This study was conducted to evaluate the effect of bupropion sustained-release (SR) on smoking cessation in patients with chronic posttraumatic stress disorder (PTSD). Fifteen veterans with chronic PTSD who desired to stop smoking enrolled in a 12-week double-blind evaluation of bupropion SR and placebo. Patients were randomly assigned in a 2:1 ratio to receive either bupropion SR or placebo. Bupropion SR was initiated at 150 mg daily for 3 or 4 days and increased to a final dose of 150 mg twice daily (300 mg daily total). Ten patients received bupropion SR and five received placebo. Nine of the patients who received bupropion SR were already being treated with at least one other psychotropic medication. One of the ten patients did not complete the study because of medication side effects. Eighty percent of patients receiving bupropion SR successfully stopped smoking by the end of week 2, and 6 (60%) of these 10 maintained smoking cessation at the study endpoint (week 12). At the 6-month follow-up, 40% of the patients (4 of 10) who received bupropion SR maintained smoking cessation. One (20%) of the five patients who received placebo stopped smoking and maintained smoking cessation at the 6-month follow-up. Bupropion SR was generally well-tolerated in combination with other psychotropic medications. Bupropion SR may be effective in helping patients who desire to quit smoking and who also have a concomitant anxiety disorder, such as PTSD. (J Clin Psychopharmacol 2001;21:94–98)
nicotine and negative mood changes associated with nicotine withdrawal, individuals with PTSD may have particular difficulty in trying to stop smoking.

Bupropion sustained-release (SR) is a unique antidepressant with a monocyclic aminoketone structure and both noradrenergic and dopaminergic activity.14 Norepinephrine and dopamine have both been hypothesized to play a key role in nicotine dependence.13 Bupropion SR is the only medication not containing nicotine that is approved by the Food and Drug Administration (FDA) for smoking cessation. Bupropion SR has been shown to be effective for smoking cessation in studies involving veterans and civilians without concomitant psychiatric disorders.15,16 In addition, bupropion possesses an adverse effects profile that is advantageous for patients with PTSD because it results in a low incidence of weight gain in studies of smoking cessation, as well as low anticholinergic, cardiovascular, sedative, and sexual effects. Given the high levels of depression and anxiety in most patients with PTSD, bupropion SR could be helpful in smoking-cessation therapy for these patients. We hypothesized that bupropion SR would be efficacious in helping patients with chronic PTSD to stop smoking. We further hypothesized that these patients would tolerate the use of bupropion SR with few adverse effects, even when added to an established regimen of antidepressant medications.

**Methods**

Fifteen male combat veterans who expressed a desire to stop smoking were recruited from the PTSD outpatient treatment program at the Durham Veterans Affairs Medical Center and were enrolled in a 12-week double-blind evaluation of bupropion SR and placebo. The institutional review board believes that a lower or underpowered control study is preferable to no control comparison group, even in a preliminary study such as this one. This was a preliminary study, and the level of funding we received only allowed 15 subjects to be studied. Each gave their consent to participate after procedures and possible side effects were explained to them. These study patients were either receiving no psychotropic medication or a stable psychotropic regimen (same dosage and drug for at least 6 months before the study). Patients were randomly assigned to receive bupropion SR or placebo using a 2:1 ratio. Bupropion SR was begun at 150 mg every morning for 3 or 4 days and then increased to 150 mg twice daily (300 mg/day). Subjects were seen at baseline, end of week (EOW) 1, EOW-2, EOW-4, EOW-8, and EOW-12. All subjects set a target quit date with drug/placebo treatment given at least 1 week before the quit date. All subjects kept a daily smoking diary and had expired carbon monoxide measurements at each visit with a level of >10 parts per million considered positive for cigarette smoking. Compliance with study medication was assessed via pill counts on each study visit. As developed in the initial trials, individual counseling sessions were based on information presented in the *How to Help Your Patients Stop Smoking* manual, which is published by the National Cancer Institute.17 In the initial counseling session (week 0), personalized messages were offered which advised the patient to stop smoking and refer to the patient’s clinical condition. Each patient received a copy of *Cleaning the Air*.17 Patients were asked to read the booklet before their target quit date for smoking cessation. Common questions and concerns about smoking and smoking cessation were discussed. In subsequent follow-up counseling sessions, the patients were asked about their smoking status. The patient’s progress and problems with smoking were discussed. Personalized messages were offered, which encouraged the patient to remain abstinent from smoking. Patients were paid $100 for their participation. Funding and placebo medication were provided by Glaxo Wellcome, Inc. All subjects met DSM-IV criteria for a primary diagnosis of PTSD as determined by the Clinician-Administered PTSD Scale, Diagnostic Version.18 The level of combat exposure was assessed using the Combat Exposure Scale (CES).19 Comorbid Axis I diagnoses were determined by the Structured Clinical Interview for DSM-III-R (SCID).20 The intrarater reliability for diagnoses was kappa = .96. At baseline, all subjects received a general psychiatric screening, as well as medical and laboratory screening.

Symptoms were also assessed by observer ratings and self-report scales before, during, and at end of treatment. These included the Davidson Trauma Scale (DTS),21 the Pittsburgh Sleep Quality Index (PSQI),22 the 24-item Hamilton Rating Scale for Depression (HAM-D),23 the Clinician Global Impressions Improvement scale,24 the Spielberger State-Trait Anxiety Scale,25 the Hughes Withdrawal Symptoms Checklist,26 and the 11-item Questionnaire on Smoking Urges.27 Somatic complaints were rated by means of a 34-item checklist rated on a 4-point Likert scale.28

**Results**

**Study patients**

Fifteen veterans were randomly assigned to receive bupropion (N = 10) or placebo (N = 5). Three of 10 patients receiving bupropion SR did not complete the full 12-week trial (one dropped out because of side effects and two failed to maintain smoking abstinence). Four of five patients receiving placebo failed to stop smoking or failed to sustain their smoking cessation and, thus, did not complete the full 12-week trial. All 15 subjects were male Vietnam combat veterans with a mean CES score...
of 29 (moderate to heavy). Eighty percent of both groups were service connected for PTSD (i.e., receiving disability payment for PTSD from the Veterans Administration). The mean age was 50 years, with a range of 47 to 58 years. Sixty percent were white and 40% were minority ethnic status. Pack-year history ranged from 21 to 203, with a mean of 57. Rates of daily smoking at baseline ranged from 15 to 99 cigarettes a day, with a mean of 33. Seven of 15 subjects reporting heavy smoking (>25 cigarettes/day). There were no significant differences between the groups for compensation status, age, ethnic minority status, pack-year history, or number of cigarettes smoked per day. Sixty-seven percent of the subjects included 40% with social phobia, and one (7%) among the 15 study subjects for each of the following diagnoses: panic disorder, obsessive-compulsive disorder, dysthymia, simple phobia, or drug abuse. Ninety-three percent had a history of alcohol abuse/dependence, and 60% had a history of drug abuse/dependence. There were no significant differences between placebo or medication groups for current or past concomitant psychiatric diagnoses. One of the placebo-treated patients was not receiving other psychotropic medications, whereas one was taking amitriptyline and another was taking paroxetine. The two other placebo-treated patients were taking a combination of psychotropic medications of lorazepam, venlafaxine, trazodone in one, and sertraline and trazodone in the other.

**Patient response**

Other psychotropic medication and response in the 10 patients receiving bupropion SR at a dose of 150 mg twice daily are presented in Table 1. No dosages of other medications were adjusted during this study. Eighty percent of the patients receiving bupropion SR had successfully stopped smoking by EOW-2, 7 (70%) of 10 continued not to smoke at EOW-8, and 6 (60%) of the 10 maintained abstinence at EOW-12. At 6-month follow-up from initiation of the study, 40% (4 of 10) of the patients who received bupropion SR maintained smoking cessation. Of those taking bupropion who stopped smoking, three (40%) were heavy smokers, and two (25%) of these maintained smoking cessation at follow-up. The single patient who received placebo and stopped smoking was a heavy smoker.

For the seven patients receiving bupropion SR who completed the 12-week study (using repeated-measures analyses of variance), there were no significant changes on their scores for the PSQI, HAM-D, DTS, STAI, or Hughes between baseline and week 12. However, QSU scores decreased significantly from baseline (5.40 ± 1.0) to week 12 (1.5 ± 0.6, F[2,14] = 125.15, p < 0.0001), indicating decreased urge to smoke. One patient who received bupropion SR was discontinued from the study upon experiencing effects of ataxia, headache, and jitteriness beginning in the second week after bupropion SR at 150 mg given twice daily (i.e., 300 mg/day) was added to his ongoing nefazodone and clonazepam treatment. These symptoms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Medication and Dosage</th>
<th>Dose at last Study Week (mg/day)</th>
<th>Smoking at EOW-2</th>
<th>Smoking at EOW-8</th>
<th>Smoking at EOW-12</th>
<th>Smoking at Six-Month Follow-Up</th>
<th>Taking Bupropion SR at Six-Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Trazodone 100 mg QHS</td>
<td>300</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>B</td>
<td>None</td>
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<td>N</td>
<td>N</td>
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<td>Y</td>
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<tr>
<td>C</td>
<td>Nefazodone 500 mg QD</td>
<td>300</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>D</td>
<td>Paroxetine 20 mg QAM</td>
<td>300</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>E</td>
<td>Nefazodone 100 mg QD</td>
<td>300</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>F</td>
<td>Nortriptyline 25 mg/day</td>
<td>300</td>
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<td>N</td>
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<td>G</td>
<td>Sertraline 100 mg QD</td>
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<td>N</td>
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<td>N</td>
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<tr>
<td>I</td>
<td>Clonazepam 3 mg QD</td>
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<td>J</td>
<td>Paroxetine 40 mg QAM</td>
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<tr>
<td></td>
<td>Trazodone 150 mg QHS</td>
<td></td>
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</tr>
</tbody>
</table>

*EOW, end of week; QHS, every bedtime; QD, every day; QAM, every morning.

*Six of 10 subjects smoking at follow-up (6-month), of which 1 of 6 was taking bupropion SR; 4 of 10 subjects not smoking at follow-up (6-month), of which 3 of 4 were still taking bupropion SR that had been prescribed after the end of study (EOW-12).

*Only smoked the last 2 days of EOW-12 (had a positive carbon monoxide reading).

*Dropped out of study with side effects.
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returned to baseline 2 weeks after bupropion SR was stopped; he also began smoking again. However, no adverse effects were experienced by two other study patients who received bupropion SR along with nefazodone. These two patients successfully completed the study and stopped smoking.

Discussion

Our results, although preliminary and small-scale, are quite positive and consistent with published larger-scale studies of bupropion SR efficacy in smoking cessation in patients with no concomitant psychiatric disorders. Several individuals who successfully stopped smoking were heavy smokers, suggesting that bupropion SR may be effective in specific populations at risk for heavy smoking.

The association of nicotine dependence with psychiatric disorders, particularly depression, has led to the consideration of antidepressants in the treatment of smoking cessation. Previous trials included imipramine, doxepin, fluoxetine, meclozine, and nortriptyline. However, bupropion SR is the only medication not containing nicotine that is FDA-approved for smoking cessation. In controlled studies using bupropion SR (which included both veterans and nonveteran patients), smoking cessation rates at 2 to 3 months have ranged from 40% to 60%. Placebo rates of quitting smoking have ranged from 15% to 35% in these same studies. Similar rates for smoking cessation have been reported in two recent placebo-controlled studies of nortriptyline versus placebo for smoking cessation in both veteran and nonveteran patients. None of these studies included patients with concomitant depressive disorders, although several included patients with a history of major depression. Our results, although based on a small sample size, are comparable to these studies with a smoking cessation rate at the end of 8 weeks of 70% for those receiving bupropion SR versus 20% of those receiving placebo. In addition, our findings of a 40% continued smoking-cessation rate at follow-up 6 months after initiation of the study for patients receiving bupropion SR is encouraging in our population of patients with PTSD. In contrast to an open trial of bupropion in PTSD patients which reported a positive response, no significant improvement in depressive, anxiety, and PTSD symptoms was demonstrated in this study. However, in contrast to the previous study, this patient sample had already been treated psychopharmacologically, so additional PTSD and depression symptom change may not be expected.

Bupropion SR was generally well-tolerated when added to a stable psychotropic medication regimen, although close follow-up and care must be taken in treating these complex patients. Our results are promising in suggesting that bupropion SR may be effective in helping a population of patients who desire to quit smoking and who also suffer with severe PTSD. These findings are preliminary and not definitive and should be confirmed by using a larger sample in a double-blind, placebo-controlled study.

Acknowledgment

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References


