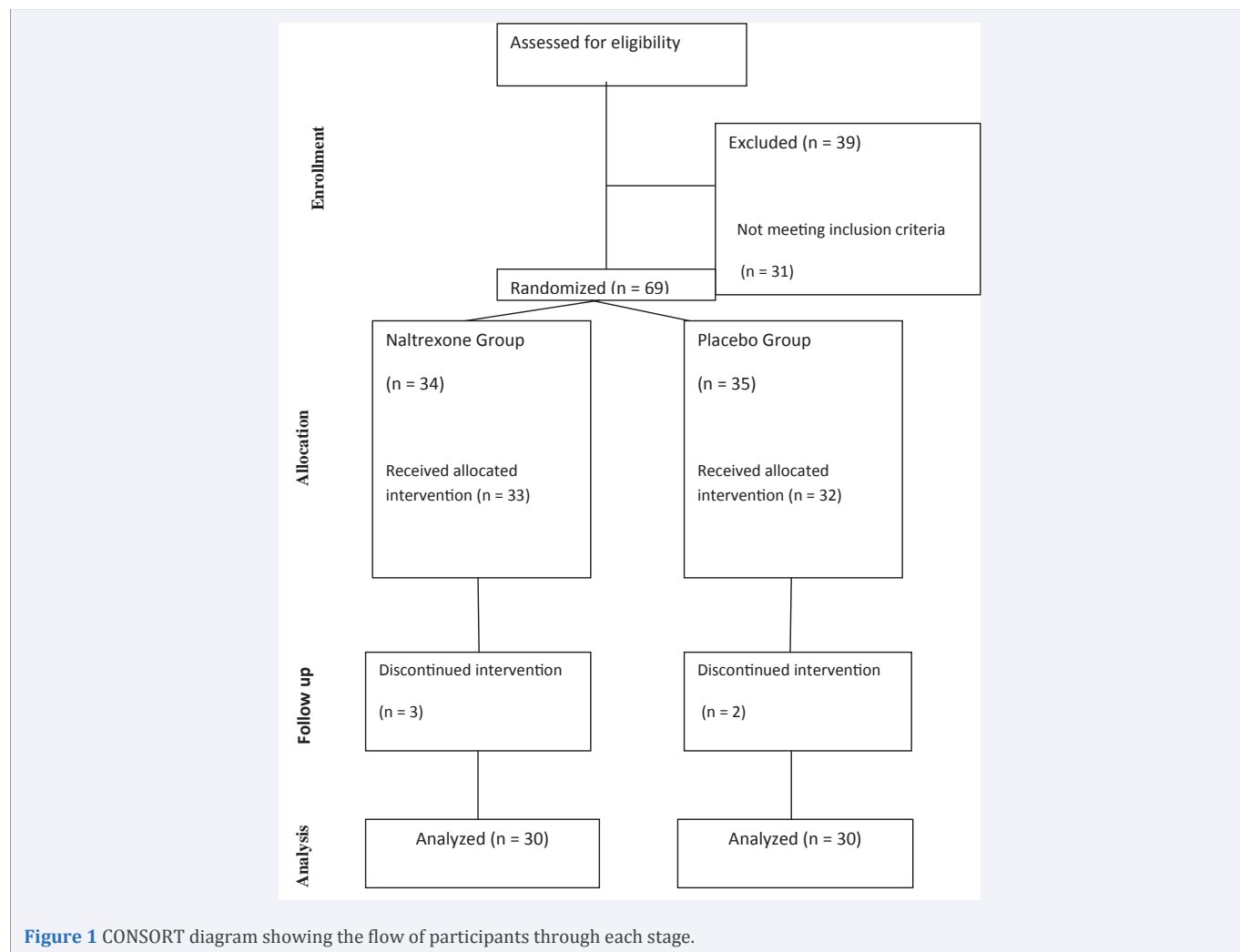
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Email: vfarnia@kums.ac.ir

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Figure 1 CONSORT diagram showing the flow of participants through each stage.

RESULTS

Baseline characteristics

108 patients were assessed for eligibility. Of these, 31 subjects did not meet inclusion criteria and a further 8 declined study participation. The remaining 69 patients were randomly assigned to either naltrexone or placebo, but 9 of these were not included in the final analysis because they refused to complete the study after randomization. (Figure 1) These left 30 participants (14 female and 16 male) in the naltrexone and 30(13 female and 17 male) in the placebo group. The mean age was 41.97 and 39.37 year in naltrexone and placebo groups respectively. Mean duration of illness was 8.4 and 7.1 years in naltrexone and placebo groups respectively. The baseline data including SAPS and SANS scores are summarized in (Table 1). Independent sample t-test revealed no differences between two groups with respect to mean age, mean duration of illness, and SAPS or SANS scores at baseline (p-value> 0.05).

Treatment response

The participants were assessed using SAPS and SANS before initiation of trial course and after 12 weeks treatment. Mean change from baseline score was used to consider treatment response in the two groups. The paired sample t-tests indicated SAPS and SANS scores were significantly lower by completion of the treatment in both groups (p-value<.001).

Although both treatment groups showed a reduction in their overall mean SAPS and SANS scores at final measurement point compared with baseline scores, there was a significant difference between the two groups. Mean SAPS score decreases in the naltrexone and placebo groups were respectively 7.67 and 4.63 by the end of the trial (p-value= 0.03; see (Table 2).

The SANS score also decreased in the two groups by completion of the treatment but more in the naltrexone group. Mean SANS score decreases in the naltrexone and placebo groups were 8.20 and 4.23 respectively and the difference was statistically significant (p-value=0.02; see (Table 2).

Results of SANS and SAPS scores in two groups summarized in table 2.

Subgroup analysis revealed no statistically significance differences in response to treatment between men and women in both groups (p-value>0.05). Regarding safety data, no major side effects were observed in either treatment group. Two patients in Naltrexone group reported transient nausea, and three reported some somnolence but no one discontinued the treatment.

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Table 1: Baseline Data* Independent sample t-test was performed to assess statistically significant differences**.**

Variables	Naltrexone group (mean± SD)	Placebo group (mean± SD)	p-value
Mean duration of illness(year)	8.4±5.7	7.1±6.1	0.19
Mean age(year)	41.9±9.5	39.3±8.9	0.11
Mean hallucination score	4.5±3.7	5.1±3.2	0.32
Mean delusion score	6.4±3.0	7.2±3.9	0.24
Mean bizarre behavior score	8.7±4.5	9.4±4.1	0.43
	9.1±3.3	10.3±4.6	0.29
Mean SAPS score	31.0±5.4	33.6±7.9	0.12
Mean affective flattening score	5.1±3.3	6.0±3.4	0.37
Mean poverty of speech score	4.1±3.0	3.7±2.9	0.14
Mean apathy score	4.0±3.7	5.4±2.7	0.33
Mean anhedonia score	6.7±3.6	6.0±2.8	0.24
Mean inattentiveness score	5.4±2.2	6.6±2.3	0.11
Mean SANS score	29.8±8.6	26.1±6.7	0.09

Table 2: SAPS & SANS mean score reduction in naltrexone and placebo augmentation to risperidone groups.

VARIABLES	Naltrexone (mean± SD)	Placebo (mean± SD)	P-value
Hallucination	3.0±0.7	1.3±0.2	0.01
Delusion	2.6±0.5	1.4±0.3	0.04
Bizarre Behavior	1.2±0.2	0.8±0.1	0.03
Thought Disorder	3.1±0.8	2.3±0.4	0.04
SAPS	7.6±1.3	4.6±0.9	0.03
Affective Flattening	1.4± 0.4	0.8±0.1	0.03
Poverty of Speech	2.9±0.5	1.4±0.2	0.02
Apathy	1.9±0.3	0.6±0.1	0.01
Anhedonia	2.3±0.5	1.0±0.2	0.02
Inattentiveness	2.1±0.2	1.7±0.3	0.05
SANS	8.2±1.4	4.2±1.1	0.02

* Independent sample t-test was performed to assess statistically significant differences

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