Bupropion in Adults with Attention-Deficit/Hyperactivity Disorder: a Randomized, Double-blind Study

Mehdi Hamedi[1], Mohammadreza Mohammadi[1], Ali Ghaleiha[2], Zahra Keshavarzi[1], Morteza Jafarinia[1], Rasool Keramatfar[3], Rosa Alikhani[1], Abolfazl Ehyaii[1], and Shahin Akhondzadeh[1]

[1] *Psychiatric Research Centre, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Research Center for Behavioral Disorders and Substance Abuse, Hamadan University of Medical Sciences, Hamadan, Iran*

[3] *Department of Psychiatry, AJA University of Medical Sciences, Tehran, Iran*

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Abstract- Attention-Deficit/Hyperactivity Disorder is one of the most common mental disorders in childhood, and it continues to adulthood without proper treatment. Stimulants have been used in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) for many years, and the efficacy of methylphenidate in the treatment of adults with ADHD has been proven to be acceptable according to meta-analysis studies. However, there are some concerns about stimulants. Finding other effective medications for the treatment of adult ADHD seems necessary. We hypothesized bupropion could be effective in the treatment of adult ADHD because some theoretical and experimental evidence exists to support efficacy of this medication. Forty-two patients with a diagnosis of ADHD, according to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, were randomized to receive 150mg/day bupropion or placebo for a 6-week double-blind, placebo-controlled clinical trial. Each patient filled the Conners' Adult ADHD Rating Scales–Self-Report-Screening version (CAARS) before starting to take medication and in weeks 3 and 6 of the study. The mean score of the two groups receiving bupropion or placebo decreased over the 6 weeks. There was a significant difference between the two groups in CAARS score after 6 weeks. Bupropion is more effective than placebo in the treatment of adults with ADHD. Bupropion can be an alternative medication for the treatment of Adults with ADHD as its clinical efficacy was proven by other studies.

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Introduction

The core symptom clusters of Attention-Deficit/Hyperactivity Disorder (ADHD), defined as inattention, hyperactivity and impulsivity, are associated with some impairments such as difficulties in sustaining attention, time management, and organization of activities (1,2). Adults with ADHD will often report that tasks are finished just at deadline, or not at all, and letters not answered. Impulsivity in adults may more dangerous consequences than childhood, such as careless driving, terminating valued relationships or impulsive job withdrawal. The aimless restlessness and childhood hyperactivity may change in adulthood. So they become more purposeful and adaptive, and restlessness may be diagnosed subjectively by the patient and not manifested overtly in their behavior (3).

Prevalence of childhood ADHD in the U.S.A. is estimated 5% to 8% (4). Based on this small and as yet incomplete evidence base, annual cost of illness due to ADHD in children and adolescents is $14,576 per individual (5-7). In reality, more than 50% of children with ADHD will carry the disorder into adulthood (8-10). Childhood ADHD is associated with a substantially higher risk of a lifetime history of nicotine and illicit substance use, in addition to nicotine dependence, or alcohol, marijuana, cocaine, and illicit drug abuse/dependence (11). ADHD in adults associated with co-morbidities such as anxiety disorders, depression, substance use disorders, personality disorders especially antisocial personality disorder. ADHD is associated with job-related problems in adulthood such as lower performance in job, less occupational status, less stability in their job and they

Corresponding Author: S. Akhondzadeh
Psychiatric Research Centre, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88281866, Fax: +98 21 55419113, E-mail address: s.akhond@neda.net

have more absence during their job period (12). In contrast, symptoms of inattention are present into adulthood and may continue into the geriatric years. While ADHD-related cognitive deficits may prolong into the advanced years of life, when they are more vulnerable for the development of dementia or minimal cognition impairment (13). People with ADHD often experience poorer long-term outcomes, and treatment may improve long-term outcomes for some individuals compared to controls (14).

Pharmacotherapy and non-pharmacological treatments such as cognitive behavioral therapy have efficacy in treatment of Attention-deficit/hyperactivity disorder. According to a 2009 meta-analysis (15), adults and children with ADHD may respond to neurofeedback, an advanced form of biofeedback (8). Only about 11% of adults with ADHD have received treatment. Stimulants are the first drug of choice of ADHD and administered for these patients. The need for multiple daily dosing, short-acting stimulant medications and risk of abuse by the patients results in cautious and restricted administration of these agents by physicians (8).

According to several controlled trials about 70% of patients with ADHD profit the useful effects of stimulants. Other medications such as atomoxetine, bupropion, guanfacine, modafinil and tricyclic antidepressantsis usually considered as second-line treatments, based on efficacy outcomes in clinical trials in different groups of patients (16). Tricyclic antidepressants and bupropion have emerged as second-line agents for treating pediatric ADHD. Bupropion is a novel aminoketone antidepressant related to the phenylisopropylamines and pharmacologically distinct from available antidepressants (17). According to the multisite, placebo-controlled, 8-week prospective trial on 162 adult patients diagnosed with ADHD who were treated with up to 450 mg/day of bupropion XL, bupropion XL was an effective and well-tolerated nonstimulant treatment for adult ADHD (18). A six-week open trial of sustained-release (SR) bupropion was performed on adults between 18 to 55 years old diagnosed with both ADHD and Substance Use Disorder. Bupropion-SR dose was 200 mg SR twice daily. This trial suggests that Bupropion-SR is effective in ADHD symptoms but has no efficacy on substance use disorder (19). Sustained-release bupropion has not a significant advantage vs. placebo in reducing ADHD symptoms or additional cocaine use in patients on methadone-maintenance therapy (20). No significant efficacy was detected between 59 participants who received bupropion-SR and placebo according to a 6-week randomized, double-blind, placebo-controlled, parallel-design clinical trial (21). A meta-analysis of 349 participants (n for bupropion treatment = 175) in five published randomized, controlled trials indicated that the bupropion is more effective than placebo for treatment of ADHD in adults (22). On the basis of accumulating evidence, we hypothesized that bupropion can be a suitable choice for treatment of adult manifestation of attention deficit/hyperactivity disorder, and we conducted this double-blind, placebo-controlled clinical trial.

Materials and Methods

This was a 6-week, parallel group, placebo-controlled trial launched at the Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran) during January 2013-March 2014.

Participants

Subjects were outpatients who were referred to a psychiatrist for psychiatric evaluation. The subject was visited by a psychiatrist and when adult ADHD diagnosis was proven to exist according to DSM-IV-TR, he/she was asked to participate in this study. All subjects were between 20 and 60 years of age. Subjects with these conditions were excluded from the study:

. Any chronic medical condition such as cardiovascular disease, epilepsy and brain organic disease
. Substance abuse or dependence during last 6 months.
. Pregnancy or breastfeeding
. Mental retardation (IQ<75) (According to psychiatrist clinical impression)
. Unstable psychiatric state (e.g. suicide, aggression, psychosis)
. Any psychotropic medication usage currently
. Any usage of methylphenidate, atomoxetine, amphetamine, and other ADHD related medication during last 3 months.
. Bipolar mood disorder

The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (TUMS) (Grant No: 20285). The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and was approved by the ethics committee at TUMS. Written informed consents were obtained from the patients before entering the trial. This trial is registered with the Iranian Clinical

Trials Registry (IRCT201302201556N51; www.irct.ir).

Measurements

CAARS utilizes short, long, and screening self-report and observer rating scale forms. The instrument is designed for individuals aged 18 to 50 years and older (23). The scales address ADHD symptoms as described in the Diagnostic and Statistical Manual Fourth Edition. This form had been translated to Farsi (Persian) and had been normalized by ICSS (Institute for Cognitive Science Studies in Tehran). Those with a total score of 30 and above were interviewed by a psychiatrist. The partners of these probable patients with ADHD were also questioned about presence and severity of symptoms to obtain an observer's view. Patients were randomized to receive bupropion or Placebo in an equal ratio. The assignments were kept in sealed, opaque envelopes until allocation.

The randomization and allocation process was accomplished by principal investigator. Each patient was randomly assigned to receive treatment either with bupropion (starting with 75mg/day to a maximum of 150mg/day) in group 1 or placebo in group 2 for a 6-week double-blind clinical trial. All people involved in the study- the psychiatrist, the rater and the patients were blind to assignments. Each patient filled the CAARS self-report screening form before starting to take medication and in weeks 3 and 6. Patients were also assessed by a psychiatrist at baseline and after 14 -day periods up to 6 weeks.

Statistical analysis

Results are presented as mean ± SD differences and were considered significant at P.value≤0.05. All data were analyzed by a two-way repeated measures analysis of variance. The two groups were considered as a between subjects factor (group), and the three measurements during treatment were considered as a within-subjects factor (time) in the analyses. Fisher's exact test was used to compare the baseline data and differences in frequency of side effects with the two treatments. With a type 1 error α=0.05 and ß=0.2 and final difference in score between the two groups of at least 5 units on the CAARS, the sample size necessary was calculated to be at least 20 patients in each group.

Results

Forty-two eligible patients were randomly allocated to either the bupropion (n=21) or a placebo (n=21) group. Table 1 illustrates baseline characteristics of the both groups patients. The mean scores of the two groups are demonstrated in Figure 1. There was no significant difference between the mean age of the two groups (P=0.604). There was no significant difference between Male/Female ratio of the two groups (P=0.334). Also, there were no significant difference between the two groups at week 0 (baseline) on CAARS self-report screening mean score (P=0.932).

Table 1. Baseline data of Participants

	Bupropion group	Placebo Group
Female	9	6
Male	12	15
Age (Mean ± SD)	33.90 ± 4.83 Year	33.19 ± 4.00 Year
CAARS week 0 Score (Mean ± SD)	41.81 ± 14.81	42.24 ± 17.43
CAARS week 3 Score (Mean ± SD)	32.86 ± 15.30	36.81 ± 10.29
CAARS week 6 Score (Mean ± SD)	23.71 ± 15.34	34.43 ± 10.09
Ethnicity	All Persian	All Persian

The bupropion group showed significant improvement over 6 weeks of treatment, and the trend seemed linear. There was a significant difference between Mean CAARS scores (Greenhouse-Geisser corrected F=4.146, df=1.303, P=0.037) according to repeated measure ANOVA. Uni-variant ANOVA was performed between groups in different weeks. The result of uni-variant ANOVA is mentioned in Table 2. There was no significant difference between the two groups in the 3rd week's mean of CAARS score (P=0.332). In the 6th week, this difference was significant (P=0.011) (Table 2).

Table 3 summarized the side effect of the two groups. Twenty-two side effects were observed during the study. No significant difference was found between the two groups in side effect of the two treatment strategies.

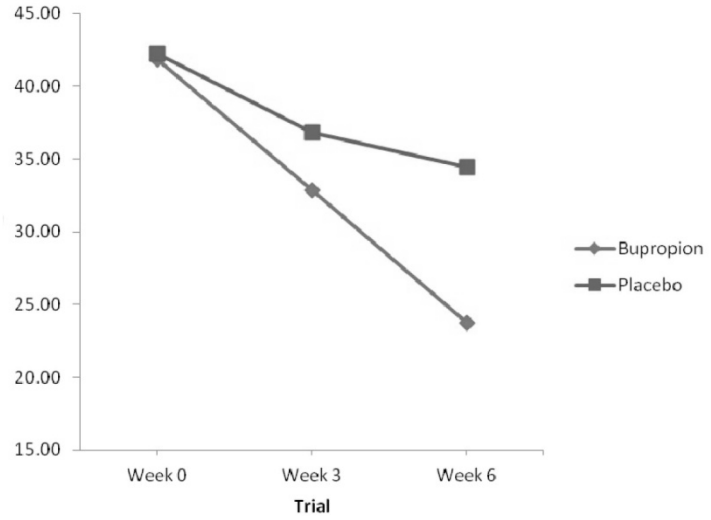

Figure 1. Mean Scores Of CAARS Self Report Screening Form Over 6 Weeks

Table 2. Uni-variant ANOVA Between 2 treatment strategies in different weeks

	CAARS Score (Mean ± SD)					
	Bupropion group	Placebo group	F	df	*P*-Value	Significance
Week 0	41.81 ± 14.81	42.24 ± 17.43	0.007	1	0.932	NS
Week 3	32.86 ± 15.30	36.81 ± 10.29	0.965	1	0.332	NS
Week 6	23.71 ± 15.34	34.43 ± 10.09	7.152	1	0.011	S

S=Significant, NS= Non-Significant

Table 3. Clinical complications and side effects (Bupropion dosage=150mg/d)

Side Effect	Bupropion group	Placebo group	P-Value (Fisher exact test)	P-Value (Chi-Square Test)	Significance
Abdominal pain	5 (23.8%)	3 (14.3%)	0.697	-	NS
Agitation	12 (57.1%)	8 (38.1%)	-	0.217	NS
Anorexia	6 (28.6%)	7 (33.3%)	-	0.739	NS
Anxiety	9 (42.9%)	6 (28.6%)	-	0.52	NS
Arthralgia	7 (33.3%)	5 (23.8%)	-	0.495	NS
Constipation	8 (38.1%)	3 (14.3%)	0.159	-	NS
Diarrhea	4 (19%)	3 (14.3%)	0.999	-	NS
Dizziness	8 (38.1%)	4 (19%)	0.306	-	NS
Dry mouth	8 (38.1%)	5 (23.8%)	-	0.317	NS
Fatigue	12 (57.1%)	7 (33.3%)	-	0.121	NS
Headache	5 (23.8%)	5 (23.8%)	-	0.999	NS
Insomnia	9 (42.9%)	7 (33.3%)	-	0.525	NS
Myalgia	6 (28.6%)	7 (33.3%)	-	0.739	NS
Nausea	6 (28.6%)	5 (23.8%)	-	0.726	NS
Palpitation	9 (42.9%)	5 (23.8%)	-	0.19	NS
Paresthesia	6 (28.6%)	1 (4.8%)	0.093	-	NS
Pruritus	8 (38.1%)	5 (23.8%)	-	0.317	NS
Somnolence	11 (52.4%)	6 (28.6%)	-	0.116	NS
Sweating	9 (42.9%)	4 (19%)	0.181	-	NS
Tinnitus	3 (14.3%)	2 (9.5%)	0.999	-	NS
Vomiting	3 (14.3%)	3 (14.3%)	0.999	-	NS
Weight loss	5 (23.8%)	1 (4.8%)	0.184	-	NS

S=Significant, NS= Non-Significant

Discussion

According to this randomized, placebo-controlled, double-blind clinical trial, bupropion was more effective than placebo to reduce Attention-deficit/Hyperactivity disorder symptoms in adults. The differences were significant at the 6th week, but not significant at the 3rd week of treatment. Therefore, bupropion can be suggested as an alternative drug for the treatment of ADHD in adults. According to the results of this study, the efficacy of this drug will appear after 3-6 weeks of treatment and not before the 3rd week. The results of our study confirmed results from previous clinical trials about effectiveness of bupropion in Adult ADHD (20,24-27). Only the results of one study, which claimed no preference for Bupropion-SR over placebo in reducing ADHD symptoms in adults, do not confirm our results (21).

The average dose of bupropion administered for cases was 150mg/d in our study. We were not able to administer more than this dose for the majority of our patients because of the side effects. The drug was not well tolerated in some patients, and these cases were dropped. Therefore, we decided not to increase bupropion dosage more than 150mg/d. Review of articles about effectiveness of bupropion on manifestation of adult ADHD showed the average dose in different studies was between 200 to 400 mg/d which is much higher than the dosage used in our study.

Bupropion is metabolized by CYP-2B6. 7.1% of females and 20% of males are poor CYP-2B6 metabolizers. CYP-2B6 activity was demonstrated to be 3.6- and 5.0-fold higher in Hispanic females than in Caucasian or African-American females (28). The bupropion metabolic ratio appears to detect known differences in CYP-2B6 activity associated with genetic polymorphism across different ethnic groups (29). Intolerance of bupropion by our patients in comparison to other studies may be due to their ethnicity. This study was conducted in Iran on Iranians. We did not find any study on CYP-2B6 activity on Iranians. Thus, investigation of CYP-2B6 activity on Iranians would be beneficial. In humans, bupropion is metabolized by the enzyme CYP-2B6 to Hydroxybupropion. Hydroxybupropion may contribute to bupropion's pharmacologic activity (30). One study recommended hydroxybupropion serum monitoring to achieve at least 700ng/ml for smoke cessation purposes because of CYP-2B6 polymorphism in different genders and ethnicities (30). It is also recommended to do hydroxybupropion monitoring in Iranian cases who receive bupropion.

Our study had some limitations such as low sample size and less powerful rating scale for measurement of ADHD manifestations. This study did not evaluate ADHD domains such as inattention, hyperactivity, and impulsivity. Further studies are recommended to address these weaknesses. In conclusion, bupropion is more effective than placebo in the treatment of adults with ADHD. Bupropion can be an alternative medication for the treatment of Adults with ADHD as its clinical efficacy was proven by other studies.

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