Eur J Clin Pharmacol (1984) 27: 75–80

European Journal of Clinical Pharmacology

The Effect of Bupropion, a New Antidepressant Drug, and Alcohol and Their Interaction in Man

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Summary. The effects of bupropion and ethanol were examined alone and in combination in a placebo controlled, double-blind, crossover study in 12 healthy volunteers. Results were subjected to analysis of variance and differences of $p < 0.05$ taken as significant. In the main study using the Wilkinson auditory vigilance test, no active treatment or combination of treatments produced significant change compared with placebo. However, when compared with bupropion 100 mg, vigilance was significantly impaired by 32 ml alcohol alone though not when combined with bupropion. No significant changes in reaction time or short term memory occurred. Visual analogue scales indicated that the subjects were mentally slower after alcohol 32 ml than after placebo. Combination of bupropion 100 mg with alcohol 32 ml abolished this difference. A similar pattern occurred with group ratings indicating mental sedation. Subjects were clearly able to differentiate between the 16 ml and 32 ml doses of alcohol when assessing their degree of inebriation. Combination of bupropion with alcohol made no difference to the ratings of inebriation. The top dose of alcohol tended to increase energy in the low frequency EEG bands. Combination of the top alcohol dose with bupropion, however, produced a significant reversal with lowered energy in the 4–7.5 Hz band. Combination of bupropion with alcohol failed to change the blood alcohol concentration achieved.

Key words: bupropion, alcohol interaction; healthy volunteers, performance, autonomic functions

Bupropion (Fig. 1) is a novel antidepressant drug (Zung 1983). Its mechanism of action is uncertain, but it is considerably weaker in inhibiting catecholamine uptake into synaptosomes than currently available tricyclic compounds (Soroko et al. 1977). These latter workers also established that the drug lacked anticholinergic properties and was unlikely to have stimulant effects of an amphetamine type. Bupropion does not produce subjective changes in normal volunteers in does up to 200 mg administered orally (Peck et al. 1979; Hamilton et al. 1983). While clinical studies reveal that improvement in ratings of anxiety occur pari passu with improvement in ratings of depression, co-prescribing of anxiolytic drugs such as diazepam may be required, and a recent study in healthy volunteers revealed no deleterious interaction when diazepam and bupropion were administered concurrently (Hamilton et al. 1982). This investigation revealed the expected subjective and objective impairment from diazepam and the lack of any changes in tests or ratings after bupropion. When administered together, however, bupropion appeared to reverse the impairment produced by diazepam.

It is extemely likely that some patients receiving bupropin during treatment for an episode of depressive illness will also take alcohol socially. This study investigates the effects of bupropion and alcohol alone and in combination on several pharmacodynamic variables, and also presents some limited pharmacokinetic data.

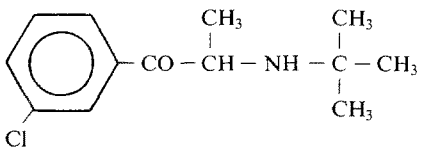

Fig. 1. Bupropion

Table 1. Analysis of d′ and β. The ratios d′ and β (Swets, Tanner and Birdsall 1961) were calculated and are approximate in that 1 false detection was added to each subject's score in each test to achieve a finite number in every case (Peck and Fowle 1980). Mean values for 12 subjects after the 6 treatments were then ranked in ascending order. Values not underlined by a common bar are significantly different ($p < 0.05$).
Abbreviations for treatments were: bupropion placebo and bupropion hydrochloride 100 mg, B0 and B100 respectively; alcohol placebo, 16 ml and 32 ml, A0, A16 and A32 respectively

Time post drug		Treatment means					
1 h–2 h	d′	B0A32	B0A0	B0A16	B100A32	B100A16	B100A0
		2.74	2.78	2.82	2.86	2.88	2.96
	β	B100A16	B0A0	B100A0	B100A32	B0A32	B0A16
		63.0	75.1	75.4	78.7	83.5	110
4 h 15 min–5 h 15 min	d′	B0A32	B0A0	B100A32	B100A16	B0A16	B100A0
		2.80	2.85	2.98	3.03	3.06	3.24
	β	B0A0	B0A32	B100A16	B100A32	B100A0	B0A16
		87.2	93.6	96.1	103	113	119

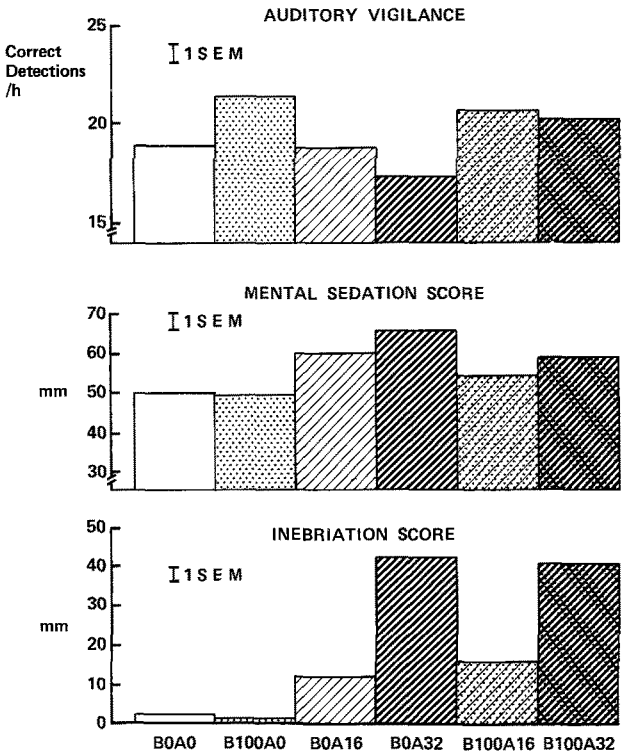

Fig. 2. Signals detected per hour by the 12 subjects in the 2 Wilkinson Auditory Vigilance tests are shown. The SEM is derived from the analysis of variance and is the same for all treatment groups. The mental sedation score is derived from the visual analogue scales: alert, drowsy; muzzy, clearheaded; mentally slow, quickwitted; and attentive, dreamy. The inebriation score was recorded on the scale, completely sober, extremely drunk. Both scores are for 2 h 40 min post treatment. – *Abbreviations* as for Table 1

Experimental Methods and Procedure

Preliminary Study

Awareness of the difficulties of producing an alcohol placebo and the problems of maintaining double blind conditions when studying alcohol prompted a short preliminary study.

Twelve healthy volunteers (5 male and 7 female) participated. The men were aged 20–57 years (mean 35) and the women 22–48 years (mean 31). The subjects were moderate social drinkers, and were allowed a normal breakfast before 09.00 h but no coffee, tea, cigarettes or alcohol after that time.

All subjects received each of the following 6 treatments at intervals of at least 1 day. The six treatments contained 0, 2, 4, 8, 12 and 16 ml ethanol all made up to 200 ml in an orange flavoured drink. Order of administration for each subject was balanced according to two, 6×6 Latin square designs. The drinks were administered at 12.00 h and immediately after consumption subjects were asked if they thought they had received alcohol. After 1 h during which the subjects ate lunch they were asked again if they thought they had received alcohol. The data were analysed by comparing the proportion of subjects who detected with those who failed to detect each dose of alcohol, using a two tailed chi-square analysis.

Main Study

Twelve healthy volunteers were recruited; the 6 women were aged 20–25 years (mean 22 years) and the 6 men were aged 20–31 years (mean 26 years). Subjects were chosen who did not regularly drink more than 3 pints of beer or 3 double measures of spirits per day. They were allowed a light breakfast before 08.00 h, but no tea, coffee, cigarettes, or alcohol (other than the test alcohol), until the end of the experimental day.

Drugs and Dosage

The study was a double blind, placebo controlled crossover trial consisting of 6 treatments as follows:

Bupropion placebo + alcohol "placebo"
Bupropion HCl 100 mg + alcohol "placebo"
Bupropion placebo + alcohol 16 ml
Bupropion placebo + alcohol 32 ml
Bupropion HCl 100 mg + alcohol 16 ml
Bupropion HCl 100 mg + alcohol 32 ml

Bupropion placebo and bupropion (Wellbutrin) were prepared as film coated tablets (100 mg size) identical in appearance and taste. The bioavailability and pharmacokinetics of this tablet have been described (Lai and Schroeder 1983). Alcohol and alcohol placebo solutions were prepared as an orange flavoured, iced drink to a total volume of 200 ml. One ml rum was applied to the rim of the glass to confuse the subjects. Alcohol or its placebo were given over 10 min, beginning 30 min after ingestion of the tablets.

The 12 subjects received all 6 treatments at weekly intervals according to two 6×6 Latin square designs which were balanced for occasion, treatment, and preceding treatment. Subjects were studied in groups of 4 on each experimental day. Each group comprised the same 4 people on each occasion and was studied on the same day of the week.

Alcohol Pharmacokinetics

"Blood" ethanol concentrations were established before the main study for the same subjects, with conditions of food, sleep, absence from other drugs etc., identical to those used during the study proper. Frequent measurements of alcohol levels during the study would have disrupted performance testing. Alcohol concentrations were measured indirectly from the expired air using an AE-DI alcolmeter (Lion Labs., Ltd.). In the double blind study measurements were made by an independent observer (with subject and experimeter unaware of values) before drug administration and 2 h 45 min and 6 h after treatment.

Variables Measured

Tests were conducted in a soundproof room which was maintained at 21($\pm$2) °C, and subjects were observed using one-way glass mirrors and TV monitors. Details of tests have been described previously (Hart et al. 1976).

Autonomic variables were:

1) Heart rate (counted over 30 s);
2) Blood pressure (supine);
3) Pupil size (recorded using a fixed focus camera)

Performance was assessed by:

1. Auditory vigilance test devised by Wilkinson (1968). The subjects listened via headphones to a tape recording for 1 h during which 0.5 s tones occurring every 2 s were replaced at random intervals by tones of 0.4 s duration. On detecting these shorter tones subjects pressed a button.
2. Auditory reaction time test of 15 min duration consisting of a randomly occurring tone. On hearing the tone subjects pressed a microswitch as rapidly as possible.
3. Short term memory test lasting 15 min consisting of 90 series of 8 digits. Subjects wrote down the series at the end in 5 s. The number of errors was counted.
4. Tapping test in which subjects tapped a microswitch as rapidly as possible for 1 min. The total number of taps was recorded.

Subjective effects were measured using visual analogue scales.

All the subjects practised the tests the week before the study began.

EEG Recordings

Bipolar surface recordings were made from positions Fz and Pz and referred to the left mastoid process, according to the method of Jasper (1958). Recordings were made using a Grass polygraph with 50 Hz filters in use and amplifier band width set at 0.1–60 Hz. The EEG was simultaneously recorded on a 7-channel FM tape recorder for subsequent playback. Analysis of the EEG was made by measuring the voltage levels in the following frequency ranges using tuned filters: 2.3–4, 4–7.5, 7.5–13.5 and 13.5–26 Hz. Voltages for 5 s epochs of each 10 s of recording were generated and the mean $\pm$ SE of these values for each subject were computed for the epochs through the 10 min of eyes opened and the 3 min of eyes closed EEG.

Analysis of Results

All measured variables were subjected to analysis of variance. Main effects of treatments (with subjects and occasions as factors) were sought. Values of $p < 0.05$ were taken as significant.

Results

Preliminary Study

The subjects detected 12 and 16 ml doses of alcohol significantly ($p < 0.05$ Chi square two tailed) more often than would have occurred by chance. Detection of the two highest doses of alcohol used was not improved by reassessment after one hour when physiological effects are likely to have been more prominent. Doses in excess of the equivalent of a single measure of spirits (in the U. K.) would be difficult to disguise.

Main Study

Analysis of variance showed a singificant main effect of treatments on auditory vigilance. No active treatment significantly altered the number of correct detections on auditory vigilance when compared with placebo but alcohol 32 ml alone significantly reduced the number of signals detected when compared with each of the 3 treatments containing bupropion 100 mg (Fig. 2). While bupropion 100 mg alone or in combination with 16 or 32 ml alcohol did not produce change in signals detected when compared with placebo the combination significantly increased the number of signals detected compared with alcohol 32 ml alone.

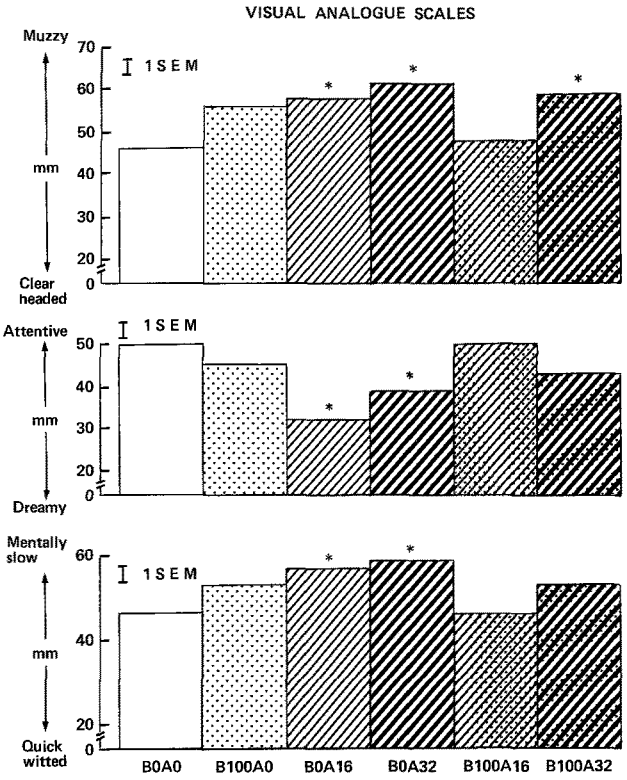

Fig. 3. Ratings on three visual analogue scale at 5 h post treatment are shown. *Abbreviations* as for Table 2. *Asterisks* indicate significant difference from placebo

Values for the ratios d′ and β reflecting the subjects' ability to discriminate between the short signal tones and the longer "noise" tones are shown in Table 1. During the first test a significant change in β indicated that subjects were more cautious in reporting signals after alcohol 16 ml than after the combination of alcohol and bupropion but no changes in d′ were seen. During the second test values of d′ indicated that after bupropion alone discrimination between signal and noise was significantly better than after the placebo or alcohol 32 ml, but there were no changes in β.

No significant changes ascribable to treatments occurred in the other performance tests.

Ratings of mental sedation and inebriation are illustrated in Fig. 2. No significant differences in the treatment groups were seen in any of the pretreatment scores. At 2 h 40 min post treatment subjects rated themselves mentally slower after alcohol 32 ml than after placebo. Combination of bupropion with alcohol 32 ml abolished this difference. A similar pattern occurred on the muzzy/clear-headed scale though here subjects rated themselves muzzier after both alcohol 32 ml treatments than after placebo.

In assessing their degree of sobriety of drunkenness subjects clearly differentiated between the treatments containing alcohol and those which did not,

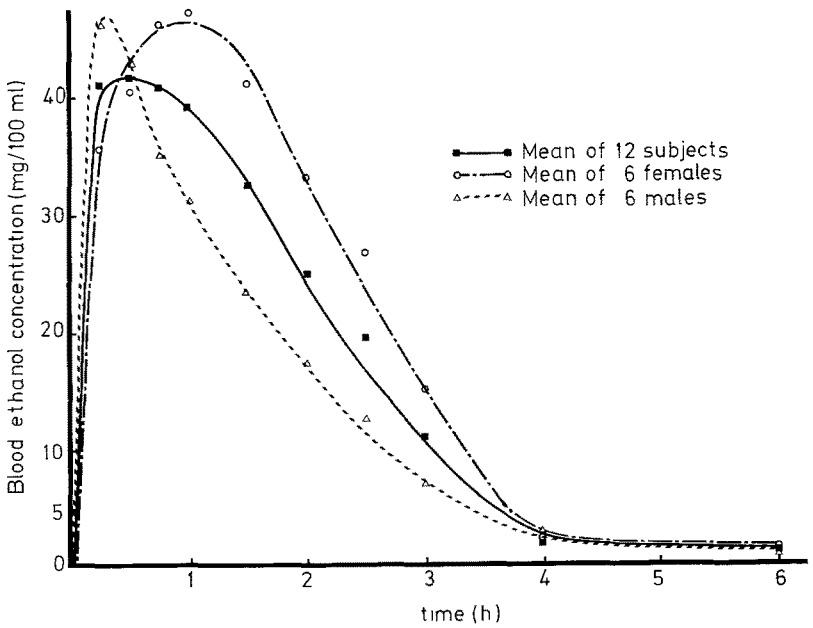

Fig. 4. Blood alcohol concentrations measured in expired air are shown for the 12 subjects and for the 6 men and 6 women up to 6 h after ingestion

and also between the 16 and 32 ml doses of alcohol. Combination of alcohol with bupropion made no difference to this assessment.

A 5 h post-treatment (Fig. 3) subjects showed similar changes on the muzzy/clear-headed dimension and also a significant difference from placebo occurred after alcohol 16 ml which appeared to be abolished by combination with bupropion. Impairment was again seen on the mentally slow/quick witted scale after both doses of alcohol and reversal of this effect when combined with bupropion. A similar pattern was seen on the dreamy/attentive dimension.

Subjects were asked whether they thought they had received alcohol and whether they thought they had received an active drug. They clearly recognised the presence of alcohol 32 ml in both treatments ($p = 0.002$). Alcohol 16 ml was recognised with less certainty and only achieved significance when combined with bupropion ($p = 0.04$). No significant differences occurred between the treatment groups in the replies to the more general question "Do you think you received an active drug?".

A significant increase in heart rate occurred 3.25 h after the combination of alcohol 32 ml and bupropion; no changes occurred in blood pressure.

A significant, though small, reduction in pupil size occurred after alcohol 16 ml both alone and in combination with bupropion.

While significant differences in the EEG between treatments and placebo were few, there was a trend for the low dose of alcohol and bupropion alone to reduce energy in the slow wave frequency bands of 2.3–4 Hz and 4–7.5 Hz. The opposite trend was seen after alcohol 32 ml alone. Again, combination of bupropion with alcohol 32 ml reversed this effect and this was significant in the 4–7.5 Hz band with the eyes closed 3 h after administration of treatment.

The pharmacokinetic characteristics of alcohol in these 12 subjects examined before the experiment proper but under very similar conditions of food ingestion, exercise and environment are shown in Fig. 4. The differences between the sexes was entirely ascribable to differences in weight. There was no significant difference between the concentrations measured after alcohol alone and with bupropion at 2.75 h under the study conditions.

Discussion

The main feature of this study is the contrast between the paucity of significant results due to administration of the active drugs alone, and the interesting pattern of significant differences which emerged when the drugs were given in combination. In the Wilkinson auditory vigilance test no treatment produced any change in signals detected which was significantly different from placebo. There was, however, a trend towards reduction of signals detected after both doses of alcohol and there was an opposite trend for signals to increase after all treatments containing bupropion. Comparing the extremes, alcohol 32 ml significantly reduced signals detected when compared with bupropion alone, bupropion and alcohol 16 ml and bupropion with alcohol 32 ml. This pattern of changes obtained in the objective test was mirrored in subjective assessments on the visual analogue scales. This is clearly seen on the quick witted-mentally slow dimension where subjects rated themselves significantly slower after the top dose of alcohol compared with placebo, but when combined with bupropion this difference had disappeared. The mental sedation score showed the same pattern quite clearly at both 2 h 40 min and 5 h post-treatment. Autonomic differences were few, but the EEG again showed a similar pattern with only one significant difference from placebo, after the combination of bupropion and alcohol 16 ml. The top dose of alcohol administered alone gave the highest mean values for energy in the two low frequency bands both with eyes open and eyes closed, 3 h after treatment. When combined with bupropion, however, mean values in the 4–7.5 Hz band were now significantly lower.

This consistent pattern of differences between alcohol alone and alcohol in combination with bupropion did not apply to ratings on the sober/drunk scale, or to recognition of alcohol or active drug by the subjects. The visual analogue scale showed clearly that subjects were able to distinguish alcohol from nonalcohol treatments, and also the 32 ml alcohol treatment from the 16 ml dose. They were not, however, able to distinguish either dose of alcohol administered alone from the same dose of alcohol administered with bupropion. Supporting the visual analogue scale ratings were the responses to the questionnaire. Alcohol containing treatments were again clearly recognised, but no effect could be attributed to bupropion administered either alone or in combination. It would have been interesting to see if effects of alcohol on eye movements and nystagmus were modified by bupropion. Eye movements are extremely sensitive to effects of alcohol and would have provided another sensitive physiological measure of effect. Unfortunately this methodology was not available in the laboratory at that time.

While studies of the interaction of alcohol with benzodiazepines are common (and often arrive at different conclusions), the interaction of alcohol with antidepressants has been studied less frequently. The effect of tricyclic antidepressants and alcohol on psychomotor skills related to driving was examined by Seppala et al. (1975). While the individual

drugs failed to impair the psychomotor skills combination of alcohol with amitriptyline and with doxepin impaired performance in cumulative choice reaction times and the latter drug also increased errors in reaction time. Co-ordination was also impaired by these combinations. Alcohol 0.5 g/kg bodyweight produced no changes in these tests on its own. Doxepin and amitriptyline are well known to be sedative antidepressants while sedation is less likely with nortriptyline and clomipramine, tricyclic drugs which failed to show any deleterious interaction with alcohol.

The relative paucity of effects observed after alcohol in our study may be attributable both to the low dosage used and to the relationship between test time and alcohol administration. Jones und Vega (1972) showed that performance on the Shipley-Hartford test was significantly worse when the blood alcohol was rising, to a peak of 80 mg/dl than when measured at the same blood concentration but on the descending part of the curve. Pohl (1978) using the Watson-Glaser critical thinking appraisal series of test exercises found that the main peak cerebral depressant effect occurred on average 25 min before the attainment of peak blood alcohol concentration. The possibility that different tests may be more or less sensitive to a rising or a falling blood alcohol level was raised by Vogel-Sprott (1979). He found that with mean peak blood alcohol levels of 82 mg/dl a coding test was disrupted on the ascending limb of the blood alcohol curve recovering quicly after the peak, while pursuit rotor performance was impaired only during the descending limb of the curve. The fact that the Wilkinson vigilance test lasts one hour meant that in our investigation observations were essentially confined to the descending limb of the alcohol curve. The test began 30 min after ingestion of alcohol had stopped, when blood alcohol for the men was declining rapidly, though the women were still achieving the peak level which occurred at approximately 1 h.

While it was not possible to obtain much information on the pharmacokinetic handling of the two drugs during the course of the behavioural study it was felt desirable to obtain some data just in case an interaction occurred which might be better explained on a pharmacokinetic rather than a pharmacodynamic basis. Blood alcohol concentrations after 32 ml alcohol were not altered by bupropion. A more detailed study of alcohol and bupropion kinetics is reported separately.

Acknowledgements. We are grateful to Dr. W. Stern and colleagues in Burroughs Wellcome Company, North Carolina, USA for supplies of bupropion and placebo tablets and colleagues in The Pharmaceutical Development Division, Dartford, England for preparations of the alcohol treatments.

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Received: December 28, 1983
accepted in revised form: May 11, 1984

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