A placebo-controlled trial of bupropion for improving the positive and negative symptoms of schizophrenia

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ABSTRACT

Background: Recently, researches have expressed renewed interest in therapeutic effects of bupropion on the positive and negative symptoms in schizophrenics.

Aim & Objective: In current study, was designed a 12-week double-blind, parallel-groups to examine the comparative efficacy of bupropion compared to placebo for improving the positive and negative symptoms of schizophrenia.

Methods/Study Design: Eligible participants were 40 patients who met DSM-IV criteria for schizophrenia and were randomly assigned to the standard therapeutic dose of bupropion (150 mg/day for the first 3 days, followed by 300 mg/day) administered orally for a total of 8 weeks (n=20) or an identical appearing placebo tablet added to their usual medication regimen (n=20). The study endpoints were the scales of positive and negative symptoms of schizophrenia by the two scales for the assessment of positive symptoms (SAPS) and negative symptoms (SANS).

Results/Finding: : After the completion of treatment schedules, both groups demonstrated similar significant improvements in all positive symptoms, adjusted for baseline variables. However, it appeared that the avolition-apathy score of negative symptoms was reduced more in the group treated with bupropion compared to the placebo group.

Conclusion: Bupropion has potential efficacy for avolition-apathy as main negative symptoms in schizophrenics who were able to tolerate bupropion and complete 12-week bupropion treatment regimen. However, no change in positive symptoms may be essentially appeared.

Keywords: placebo, bupropion, positive symptoms negative symptoms, schizophrenia,

Introduction:

Schizophrenia is a debilitating psychiatric disorder that consists of severe disturbances in thoughts, cognitions, mood, perceptions, and relationships with others[1]. The hallmark symptoms of schizophrenia are mainly classified as positive symptoms including delusions, paranoia, hallucinations and disorganized thoughts and also negative symptoms including poor motivation, lack of emotional expression, and inability to form appropriate social relationships[2].

Several randomized and controlled trials revealed the efficacy of some classic and conventional antipsychotic agents such as second-generation antipsychotics and adjunctive agents for improving the positive and negative symptoms in treatment-refractory inpatients with schizophrenia[3-7]. However, some others could demonstrate that the current available treatment protocols appear to have modest benefits[8]. Because of the notable limitations of routine antipsychotics in treatment responsiveness, the use of other medications targeting positive and negative symptoms besides or in conjunction with antipsychotic agents is expected.

In the recent decade, researchers have expressed renewed interest in therapeutic effects of bupropion an atypical antidepressant and smoking cessation aid on these symptoms. This agent as a strong norepinephrine and dopamine reuptake inhibitor, as well as nicotinic receptor antagonist[9-10] . Investigations about the impact of bupropion administration on positive and negative symptoms have been little. In a study by George et al, it was demonstrated that negative symptoms scores of schizophrenia were reduced by about 15% in the bupropion group which were treated with 300mg/day for 10 days compared to the placebo group. However, positive symptoms of these patients were not affected[11]. In another study, patients diagnosed with schizophrenia were examined for the effects of bupropion and supportive group therapy on schizophrenia symptoms. Bupropion treatment was associated with an 18% drop in the negative symptoms scores; however, the difference was not significant. But a significant decrease was seen in the negative symptom of alogia factor score[12]. However, in some reports, it was even suggested that the patients with no previous psychiatric history may experience positive psychotic symptoms after treatment with 300 mg/day bupropion[13].

The current study was designed to examine the comparative efficacy of bupropion for positive and negative symptoms. We used a 12-week double-blind, parallel-groups design to examine the comparative efficacy of bupropion compared to placebo.

Material and Method:

Current study was a double-blind, placebo-controlled randomized clinical trial conducted in at the Razi Psychiatric Teaching Hospital, University of Social Welfare and Rehabilitation Sciences in Iran in compliance with the ethical principles of the Declaration of Helsinki. Eligible participants were 40 patients who met DSM-IV criteria for schizophrenia. Exclusion criteria were:

1) Concurrent drug abuse or alcoholism;

2) organic brain disorders or mental retardation; 3) any medical condition that contraindicated use of bupropion; 4) history of seizure disorder; 5) an allergy to bupropion

6) any cancer in the year prior to randomization; 7) pregnancy, lactating or likely to become pregnant. We were also excluded the subjects who had previously used bupropion. All participants or their families provided written informed consent before participating in the study.

Participants were randomly assigned to the standard therapeutic dose of bupropion (150 mg/day for the first 3 days, followed by 300 mg/day) administered orally for a total of 8 weeks (n=20) or an identical appearing placebo tablet added to their usual medication regimen (n=20). Participants, investigators, and study staff were blinded to treatment assignment.

Baseline data were collected from the hospital recorded files, including demographics, medical history, education level, marital status, age of disease onset, and laboratory parameters. Cigarette smoking was defined as tobacco use within the 12 months prior to the interview and daily use of cigarettes was recorded[14]. The study endpoints were the scales of positive and negative symptoms of schizophrenia by the two scales for the assessment of positive symptoms (SAPS) and negative symptoms (SANS). These scales are designed to assess positive and negative symptoms principally those that may be occurred in schizophrenia. These two instruments were collected based on a standard clinical interview in order to evaluate the subject's symptoms. The positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Also, the negative symptoms include affective flattening or blunting, alogia, avolition-apathy, and anhedonia-asociality. All assessments are conducted on a six-point scale (0=no symptom to 5=very severe symptom) and the higher the score in each subscale, the more symptomatic the individual is. Positive and negative symptoms were assessed by the sum of scores on the four positive symptoms items as well as the four negative symptoms items[15].

Data are expressed as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using *t* test or non-parametric Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. Categorical variables across the two groups were compared using the Chi-square test or Fisher's exact test if required. To compare the differences in the improvement of outcome between the bupropion and placebo groups, analysis of covariance (ANCOVA) was used on the positive and the negative symptoms scores adjusting for demographic characteristics, marital status, education level, age of disease onset, duration of drug use and cigarette smoking as well as number of smoked cigarette before drugs administrating. Statistical significance level was set at P G 0.05. For the statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) was used.

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RESULTS:

The mean age of the total study population was 46.78 ± 7.16 years (aged 31-60 years) and the mean weight was 66.35 ± 13.66 kg (range 46-114 kg). Twenty two patients (55.0%) were single and only 7.5% of them had college degree. The mean age of disease onset was 23.35 ± 7.08 years that in 25% was less than 20 years. Eighty percent of subjects reported daily smoking in the previous 12 months with the average consumption of 11.13 ± 10.02 cigarettes per day.

There were no importance baseline differences between the two study groups regarding demographics, education level, marital status, disease duration, history of tobacco use, number of daily consumed cigarette as well as laboratory parameters (Table 1). After the completion of treatment schedules, both groups demonstrated similar significant improvements in all positive symptoms, adjusted for baseline variables. However, it appeared that the avolition-apathy score of

negative symptoms was reduced more in the group treated with bupropion compared to the placebo group (Table 2).

Discussion:

Little evidence has been suggested for the efficacy and effectiveness of bupropion on the positive and negative schizophrenia symptoms. The major finding of current study was that bupropion had potential efficacy for avolition-apathy as main negative symptoms in schizophrenics who were able to tolerate bupropion treatment and complete our 8-week double-blind study. However, no change in positive symptoms was essentially observed. Despite very sample size and low power of our study to detect differences between the two treatment approaches, we revealed a significant effect of bupropion on avolition-apathy symptom. This result is consistent with some other interventional studies. In a study by Evins et al, bupropion treatment was associated with improvement in the negative symptoms and greater stability of psychotic and depressive symptoms, compared with placebo[16]. But, some others failed to demonstrate a significant advantage for this medication[17]. Avolition-apathy generally manifests as lacking desires, lack of energy, motivation and persistence in schizophrenic patients. In avolition, patient is not able to start or complete any major tasks and in apathy appearance, entire lack of emotions or motivation is occurred. Based on different aspects of these symptoms, patients might suffer from severe social and economic impairment during their live. Patients may display less attention to hygienic habits than normal and clothing may appear untidy and begrimed. They may bathe infrequently and overall may be appeared as dilapidated and disheveled[18].

Little empirical investigation has been conducted on potential psychological or pharmacological treatment protocols for apathy. It seems that the agents that induce dopamine release and/or delay dopamine reuptake in the central nervous system can promise to use in apathy. Among these, atypical antipsychotics have received especially attention and have been demonstrated to reduce apathy in several schizophrenic populations.

The preclinical and clinical researches have been demonstrated that bupropion acts via dual inhibition of dopamine reuptake. Studies on animal samples also confirmed that acute administration of bupropion could decrease firing of dopamine neurons in the brain stems in a dose-dependent manner. Therefore this inhibitory effect may be associated with a unique clinical profile for improving avolition-apathy in schizophrenia. Besides, because bupropion is a selective norepinephrine and dopamine reuptake inhibitor that has no effect on serotonergic system, common observable side effects which related to other antidepressants, such as weight gain, sexual dysfunction or sedation are not associated with bupropion use and therefore this drug can be superior to other agents for preventing avolition-apathy.

Despite these hypotheses, the mechanism by which bupropion may stabilize this symptom among schizophrenics is already unknown and need to more investigation on human models.

In conclusion, our finding suggests that the bupropion therapy can be a clinically useful treatment for improving negative symptoms particularly avolition-apathy in patients with schizophrenia and also appears to be safe and well-tolerated. However, it was no evidence of any benefit of this drug for positive symptoms in these patients, which suggests that the field still lacks an effective treatment for these symptoms.

References

1. Salokangas RK. *Medical problems in schizophrenia patients living in the community (alternative facilities)*. Curr Opin Psychiatry 2007; 20:402-5.
2. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th* ed. Washington, DC: American Psychiatric Press; 2000.
3. Fleischhacker WW. *New drugs for the treatment of schizophrenic patients.* Acta Psychiatr Scand Suppl 1995; 388:24–30.
4. Lauriello J, Lenroot R, Bustillo J. *Maximizing the synergy between pharmacotherapy and psychosocial therapies for schizophrenia*. Psychiatr Clin North Am 2003; 26:191–211.
5. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. *Efficacy and extrapyramidal side effects of the new antipsychotics olanzapine, quetiapine, risperidone and sertindole compared to conventional antipsychotics and placebo. A metaanalysis of randomized controlled trials. Schizophr* Res 1999; 35:51–68.
6. Tollefson G, Bealey C, Tran P, Street J, et al. *Olanzapine versus Haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial*. Am J Psychiatry 1997; 154: 457–474.
7. Davis J, Chen N. *Clinical profile of an atypical antipsychotic: Risperidone. Schizophr* Bull 2002; 28:43–61.
8. Erhart SM, Marder SR, Carpenter WT. *Treatment of schizophrenia negative symptoms: future prospects*. Schizophrenia Bulletin 2006; 32:234–7.
9. Slemmer JE, Martin RM, Damaj MI. *Bupropion is a Nicotinic Antagonist*. J Pharmacol Exp Ther 2000; 295: 321–7.
10. Fryer JD, Lukas RJ. *Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine*. J Pharmacol Exp Ther 1999; 288: 88–92.
11. George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, Kosten TR. *A placebo controlled trial of bupropion for smoking cessation in schizophrenia*. Biol Psychiatry 2002; 52:53-61.
12. Weiner E, Ball P, Summerfelt A, Gold J, Buchanan RW. *Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia*. Am J Psychiatry 2001; 158: 635-7.
13. Neumann M, Livak V, Paul HW, Laux G. *Acute Psychosis after Administration of Bupropion. Pharmacopsychiatry* 2002; 35: 247-48.
14. Ratto LRC, Menezes PR, Gulinelli A. *Prevalence of tobacco use in individuals with severe mental illnesses*, São Paulo, Brazil. Rev Saúde Pública 2007; 41:51-6.
15. Andreasen, N., and Olsen, S. *Negative versus positive schizophrenia: Definition and validation*. Arch General Psychiatr 1982; 39:789–94.
16. Evins AE, Mays VK, Cather C, Goff DC, Rigotti NA, Tisdale T. *A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia*. Nicotine & Tobacco Research 2001 3:397-403
17. George TP, Vessicchio JC, Sacco KA, Weinberger AH, Dudas MM, Allen TM, Creeden CL, Potenza MN, Feingold A, Jatlow PI. *A Placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia.* Biol Psychiatry 2008; 63: 1092–6.
18. Foussias G, Remington G. *Negative Symptoms in Schizophrenia: Avolition and Occam's Razor*. Schizophrenia Bulletin Advance Access published online on July 21, 2008.
19. Roth RM, Flashman LA, McAllister TW. *Apathy and its treatment.* Curr Treat Options Neurol 2007; 9: 363-70.
20. Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. *A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor.* Prim Care Companion J Clin Psychiatry 2004; 6:159–66

21. Ferris RM, Cooper BR. *Mechanism of antidepressant activity of bupropion*. J Clin Psychiatry Monograph 1993; 11:2–14.
22. Ascher JA, Cole JO, Colin J-N, et al. *Bupropion: a review of its mechanism of antidepressant activity*. J Clin Psychiatry 1995; 56: 395–401.

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Table1. Baseline characteristics of smoker schizophrenic groups administered bupropion or placebo

Item	*Bupropion group (n=20)*	*Placebo Group (n=20)*	*p-value*
Age (yr)	47.70±7.85	45.85±6.46	0.414
Weight (Kg)	67.30±15.50	65.40±11.87	0.666
Marital status			
Single	10 (50.0)	12 (60.0)	
Married	5 (25.0)	1 (5.0)	0.204
Widow	5 (25.0)	7 (35.0)	
Education (yr)	8.35±4.49	8.65±3.71	0.799
Duration of disease (yr)	22.80±7.76	24.05±7.57	0.718
Duration of smoking (yr)	16.65±11.60	16.40±13.60	0.950
Number of cigarette (/day)	12.00±9.21	10.25±10.93	0.383
Laboratory indices			
White blood count ($\times 10^3$)	7.86±1.94	6.83±1.78	0.091
Hemoglobin	15.17±1.33	14.55±1.10	0.076
Platelet ($\times 10^3$)	212.15±45.37	213.90±61.15	0.565
Systolic blood pressure	11.30±1.38	11.45±1.10	0.265

Data are presented as mean ± SD or n (%)

Table2. Scales for the assessment of positive and negative symptoms in the groups treated with bupropion and placebo

Positive symptoms	*Bupropion group*		*Placebo group*		*p-value*
	Before treatment	After treatment	Before treatment	After treatment	
Hallucinations	3.00±5.49	2.55±4.15	6.35±6.68	5.25±6.41	0.850
delusions	9.00±12.29	8.90±12.07	16.75±12.80	16.75±12.99	0.961
Bizarre behavior	3.80±3.16	3.55±2.98	5.05±2.93	4.85±2.85	0.738
Positive formal thought disorders	6.55±7.88	5.15±6.51	15.80±10.98	14.70±12.71	0.716

Negative symptoms	*Bupropion group*	*Placebo group*	*p-value*

Affective flattening or blunting	16.75±5.16	14.05±5.39	17.65±6.28	14.40±6.67	0.822
Alogia	6.80±5.74	5.00±3.97	6.25±3.93	5.05±3.20	0.453
Avolition-Apathy	7.75±3.37	7.20±3.25	8.40±2.96	8.30±3.13	0.019
Anhedonia-Asociality	13.15±8.51	12.25±6.57	16.65±6.61	16.15±6.63	0.371

Data are presented as mean ± SD or n (%)