Buspirone Effect On Tobacco Withdrawal Symptoms: A Randomized Placebo-Controlled Trial

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Abstract: Background: Withdrawal symptoms hinder smoking cessation in nicotine-dependent smokers. This prospective, double-blind, placebo-controlled clinical trial was conducted to evaluate buspirone for nicotine withdrawal symptoms.

Methods: Fifty-four heavy smokers (mean 33.1 cigarettes per day for 24 years) were randomly prescribed 30 mg/d of buspirone or placebo beginning 3 weeks before abrupt smoking cessation. Validated nicotine withdrawal and anxiety scales were administered at baseline and serially for 2 weeks after cessation.

Results: Baseline demographic and nicotine-dependence measures were similar for each group. Three smokers (1 on buspirone, 2 on placebo) dropped out of the protocol prior to the quit date. Both groups had significant withdrawal effects over time (analysis of variance [ANOVA] $P = 0.0001$). There was no significant buspirone effect on any nicotine withdrawal symptoms (ANOVA, $\alpha = 0.05$). Smokers who relapsed, regardless of group, reported significantly worse craving, irritability, anxiety, and difficulty concentrating than abstainers ($P < 0.05$). Relapse rates at follow-up visits were not significantly different between groups. Two-week abstinence rates were 52 percent for placebo and 62 percent for buspirone (chi-square, $P = 0.760$).

Conclusions: In these heavy smokers, buspirone offered no relief from nicotine withdrawal symptoms. Regardless of treatment, relapsing smokers experienced more intense nicotine withdrawal. (J Am Board Fam Pract 1992; 5:1-9.)

Nicotine withdrawal symptoms make smoking cessation extremely difficult for the nicotine-dependent smoker. The nicotine withdrawal syndrome is marked by four or more of seven signs and symptoms: craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, decreased pulse rate, and increased appetite.[1-3] Any agent with proved efficacy in relieving these symptoms may help prevent early relapse to smoking.

Pharmacologic agents currently used for this purpose have limitations. Nicotine gum is not as effective in the primary care setting as it is in formal smoking-cessation programs.[4] In a randomized clinical trial of smoking-cessation interventions delivered by primary care physicians, smokers in the control group (n = 112) received the "basic intervention" in which the smokers set a quit date and received advice, self-help materials, and supportive follow-up visits. Smokers in the treatment group (n = 111) received the same basic intervention and were offered a prescription for 2-mg nicotine chewing gum. Validated 1-year abstinence rates were no greater for smokers offered 2-mg nicotine gum (8.1 percent) than for those with the basic intervention only (9.8 percent).[5]

Tønnesen, et al. in Denmark have shown that the effectiveness of nicotine gum is dose related.[6] In a clinical trial of 60 highly nicotine-dependent smokers, chemically validated 1- and 2-year abstinence rates were 44.4 percent and 33.3 percent

for those receiving 4 mg of gum versus 12.1 percent and 6.1 percent for those receiving 2 mg of gum. Nevertheless, 15 percent of all the abstainers were still using nicotine gum after 2 years, indicating ongoing nicotine dependence.

Alprazolam and clonidine have been shown to relieve withdrawal symptoms in the first 24 hours of abstinence,[7] but each agent has undesirable side effects. Alprazolam has substantial addictive potential, clonidine causes hypotension, and both cause sedation. Clonidine therapy has increased 6-month cessation rates over placebo in one randomized, controlled 4-week trial.[8] Presumably, this effect was related to the ability of clonidine to relieve craving and perhaps other withdrawal symptoms, but withdrawal data were not provided in this trial.[8]

Buspirone is a nonbenzodiazepine, anxiolytic agent that is as effective as diazepam in treating selected patients with generalized anxiety disorder.[9] Unlike traditional anxiolytics, buspirone has a favorable side effect profile and lacks sedative, muscle relaxant, and addictive properties.[10] Buspirone does not produce withdrawal effects, even when abruptly stopped after 6 months of continuous use.[11] If buspirone is proved beneficial for smoking cessation, these advantages would make buspirone a valuable addition to currently available pharmacologic aids for smoking cessation.

Buspirone has been studied for the treatment of other withdrawal syndromes with mixed results. Buspirone does not block the symptoms of benzodiazepine withdrawal and should not be used as primary therapy for this purpose.[12,13] To date, two studies have examined buspirone for treating alcohol withdrawal symptoms. Bruno[14] performed a randomized controlled trial of buspirone for alcohol withdrawal. In this group of 50 outpatients who were alcoholic, buspirone therapy decreased scores for alcohol craving and increased the percentage of patients remaining in treatment. After 8 weeks of treatment, however, self-reported daily ethanol consumption was similar for the buspirone and placebo groups at 11.7 oz/d and 12.9 oz/d, respectively. Dougherty[15] used buspirone in an open, uncontrolled clinical trial to treat 60 selected inpatients for acute alcohol withdrawal. Buspirone therapy was well-tolerated and produced less sedation than traditional benzodiazepine treatment.

Uncontrolled trials of buspirone for smoking cessation have been favorable. In one study, 7 of 8 smokers given buspirone in up to 60 mg/d doses smoked less without other behavioral intervention.[16] We previously reported a pilot study finding that all smokers (n = 11) indicated some relief of withdrawal symptoms with 30 mg/d of buspirone therapy.[17]

At the time this study was performed, there were no controlled trials of buspirone therapy for the nicotine withdrawal syndrome. This study evaluated buspirone therapy for nicotine withdrawal symptoms in a prospective, randomized, double-blind, placebo-controlled trial.

Methods
Recruitment and Entry Criteria
Our target population consisted of smokers with a self-reported history of nicotine withdrawal during an earlier attempt to quit. Subjects were drawn from the population of adults eligible for care at Eisenhower Army Medical Center, Ft. Gordon, GA. A study eligibility questionnaire was mailed to those responding to a newspaper article and posted advertisements recruiting subjects for the study. No attempt was made to contact nonresponders.

Subjects were included if they were between 18 and 65 years old, smoked more than 10 cigarettes daily for at least 1 year, had at least one attempt to quit smoking in the past, and reported at least three of the following six withdrawal symptoms on previous attempts: craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, and increased appetite.

To avoid potentially confounding organic or psychic sources of anxiety, subjects were excluded if they were taking psychotropic medications or had ill health, active alcoholism, depression, or anxiety disorder. In addition, women were excluded if they were pregnant or lacked a birth control method. The self-administered Short Michigan Alcoholism Screening Test (SMAST) questionnaire was used to screen for alcoholism.[18] The Zung self-rating depression scale was used to screen for depression.[19]

Medical records of those meeting entry criteria were reviewed to confirm medical histories. Subjects meeting the entry criteria signed an informed consent and were enrolled in the study. This protocol was approved by the local in-

stitutional review board and human subjects committee.

Study Visits and Nonpharmacologic Smoking Cessation Aids

Smokers were seen in groups of approximately 20 persons at an orientation on the first day of the study. Simple aids to smoking cessation from the Stop Smoking Program of the American Academy of Family Physicians[20] were discussed at this meeting and at subsequent individual encounters with physicians.

Patients were advised not to change their smoking pattern prior to the quit date, which was 3 weeks after initiation of buspirone or placebo therapy. Smokers were then expected to quit abruptly. No group therapy, buddy system, or relaxation techniques were employed. Each subject signed a contract to quit smoking on the designated quit date and to attend each of the study visits.

After the orientation, patients were seen individually on the following schedule of visits: after 10 days of buspirone or placebo therapy (day 11), on the designated quit date (day 22), and after 24 hours of abstinence (day 23), 48 hours of abstinence (day 24), 1 week of abstinence (day 29), and 2 weeks of abstinence (day 36).

Drug Therapy

Using a random number table, smokers were randomly assigned by the hospital pharmacist to receive buspirone or placebo when enrolled in the study.[21] All tablets appeared identical to patients and prescribing physicians. Both the study physicians and patients were blinded to treatment group assignment.

Subjects began buspirone or placebo therapy on the first day of the study at 15 mg/d administered in three 5-mg doses taken with meals. The total daily dose was increased by 5 mg every 3 days until reaching the target dose, 30 mg/d, after 10 days of therapy. This dose was maintained for the rest of the study unless the patient experienced two or more severe withdrawal symptoms or a doubling of their baseline score on the Spielberger state-anxiety scale (described below). Medication dose was increased by 5 mg/d for these patients. Titrations were not allowed more frequently than every 3 days.

Drug therapy compliance, adverse effects, and efficacy were evaluated during patient office visits during the course of the study. At the final visit, subjects were asked to indicate, if possible, whether they were receiving buspirone or placebo.

Nicotine Withdrawal Measures and Study Instruments

Nicotine dependence, nicotine withdrawal, trait and state anxiety, and smoking levels were measured at baseline for both groups. At each subsequent study visit (except the day 11 visit, which was solely for medication titration), withdrawal, state anxiety, and smoking levels were measured again.

The Fagerstrom Tobacco Tolerance Questionnaire (FTQ), a widely used validated paper-and-pencil test, was used to measure baseline nicotine dependence.[22] The FTQ numerical score ranges between 0 (minimal dependence) and 11 (maximal dependence) and correlates with biochemical markers of nicotine dependence (carbon monoxide, nicotine, and cotinine levels). The mean score for smokers seeking treatment is usually between 6 and 7. Scores of 7 or greater indicate nicotine dependence.

Nicotine withdrawal was measured with a tobacco withdrawal scale previously validated by Hughes, et al.[23] This scale lists the DSM III-R[2] nicotine withdrawal symptoms (craving, irritability, anxiety, difficulty concentrating, restlessness, and increased appetite), common somatic complaints (insomnia, drowsiness, headache, gastrointestinal disturbances), and somatic symptoms of anxiety (tremor, sweating, and palpitations). Subjects rate the severity of each symptom on a 0- to 3-point scale where 0 = not present, 1 = mild, 2 = moderate, and 3 = severe. At each visit, subjects were asked to rate these symptoms for the previous 24-hour period. Pulse rate was measured for each subject at every visit to monitor for decreased pulse rate, another sign of nicotine withdrawal. On the final visit, subjects rated the overall effectiveness of the medicine in relieving nicotine withdrawal compared with previous cessation attempts using the following four-point Likert scale: no relief at all, slight relief, moderate relief, and very definite relief.

To evaluate specifically buspirone's effect on withdrawal-induced anxiety, we used the

Spielberger trait and state anxiety scales.[24] These validated scales consist of 20 statements that measure anxiety. The trait-anxiety scale, administered at baseline only, assesses how anxious the respondent usually feels. By contrast, the state-anxiety scale, administered at every study visit, assesses how anxious the respondent feels "right now, at this moment."

To determine whether buspirone affected smoking urges during the 3-week medication titration period, all smokers were surveyed on the quit date and asked to rate their urge or craving for cigarettes over the previous 3 weeks as increased, unchanged, or decreased from baseline.

To validate self-reported smoking abstinence or lapses, biochemical measures of expired carbon monoxide and urinary cotinine were taken at every visit (except on day 11) in addition to self-reports of smoking. Expired carbon monoxide was measured with a Mini-Co™ breath analyzer (Catalyst Research, Owings Mills, MD). Cotinine analysis was performed using a Waters High-Performance Liquid Chromatography System™ following a liquid-liquid extraction with methylene chloride.[25] Urine creatinine was measured using a Beckman Astra-8™ multichannel clinical analyzer. Cotinine to creatinine ratios were then calculated to control for varying urine concentration.

Statistical Analysis
We performed a power analysis using an expected effect size of 0.7 standard deviations, a power of 0.80, and an $\alpha = 0.05$ to derive the sample size needed for this study: 26 subjects per group. This effect size of 0.7 standard deviations would be a moderately large treatment effect as described by Cohen.[26]

The self-reported ratings for each symptom in the tobacco withdrawal questionnaire were added to produce a daily withdrawal discomfort score for each visit.[23]

Serial measures of each withdrawal symptom, daily discomfort scores, pulse rate, and state-anxiety scores were compared using repeated measures analysis of variance (ANOVA). Univariate analysis for each time period was also performed.

The Pearson chi-square statistic was used to compare dichotomous variables. The independent samples t-statistic was used to compare the

baseline means of nondichotomous variables between groups.

Definition of Abstinence
Smokers were considered abstinent at the 24-hour visit (day 23) if the expired carbon monoxide level was less than 14 ppm. At all subsequent visits, smokers were considered abstinent if the expired carbon monoxide level was less than 11 ppm and they reported smoking less than one cigarette per day since the previous visit.

Results
Enrollment and Baseline Demographics
Three hundred sixty-four persons responded to the posted advertisements and were mailed eligibility questionnaires. One hundred thirty-three questionnaires were returned for a response rate of 37 percent. Of those responding, 79 were excluded as a result of one or more of the exclusion criteria outlined in Table 1. Fifty-four smokers were entered into the protocol, 27 in the buspirone group and 27 in the placebo group.

The baseline demographic characteristics and smoking history of the smokers in the protocol are outlined in Table 2. There were no significant differences between the groups at baseline; however, although not statistically significant, on average the buspirone group smoked five fewer cigarettes per day than the placebo group (t-test, $P = 0.09$). In addition, the buspirone group had smoked for 21.8 years versus 26.0 years for the placebo group (t-test, $P = 0.15$).

Table 1. Study Exclusions.

Reason Excluded	Number*	Percent of Total Returns (n = 133)
Prescription medicine use	30	23
Fewer than 3 previous withdrawal symptoms	23	17
Ill health	18	14
Depression	13	10
Unable to attend meetings	11	8
Alcoholism	10	8
Anxiety disorder	10	8
Smoke < 10 cigarettes per day	7	5
Older than 65 years	4	3
Pregnant or not using birth control	4	3
No prior quit attempts	2	2

*Some subjects were excluded for more than one reason.

Table 2. Baseline Demographic Characteristics and Smoking History.

Variable	Buspirone (n = 27)	Placebo (n = 27)
Demographics		
Men, number (%)	20 (74)	17 (63)
Mean age, years (SD)	39.7 (10.9)	42.9 (9.6)
Smoking history, mean (SD)†		
Cigarettes per day	30.4 (11.9)	35.9 (11.8)
Years smoked	21.8 (10.7)	26.0 (10.2)
Prior quit attempts	4.4 (2.1)	4.2 (3.0)

*$P > 0.05$ for chi-square test on sex and t-test on age.
†$P > 0.05$ for t-test on smoking history variables.

Table 3 gives the baseline measures of nicotine dependence. There were no significant differences between groups at baseline on these measures. Spielberger trait-anxiety scores were similar and within normal limits for each group (32.0 ± 6.9 for the buspirone group and 31.7 ± 7.6 for the placebo group). Zung self-rating depression scores were also normal and not significantly different between groups.

Three smokers (1 receiving buspirone, 2 receiving placebo) dropped out of the protocol before attempting cessation. Of these, 1 from each group dropped out because of intolerable adverse effects. The placebo subject experienced dream disturbance, and the buspirone subject experienced myalgias and dizziness. The other patient in the placebo group was unwilling to quit because of family stress and dropped out prior to cessation. The remaining 51 smokers (26 in the buspirone group and 25 in the placebo group) attempted cessation and were included in the withdrawal and abstinence data analysis.

Reanalysis of the baseline smoking, demographic, and nicotine dependence measures, excluding the 3 smokers who dropped out prior to cessation, showed that the placebo group reported smoking significantly more cigarettes per day on average (37.0) compared with the buspirone group (30.0) (t-test, $P = 0.04$). There were no other significant differences between treatment groups for any of the other baseline measures outlined in Tables 2 and 3.

There were 9 patients (4 buspirone, 5 placebo) who had missing data at either the 48-hour (day 24), 1-week (day 29), or 2-week (day 36) visits. This left 42 patients (22 buspirone, 20 placebo) with complete data for the repeated measures ANOVA.

Compliance

Medication compliance rates were not significantly different between treatment groups. On average, pill counts during the course of the study were correct in 85 percent of subjects.

Effect on Tobacco Withdrawal

Both groups reported significant nicotine withdrawal symptoms over time (ANOVA, $P = 0.0001$), but there was no significant difference in nicotine withdrawal between treatment groups for any of the measurements we examined (ANOVA, $P > 0.05$).

Figure 1 shows mean withdrawal discomfort over time by treatment group. At baseline the placebo group had slightly higher withdrawal discomfort scores, but this difference was not significant (t-test, $P > 0.05$). As plotted in Figure 1, smokers in the buspirone group reported slightly more intense withdrawal discomfort than placebo at each of the abstinence visits, but this difference

Table 3. Baseline Measures of Tobacco Dependence.*

Tobacco Dependence Measurement	Buspirone (n = 27) Mean (SD)	Placebo (n = 27) Mean (SD)
Carbon monoxide (ppm)	26.6 (7.8)	27.7 (7.9)
Urine cotinine (ng/mL)	1856 (752)	1878 (882)
Cotinine:creatinine (μg/mg)	1.61 (1.3)	1.98 (1.3)
Fagerstrom tolerance scores (range: 0–11)	7.1 (1.6)	7.4 (1.8)

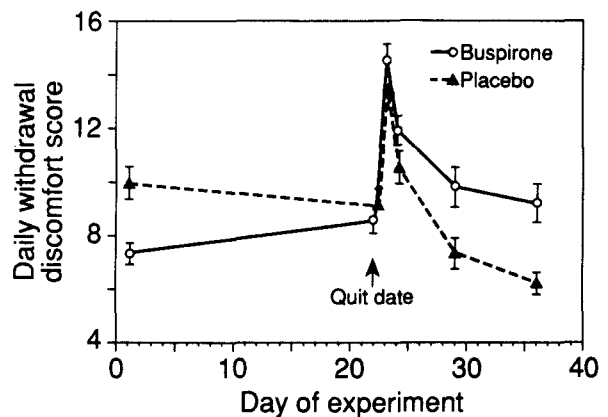*$P > 0.05$ for independent samples t-test of tobacco dependence variables.

Figure 1. Withdrawal discomfort versus time by treatment group (means with standard error of the mean bars).
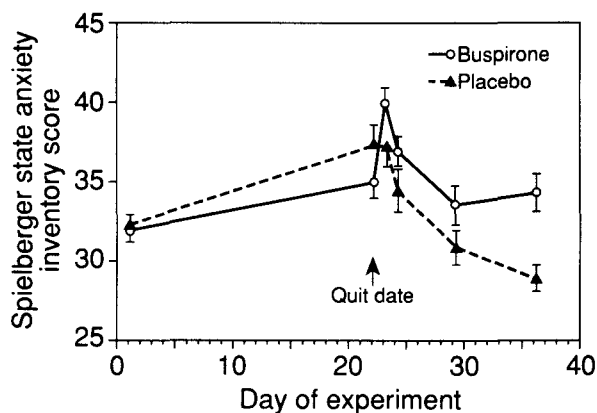
Figure 2. State anxiety versus time by treatment group (means with standard error of the mean bars).

Figure 4. Group abstinence rate versus time.

was not statistically significant. Figure 2 shows mean state-anxiety over time by treatment group and shows no difference between groups. The withdrawal data were analyzed with and without the partially abstinent smokers. Neither analysis yielded any significant difference between the placebo and buspirone groups. Figure 3 shows the
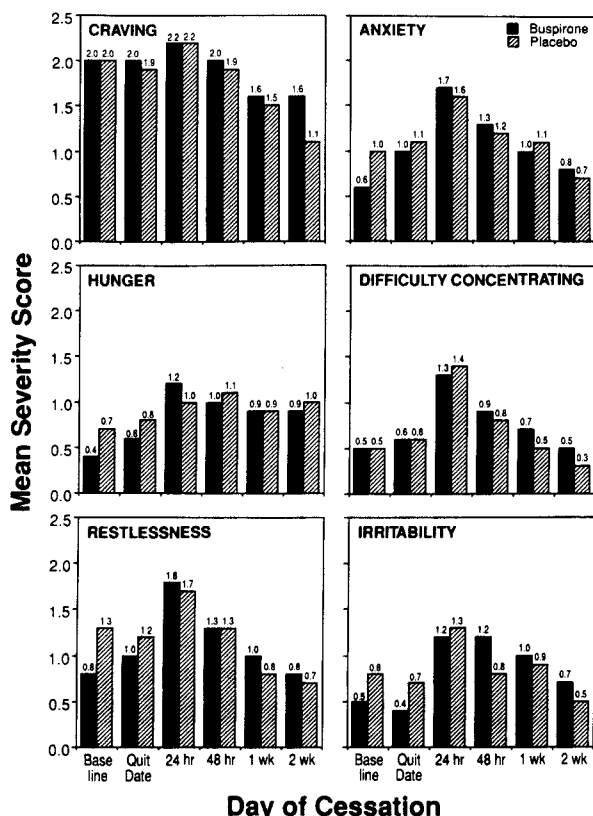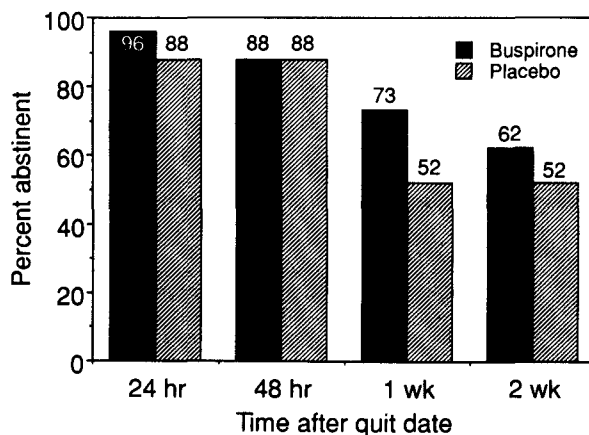
mean withdrawal symptom scores by treatment group for each of six withdrawal symptoms. Withdrawal scores were not significantly different between groups for any of these symptoms. There was no significant difference in pulse rate between groups. There was also no significant difference at the final visit between the buspirone and placebo groups in overall withdrawal relief (chi-square, $P = 0.28$).

During the precessation medication period, 13 (50 percent) buspirone recipients reported decreased smoking urge compared with 5 (20 percent) in the placebo group (chi square, $P = 0.08$).

Figure 3. Mean withdrawal symptom severity scores by group: 0 = not present, 1 = mild, 2 = moderate, 3 = severe.

Effect on Relapse

Relapse rates at each follow-up visit were not significantly different between groups (Figure 4). The 2-week abstinence rates were 52 percent for placebo and 62 percent for buspirone (chi-square, $P = 0.760$).

Smokers who had relapsed by either the 1- or 2-week visit, regardless of treatment, reported significantly worse craving, irritability, anxiety, restlessness, and difficulty concentrating than the abstainers (two-tailed t-test, $P < 0.05$). Withdrawal discomfort scales pooled from each treatment group for 2-week relapsers versus 2-week abstainers are plotted in Figure 5. Relapsers reported significantly more intense withdrawal discomfort than abstainers (ANOVA, $P < 0.05$).

There were no significant baseline differences between 2-week abstainers and relapsers on any of the following measures: age, number of smoking family members, years smoked, age of smoking initiation, number of cigarettes smoked per

day, baseline expired carbon monoxide, number of previous quit attempts, baseline withdrawal discomfort, state-anxiety, trait-anxiety, Zung self-rating depression score, and SMAST alcohol dependence scores (t-test, $P > 0.05$).

Figure 6 shows serial carbon monoxide over time for 2-week abstainers and relapsers in the buspirone and placebo groups, respectively. The curves are similar for each treatment group, showing that abstainers and relapsers behaved similarly regardless of treatment. Carbon monoxide levels for abstainers in each group were significantly different than for relapsers (ANOVA, $P = 0.006$). Figure 7 plots the serial cotinine to creatinine ratios for abstainers and relapsers by treatment group. As shown in Figure 6, abstainers and relapsers had similar ratios regardless of treatment group. Relapsers had significantly higher ratios than abstainers, confirming the definition of abstinence (ANOVA, $P = 0.01$).

Adverse Drug Effects

On the quit date visit, 10 of 26 (38 percent) buspirone-treated smokers reported one or more adverse effects compared with 1 of 25 (4 percent) in the placebo group. This was a significant difference (chi-square, $P = 0.0028$). At all of the subsequent visits, there was no significant difference in side effects between treatment groups. At the final study visit, 21 percent of the buspirone group reported one or more adverse effects versus 10 percent of the placebo group (chi-square, $P = 0.30$). In general, the medication was well tolerated. The most frequently reported adverse effect was transient dizziness or lightheadedness after
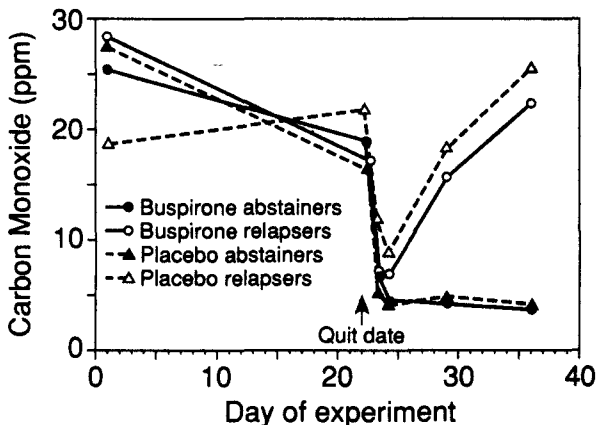
doses. After 10 days of therapy, 6 patients (23 percent) in the buspirone group reported dizziness versus none in the placebo group (chi-square, Fisher's exact test, $P = 0.01$). At the final study visit, 4 buspirone subjects (15 percent) still reported transient dizziness. As reported above, 1 buspirone subject withdrew before cessation because of adverse effects. None of the 51 smokers who actually attempted smoking cessation, however, dropped out due to adverse drug effects.

Blinding

Fifty-eight percent of the buspirone group and 27 percent of the placebo group correctly identified their treatment assignment. One-quarter of the buspirone patients and one-third of the placebo patients were unsure of treatment assignment. These differences were not statistically significant (chi-square, $P = 0.09$).

Figure 6. Mean carbon monoxide levels versus time by group and smoking status.
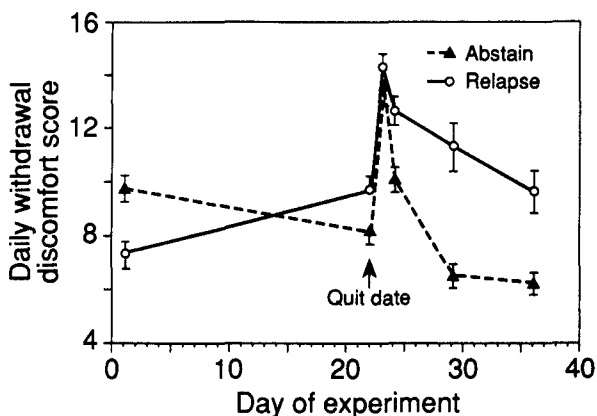

Figure 5. Withdrawal discomfort versus time by smoking status (means with standard error of the mean bars).
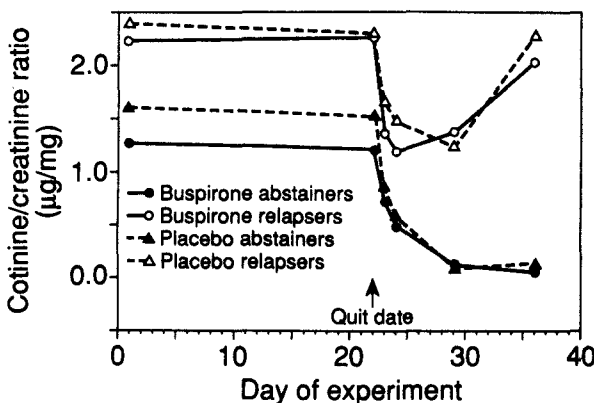

Figure 7. Mean urine cotinine:creatinine ratio versus time by group and smoking status.

Discussion

In this prospective double-blind trial, buspirone showed no advantage over placebo for relieving any symptoms of nicotine withdrawal. Unexpectedly, the treatment group experienced slightly more intense withdrawal discomfort (Figure 1) even though they reported smoking less than the placebo group at study entry (Table 2). The sample size used in the study was adequate to detect a moderately large drug effect. Smaller treatment effects might be detected with a larger sample size but would be of questionable clinical significance.

West, et al.[27] reported similar withdrawal symptom results in a prospective double-blind trial that was published while this paper was in press. They premedicated their subjects with 15 mg/d of buspirone or placebo for 2 weeks prior to cessation and maintained the same dosage for 4 weeks after cessation. As in our study, West, et al. found no significant buspirone effect on any nicotine withdrawal symptoms. The buspirone group experienced significantly stronger urges to smoke after 2 and 3 weeks of abstinence. Paradoxically, the buspirone group in the West, et al. study achieved a significantly greater 4-week abstinence rate over placebo (47 percent versus 16 percent, $P < 0.025$). In our study, the 2-week abstinence rates were similar at 52 percent for placebo versus 62 percent for buspirone ($P = 0.76$). Discussion of the puzzling beneficial abstinence effect for buspirone reported by West, et al. is beyond the scope of this paper.

The smokers enrolled in this study were heavily addicted to nicotine. Both groups had smoked an average of more than 30 cigarettes per day for more than 21 years. Both groups had experienced nicotine withdrawal on previous attempts and had failed smoking cessation an average of four times or more. Smokers with these characteristics are the most recalcitrant to current therapy. Less heavily addicted smokers often quit without assistance.[28] Favorable drug effects might be seen in a less-addicted population.

Tønnesen, et al.[6] have reported that heavily addicted smokers require higher doses of nicotine gum. A modest buspirone dosage was used in this trial. Gawin, et al.[16] used up to 60 mg/d in his open buspirone trial. At study completion, the mean dose of buspirone was 32.3 mg (standard deviation 3.5 mg). Using the maximum buspirone dosage might yield beneficial treatment effects.

The intensity of abrupt withdrawal might have overwhelmed a subtle, but valuable drug effect. One-half of the buspirone group reported decreased smoking urge during the precessation medication period versus less than a quarter of the placebo group ($P = 0.08$). In our pilot study,[17] 45 percent (n = 11) of the smokers reported a decreased urge to smoke over the 2-week precessation period of buspirone therapy. Bruno[14] observed decreased craving for alcohol in his trial of buspirone for the outpatient treatment of alcohol. Anxiolytic therapy could block some dependency-related urges experienced by heavy smokers and drinkers. This possibility should be explored in future studies because any agent that decreases such urges has potential benefit in relapse prevention.

Smokers who had relapsed by 2 weeks reported more intense withdrawal symptoms than those who were successful (Figure 5). This finding lends credence to the belief that withdrawal symptoms contribute to early relapse. The 1990 Surgeon General's Report on Smoking[29] cites several recent studies that have also found severe withdrawal symptoms to be an important factor in early relapse. Whereas severe withdrawal symptoms predict early relapse, there is no evidence to show that withdrawal experience predicts long-term abstinence rates. If more smokers successfully hurdle the first 2 weeks of nicotine withdrawal, more should achieve long-term abstinence.

These data show that for heavy smokers the 30-mg/d dosage of buspirone does not reduce acute nicotine withdrawal symptoms or prevent early relapse in highly nicotine-dependent smokers. For the primary care physician, the treatment of nicotine withdrawal remains a vexing problem. The search for potential therapeutic agents should continue.

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