

# Bupropion Hydrochloride in Attention Deficit Disorder with Hyperactivity

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## ABSTRACT

**Objective:** This is a multisite, double-blind, placebo-controlled trial to determine the safety and efficacy of bupropion in the treatment of children with attention deficit disorder with hyperactivity (ADHD). **Method:** In a four-center, double-blind comparison of bupropion ( $n = 72$ ) and placebo ( $n = 37$ ), children aged 6 to 12 years meeting *DSM-III* criteria for ADHD were randomized to receive bupropion 3 to 6 mg/kg per day or placebo, administered twice daily, at 7 A.M. and 7 P.M. Measures of efficacy included the Conners Parent and Teacher Questionnaires (93-item, 39-item, and 10 item), Clinical Global Impressions Scales of Severity and Improvement, the Sternberg Short-Term Memory Task, and the Continuous Performance Test. Screen and posttreatment physical examinations, electrocardiograms, electroencephalograms, and clinical laboratory evaluations were performed. Height, weight, and vital signs were measured and adverse experiences were assessed weekly. **Results:** A significant treatment effect, apparent as early as day 3, was present for both conduct problems and hyperactivity on the Conners 10-item and 39-item teacher's checklist, and at day 28 for conduct problems and restless-impulsive behavior on the 93-item parent questionnaire. Findings were of smaller magnitude for parent ratings than teacher ratings. Significant treatment effects were present on both the Continuous Performance Test and memory retrieval test. Effect sizes of bupropion/placebo differences for teacher and parent ratings in this study were somewhat smaller than for standard stimulant drugs used to treat ADHD. Bupropion appeared to be well tolerated in most children. Dermatological reactions were twice as frequent in the drug group as the placebo group, with four reactions involving rash and urticaria that were serious enough to require discontinuation of medication. **Conclusions:** Bupropion may be a useful addition to available treatments for ADHD. Comparative trials with such standard drugs as methylphenidate are warranted to determine the relative clinical merits of bupropion. *J. Am. Acad. Child Adolesc. Psychiatry*, 1996, 35(10):1314–1321. **Key Words:** bupropion, attention deficit disorder with hyperactivity, attention-deficit hyperactivity disorder.

Bupropion hydrochloride is a monocyclic phenylamino ketone structurally related to the phenylisopropylam-

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ines, with significant antidepressant effects (Preskorn and Othmer, 1984) (Fig. 1). Its mechanism of action is unclear. Bupropion does not interact with neurotransmitters or inhibit monoamine oxidase. A weak indirect dopamine agonist effect has been reported from animal studies but does not seem sufficient to explain its antidepressant activity (Cooper et al., 1980; Ferris et al., 1983). Recent data indicate that in humans, bupropion decreases whole body norepinephrine turnover, but effects do not appear to depend on reuptake blockade (Golden et al., 1988). In rats, bupropion decreases the firing rates of noradrenergic neurons in the locus ceruleus (Shea and Wang, 1985) at doses found to be active in animal models of antidepressant activity. These data suggest that bupropion's effects on the noradrenergic system may be responsible for its antidepressant activity.

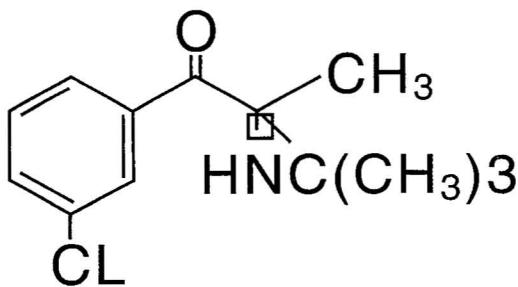
Both dopaminergic and noradrenergic mechanisms have been postulated in attention deficit disorder with hyperactivity (ADDH) (Shekim et al., 1983; Zametkin and Rapoport, 1987). Interest in the use of bupropion in children with ADDH derives from these putative catecholamine actions. In a previous single-blind trial of bupropion, Simeon et al. (1986) reported moderate to marked improvement in global behavioral measures in 12 to 17 inpatient child subjects with ADDH or conduct disorder. This article will report on the results of a multicenter, double-blind trial of bupropion hydrochloride in children with ADDH and a possible secondary diagnosis of conduct disorder.

## METHOD

The study was a 6-week, parallel-group, randomized, double-blind comparison of bupropion ( $n = 72$ ) and placebo ( $n = 37$ ). Four centers collaborated in the investigation. Subjects were children aged 6 to 12 years who met the *DSM-III* criteria for ADDH. A 1-week, single-blind washout period with placebo preceded the double-blind randomization to bupropion or placebo and was repeated at the conclusion of the active drug trial.

### Subjects

The following inclusion criteria were used for subject selection: (1) a score of moderate illness severity on the Child Diagnostic Scale; (2) a physician diagnosis of ADDH, based on history and examination; (3) occurrence of mean parent and teacher scores of at least 1.5 on the Conners Parent Questionnaire Hyperactive-Immature or Conduct Disorder factors, and the Hyperactive or Conduct Disorder factors from the Conners Teacher Questionnaire; and (4) in good physical health and without evidence of laboratory, electroencephalographic (EEG), or electrocardiographic (ECG) abnormalities. Subjects were all recruited from university-based outpatient psychiatry clinics, and at one site some were recruited from child psychiatric inpatient admissions ( $n = 6$ ). All sites also placed local advertisements. Subjects were not reimbursed or charged for services connected with the study. Recruitment took place over a 3-year time period because of a temporary discontinuation of the study due to regulatory issues involving concurrent adult studies with the drug. The number of subjects screened generally far exceeded the number accepted, owing to the strict entrance criteria.



**Fig. 1** Structure of bupropion hydrochloride.

For example, at the senior author's site there were 165 patients screened, or about one fifth of the total entered.

Exclusion criteria were as follows: (1) WISC-R IQ <70; (2) body weight <20 kg; (3) girls who had passed menarche; (4) known hypersensitivity to psychotropic medications; and (5) history or presence of seizure or tic disorders. All subjects had to be free of psychotropic medications for a minimum of 14 days prior to study entry. Permission for study participation was obtained from the parents of all subjects prior to enrollment.

### Medication

Subjects were randomly assigned to bupropion or placebo in a 2:1 ratio to allow increased assignment to active drug while maintaining statistical power and sound double-blind conditions. Bupropion, consisting of 50-mg and 75-mg tablets, or matching placebo tablets were dispensed weekly to the parent in bottles for supervised administration. Three weight ranges (20 to 30 kg, 31 to 40 kg, and >40 kg) were used to determine medication dosage schedules. All treatment-phase medications were administered twice daily at 7 A.M. and 7 P.M. During the initial 1-week single-blind phase, all subjects received placebo tablets once daily. Subjects were then randomized for the 4-week, double-blind, flexible-dose treatment phase of the trial. Dosage was escalated from 3 mg/kg of body weight from day 1 to day 3 to 6 mg/kg from day 15 to day 28.

A maximum total dose of 150 mg/day was established for the lowest weight range, 200 mg/day for the middle range, and 250 mg/day for the heaviest weight range. A log of medication administration was kept by the parent and reviewed weekly by the research assistant and study physician, together with tablet counts of medication remaining in the returned bottle to monitor medication compliance.

### Efficacy Assessments

*Parent and Teacher Questionnaires.* The 93-item version of the Conners Parent Questionnaire and the 39-item version of the Conners Teacher Questionnaire were used (Conners, 1969, 1970). Each contains symptoms rated by the observer on a 4-point Likert scale (not at all, just a little, pretty much, very much). Three factors were used from the Parent Form (Hyperactive-Immature, Restless-Impulsive, and Conduct Disorder), and two factors were chosen from the Teacher Form (Hyperactivity and Conduct Disorder). These questionnaires were used to establish initial symptom severity for subject selection and were completed at screening, day 0, day 14, day 28, and day 35 by both parent and teacher.

*Abbreviated Parent and Teacher Questionnaires.* Ten items known as the "Hyperactivity Index" comprise the highest-loaded items from the other factor scales, and these were rated at all assessments by parent and teacher. Items from the abbreviated teacher form have been further separated into two distinct subfactors for analysis purposes, one relating to aggression and the other to hyperactivity (Loney and Milich, 1982; Pelham et al., 1989).

*Clinical Global Impressions Scales.* The Clinical Global Impressions-Severity Scale (CGI-S) is a measure of symptom severity on a 7-point scale (1 = "normal, not at all ill" to 7 = "among the most extremely ill patients"). It was completed by the study physician at initial subject assessment and at each assessment thereafter for each subject (NIMH, 1985). A separate global rating of improvement, the Clinical Global Impressions-Improvement Scale (CGI-I), was made at each assessment beginning with baseline (1 = "very much improved," 4 = "no change," 7 = "very much worse").

*Short-Term Memory Test.* A computerized test of memory retrieval time, requiring a "yes/no" response to a probe letter, was completed at baseline on day 0, and again on day 28. The probe was randomly present 50% of the time in the memory set that preceded it. Memory set size was either one, three, or six letters. Each test was composed of 60 trials, 20 at each set size. This is a test widely used in experimental cognitive psychology that is not normed. However, it was included in the study because a comparison of the active drug and placebo effects on short-term memory processes would be informative with respect to the question of possible interactions between memory load and drug effect. This is similar to the testing paradigm used in Sprague and Sleator's (1977) classic paper on methylphenidate and cognitive load.

*Continuous Performance Test.* A test of vigilance presented letters on a computer monitor at 1-second intervals, using subject responses to visual "X" or "B-X" targets occurring 20% of the time in a series of letters (Conners, 1985; Swanson, 1985). Fifty targets were presented in each segment of the test. Correct responses, and errors of omission and commission, were recorded on day 0 and day 28.

### Safety Examination

*Physical Examination.* A medical history, review of systems, and complete physical examination were done at screening, including height, weight, and vital signs. Subsequently, height, weight, and vital signs were measured at each assessment throughout each subject's study participation.

*Laboratory Battery.* Routine laboratory tests were obtained at day 0 and again at day 28, and these included (1) hematology (platelet estimation, hemoglobin, hematocrit, total red blood cell count, and total white blood cell count with differential); (2) blood chemistry (calcium, creatinine, glucose, uric acid, blood urea nitrogen, total cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase); (3) blood sample for plasma prolactin and growth hormone levels; (4) routine urinalysis; (5) ECG; and (6) EEG.

### Statistical Analysis

All variables were first examined for site by treatment by day interactions. If interactions with site were nonsignificant, then data were pooled across sites in subsequent analyses. Efficacy measures were examined in a repeated-measures analysis of covariance (ANCOVA), with treatment being a between-subjects factor (drug versus placebo), with day (0, 3, 7, 14, 21, 28) and treatment by day interaction being within-subject factors. The baseline assessment (day 0) was used as a covariate. For the Conners Parent-Teacher Abbreviated (10-item) Questionnaire and the CGI scales, days 3, 7, 14, 21, and 28 were used for the within-subject repeated measure. For the longer forms of the Conners Parent and Teacher Questionnaires, days 14 and 28 were used for the repeated measure. Planned comparisons for examination of significant treatment by day interactions were carried out with unidirectional *t* tests. All analyses were carried out for both the final sample (observed), and for the original sample with last observation carried forward (LOCF). Where results differ for the two methods, they are reported separately.

## RESULTS

### Sample Description

The sample consisted predominantly of white (75%) male (90%) schoolchildren of about 8.5 years of age

in the third grade or lower (66%), with slightly more than half performing in an average to superior range in school. Drug and placebo groups were comparable in birth order, paternal education, and previous treatments.

The 10 to 1 ratio of males to females in this sample was typical of clinic samples of *DSM-III ADDH* in many outpatient settings at the time recruitment for the study began. Epidemiological studies indicate a somewhat smaller ratio of boys to girls than appear in clinical settings. The fact that patients could be entered with either a high Hyperactivity or Conduct Problem parent rating probably favored the recruitment of subjects with higher levels of externalizing symptomatology, more of whom are males. The parents were predominantly high school or college educated (81%). Most children (85%) had had symptoms of ADDH for more than 2 years, and almost half (45%) had received some form of psychiatric treatment for their problems. Tests of differences between the drug and placebo groups for these variables by *t* test and  $\chi^2$  showed no significant differences. There was, however, a trend for the bupropion group to contain more of the children with above-average school performance (40% versus 15%;  $\chi^2 = 3.15$ ,  $p < .076$ ).

### Efficacy Measures

Table 1 presents the observed scores for the teacher and parent 10-item scales, and Table 2 presents the results of the ANCOVA for all parent and teacher rating scales. Figure 2 presents Hyperactivity factor scores for the 39-item teacher and 93-item parent scales. A significant treatment by day interaction indicates that the two treatments differ in their effects at different time points of the study.

*Teachers.* The results indicate that a significant treatment effect is present for both Conduct Problems and Hyperactivity on the 10-item teacher checklist and the longer Conners Teacher Questionnaire. However, this latter finding with the Hyperactivity factor scale is somewhat tempered by the failure of this measure to attain significance in the LOCF analysis ( $p < .08$ ). Nevertheless, the treatment effect noted on the 10-item form indicates that teachers clearly discerned a positive bupropion effect. Analysis of differences for each evaluation day using *t* tests indicates that teachers noticed the effect as early as the third treatment day ( $p < .02$ ). The teachers failed to detect any significant

**TABLE 1**  
10-Item Teacher and Parent Ratings: Observed Scores

Period	Day	<i>n</i>	Placebo		Bupropion		
			Mean	SD	<i>n</i>	Mean	SD
<b>Parent</b>							
Screen	-7	34	22.53	4.72	67	21.64	5.00
Baseline	0	36	20.67	6.07	69	19.55	5.62
Drug	3	31	16.68	6.86	61	16.10	6.23
	7	34	17.32	7.27	68	15.79	6.35
	14	35	16.97	7.28	64	16.02	6.53
	21	33	16.33	6.53	63	15.19	6.78
	28	34	16.91	7.57	62	13.81	6.83
	Post	35	17.29	7.43	61	15.21	7.52
	Teacher						
Screen	-7	32	21.50	4.08	62	20.35	5.21
Baseline	0	36	20.58	5.89	69	20.03	5.62
Drug	3	28	19.32	6.64	59	16.78	6.13
	7	31	19.61	5.79	61	16.23	5.86
	14	30	19.23	7.01	62	15.95	6.07
	21	30	18.73	5.79	57	15.37	7.05
	28	27	19.11	6.15	54	14.67	6.97
	Post	35	19.40	8.30	52	16.37	6.62

difference between treatment groups on day 35, the last day of a week of treatment in which both groups received placebo.

Further analysis was undertaken of the Aggression and Hyperactivity subfactors for the 10-item teacher

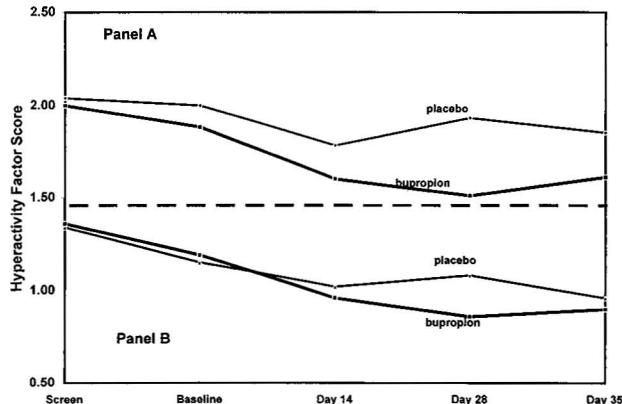
questionnaire. Net changes were examined comparing baseline and days 14, 28, and 35. Results indicate that significant treatment effects on the aggression subscale were present at day 28 ( $p < .015$  and  $p < .027$  for observed and LOCF scores, respectively) and at day 14 and day 28 for the Hyperactivity subscale ( $p < .01$  on both days for observed scores;  $p < .01$  on day 14 and  $p < .06$  on day 28 for LOCF scores).

**Parents.** Parents did not distinguish any treatment effects on the weekly 10-item checklist. However, on

**TABLE 2**  
Teacher and Parent Ratings: Probability Values for Treatment and Day Effects

	Treatment	Treatment $\times$ Day
<b>10-Item form (LOCF)</b>		
Teacher	.0003	NS
Parent	NS	NS
<b>10-Item form (observed)</b>		
Teacher	.001	NS
Parent	NS	NS
<b>39-Item teacher form (LOCF)</b>		
Conduct Disorder	.05	NS
Hyperactivity	.08	NS
<b>39-Item teacher form (observed)</b>		
Conduct Disorder	.02	NS
Hyperactivity	.03	NS
<b>93-Item parent form (LOCF)</b>		
Conduct Disorder	NS	.01
Restless-Impulsive	NS	.01
Hyperactive-Immature	.06	NS
<b>93-Item parent form (observed)</b>		
Conduct Disorder	.09	.017
Restless-Impulsive	.096	.013
Hyperactive-Immature	.02	NS

*Note:* LOCF = Last observation carried forward; NS = not significant.



**Fig. 2** Hyperactivity-Impulsivity factor scores from 39-item teacher scale (A) and 93-item parent rating scale (B). Post hoc *t* tests indicate a significant difference between drug and placebo at day 28 for the parent scale ( $p < .02$ ) and at days 14 and 28 for the teacher scale ( $p < .01$  for both days for observed scores, and  $p < .01$  and  $p < .06$  for last-observation-carried-forward scores).

the 93-item Conners Parent Questionnaire, there were significant treatment by day interactions for Conduct Problems and Restless-Impulsive behavior at day 28 ( $p < .01$ ).

**Clinical Global Impressions.** Both the CGI-S and CGI-I showed significant treatment by site interactions throughout the course of treatment. While two sites showed a significant effect of bupropion on the CGI-S and one site reported a significant CGI-I, the pooled results from the four sites failed to demonstrate a significant treatment or treatment by day interaction on either measure using repeated-measures ANCOVA. Results were identical for LOCF and observed data.

#### Cognitive Measures

**Continuous Performance Test.** This test was administered at baseline and on day 28 only. Data were log-transformed prior to analysis because of severe skewness. Pre- and posttest scores were used as repeated measures, with treatment and site as between-subjects variables. Age was also used as a covariate because of a strong age correlation with scores. Of main interest is the treatment by day interaction. There was a slight improvement in the bupropion group, accompanied by a slight worsening in the placebo group. This was significant for the more difficult "B-X" task ( $F[1,89] = 4.50, p < .037$ ). Results did not differ for LOCF and observed data. There was a near-significant site effect ( $p < .095$ ) due to one site, which mistakenly administered only half as many trials as other sites, but no treatment by site interaction. Part of the treatment effect appeared to be due to the offsetting of a performance decline associated with repeated administration of the test.

**Memory Retrieval Time.** Analysis of errors indicates that there were no treatment effects on errors. (This is a desirable effect in this type of test because the main interest centers on the speed of response to the probe stimulus as a function of set size for accurate responses.) Reaction time scores were log-transformed. Data were analyzed with treatment and site as between-subjects factors, and pre/post and set size (one, three, or six items per set) as repeated-measures factors. Age was used as a covariate. There were no significant treatment by site interactions, indicating similar patterns of response at all four sites. Main interest centers on interactions with treatment. There was a significant treatment effect interaction (treatment by pre/post  $F[1,62] = 4.14, p < .046$ ). Since there was no further

interaction of this effect with set size, it appears that speed of memory retrieval was enhanced irrespective of memory load.

#### Safety and Tolerance

**Vital Signs.** Vital signs from baseline to each return visit were examined by  $t$  tests for net difference between bupropion and placebo changes. There were no statistically significant effects on height, weight, or standing systolic or diastolic blood pressure. However, statistical trends were noted for supine blood pressure ( $p < .06$ ). There was a minor relative increase in supine systolic blood pressure on day 28 (a decrease of 2.3 mm Hg in the placebo group, compared with an increase of 2.4 mm Hg in the bupropion group). A relative increase of 4.7 beats per minute (bpm) in standing pulse was noted on day 28 (a decrease of 2.9 bpm in the placebo group, compared with an increase of 1.8 bpm in the bupropion group) ( $p < .04$ ).

**Electrocardiogram.** There was a mean heart rate increase of approximately 2 bpm in the bupropion group and a mean decrease of approximately 5 bpm in the placebo group. The net difference was statistically significant ( $p < .009$ ). There was no change in the QT interval in the bupropion group, but a slight increase was observed in the placebo group (from 0.36 second to 0.37 second); the net difference was significant at  $p < .02$ . There was a decrease of about 4 degrees in the *R* axis for the placebo group, and an increase of about 5 degrees in the bupropion group. This net difference reached statistical significance ( $p < .015$ ). No statistically significant differences in PR interval or QRS duration were observed.

**Hematology.** Hematological results were compared between screening and drug termination days. There was a slight drop in monocytes in the placebo group (mean change = 0.25%) and a slight increase in the bupropion group (mean change = 0.41%), which resulted in a significant net difference ( $p < .04$ ). No other measures showed statistically significant mean changes.

**Blood Chemistry.** There was a slight mean increase of blood urea nitrogen levels in the placebo group (mean change = 0.24 mg/dL) and a decrease of 1.55 mg/dL in the bupropion group ( $p < .005$ ). Bilirubin was unchanged in the bupropion group but slightly increased in the placebo group ( $p < .02$ ). There were no treatment-related effects for either growth hormone or prolactin.

None of the statistically significant differences noted on the above safety parameters were considered to be clinically important.

*Treatment-Emergent Adverse Experiences.* In general, side effects were infrequent. Dermatological and gastrointestinal complaints were the most frequently encountered symptoms in the bupropion group. Although 16.7% of the bupropion patients complained of nausea and vomiting, there was almost an equal rate of such complaints (13.5%) in the placebo group. Twelve bupropion patients, or 16.7%, had a rash versus 8.1% in the placebo group. Four patients were discontinued from the study because of apparent allergic reactions to bupropion (skin rash with urticaria). One of these four patients had a low-grade fever with flushing, swelling of the lower extremities, and pruritus. All other adverse experiences were managed by lowering the dose or adding a concomitant medication allowed in the protocol (such as mild topical anesthetics, aspirin). Four additional bupropion patients discontinued the study prematurely, three because of ineffectiveness and one who did not return for scheduled visits. Two placebo patients discontinued the study prematurely, one because of ineffectiveness and one who did not return.

*Electroencephalogram.* All patients received an EEG at baseline and again on the final day of active treatment. No patients showed any evidence of clinical seizure activity during treatment. Abnormal findings are reported in Table 3.

All EEGs were collected and read by local pediatric neurologists at each site. Ten cases with abnormal findings that warranted further investigation were reviewed by a pediatric neurologist. Of the 10 cases with abnormal findings, 4 were judged abnormal at both baseline and day 28 and appeared not to be drug-related. Two of those four patients demonstrated diffuse background slowing at each recording, and one displayed potentially biphasic waves at baseline and occipital sharp waves at both discontinuation and a follow-up EEG. One patient in the placebo group displayed rolandic discharges, which are common to this age group and often not associated with clinical seizures.

EEGs of six patients receiving bupropion went from normal to abnormal. Slow waves appeared after treatment in one patient, and though the patient may simply have been drowsy at the recording, a drug effect cannot be ruled out. Two patients showed spike-and-wave discharges at day 28 after a normal recording at

baseline. One patient showed spike-and-wave discharges at day 28 but showed no abnormalities at baseline or at a 3-month follow-up visit. Two other patients who had normal EEGs at baseline showed rolandic discharges at day 28. Neither of these children achieved sleep at the baseline EEG. Since rolandic discharges are very often only present in light sleep, both patients may have had rolandic activity prior to drug administration that was not detected.

The regulatory agreement for this study did not permit continued open-label follow-up of the drug. At the end of the study all subjects were discontinued from bupropion and placebo. They were then given appropriate clinical referral information and no further study follow-up was maintained.

## DISCUSSION

The teacher rating scales in this study provide strong evidence that bupropion reduced hyperactivity and aggression in a group of children with conduct and attention problems. Parents also reported significant reductions of symptoms, but these effects were less reliable and of less magnitude. Whereas teachers saw an immediate effect after day 3 of treatment, parents did not reliably detect improvement until the fourth week of treatment (day 28). Part of this difference between parents and teachers may reflect the sizable placebo effect in the parent ratings. For example, whereas the decrease in the placebo group for the parents' 10-item ratings averaged about 7 points, the teachers' ratings in the placebo group never declined more than 2 points. This represents a difference of more than three standard errors in the placebo effect.

The teacher and parent rating scale data stand in contrast with the results of the investigator-rated CGI scales. For the latter there were sizable treatment by site interactions, indicating that some sites were detecting global effects that others did not. Stimulant drug studies of hyperactive and aggressive children have generally shown that clinical global impressions are sensitive and reliable indicators of drug effect (Werry et al., 1976). No satisfactory explanation can be offered for the failure of the CGI results to be consistent across sites in this investigation. The study procedures should have made it difficult to confound improvement ratings by knowledge of side effects. While all investigators were experienced clinicians, the results underscore the need

**TABLE 3**  
Electroencephalogram Results

Patient	Tx	Baseline EEG		Discontinuation EEG		Follow-up	
		Result	Description	Result	Description	Result	Description
102	B	Normal		Abnormal	Slow waves	Abnormal	
303	B	Abnormal	Posterior polyphasic; potentially biphasic	Abnormal	Occipital sharp waves R>L	Abnormal	Sharp waves R>L; no change from previous EEG
311	B	Normal	No sleep achieved	Abnormal			
325	B	Normal		Abnormal	Spike and wave complexes	Normal	
405	B	Normal	No sleep achieved	Abnormal	Rolandic spike		
410	B	Normal		Abnormal	Spike and wave		
413	B	Abnormal	Diffuse background slowing	Abnormal	Diffuse background slowing		
415	B	Abnormal	Diffuse background slowing	Abnormal	Diffuse background slowing		
421	B	Normal		Abnormal	3/sec spike and wave		
423	P	Abnormal	Rolandic spikes	Abnormal	Spike & slow wave considered to be rolandic		

Note: B = bupropion; P = placebo.

for all multisite investigations to require rater training-in-common prior to the enrollment of subjects, to ensure acceptable interrater reliability. Furthermore, these between-site findings of varying sensitivity on the CGI scale emphasize the importance of relying on standardized instruments in drug trials.

The results of the cognitive studies are weakened to some extent by the smaller number of occasions on which they were administered and by substantial amounts of missing data due to technical problems or administrative errors. Nevertheless, the most demanding part of the CPT, the "B-X" task, showed a significant drug effect in reducing errors of omissions. Thus, like stimulant drugs, which often reduce errors of omission in studies of hyperactive children, bupropion appeared to do more than simply calm the child behaviorally.

Results of the Sternberg Short-Term Memory Task are consistent with the demonstrations by Sergeant and colleagues (Sergeant and van der Meere, 1988) that stimulants alter the intercept of the response function relating reaction time to memory load, not its slope. This suggests bupropion is primarily acting upon response processes, rather than stimulus encoding or memory capacity. There is an overall improvement in response efficiency, without change in performance in relation to the size of the memory load. However, it should be noted that the memory load (load = set

size × probe size) is relatively small compared with the load employed in Sprague and Sleator's classic study, which showed a curvilinear relation of set size to stimulant dosage (Sprague and Sleator, 1977).

An important issue is the magnitude of the clinical effect achieved by bupropion. First, it should be noted that the bupropion group improved below the subject selection cutoff of 15 points of the 10-item Conners scale commonly used for clinical identification of patients. The observed improvement of about 5 to 6 points on this scale with bupropion may be compared with the 10-point change seen by teachers with pemoline (Conners et al., 1972). The change with bupropion is approximately the same as the effects of a good behavior therapy program (Pelham et al., 1980). The changes on the Aggression and Hyperactivity subfactors of the 10-item scale are approximately half a standard deviation. In behavioral research, this is considered a moderate size effect (Cohen, 1987). Meta-analyses of stimulant drug effects consistently show effect sizes of 0.8 to 0.9 for behavioral measures—a very large effect in Cohen's terminology (Kavale, 1982; Ottenbacher and Cooper, 1983; Thurber and Walker, 1983). Although comparisons across different methodologies, subjects, dosing, etc., are hazardous, these studies suggest that the effects in the present study are somewhat less robust than the standard stimulant drugs used to treat ADDH.

Bupropion appeared to be well tolerated in most children receiving the drug. The most frequently encountered adverse effects were dermatological (16.7% in the bupropion group versus 8.1% in the placebo group) and nausea/vomiting (17% for bupropion versus 13.5% for placebo). That four children had an allergic response to the medicine underlines the importance of careful follow-up evaluations. Minor differences were noted for ECG, hematological, and liver function findings, but these were thought to be of no clinical significance. Six patients showed an abnormal EEG at day 28 that was not present at baseline. Three of these were spike-and-wave discharges. Since these abnormalities are often missed in a single 20-minute recording, it is possible that they were present but missed in the baseline sampling. One patient showed an increase in slow waves at day 28. This was a child in a single-parent family whose biological mother had a history of diazepam and alcohol abuse during pregnancy. The three patients with spike-and-wave discharges had no family psychiatric or medical history factors related to their condition.

Experience with seizures in depressed adults receiving bupropion has shown the rate to be approximately 0.4%. Because the current trial in children with ADDH was limited to 4 weeks of bupropion treatment, no generalization to possible occurrence of seizures with treatment over a longer period of time can be made. Although the role of the drug in inducing observed EEG changes must remain uncertain because of the many factors that influence recordings in children, the overall rate of such findings in the study is quite small. Most importantly, no actual clinical seizure abnormalities were observed in any of the study subjects.

The results of this investigation indicate that bupropion may be a potentially useful addition to the available clinical treatments for ADDH and, perhaps, for conduct disorder in children. The present study offers evidence that clinically meaningful changes are detected by teachers, and to a lesser extent by parents, within a few days of initiating treatment. There are also signs of modest improvements in cognitive functions of attention and memory retrieval. As with all new treatments, however, a conservative approach is advised, involving careful physical examinations at baseline and during treatment, continuous monitoring of parent and teacher observations, frequent recording of side effects, and other objective measures of improvement,

such as academic progress, when these are available. It will now be important to undertake comparative drug trials with standard drugs such as methylphenidate, dextroamphetamine, and pemoline in order that the relative clinical merits of bupropion can be determined.

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