ORIGINAL RESEARCH

The Impact of Bupropion on Psychomotor Performance

MICHEL A. PAUL, GARY GRAY, GORD KENNY, AND MARVIN LANGE

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Introduction: The NDRI (noradrenalin-dopamine re-uptake inhibitor) bupropion SR (sustained-release) is marketed as Wellbutrin® for treatment of depression or Zyban® as a smoking cessation aid. There has been considerable interest in the possibility of returning aircrew to restricted flying duties once stabilized on bupropion SR after resolution of depressive symptoms, or while taking bupropion SR for smoking cessation. This study was undertaken to determine whether bupropion SR affects psychomotor performance. ***Method:*** There were 24 subjects (18 men and 6 women) who were assessed for psychomotor performance during placebo and bupropion SR treatment, in a double-blind cross-over in counter-balanced order. Each treatment arm lasted 5 wk. The daily bupropion SR dose was 150 mg during week 1, and 300 mg during weeks to 2 to 5. Subjects completed a drug side-effect questionnaire and were tested on two psychomotor test batteries once per week during each of the placebo and drug arms. ***Results:*** There was no significant impact of bupropion SR on serial reaction time, logical reasoning, serial subtraction, or multitask performance. With respect to drug side effects there was a main effect of drug on "number of awakenings" ($p < 0.048$), "difficulty returning to sleep" ($p < 0.004$), and "dry mouth" ($p < 0.049$). There was no impact of bupropion SR on dizziness. ***Discussion:*** While we found some of the expected side effects due to bupropion SR, there was no effect on psychomotor performance. These findings support the possibility of returning aircrew to restricted flight duties (e.g., in non-fast jet aircraft) under close observation once stabilized on bupropion SR.

Keywords: antidepressants, aircrew, side effects, smoking cessation, psychomotor performance

ADVANCES IN NEUROSCIENCE research have yielded new treatment options for depression, including selective serotonin re-uptake inhibitors (SSRIs) and related compounds such as noradrenaline and dopamine re-uptake inhibitors (NDRIs). These medications are similar in efficacy to the older tricyclic antidepressants, but their different mechanisms of action result in distinctly different side effect profiles (7). Bupropion is an NDRI which has both noradrenergic and dopaminergic activity. Bupropion sustained release (SR) is marketed as Wellbutrin SR® for depression and as Zyban® for nicotine dependence.

Because of the requirement for extended maintenance therapy in the treatment of depression, generally long after symptoms have resolved, there has been increasing interest in the aeromedical community regarding the possibility of returning aircrew to at least restricted flying duties while taking SSRIs or related compounds such as bupropion. Currently, most aeromedical agencies require aircrew to be grounded throughout the period of antidepressant treatment, and then for an observation period. Aircrew requiring long-term maintenance treatment to prevent a recurrence of depression have been permanently removed from flying duties. This prolonged period of grounding makes aircrew reluctant to come forward for treatment except under the most dire circumstances. Further, the clinical observations of most flight surgeons suggest that aircrew, by nature, tend to try to control rather than express affective symptoms including depression. The end result is that aircrew tend not to seek medical attention for even significant depression, "toughing it through" symptoms such as difficulty in concentrating, difficulty with decision-making, interference with sleep, and fatigue, all of which constitute potentially significant risks to flight safety which may be more worrisome than the pharmacologic side effects of SSRIs or NDRIs.

Tobacco addiction is the leading cause of preventable death, disability, and unnecessary health care expense in the United States and the developed world (23). Currently, approximately 45,200 Canadians die annually as a consequence of tobacco addiction (5), while ten times that number die prematurely in the United States (18). Annually, only about 6% of the 20 million smokers in the United States who try to quit smoking succeed in quitting in the long term (16,25). Review articles on bupropion and smoking cessation confirm that bupropion is more effective than nicotine replacement therapy (13,22) and represents a significant advance in the medical management of the world's most deadly addiction (22). Smoking cessation is a key ingredient in virtually all preventive health programs, but few if any aeromedical agencies allow the use of systemic smoking cessation aids.

The question of possible impact of bupropion on psychomotor performance has not been studied exten-

From Defence Research and Development Canada, Toronto, Ontario, Canada

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Address reprint requests to: Michel A. Paul, M.Sc., who is a Defence Scientist at DRDC Toronto, 1133 Sheppard Ave. West, P.O. Box 2000, Toronto, Ontario, Canada M3M 3B9, michel.paul@drdc-rddc.gc.ca

sively. In 1984 a cognitive test battery was administered to children on therapeutic doses of bupropion (Wellbutrin®) for depression in order to determine whether bupropion might affect classroom performance (6). The results of this study indicated no effect of bupropion on cognition. More recently, 91 subjects were randomly assigned to 3 treatment groups (placebo, 150-mg bupropion, and 300-mg bupropion) and assessed on 3 psychomotor tasks (simple reaction time, mental arithmetic, and logic) during smoking cessation (24). There was no effect of bupropion on reaction time or mental arithmetic; however, the response latencies on the logic task for the 300-mg bupropion group suggested a positive effect on logic performance during the stress of withdrawal.

The present protocol was designed to evaluate the effect of bupropion SR on psychomotor performance using three traditional psychomotor tasks (SRT, serial reaction time; LR, logical reasoning; and SS, serial subtraction) and a recently developed multitask designed to simulate aviation-relevant performance.

METHODS

The study protocol was approved by the DCIEM Human Ethics Committee. The 24 volunteer subjects (18 men and 6 women), who were between 22 and 52 yr of age, passed a screening medical, provided written informed consent, and were studied in a double-blind repeated-measures design in which subjects received bupropion SR and placebo in counter-balanced order. One male subject withdrew from the study because of difficulties with insomnia. One female subject withdrew because of eye irritation. The study medications (placebo and bupropion) were prepared by a contract pharmacy in identical capsules for blinding purposes. Each study arm (placebo and bupropion) lasted 5 wk.

The subjects took a single daily dose of placebo or bupropion (150 mg) in identical capsule format for the first 7 d, after which they took two daily doses of placebo or bupropion (150 mg · dose ^{1} for a total daily dose of 300 mg) for the following 4 wk. The subjects were evaluated for psychomotor performance once each week, on the same weekday, at the same time of day throughout each 5-wk treatment period. At the beginning of each psychomotor test session the subjects were asked to provide their subjective estimates of sleepiness (Stanford Sleepiness Scale) (12) as well as mental and physical fatigue levels (9). The first 5-wk treatment session was followed by a 2-wk drug-free washout period prior to commencement of the second 5-wk treatment period during which the subjects took the alternate medication and again underwent weekly psychomotor testing similar to the first 5-wk treatment session. Each time the subjects underwent a psychomotor performance session, they were asked to complete a questionnaire soliciting their subjective responses to questions regarding any medication-induced side effects.

Because bupropion could be potentially harmful to a fetus, prior to participation, all female subjects were screened for pregnancy and were advised to take precautions to avoid pregnancy during this study.

Immediately prior to the study, all subjects were trained to best performance on two psychomotor test batteries. One test battery was a subset of the DCIEM SUSOPS (sustained operations) battery involving SRT (28), LR (2), and SS (11) tasks. The other test battery was a recently developed multitask designed to simulate the information processing characteristics of flight performance (27). The task simulated flying an aircraft to specific targets or "waypoints." The computer screen showed four separate displays representing four subtasks to be performed simultaneously. Three of these four tasks interacted. There were vigilance sub-tasks with altitude assignment changes visible for only 5 s; the subjects also had to be vigilant in order to determine when the two "attitude indicators" disagreed with each other and then determine which of the attitude indicators accurately reflected the "aircraft attitude." A bar task (analagous to managing the power quadrant of a large multi-engine transport) did not interact with the other three sub-tasks. The measures of performance included scores related to error detection and selective attention, visuo-motor tracking and co-ordination, short-term memory, mental arithmetic, and scanning strategies. The raw output data file was merged with a computer reduction algorithm to yield a single weighted composite score that reconciled correct responses and errors. This task is explained in more detail elsewhere (21).

Statistical Analysis

The subjective levels of sleepiness and fatigue, as well as the dependent variables (# correct responses for the SUSOPS tasks and 'total score' for the multitask) from the psychomotor tasks, are plotted over trials for each of the two 5-wk treatment sessions. The dependent variables from the questionnaires are also plotted over trials. The subjective sleepiness and fatigue data, psychomotor data, and the side-effect questionnaire data were submitted to two-factor (drugs × trials) repeated-measures analysis of variance. The Least Significant Difference Test was used to assess planned comparisons. The acceptable level of significance for all main effects or interactions is 0.05.

RESULTS

Subjective Sleepiness and Fatigue

There were no significant main effects or interactions for subjective sleepiness, mental or physical fatigue. The subjective sleepiness and fatigue data are illustrated in **Table I.**

Psychomotor Data

A completely repeated-measures analysis of variance reduces overall variability by removing between-subject differences from the error term. Note that all figures are graphed with z-scores in order to better demonstrate the within-subjects treatment effects. The analyses of variance were equivalent whether done with z-scores or with original units.

With respect to SRT performance (**Fig. 1**), the main

TABLE I SUBJECTIVE SLEEPINESS AND FATIGUE SCORES (MEAN ± SEM)* ACROSS WEEKS FOR PLACEBO AND BUPROPION SR.

	Subjective Scores				
	Week 1	Week 2	Week 3	Week 4	Week 5
Sleepiness					
Placebo	2.09 ± 0.20	2.24 ± 0.23	2.23 ± 0.20	2.18 ± 0.19	2.18 ± 0.19
Bupropion SR	2.32 ± 0.25	2.27 ± 0.22	2.32 ± 0.19	2.18 ± 0.21	2.23 ± 0.17
Mental Fatigue					
Placebo	2.33 ± 0.24	2.64 ± 0.31	2.50 ± 0.24	2.52 ± 0.25	2.34 ± 0.20
Bupropion SR	2.45 ± 0.24	2.44 ± 0.24	2.44 ± 0.23	2.40 ± 0.25	2.48 ± 0.29
Physical Fatigue					
Placebo	2.26 ± 0.22	2.32 ± 0.26	2.42 ± 0.25	2.47 ± 0.23	2.27 ± 0.19
Bupropion SR	2.38 ± 0.23	2.42 ± 0.23	2.38 ± 0.21	2.35 ± 0.27	2.31 ± 0.21

*Score scale from 1 to 7, the higher the number, the more sleepiness/fatigue.

effect of drugs $F(1,21) = 0.048$, $p < 0.83$ was not significant, the main effect of trials $F(4,84) = 2.22$, $p < 0.074$ was not significant, nor was the drug × trials interaction $F(4,84) = 1.09$, $p < 0.37$. This demonstrates that bupropion has no effect on SRT performance.

For LR performance (**Fig. 2**) the main effect of drugs $F(1,21) = 2.51$, $p < 0.13$, the main effect of trials $F(4,84) = 0.27$, $p < 0.89$, and the drug × trials interaction $F(4,84) = 2.29$, $p < 0.07$ were all not significant. This indicates that bupropion has no effect on LR performance.

For SS performance (**Fig. 3**), the main effect of drugs $F(1,21) = 1.84$, $p < 0.19$, the main effect of trials $F(4,84) = 2.13$, $p < 0.08$, and the drug × trials interaction $F(4,84) = 0.34$, $p < 0.85$ were not significant, thus indicating no effect of bupropion on this task.

With respect to multitask performance (**Fig. 4**) the main effect of drugs $F(1,21) = 0.001$, $p < 0.97$, the main effect of trials $F(4,84) = 0.41$, $p < 0.80$, and the drug × trial interaction $F(4,84) = 0.87$, $p < 0.48$ were not significant, indicating that bupropion has no effect on multitask performance.

Questionnaire Side-Effect Data

The questionnaire side-effect data are illustrated in **Table II**. With respect to sleep hygiene issues, bupropion caused a significant main effect on the number of awakenings (relative to placebo) $F(1,21) = 2.06$, $p < 0.048$, and a significant main effect on difficulty returning to sleep after awakening $F(1,21) = 10.67$, $p < 0.004$.

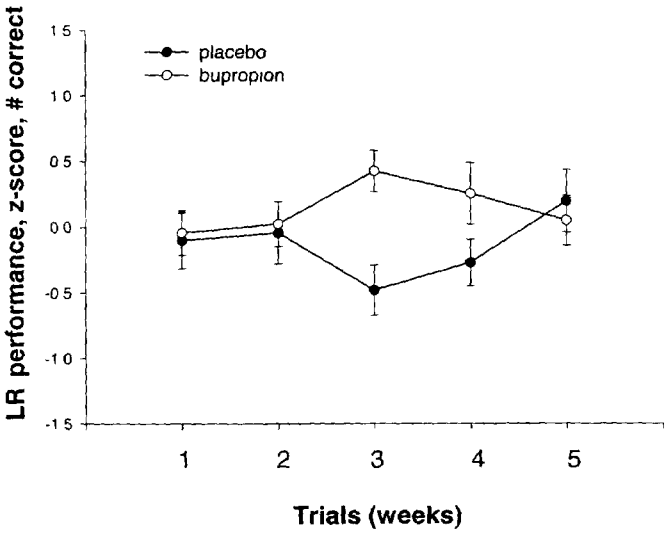

Fig. 2. The z-score for number of correct responses to the Logical Reasoning (LR) task. All values are mean ± SEM and are plotted across drugs and trials.

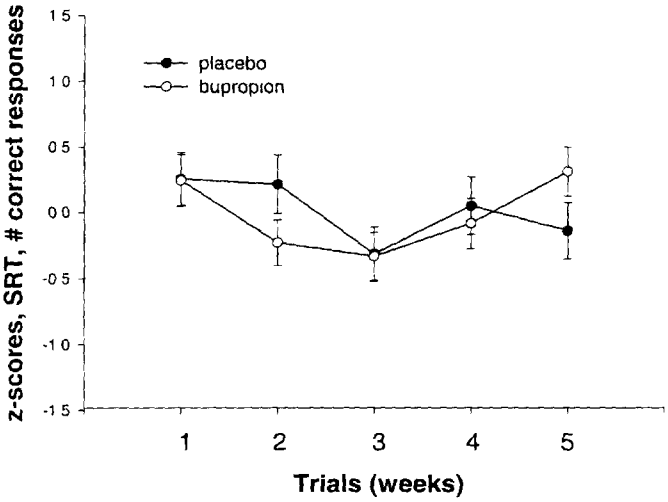

Fig. 1. The z-scores for number of correct responses to the Serial Reaction Time (SRT) task. All values are mean ± SEM and are plotted across drugs and trials.

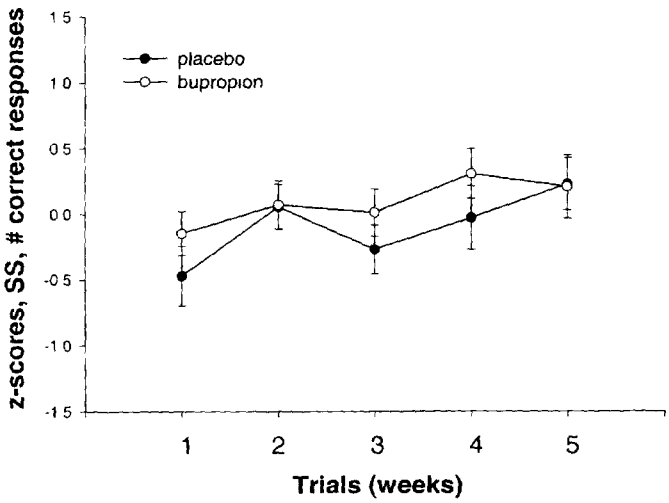

Fig. 3. The z-scores for number of correct responses to the Serial Subtraction (SS) task. All values are mean ± SEM and are plotted across drugs and trials.

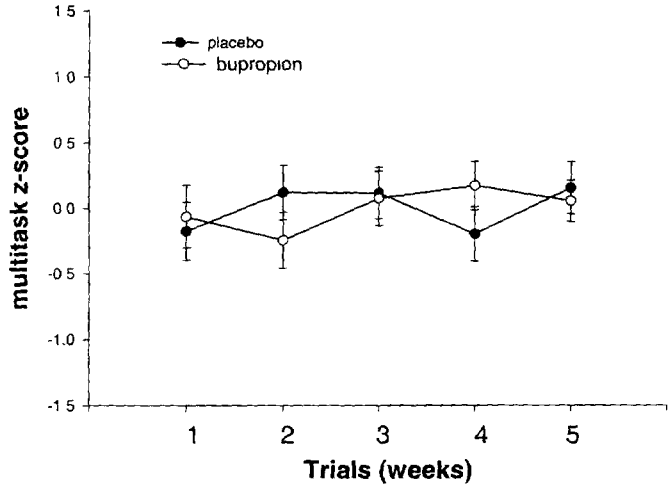

Fig. 4. The z-scores for multitask "score."All values are mean ± SEM and are plotted across drugs and trials.

Subjects awakened on average 0.8 times per night while on placebo and 1.3 times per night while on bupropion, and once awakened, had more difficulty returning to sleep while on bupropion than while on placebo.

Relative to placebo, bupropion caused a significant main effect on dry mouth $F(1,21) = 4.37$, $p < 0.049$.

DISCUSSION

Earlier studies of bupropion have confirmed its efficacy as an anti-depressant (1,3,17) which may also prevent relapse/recurrence of depression (26), and as a smoking cessation aid (7,8,10,14–16). Ferry and Burchette first noted spontaneous smoking cessation in patients treated with bupropion for depression in a Veteran's Administration Hospital Clinic in California. They then went on to conduct the first placebo-controlled trial in 190 non-depressed veterans over a 12-wk course of a 300 mg · d^{-1} bupropion dose. They found that 40% of the bupropion group achieved abstinence in 4 wk vs. 24% in the placebo group (7). As an inhibitor of synaptic re-uptake of norepinephrine and dopamine, bupropion may result in attenuation of withdrawal symptoms. These two neurotransmitters are hypothesized to create the rewarding and positive effects of the dopamine reward pathway and the noradrenergic withdrawal pathway of nicotine addiction (8). Enhanced dopamine activity in the nucleus accumbens may maintain stimulation of pleasure-response areas in the absence of nicotine.

However, to date, very little work has been done to evaluate the psychomotor effect of bupropion. In the current study, using our SUSOPS battery we found no effect of bupropion on SRT, LR, and SS performance.

TABLE II. SIDE-EFFECT QUESTIONNAIRE SCORES (MEAN ± SEM)† ACROSS WEEKS FOR PLACEBO AND BUPROPION SR

	Subjective Scores				
	Week 1	Week 2	Week 3	Week 4	Week 5
Difficulty getting to sleep					
Placebo	1.48 ± 0.20	1.38 ± 0.18	1.64 ± 0.23	1.39 ± 0.16	1.36 ± 0.14
Bupropion SR	1.36 ± 0.17	1.86 ± 0.27	1.86 ± 0.28	1.91 ± 0.24	1.71 ± 0.20
Number of awakenings					
Placebo	0.86 ± 0.19	0.93 ± 0.21	0.57 ± 0.12	0.86 ± 0.19	0.83 ± 0.16
Bupropion SR	1.07 ± 0.27*	1.64 ± 0.43*	1.26 ± 0.32*	1.29 ± 0.24*	1.29 ± 0.23*
Difficulty returning to sleep					
Placebo	1.28 ± 0.12	1.38 ± 0.14	1.57 ± 0.22	1.40 ± 0.17	1.50 ± 0.13
Bupropion SR	1.84 ± 0.30*	2.57 ± 0.44*	2.29 ± 0.37*	2.13 ± 0.31*	2.13 ± 0.30*
Dry mouth					
Placebo	1.14 ± 0.07	1.29 ± 0.13	1.42 ± 0.17	1.39 ± 0.18	1.32 ± 0.16
Bupropion SR	1.38 ± 0.13*	1.71 ± 0.22*	1.95 ± 0.24*	1.81 ± 0.20*	1.71 ± 0.18*
Nausea					
Placebo	1.05 ± 0.05	1.14 ± 0.14	1.23 ± 0.13	1.09 ± 0.09	1.23 ± 0.15
Bupropion SR	1.19 ± 0.11	1.10 ± 0.07	1.24 ± 0.12	1.02 ± 0.02	1.00 ± 0.00
Constipation					
Placebo	1.09 ± 0.06	1.33 ± 0.17	1.23 ± 0.11	1.41 ± 0.20	1.41 ± 0.25
Bupropion SR	1.19 ± 0.11	1.24 ± 0.12	1.43 ± 0.23	1.45 ± 0.18	1.21 ± 0.12
Tremors					
Placebo	1.00 ± 0.00	1.24 ± 0.23	1.18 ± 0.18	1.18 ± 0.14	1.09 ± 0.06
Bupropion SR	1.14 ± 0.10	1.07 ± 0.05	1.26 ± 0.17	1.18 ± 0.11	1.22 ± 0.11
Skin rash					
Placebo	1.14 ± 0.14	1.24 ± 0.15	1.05 ± 0.05	1.09 ± 0.06	1.14 ± 0.10
Bupropion SR	1.00 ± 0.00	1.09 ± 0.09	1.18 ± 0.18	1.14 ± 0.14	1.05 ± 0.05
Difficulty concentrating					
Placebo	1.25 ± 0.11	1.33 ± 0.12	1.45 ± 0.16	1.39 ± 0.17	1.43 ± 0.17
Bupropion SR	1.41 ± 0.23	1.41 ± 0.19	1.57 ± 0.19	1.40 ± 0.14	1.49 ± 0.19
Dizziness					
Placebo	1.18 ± 0.14	1.10 ± 0.06	1.09 ± 0.06	1.09 ± 0.06	1.09 ± 0.06
Bupropion SR	1.10 ± 0.07	1.24 ± 0.10	1.14 ± 0.08	1.10 ± 0.07	1.10 ± 0.07
Nervousness					
Placebo	1.36 ± 0.14	1.07 ± 0.05	1.17 ± 0.08	1.17 ± 0.11	1.21 ± 0.11
Bupropion SR	1.45 ± 0.22	1.26 ± 0.14	1.40 ± 0.16	1.18 ± 0.08	1.13 ± 0.07

† Score scale from 1 to 7, the higher the number, the more pronounced side effects
* Significant difference, $p < 0.05$

Further, we found no effect of bupropion on the multitask which assesses aviation-relevant performance including scores related to error detection and selective attention, visuo-motor tracking and coordination, short-term memory, mental arithmetic, and scanning strategies.

In clinical studies, side effects with bupropion therapy are few and appear to be well tolerated The most common are insomnia and dry mouth. Insomnia may occur, but generally resolves after 1 to 2 wk, and can be minimized by taking the evening dose at least 4 h before bedtime. Cardiovascular and sexual side effects are relatively uncommon. Although SSRIs including sertraline may cause decreased libido and delayed orgasm, these side effects are uncommon with bupropion which, in fact, may increase libido, level of arousal, intensity of orgasm, and duration of orgasm (19). Bupropion is, thus, likely to result in better compliance in an aircrew population than SSRIs. Model et al. suggest that bupropion should be seriously considered as the first-line antidepressant for the treatment of depression in sexually active individuals (19).

Our side effect questionnaire solicited subjective responses to questions regarding the known side effects of bupropion including sleep disruption, dry mouth, constipation, nausea, tremors, skin rash, concentration difficulties, dizziness, and nervousness. In our subjects, bupropion caused a slightly increased number of awakenings, middle insomnia (difficulty returning to sleep after awakening), and an increase in dry mouth but nothing else.

In contrast to these side effects, our recent study on the effects of sertraline (20) indicates that it caused more severe sleep problems than bupropion SR, with more awakenings and more severe middle insomnia. Further, sertraline caused initial insomnia whereas bupropion did not. Sertraline also caused significant nausea, diarrhea, tremors, sweating, and sexual dysfunction, none of which were caused by bupropion SR.

Because seizures have been reported in about 1 of 1,000 patients, careful screening for any of the factors that place patients at high risk of seizure is important (4). These factors include an active seizure disorder or any history of seizures, and any history of central nervous system trauma including head injury with loss of consciousness, or concurrent use of other medications that might lower the seizure threshold, including alcohol. Additional contraindications to the use of bupropion SR are history of anorexia nervosa or bulimia, hypertension, recent myocardial infarction, congestive heart failure, allergy to bupropion, breast feeding, use of insulin or oral hypoglycemics, street drugs—cocaine in particular, monoamine inhibitor use in the last 2 wk, cessation of heavy alcohol intake, or recent cessation of benzodiazepenes While these are important contraindications in a clinical population, they are generally not relevant in a prescreened aircrew population, in which the risk of seizure on bupropion SR is less than 0.1%.

CONCLUSIONS

The current study found no impact of bupropion SR on traditional psychomotor tests nor on a complex battery simulating flying performance. The side effects evident from our questionnaire data are limited to a small increase in the number of nocturnal awakenings, some increased difficulty returning to sleep after awakening, and an increase in dry mouth.

These findings support the possibility of returning aircrew to restricted flight duties while on bupropion for smoking cessation. Eventually, long-term bupropion cognitive and psychomotor studies may support the possibility of returning aircrew to their duties after longer-term use for the maintenance treatment of depression.

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