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Effects of Bupropion on Cognitive Function in Schizophrenia: A Double Blind Randomized Controlled Trial

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Abstract

Smoking habits are common in schizophrenic patients. Nicotine can suppress negative symptoms and cognitive impairments. The aim of this study was to determine the efficacy of bupropion on cognitive function in schizophrenic patients. This study is a double blind randomized controlled trial in a large referral psychiatric university hospital in Iran. Ninety smoker schizophrenic patients were randomly allocated (based on DSM -IV TR criteria) in two groups (46 patients for case group and 44 patients in control group). They get risperidone up to 6 mg/d and bupropion up to 400 mg/d .clinical assessment (Positive and Negative Syndrome Scale (PANSS), Brief psychiatric rating scale (BPRS) were taken in beginning of study, 14th and 28th days of study. Cognitive assessment (Stroop, Digit Span, and Wechsler, Wisconsin) were taken in begging of study, the days 2nd, 7th, 14th, 28th. All data were analyzed by SPSS Ver. 17 with analytic and descriptive tests. Mean age of patients was 37.66±1.01. Mean duration of disorder was 11.63±.98 years. The scores were significantly lower at the day 28th compared to the beginning of the study in both groups in Wechsler, Stroop color word , Stroop word , Stroop color , BPRS, PANSS p value ≤0.05 .The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor **p** value ≥0.05. In this study, the side effects were examined and there was no significant difference between the two groups p value ≥0.05. Augmentation of bupropion to routine treatment improves cognitive symptoms of schizophrenia in abstinence of tobacco.

Keywords: schizophrenia, smoking cessation, bupropion, cognitive functions

1. Introduction

Smoking among patients with schizophrenia is much higher than in the general population and in other psychiatric patients (de Leon & Diaz, 2005). In the US, more than 80% of schizophrenic patients smoke compared to approximately 20% of the general population (Keltner & Grant, 2006). It has been suggested that nicotine enhances cognitive function indicating that smoking may improve neurocognitive dysfunction inherent in schizophrenia (Vernon et al., 2014). High cigarette consumption also causes heart disease, respiratory diseases, lung cancer and high blood pressure (Evins, Cather, et al., 2005). This is even more important among the schizophrenic population as negative long-term metabolic effects of antipsychotic medications which are also a concern (Beary, Hodgson, & Wildgust, 2012). Smoking behavior in schizophrenia has been suggested to include psychopathological, biochemical, and neuropharmacological processes (Dervaux & Laqueille, 2008; Freedman et al., 2003; McCloughen, 2003; Winterer, 2010). Agonists of nicotinic alpha-7 receptors have shown positive effects on neurophysiological and neurocognitive deficits associated with schizophrenia (Harris et al., 2004; Olincy et al.,

2006). Cognitive dysfunction is responsible for significant psychosocial disability in schizophrenia. (Cullum et al., 1993).

1.1 Smoking Cessation

Smoking cessation is a challenge in general population with 23% of high relapse rate. This is even more difficult in patients with schizophrenia where the smoking relapse rate is as high as 75% to 85%. (Evins, Cather, et al., 2005).

Bupropion is an antidepressant with both dopaminergic and adrenergic actions. It is a FDA approved anti-craving medication for smoking cessation and may benefit psychiatric groups such as what which is under consideration (Susanne Englisch, Morgen, Meyer-Lindenberg, & Zink, 2013; D. T.-y. Tsoi, M. Porwal, & A. C. Webster, 2010; D. T. Tsoi, M. Porwal, & A. C. Webster, 2010; Weinberger et al., 2009; Weiner et al., 2012).

Bupropion has also been found to enhance cognitive performance in healthy individuals as well as in those with major depressive disorder, dementia, and attention deficit/hyperactivity disorder (ADHD). Patients, treated with this medication, have also shown improvement in visual memory measures, mental processing speed, symptoms of sleepiness, fatigue, and executive dysfunction- all these areas are negatively influenced by the schizophrenic illness (Bragin et al., 2005; Gobbi, Slater, Boucher, Debonnel, & Blier, 2003; Herrera-Guzmán et al., 2008; Stahl, Zhang, Damatarca, & Grady, 2003). Weiner and colleagues (71, 74) were the first to investigate cognitive function among a pilot sample of nine smoker schizophrenic patients. Despite reduced nicotinergic stimulation as a result of a restrained use of tobacco products, cognitive performance tested in all subdomains remained stable during bupropion treatment (Weiner et al., 2012).

The objective of this study was to assess the effects of bupropion on cognitive function in smoker schizophrenic patients.

2. Methods

2.1 Study Design

This study was an inpatient double blind, 4-weeks clinical trial. The research was conducted in a large referral psychiatric university hospital in Iran, and was approved by the research review board of the Mashhad University of Medical Sciences (MUMS).

2.2 Participants

Patients were recruited based on DSM-IV-TR criteria and based on a semi-structured interview, performed by an expert psychiatrist. Criteria included here were: a DSM-IV-TR diagnosis of schizophrenia, smoking at least 10 cigarettes a day, patients' agreement on examining them or their legal guardian, absence of a major depressive, manic, or hypomanic episode, and absence of a seizure disorder. Patients accepted to take bupropion add on routine treatment including participate in the study. Of 136 patients eligible for screening, 93 patients met the inclusion and exclusion criteria and agreed on being examined for the research (Evins, Deckersbach, et al., 2005).

The study was done in accordance with the Declaration of Helsinki and subsequent revisions (World Medical Association. Declaration of Helsinki, 2000) and was approved by the ethics committee of Mashhad University of Medical Sciences. Written informed consent was obtained from the participants or their legal guardian before entering the study.

2.3 Intervention

Patients were randomly assigned to two groups by using table random numbers and treated by a psychiatrist blind to the group assignments and also patient were blind to study . They were started taking 2mg of risperidone daily. Dosage was prescribed up to 6 mg/d based on the symptoms response and side effects. All patients stopped smoking at the beginning of the treatment. Forty seven (n=47) patients in the study group were started on bupropion 100mg/per day. Forty six (n=46) patients assigned to the placebo group received a similar placebo tablet daily. On the second week, bupropion dosage was increased to 200mg (two tablets) a day, and placebo was increased to 2 tablets.

2.4 Neuropsychological Testing and Rating Scales

The present research aims to examine the effects of bupropion on cognitive and clinical symptoms. Cognitive Rating scales were administered at baseline, 14, and 28 days by a psychologist. Cognitive and executive functioning were assessed by Wechsler Memory Scale (Third Edition Spatial Span, WMS-III SST) to evaluate attention span and working memory (dependent variable: digit forward and backward) (Wechsler, 2008), Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and Stroop Color and Word Test (Buchanan, Holstein, & Breier, 1994) for checking probable effects of bupropion on psychotic symptom of

schizophrenia (Buchanan, Holstein, & Breier, 1994). Symptoms severity was assessed by the Positive and Negative Symptoms Scale (PANSS) (Kay, Flszbein, & Opfer, 1987) and by Brief Psychiatric Rating Scale (BPRS) at baseline, 14 and 28 days (Kay et al., 1987) as a secondry outcome . Safety evaluations included physical examinations, electrocardiography, vital signs check, and adverse drug reactions. All test used as the primary outcome measure

2.5 Statistical Analysis

All analyses were conducted using the SPSS software version 17.0. Threshold for statistical significance was set at P=0.05. Data analysis was based on the intent-to-treat, including all recruited patients with at least one follow-up assessment. Using the Student's t-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, between-group comparisons of demographic and clinical characteristics at baseline were performed. The χ^2 test or Fisher's exact test was used to compare between-group differences in adverse events.

3. Result

Ninety-three patients were randomized to the trial. Patients of both groups (Bupropion vs. Placebo) were statistically identical according to basic demographic data, including age and gender (Figure 1). Nineteen patients completed the trial and three patients refused participation (Two of them because of early discharge and one patient because of immigration).

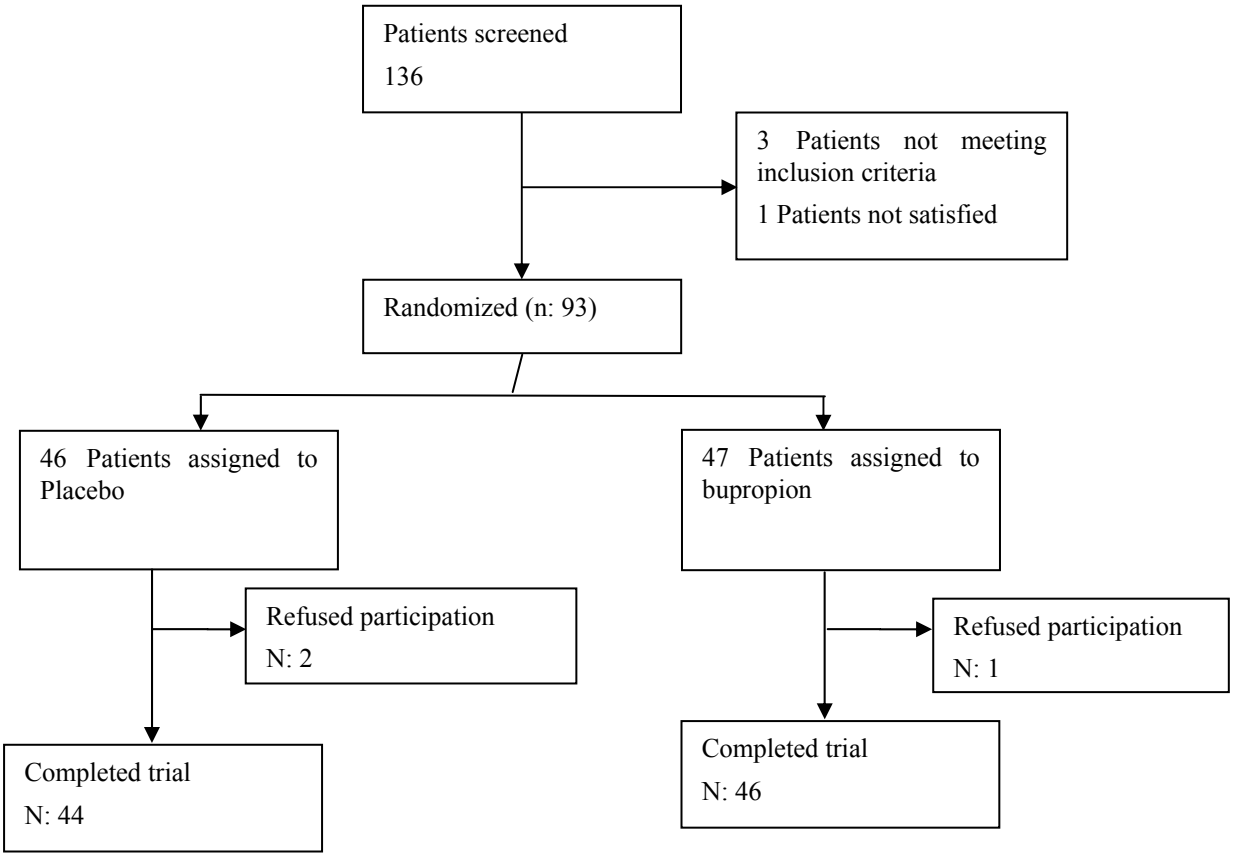

Figure 1. CONSORT diagram showing the disposition of all subjects screened for the study

Demographic data of the 90 participants are shown in table 1. There was no difference in the level of education between the two groups (P=0.92). There was also no difference in baseline of Wechsler (P=0.51), PANSS (P=0.12), Digit Span (P=0.62) BPRS (P=0.72), Wisconsin Card Sorting (P=0.31) scores. The average number of cigarettes smoked daily was 15.10 (SD = 7.1) in case group and 16.02 (SD = 8.0) in control group.

Table 1. Characteristics of the patients

Variable	Bupropion group	Control group	P
Age	36.94±8.17	38.36±11.00	0.49
Length of illness (years)	11.02± 7.26	12.20± 8.45	0.82
Smoking duration (years)	13.87 ±7.32	14.37 ±9.54	0.29
# Cigarettes smoked daily	15.10± 7.04	16.02± 8.00	0.29

3.1 Cognitive Assessment

The average Digit span baseline was 9.08 score (SD: 6.06) in patients and 10.56 score (SD: 7.54) in the control group. The baseline scores were not significantly different t(88):-0.35 ,p:0.72. No statistical difference was found between the two groups at day 7 t(88):-1.29 ,p:2.00 , day 14 t(88):-0.93 ,p:0.35 , and end of the study day 28 t(57):-0.50, p:0.61.

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (df: 1, F: 0.3, P: 0.57)

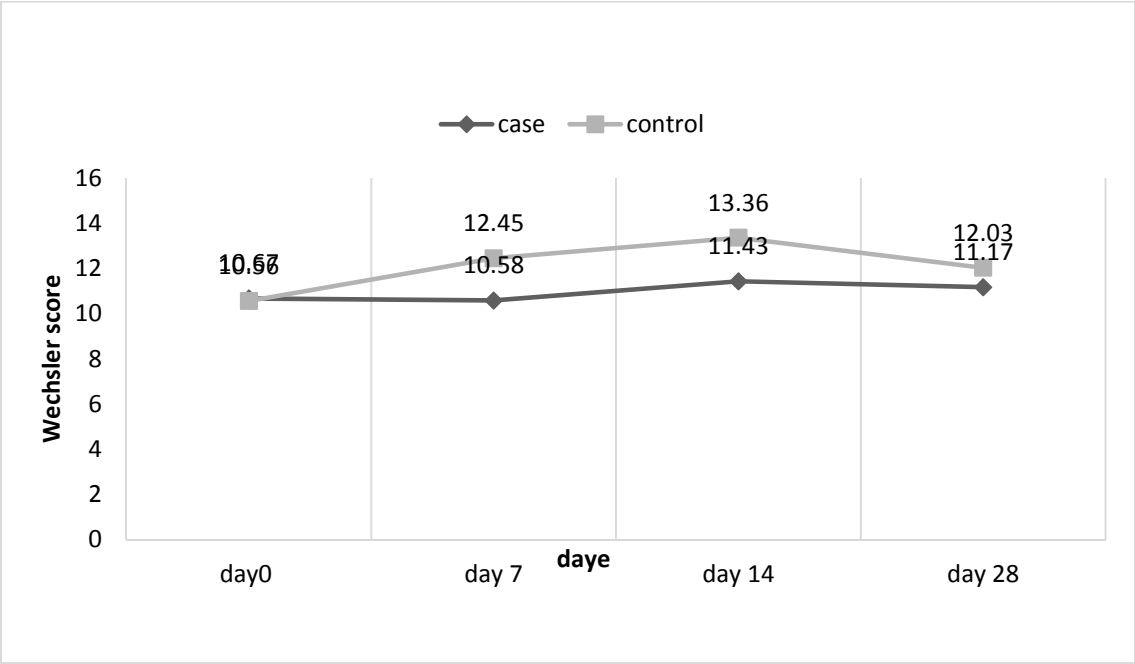

Figure 2. Changes in the digit span scores in both groups during the study

The average Wechsler baseline was 59.67 score (SD: 15.94) in the case and 60.18 score (SD: 19.27) in the control group. The baseline scores were not significantly different t (88):-0.13, p: 0.99. They were not also different between the two groups at day 2 t(88):-0.42 ,p:0.67 , day 7 t(88):--1.26 ,p:0.21 , day 14 t(57):-0.88 ,p:0.37 , day 28 t(55):-1.81 ,p:0.07. This score was significantly lower in the day 28 compared to the beginning of the study in both groups (case: p value ≤ 0.001 and control p value: 0.006)

The difference of score between first and end of study case: $p < .001$, control: $p < .006$

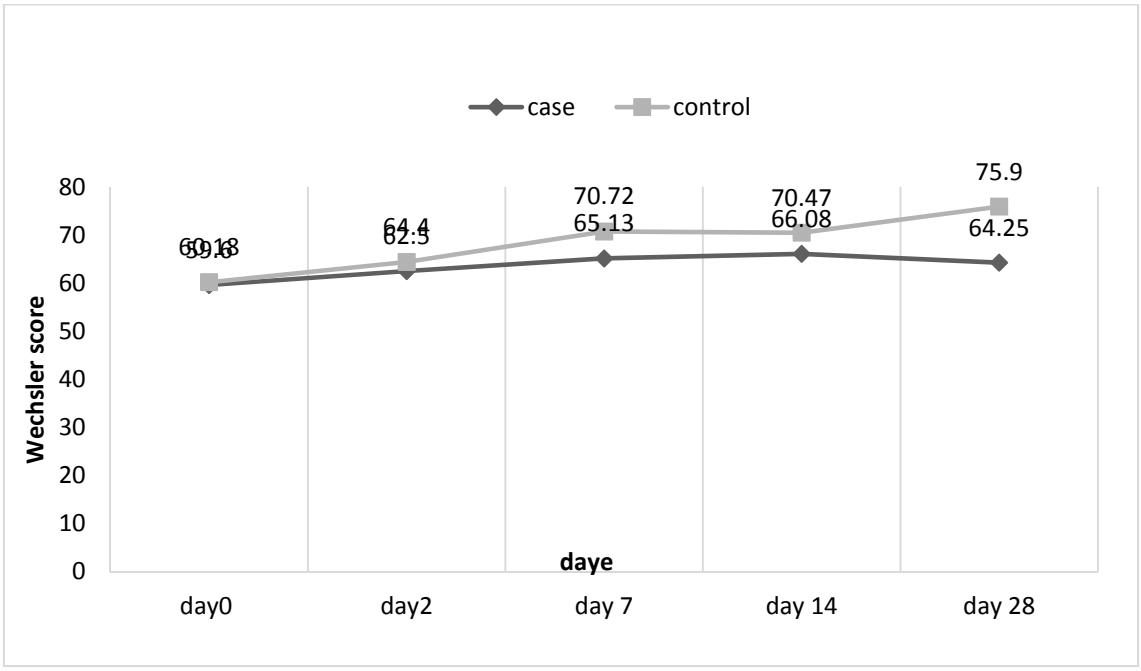

Figure 3. Changes in Wechsler scores in both groups

The average Stroop Color Word baseline was 15.67 score (SD: 9.35) in the case (patient) and 16.38 score (SD: 9.43) in the control group. The baseline scores were not significantly different t (88):-0.36, p: 0.72. They were not also different between the two groups at day 2 t(88): 0.36 ,p:0.71 , day 7 t(88):0.45 ,p:0.65 , day 14 t(88):1.42 ,p:0.15 , day 28 t(58):0.22 ,p:0.82. This score was significantly lower in the day 28 compared to the beginning of the study in both groups (case: p value: 0.003and control p value: 0.03)

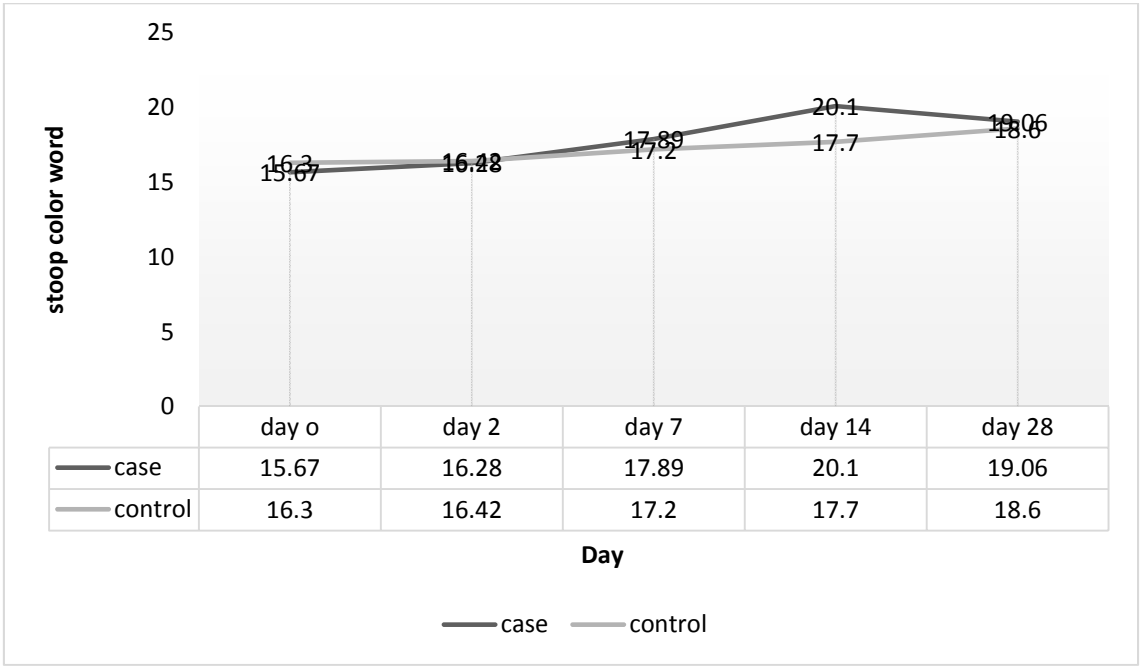

Figure 4. Changes in Stroop Color Word Test scores in both groups

The average Stroop word baseline was 15.67 score (SD: 9.99) in the case (patient) and 16.29 score (SD: 9.37) in the control group. The baseline scores were not significantly different baseline t(88):-0.30 ,p:0.76. They were not

also different between the two groups in the day 2 t(87): 0.41 ,p:0.67 , day 7 t(88):0.44 ,p:0.65 , day 14 t(88):1.30 ,p:0.19 , day 28 t(58):0.01 ,p:0.98. This score also was significantly lower in the day 28 compared to the beginning of the study in both groups (case: p value ≤ 0.01and control p value: 0.06)

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor df: 1, F: 0.001, P: 0.985)

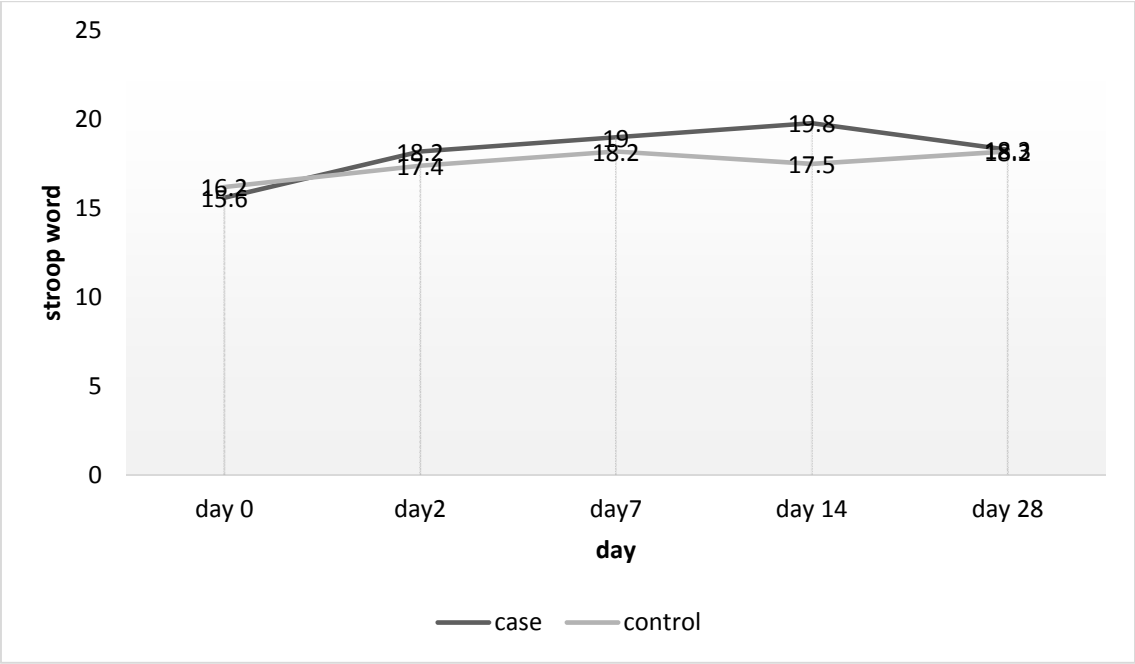

Figure 5. Changes in Stroop Word Test

The average Stroop Color baseline was 10.28 score (SD: 8.60) in the case (patient) and 9.45 score (SD: 8.75) in the control group. The baseline scores were not significantly different t(88): 0.45 and p: 0.65 respectively. There were also no significant difference between the two groups in the day 2 t(88): 0.36, p:0.71, day 7 t(88): 0.45, p: 0.65, day 14 t(88): 1.42 ,p:0.15 , and day 28 t(58): 0.22 ,p:0.82. This score was significantly lower in the day 28 compared to the beginning of the study in both groups (case: p value: 0. 01 and control p value: 0.001)

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor df: 1, F: 0.01, P: 0.9).

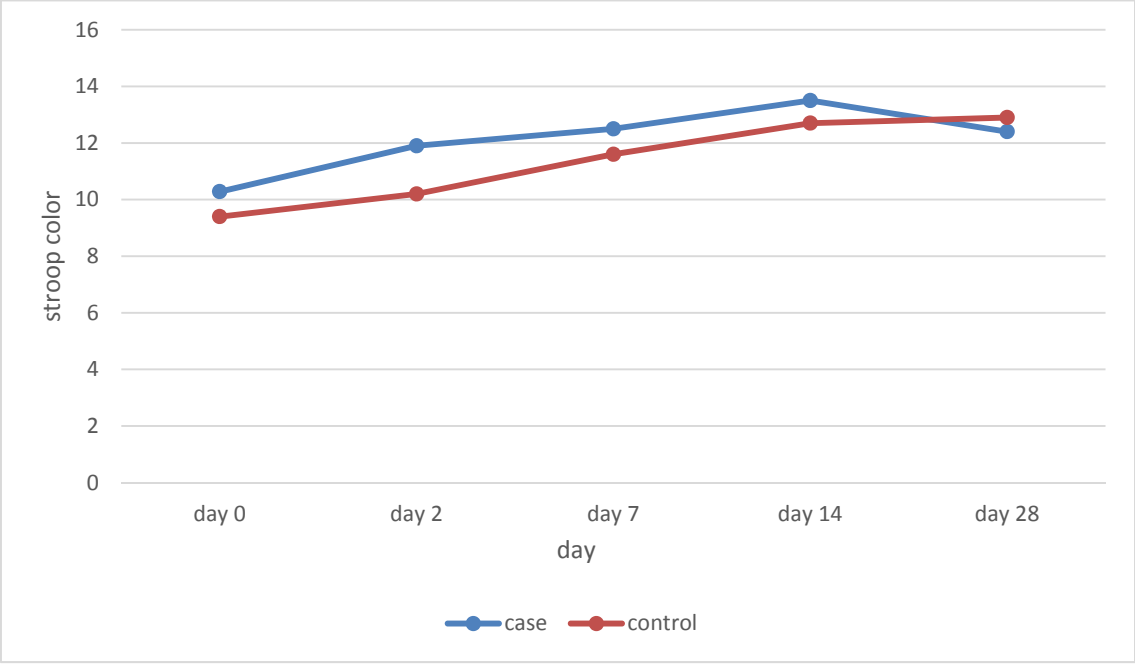

Figure 7. Changes in Stroop Color Test

The average Wisconsin baseline scores were 16.28 (SD: 4.5) in the case (patient) and 16.42 (SD: 4.15) in the control group. The baseline scores were not significantly different t(77): -0.14, p: 0.88. They were not also different between the two groups in the day 2 t(80): -0.47, p: 0.63, day 7 t(82): -0.80, p: 0.42, day 14 t(83): 0.82, p: 0.40 , day 28 t(56): 0.38, p: 0.70.

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (df: 1, F: 1.5, P: 0.22)

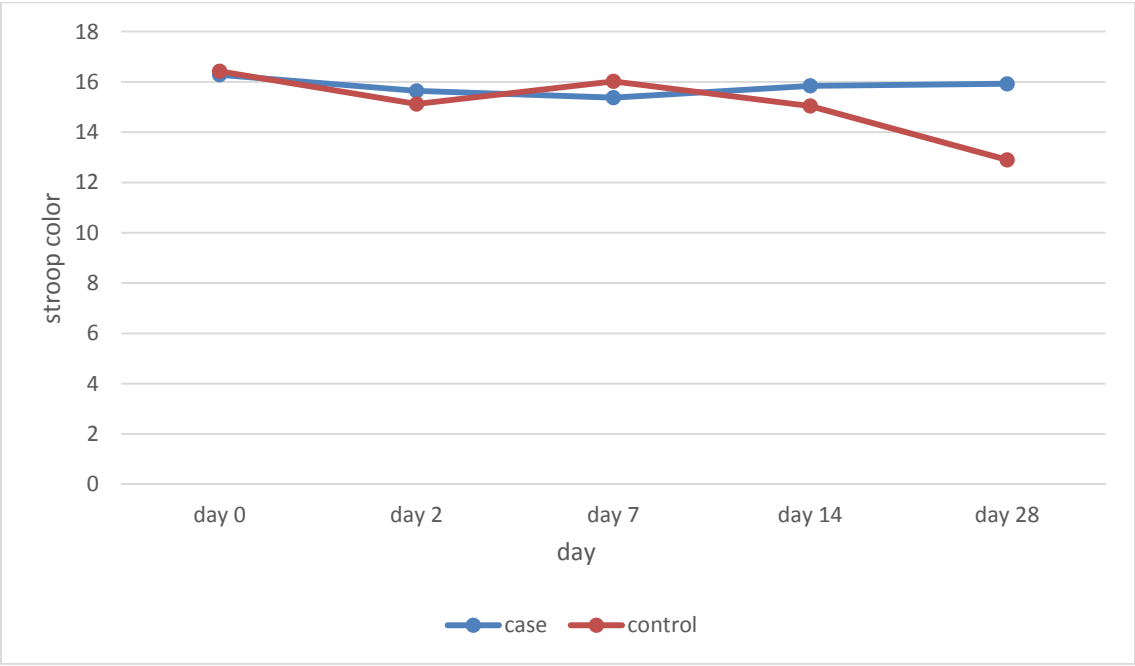

Figure 8. Changes in Wisconsin Test

3.2 Clinical Assessment

The average PANSS baseline scores were 68.78 (SD: 8.53) in the case (patient) and 70.20 (SD: 10.31) in the control group. The baseline scores were not significantly different t (88): -0.71, p: 0.47. They were not also different between the two groups in second week t (88): -0.40, p: 0.69. At the end of the study, there was no statistically significant difference between the two groups (day 28) t(58): 0.68 ,p:0.49

This score also was significantly lower in the day 28 compared to the beginning of the study in both groups (case: p value 0.002 and control p value ≤ 0.001).

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (df: 1, F: 0.79, P: 0.65)

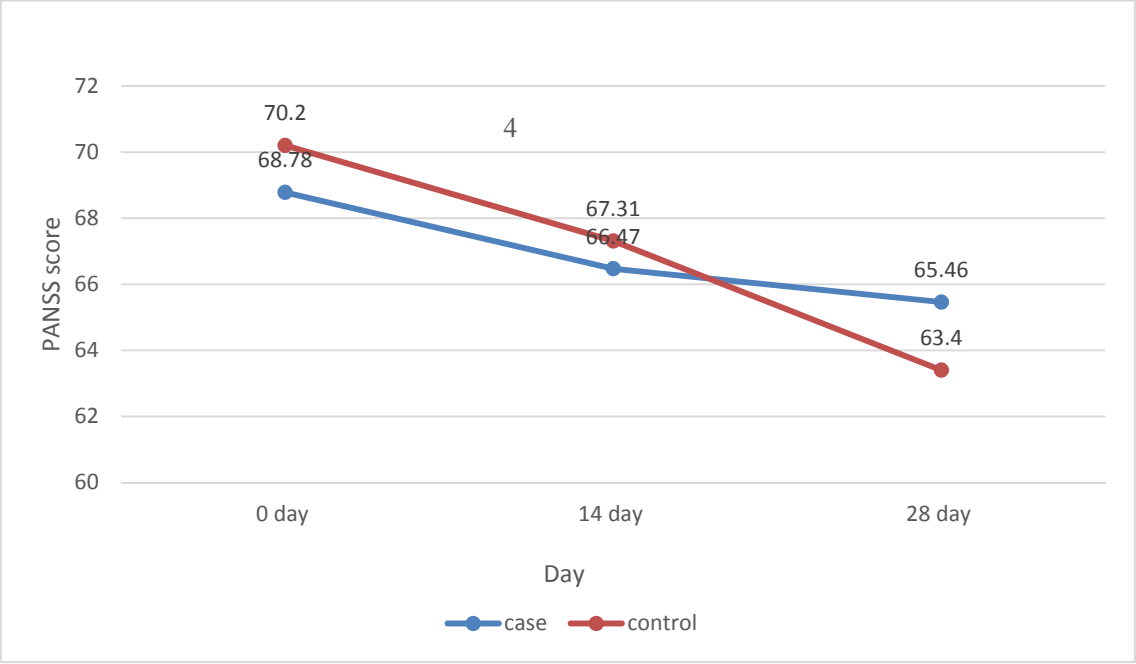

Figure 9. Changes in the PANSS scores in both groups during the study

The average BPRS baseline scores were 73.43 (SD: 8.68) in the case (patient) and 74.50 (SD: 10.73) in the control group. The baseline scores were not significantly different t (88):-0.51, p: 0.60. They were not also different between the two groups in second week t (88):-0.37, p: 0.97. They were not also different between the two groups at the end of the study (day 28) t (58):0.85, p: 0.39. Likewise, this score was significantly lower at day 28 compared to the beginning of the study in both groups (case: p value ≤ 0.001and control p value ≤ 0.001)

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (df: 1, F: 0.127, P: 0.72).

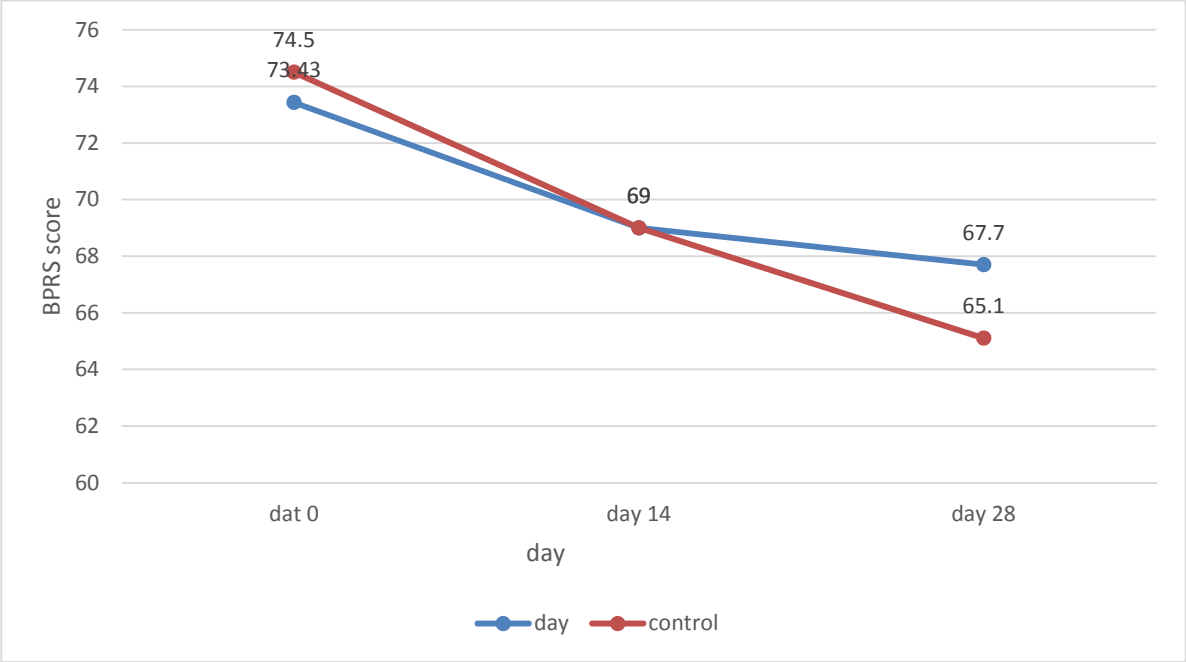

Figure 10. Changes in the BPRS scores in both groups

The average score of Negative PANSS was 30.3 (SD: 3.99) in case group and 29.37 (SD: 4.73) in control group. During the study, positive and Negative PANSS have been reduced; the values are lowered in the control group, though. This scores were not significantly different in both group

3.3 Clinical Complications and Side Effects

In this study, the Bupropion was well tolerated and there weren't any serious physical side effect in any group. In addition, there were no side effects needed treatment in the two groups.

4. Discussion

The present study examines the effects of bupropion on cognitive and clinical symptoms in patient with schizophrenia and nicotine consumption. The number of cigarettes smoked daily was between 14-16, which is less than the previous reports in which 45% of patients smoke more than 20 cigarette a day (McCreadie, 2003).

Considering both the Digit Span Test and Stroop Test in the research group, comparing inter group from the beginning to the end shows no significant changes. This is similar to the results obtained through Evins et al.'s study. In the research done by Evins et al, test on functional memory (Digit Span) or action-inhibition performance (Stroop Test) did not worsen. Bupropion therapy may be associated with an improvement in attention (Evins, Cather, et al., 2005).

In cross-sectional comparison of the Wisconsin Test, there was no change in case (patient) and control group from the beginning toward the end of the research. This is consistent with Evins et al.'s study in which any statistically significant difference was not observed (Evins et al., 2007; Evins, Deckersbach, et al., 2005).

Using Wechsler Test for the cross-sectional evaluation, the score was significantly lower in the day 28 compared to the beginning of the study in both groups. It means that Bupropion, in general, improves the memory of the patient during treatment. Also this may result from other factors such as an improvement in clinical symptoms, or the practice effects due to serial cognitive assessments

Through cross-sectional comparison, neither the case (patient) nor the control groups varied at any time in terms of positive and negative symptoms as well as psycho-pathological symptoms. Total changes in both case and control groups were studied and compared by PANSS, BPRS Tests; and there was statistically no significant difference. This was similar to the research performed by Evins and his colleagues; applying this test, they also used PANSS Test to examine the relationship between smoking cessation and cognitive symptoms in schizophrenic patients. The results of the mentioned tests performed in both groups did not suggest significant differences statistically. In Evins et al.'s study, mean PANSS scores were 8.60 for the case group and 4.56 for control group (Evins, Deckersbach, et al., 2005).

Research on both groups showed that Bupropion increases the rate of smoking cessation during treatment and 6 months after treatment. However, it does not worsen the mental status (Positive and Negative symptoms) (Dervaux & Laqueille, 2007; D. T. Tsoi et al., 2010). Likewise, experiencing another investigation conducted by Evins et al, the patients who were taking Bupropion did not clinically deteriorate; in contrary, they showed improvement in terms of negative symptoms and depression (Evins, Cather, et al., 2005). The present study does not demonstrate any change in negative symptoms, yet some improvements were also found in positive and general symptoms.

In addition, according to the present study, Bupropion postpones the progress of negative symptoms after the second week. It worth mentioning that there are few studies similar to the present one that deal with the patients' cognitive performance; and most researches have focused on the effects of Bupropion on schizophrenic patients who are quitting smoking cigarette.

This study indicates that Bupropion does not worsen the psychotic symptoms. However, it suggests that the negative symptoms, while remaining rather constant, demonstrate a gradual improvement after 14 days. On the other hand, the other memory tests as well as the cognitive tests showed improvement after Bupropion was taken.

Wisconsin test (examining cognitive performance) suggests considerable improvement after the first week of the study.

The Wechsler Memory Test showed improvement in the control and case group. Regarding the comparison throughout the research, changes in memory got better in case/study group at the end of research.

It seems that Bupropion can be helpful in improving cognitive disorder without worsening the clinical symptoms; in fact, cognitive effects of smoking cessation is challenging for the patien. Therefore, if Bupropion is taken, it is better to continue this medication for more than two weeks.

Reported bupropion effects on negative symptoms are less consistent but both cases reports show progress in both affective and negative symptoms (S Englisch, Esser, & Zink, 2010; Susanne Englisch, Inta, Eer, & Zink, 2010). Other studies revealed a tendency toward improvement of negative symptoms in response to Bupropion treatment (Susanne Englisch et al., 2010; Evins, Cather, et al., 2005; Weiner et al., 2012; Weiner, Ball, Summerfelt, Gold, & Buchanan, 2001).

Limitations'

There are a few issues to consider in this review. The sample size is one of the limitations of the study. So, the results of this review may also not apply to all the people with schizophrenia; in Iran most of smoker in hospital were men so the study was conducted on men who are not generalizable. This research was performed in patients group and results may vary in outpatient group.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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