

## Double-Blind Randomized Controlled Trial of Bupropion versus Methylphenidate for Children and Adolescents with Attention-Deficit Hyperactivity Disorder

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**Objective.** The primary aim of this study was to compare the efficacy of bupropion with that of methylphenidate in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). **Method.** A double-blind clinical trial was used in this study. The study was performed in the child and adolescent psychiatric clinics of the Roozbeh and Imam Hossein hospitals during 2000 and 2001. By means of clinical psychiatric evaluations, DICA interviews, and DSM-IV diagnostic criteria, 40 children and adolescents (ages 6 to 16 years) were diagnosed with ADHD (excluding participants who were taking medication or who had comorbid mental retardation, epilepsy, abnormal EEGs, or any other psychiatric disorder, with the exception of oppositional defiant disorder, ODD). The 40 participants were randomly assigned to groups receiving either methylphenidate or bupropion for a six-week period. Methylphenidate was titrated to an effective dose ranging from 0.4 to 1.3 mg/kg per day, and bupropion was titrated to an effective dose ranging from 1.4 to 5.7 mg/kg per day. **Results.** The comparison of pre- to post-treatment changes in the IOWA Conners' Teacher and Parent rating scales in both groups suggested that the effectiveness of bupropion in the treatment of ADHD is equivalent to that of methylphenidate. However, when comparing pre- and post-treatment CGAS test scores, a significantly greater improvement during treatment was obtained for the methylphenidate group ( $p < .05$ ). The side effects of bupropion, however, were significantly lower than for methylphenidate ( $p < .05$ ). **Conclusion.** In this double-blind clinical trial, both bupropion and methylphenidate were effective in the treatment of ADHD. These results indicate a need for further comparative studies.

**Keywords:** ADHD; Bupropion; Methylphenidate; Conner's rating scale.

### Introduction

Attention deficit-hyperactivity disorder (ADHD) is one of the most common disorders in child psychiatry. Epidemiological studies report that about 3 to 5 per-

cent of school-age children suffer from ADHD (Kaplan & Sadock, 2000). The disorder causes severe dysfunctions in the family, at school, and in society. Leaving this disorder untreated would make it a devastating life-long challenge. ADHD can co-exist with psychiatric disorders such as conduct disorder (CD), antisocial personality disorder (APD), mood disorders, and learning disorders (Weiner, 1994).

Pharmacotherapy usually results in significant clinical recovery, thus making it the first step in ADHD treatment. Among psychoactive drugs used for treating ADHD, central nervous system (CNS) stimulants such as methylphenidate, dextroamphetamine, and pemolin,

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are the most common drugs in use (Kaplan & Sadock, 2000). Although these drugs are highly effective in the treatment of ADHD, they can cause troublesome side effects, thus limiting their use. Such side effects include headaches, vomiting, insomnia, possible failure to thrive (FTT), aggravation of tic disorders, anxiety, and psychosis; furthermore, patients may fail to respond to treatment altogether (Kaplan & Sadock, 2000).

Hence, it is important to keep investigating the usefulness of alternative pharmacological agents. The therapeutic effects of bupropion have been emphasized in many studies. Simeon, Ferguson, and Van Wyck Fleet (1986), for instance, showed that using bupropion in 17 children with severe ADHD resulted in moderate recovery. In another study, in which participants were assessed using the Parent Conner's Rating Scale (PCRS), Teacher Conner's Rating Scale (TCRS), and Children's Global Assessment Scale (CGAS; Shaffer et al., 1993), it was found that, in comparison with a placebo group, no changes could be observed in EEG and vital signs (Dulcan et al., 1999). The side effects of bupropion in this study were only transient.

Casat, Pleasants, and Van Wyck Fleet (1987) studied 20 children suffering from ADHD who were resistant to treatment with common stimulant drugs. The investigators found that bupropion yielded improvement, compared to a placebo, on the CGAS and the hyperactivity scale of the TCRS.

According to the results of Wolf's (1993) six-week double-blind study, no significant differences could be observed between the placebo group and a group of 16 ADHD cases receiving bupropion based on PCRS and TCRS scores. However, three children in the experimental group in this study did respond quite positively to bupropion. In a double-blind clinical trial by Conners et al. (1995), bupropion and placebo were compared, and positive results were seen when assessing patients using the PCRS and TCRS. The study group tolerated bupropion very well, as transient skin reactions were the only side effects observed. In Barrikman et al.'s (1995) double-blind study comparing bupropion and methylphenidate in ADHD, assessments using the PCRS, TCRS, and CGAS showed similar recovery patterns after six weeks of treatment in 15 teenagers suffering from ADHD.

The aim of the present study was to compare the efficacy and side effect profiles of bupropion and methylphenidate in the treatment of ADHD.

## Method

Forty patients with ADHD drawn from a convenience sample were examined at the child psychiatry outpatient clinic of the Roozbeh and Imam Hossein hospitals during 2000 and 2001.

Participants were consecutive attendees with a clinical psychiatric diagnosis of ADHD based on DSM-IV criteria, as determined following an interview using the DICA questionnaire. Those who had history of organic disorders, abnormal EEGs, or IQs of less than 70 were excluded from the study. At intake, patients underwent a two-week washout period. Written consents were obtained from patients, as well as from their parents. Participants' ages ranged from 6 to 16 years.

Methylphenidate and bupropion were prescribed on a random, double-blind basis for six weeks. Drug dosages were based upon the recommendations of previous studies (e.g., Barrikman et al., 1995). Bupropion (1.4-5.7 mg/kg/day or 50-200 mg/day) was given as one tablet per day (one-half in the morning and the other half at noon) for the first week, and two tablets per day (one in the morning and one at noon) for the second week. If the participant's weight was over 30 kg, three tablets were given daily.

In the other treatment group, methylphenidate (0.4-1.3 mg/kg/day) was given as one tablet per day (one-half in the morning and the other half at noon) in the first week, and two tablets per day (one in the morning and one at noon) for the second week. If the participant's weight was more than 30 kg, this dosage was increased to three tablets in the third week.

## Psychological Measures

*Conner's Questionnaire.* Conner's questionnaire consists of two forms, the Parent form and the Teacher form. The Parent form consists of 48 questions, while the Teacher form includes 38 items. This instrument assesses ADHD symptoms, and has well-documented validity and reliability (Conners et al., 1995; Lewis, 1996; Kaplan & Sadock, 2000).

*Children's Global Assessment Scale (CGAS).* The Children's Global Assessment Scale (CGAS) is designed for the simultaneous evaluation of the disorder's

Table 1  
*Mean PCRS scores and score changes after the third and sixth weeks.*

Week	Treatment	Mean PCRS score (SD)	Mean PCRS score change (SD)
3	Bupropion ( <i>n</i> = 20)	63.60 (5.15)	-10.15 (4.90)
	Methylphenidate ( <i>n</i> = 19)	63.16 (7.96)	-7.740 (6.70)
6	Bupropion ( <i>n</i> = 20)	57.00 (5.20)	-16.27 (4.66)
	Methylphenidate ( <i>n</i> = 19)	57.17 (7.77)	-13.44 (8.05)

Table 2  
Mean TCRS scores and score changes after the third and sixth weeks.

Week	Treatment	Mean TCRS score (SD)	Mean TCRS score change (SD)
3	Bupropion ( <i>n</i> = 20)	63.45 (4.54)	-6.150 (3.67)
	Methylphenidate ( <i>n</i> = 19)	67.05 (7.12)	-5.680 (5.02)
6	Bupropion ( <i>n</i> = 20)	58.11 (6.98)	-16.75 (4.66)
	Methylphenidate ( <i>n</i> = 19)	62.94 (8.93)	-13.44 (8.05)

symptoms and the child's functioning, as determined from family, educational, psychological, and social perspectives. The CGAS assesses the child's global functioning, with a minimum score of 70 out of 100 considered as normal. Its validity has been confirmed as an outcome measure in clinical trials (Lewis, 1996; Kaplan & Sadock, 2000; Shaffer et al., 1997)

## Results

Thirty-eight out of 40 patients (95%) completed the study (*N* = 20 for the bupropion group, *N* = 18 for the methylphenidate group). One participant from each of the two treatment groups failed to complete the study. The mean ages of participants in the bupropion and methylphenidate groups were 7.86 (*SD* = 1.28) and 9.26 (*SD* = 2.98), respectively. The age range of participants was 6 to 16 years, with mean age of 8.5 years. Males constituted 57.1% and 63.2% of the bupropion and methylphenidate groups, respectively, while females constituted 42.9% and 36.8%, respectively. To determine whether the groups were similar in terms of demographic variables, and to assure that these variables were distributed normally, the Kolmogorov-Smirnov test was used. On the basis of the results using this test, we could assume a normal distribution among the groups, and thus use *t*-tests for further analyses.

Mixed-type ADHD was the most prevalent, constituting 57.1% and 63.2% of cases in the bupropion and methylphenidate groups, respectively; hyperactivity was found in 23.8% and 21.1%, while attention-deficit characterized 19.0% and 15.8% of the bupropion and methylphenidate groups, respectively. The two groups were also similar in terms of comorbid disorders, with 52.4% and 47.4% of the bupropion and methylphenidate groups, respectively, experiencing comorbid oppositional-defiant disorder (ODD).

Age and sex distributions, as well as disorder types and co-morbid disorders (e.g., oppositional defiant disorder, ODD) in the two groups are shown in Tables 1 and 2). As shown in these tables, the groups were matched on all relevant variables (all *ps* > .05).

As of the third and sixth weeks of the study, the two groups did not differ significantly in terms of either PCRS scores or PCRS score changes (see Table 1). These findings also held true for score changes in the TCRS scores and TCRS score changes (all *ps* > .05) (see Table 2). However, an analysis of CGAS scores revealed significant differences for methylphenidate versus bupropion users after six weeks (*t* = 2.22, *p* < .05), indicating the superiority of methylphenidate over bupropion (see Table 2)

At the end of the third week, seven out of 21 bupropion users reported no side effects (33.3%). Ten subjects (47.6%) reported minor side effects, while four experienced moderate side effects (19%). No severe side effects were reported. On the other hand, all 19 methylphenidate users experienced side effects: 10 (52.6%) reported minor severity, 7 (36.8%) reported moderate severity, and two presented with severe side effects (10.5%).

A comparison of the profile of side effects showed that 17 out of 21 bupropion users were free from side effects (81%), while only seven in the methylphenidate group showed no side effects (36.8%); this difference was significant (*p* = .005) (see Table 4).

## Conclusion

In the present study, the efficacy of two drugs (methylphenidate and bupropion) in the treatment of ADHD was assessed. Both medications proved effective, with bupropion producing considerably fewer side effects, a finding consistent with previous research (Casat et al., 1987; Conners et al., 1995; Simeon et al., 1985).

Interestingly, although both medications yielded significant improvements, CGAS score changes were more robust in the methylphenidate group. On the

Table 3  
Mean CGAS scores at baseline and after six weeks.

Week	Treatment	Mean CGAS score (SD)
0	Bupropion ( <i>n</i> = 21)	45.38 (5.02)
	Methylphenidate ( <i>n</i> = 19)	45.68 (6.73)
6	Bupropion ( <i>n</i> = 20)	51.75 (6.17)
	Methylphenidate ( <i>n</i> = 18)	56.56 (7.18)

Table 4  
*Drug side effects at third and sixth weeks of treatments.*

Week	Treatment	Side effects	Number of participants experiencing side effects (%)	
3	Bupropion (n = 21)	None	17 (81.0%)	
		Mild	4 (19.0%)	
		Moderate	0 (0.00%)	
		Severe	0 (0.00%)	
		Methylphenidate (n = 19)	None	7 (36.8%)
6	Bupropion (n = 21)	Mild	6 (31.6%)	
		Moderate	6 (31.6%)	
		Severe	0 (0.00%)	
		Methylphenidate (n = 19)	None	7 (33.3%)
		Mild	10 (47.6%)	
	Bupropion (n = 21)	Moderate	4 (19.0%)	
		Severe	0 (0.00%)	
		Methylphenidate (n = 19)	None	0 (0.00%)
		Mild	10 (52.6%)	
		Moderate	7 (36.8%)	
	Bupropion (n = 21)	Severe	2 (10.5%)	
		Methylphenidate (n = 19)	Severe	2 (10.5%)

other hand, a comparison of TCRS and PCRS scores at the third and sixth weeks showed that bupropion was not significantly different from methylphenidate in terms of its efficacy.

It is possible that variability among ADHD patients could have resulted in variable treatment responses. However, it is not clear why different subgroups would respond differently to various treatments. In naturalistic settings, treatment should be based on co-morbid disorders, common symptoms, and characteristics of the family, societal, and school settings.

While the cost of bupropion is a major limitation to its liberal use, its superior safety profile would make it a viable alternative to psychostimulants.

Further studies are needed to address the limitations of the present study, such as its limited sample size, short follow-up period, and limited comparisons.

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