

ADHD Through the Life Span: The Role of Bupropion in Treatment

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Attention-deficit/hyperactivity disorder (ADHD) is a common problem that begins early in life and in many cases persists through the life span. Psychostimulants have been the psychopharmacologic treatment of choice. Not all patients respond to psychostimulants, and some patients have significant side effects. This paper reviews the use of a nonstimulant psychopharmacologic agent, bupropion, to treat ADHD in both children and adults. *(J Clin Psychiatry 1998;59[suppl 4]:92-94)*

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood. It is important because it is highly prevalent, interferes with development in a variety of areas, and is relatively persistent across settings such as home, school, and leisure time activities. It is also relatively persistent across the life span. Although the condition has undergone multiple name changes throughout history, the core symptoms have always been considered to be developmentally inappropriate levels of inattention, impulse control, and motor activity disturbance. A variety of associated symptoms and comorbid conditions complicate the clinical picture. There is also a suggestion that developmental differences exist in manifestations of the disorder across the life span from preschool to adulthood.^{1,2}

Since the original work of Bradley³ in the 1930s, psychostimulants have been the psychopharmacologic treatment of choice for ADHD. Most data on psychostimulant treatment of ADHD come from grade school-aged children, although there is a published literature on their use in preschoolers, adolescents, and adults. Clinical studies have suggested that approximately 70% of individuals with ADHD will have a positive response to one of the psychostimulants.¹ The percentage of response goes up if multiple psychostimulants are tried. However, there are always individuals who do not respond at all or respond incompletely to stimulant medication. In addition, there are those who cannot take stimulant medication because of intractable

side effects such as insomnia and appetite suppression. Thus, there is a need for alternative nonstimulant treatment for ADHD. This paper will review the utility of bupropion in the treatment of ADHD throughout the life span.

TREATMENT STUDIES

There are a number of studies of bupropion, both controlled and open, across the life span in individuals with ADHD. The most recent is a multisite study published by Conners et al.⁴ This was a double-blind placebo-controlled study that took place at four sites. Seventy-two youngsters were taking bupropion, and 37 were taking placebo. The age range was 6–12 years, 75% were male, and 90% were white. DSM-III criteria were used as the categorical diagnosis for inclusion, but a dimensional cutoff score was also used.

After a 1-week placebo washout, children were randomly assigned to 4 weeks of placebo or bupropion treatment at dosages of 3 to 6 mg/kg/day. The doses were administered twice a day at 7:00 a.m. and 7:00 p.m. Dosage began at 3 mg/kg/day from Days 1 to 3 and was increased up to 3–6 mg/kg at Days 15–28. Children weighing 20–30 kg received about 150 mg/day, those weighing 31–40 kg received about 200 mg/day, and those weighing more than 40 kg received about 250 mg/day.

Efficacy assessments included standard measures used in other drug studies of ADHD. These included the Conners Parent and Teacher Questionnaires (including the Hyperactivity Index), the Clinical Global Impressions (CGI) scale, the Sternberg Short-Term Memory Task, and the Continuous Performance Test. Results indicated that, by Day 3, the conduct and hyperactivity factors of the Conners 10- and 39-item teacher rating scales showed significant treatment effect. By Day 28, conduct disorder and the restless-impulsive factors were positively impacted on the Conners 93-item rating scale. At Day 28, teachers noticed significant treatment effects on the aggression and on

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the hyperactivity subscales. Parents did not distinguish any treatment effects between active drug and placebo on the 10-item checklist completed weekly.

The data from all four sites taken together failed to reveal a significant effect on the CGI scale, but two sites did reveal a significant effect on CGI symptom, and one site reported a significant effect on the CGI-Improvement. These findings suggested site differences in utilization of the CGI scale.

On the Continuous Performance Test, there was a slight worsening with placebo treatment and a slight improvement for the bupropion group. On the memory task, it appears that speed of memory retrieval was affected positively, irrespective of memory load and with no effect of treatment on errors. Vital signs, electrocardiogram (ECG), hematological studies, and blood chemistry studies revealed no clinically significant problems in either group and no significant difference between groups.

Treatment-emergent adverse experiences included nausea and vomiting, which were quite frequent (16.7% in the drug group, but also 13.5% in the placebo group). Twelve bupropion patients (16.7%) had a rash compared with 3 (8.1%) in the placebo group. Rashes led to discontinuation of the medication in four cases. Electroencephalogram (EEG) readings of 6 patients receiving active drug changed from normal to abnormal. These changes were not accompanied by clinical symptoms.

The authors indicate that the study revealed that bupropion lowered hyperactivity and improved aggression in children who had both conduct and attention problems as rated by the teachers. Significant reduction of symptoms was reported by parents. These measurements, however, were less reliable and strong; there was a sizable placebo effect in parent ratings. The results of the Sternberg Short-Term Memory Task were interpreted as suggesting that bupropion acts on response processes rather than acting on memory capacity or stimulus encoding. The authors note that the memory load was relatively small compared with the higher memory load used in Sprague and Sleator's classic study,⁵ which revealed a curvilinear relationship between set size and stimulant dosage. The effect size of the bupropion intervention was considered to be moderate.

Studies reported by Casat et al.,^{6,7} Clay et al.,⁸ and Wolfe et al.⁹ present subsets of the same total data set reported by Conners. The Casat et al. papers reported on 20 subjects receiving active treatment and 10 receiving placebo. The results of this site showed significant improvements in the CGI and Conners Teacher Questionnaire hyperactivity scores, while the other scores were similar between the two groups. One patient in the active drug group withdrew because of rash and periorbital edema. Cognitive measures at this site were compromised by methodological problems.

Clay et al.⁸ reported on 18 children receiving active drug treatment and 10 receiving placebo. At their site, the CGI-Improvement, CGI-Severity, and various self-ratings

showed significant improvement for patients receiving active drug treatment versus those receiving placebo. The other scales showed no statistically significant differences. Rashes were reported in 2 of the 18 patients receiving active drug treatment. Marginal effects were reported on the Continuous Performance Test.

Simeon et al.¹⁰ reported on a single-blind trial of 17 white boys, 7–13 years of age. Fourteen of them were treatment resistant and/or had conduct disorder. There was a 4-week placebo lead-in with active drug being given at dosages between 50 and 150 mg/day. Mean dose was 135 mg/day for 8 weeks. Fifteen of the 17 subjects completed the study. Significant improvement was reported by trends in the behavioral rating scores and by improvements in cognitive performance, the CGI, and the Conners Parent and Teacher Questionnaires. There was deterioration on most of these measures during a posttreatment placebo phase. Eight patients reported mild nausea. Increased appetite and vomiting were reported as side effects, but the number who had these symptoms was not reported.

Another open study was conducted by Wender et al.¹¹ on adults diagnosed by Utah criteria as having ADHD. Mean age was 40 years. A total of 19 patients entered an open trial after a 2-week washout. The treatment phase was 6 to 8 weeks at initial dosages of 150 mg/day increased to a maximum dosage of 450 mg/day. There was a significant improvement in the Targeted Attention Deficit Disorder Symptoms scale reported in 14 patients. The CGI scores showed marked response in 8 patients and moderate response in 6 patients. Five patients withdrew due to adverse effects, primarily agitation. At the end of the trial, 4 of 14 returned to stimulant treatment. The others chose to remain on bupropion treatment. The subjects in this study were all known stimulant responders. Subjects in the Simeon et al.¹⁰ group were treatment resistant, and in the multisite study with reports by Conners et al.,⁴ Casat et al.,^{6,7} Clay et al.,⁸ and Wolfe et al.,⁹ subjects were treatment resistant or naive.

A comparative study¹³ of bupropion and methylphenidate in 15 subjects, 7–17 years of age with a mean age of 11.8 years, has been reported. Nine patients had comorbid conduct, oppositional defiant, or developmental learning disorders. Ten had received previous treatment with methylphenidate.

The study was a double-blind crossover design: 2 weeks at baseline for a washout, 6 weeks of treatment, another 2-week washout, and then crossover to the alternative drug for 6 weeks. Bupropion was used in initial doses of 1.5 mg/kg/day titrated to the maximum effective dose at Week 4. The mean maximum dose was 3.3 mg/kg/day with a range of 1.4 to 5.7 mg/kg/day. The initial dose of methylphenidate was 0.4 mg/kg/day titrated to a maximum effective dose at Week 2, which averaged 0.7 mg/kg/day with a range of 0.4 to 1.3 mg/kg/day. The authors reported significant improvements over baseline in Conners Parent and Teacher Questionnaires for both medications. There were

similar improvements on the CGI, Kagan's Matching Familiar Figures Test, the Continuous Performance Test, the Children's Depression Inventory, the Children's Manifest Anxiety Scale, and the Rey Auditory-Verbal Learning Test. No significant differences between treatments were noted for any measure of efficacy. However, all rating scales except for the Children's Manifest Anxiety Scale slightly favored methylphenidate.

Nine patients reported adverse effects during the bupropion treatment. These included anxiety, anorexia, drowsiness, fatigue, dizziness, headaches, nausea, a "spacey" feeling, and tremors. Five reported adverse effects during methylphenidate treatment including anxiety, anger, crying, drowsiness, headaches, insomnia, irritability, low moods, nausea, and stomach aches. Ten of the 15 subjects elected to remain on methylphenidate treatment rather than on bupropion treatment at the end of the study. The study is complicated by having no placebo control and a significant treatment order by medication interaction effect.

Finally, case reports^{12,14} suggest some possible adverse effects of bupropion use. These include possible exacerbation or new manifestation of tics that resolve after bupropion is withdrawn, the development of repetitive and compulsive behaviors in patients who may be vulnerable to the development of obsessive-compulsive disorder (OCD) and/or tics, and, in one case, hypomanic symptoms.

DISCUSSION

The results reported above from open and controlled studies suggest possible usage of bupropion in the treatment of ADHD throughout the life span. There are some methodological issues that need to be discussed in evaluating the literature in total. The total number of studies is relatively small, and the total number of patients enrolled in all the studies combined and in some of the individual studies is quite small as well. Different inclusion and exclusion criteria were used across studies. If categorical criteria were used to make the diagnosis of ADHD, it makes a difference as to whether DSM-III, DSM-III-R, or DSM-IV criteria are used because each of these sets of criteria is likely to include different subjects. Some studies, such as the Conners et al.⁴ study, required a dimensional cutoff on rating scales, while others did not. Patients in some studies were drug naive and others were stimulant resistant, while patients in other studies were positive stimulant responders. The age range in the studies as a whole was quite wide, most of the patients studied were male, and issues such as ethnicity and comorbidity were not fully explored with regard to treatment response in the studies in general.

The dose of the medication, the duration of treatment, the dosing frequency (e.g., b.i.d. or t.i.d.), and the method used to determine efficacy of the medication differed from study to study. All of the studies published thus far have used the immediate-release form of bupropion. Bu-

propion SR (sustained release) is now on the market and should be studied because it is as or more effective than the immediate-release form. It offers the advantage of the child not having to take medication at school. Further studies of both immediate- and sustained-release bupropion are warranted in which tight control over exclusion and inclusion criteria, dosing, timing, and duration of treatment is exercised. Modern diagnostic criteria and both behavioral and cognitive modern assessment measures should be used in these studies.

In the author's clinical experience, bupropion offers a useful alternative to stimulant medication in the treatment of some ADHD children. The side effect profile is generally better than with stimulants, and it is better than those of the tricyclics, particularly with regard to cardiovascular effects, although rashes were reported in a number of studies at a higher level than placebo and at a higher level than apparently occurs with stimulants and tricyclics. Because some ADHD individuals do not respond to stimulants, and because some stimulants have prohibitive side effects and in some cases there is parental concern about usage of controlled drugs, future studies of nonstimulant treatment, including those with bupropion, are much needed.

Drug names: bupropion (Wellbutrin), methylphenidate (Ritalin).

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