

Buspirone Effect On Tobacco Withdrawal Symptoms: A Pilot Study

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Abstract: Tobacco withdrawal symptoms hamper smoking cessation. This was a pilot study of buspirone, a new azapirone anxiolytic, for tobacco withdrawal. Thirteen smokers entered an open clinical trial. Smokers were titrated to 30 mg/day of oral buspirone for 2 weeks prior to cessation. Tobacco withdrawal and Spielberger state-anxiety scales were used at baseline, on the quit date, and then at 24 hours, 48 hours, 1 week, and 2 weeks after abrupt cessation. At the final visit, smokers compared their withdrawal experience with previous cessation attempts.

Two patients (15 percent) could not tolerate the medication and did not attempt smoking cessation. Of the remaining 11 smokers, 3 (27 percent) rated withdrawal relief "very definite," 6 (55 percent) "moderate," and 2 (18 percent) "slight." More than two-thirds of the smokers believed that their difficulty concentrating, craving, restlessness, and anxiety were improved compared with earlier tobacco withdrawal attempts. Five patients (46 percent) reported decreased smoking urges during the 2-week medication titration period. Tobacco withdrawal symptoms and state-anxiety scores changed significantly during the study ($P < 0.05$).

These results are encouraging, but they should be interpreted with caution because of the small sample size and lack of placebo control. Buspirone effect on tobacco withdrawal symptoms should be studied in a randomized, controlled clinical trial. (J Am Board Fam Pract 1991; 4:89-94.)

Smoking is a dependence disorder,¹ and tobacco withdrawal is a well-recognized syndrome characterized clinically by the onset of four or more of the following symptoms within 24 hours after abrupt cessation or marked reduction in nicotine intake: craving for nicotine, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite, and weight gain.¹⁻³

Nicotine gum has relieved tobacco withdrawal symptoms in a number of prospective, randomized, placebo-controlled trials,^{4,7} but the 2-mg nicotine gum currently available in the United States does not relieve craving.^{4,6,7} Nicotine gum requires specific patient training, and minor side effects are common.^{5,7} A meta-analysis of 14 randomized controlled nicotine gum trials showed

no significant efficacy over placebo gum in the general medical setting.⁸

Glassman, et al.⁹ compared alprazolam (1 mg p.o.), clonidine (0.2 mg p.o.), and a placebo in the first 24 hours of abstinence and found that both drugs decreased anxiety, irritability, difficulty concentrating, tension, and global difficulty not smoking. Both drugs caused sedation, and alprazolam, a benzodiazepine, is addicting. The need remains for developing nonaddicting, non-sedating, well-tolerated drugs for the relief of tobacco withdrawal symptoms.

This pilot study explored the effect of buspirone on tobacco withdrawal symptoms in an open, uncontrolled clinical trial performed in a family practice setting. Buspirone is a new, non-benzodiazepine, anxiolytic agent that is equally as effective as diazepam in treating patients with generalized anxiety disorder.¹⁰ Buspirone's advantages are that it lacks the sedative, muscle relaxant, and addictive properties of the benzodiazepines,¹¹ and, overall, it has a favorable side effect profile.¹² It has no addictive potential,¹³ and no withdrawal symptoms occurred even with abrupt cessation after 6 months of continuous use.¹⁴

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Gawin, et al.¹⁵ reported significant decreases in both smoking and tobacco craving in 7 smokers who received bupirone in doses up to 60 mg per day in an open, uncontrolled 6-week trial without behavioral intervention. The mean time of onset of decreased smoking was 19 days of therapy. No biochemical markers were used to confirm the smokers' reports. The effect on other withdrawal symptoms was not reported.

Methods

We recruited cigarette smokers from a population of active duty and retired military beneficiaries at Fort Gordon, GA. Smokers were recruited by publishing an article in the post newspaper and by posting advertisements. Smokers were included if they smoked more than 10 cigarettes per day for more than 1 year, had at least four of the six tobacco withdrawal symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*¹ on a previous unsuccessful quit attempt, and desired to quit smoking.

Exclusion criteria were pregnancy or potential to conceive during the study, age less than 18 years, use of psychotropic medication, ill health, alcoholism, depression, history of panic attacks, chronic anxiety, bipolar illness, or recent major depression. All applicants signed an informed consent before entering the study.

Thirty smokers were arbitrarily selected from 187 study applicants and screened by telephone. Fifteen were excluded for failing one or more of the entry criteria, and the qualifying 15 smokers were screened for alcoholism using the Short Michigan Alcoholism Screening Test (SMAST)¹⁶ and for depression using the Zung Self-Depression rating scale.¹⁷ At the initial visit, the Spielberger trait-anxiety scale¹⁸ was administered to assess baseline general anxiety, and the Fagerstrom tobacco tolerance questionnaire¹⁹ was administered to assess nicotine dependence. In addition, medical and pharmacy records were reviewed, and patients were interviewed about their medical and psychiatric histories. Of the 15 patients invited for evaluation, one did not attend the interview, and one was excluded for alcoholism.

We prescribed oral bupirone for the 13 remaining smokers for 2 weeks prior to the quit date. The initial dose was 5 mg three times daily. This was increased 5 mg every 3 days until the target dosage of 30 mg/day was achieved. A min-

imum dosage of 20 mg/day was required. One patient needed 40 mg/day 1 week after cessation to decrease withdrawal symptoms, but no others had their dosage increased. The target dosage was continued for the remainder of the 4-week study. Patients were instructed not to change their smoking habits before the quit date. At that time, they were expected to quit "cold turkey."

Patients were seen at the initial screening, on the quit date (14 days later), and then at 24 hours, 48 hours, 1 week, and 2 weeks after cessation. At each visit, the following data were collected: a 13-item tobacco withdrawal questionnaire previously validated by Hughes and Hatsukami,² the Spielberger state-anxiety scale,¹⁸ resting pulse, blood pressure, and weight. A urine sample for cotinine analysis to confirm abstinence was collected at each visit. Cotinine analysis was performed using a Waters High Performance Liquid Chromatography System[™] following a liquid:liquid extraction with methylene chloride. 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.

We collected the data from January 31 to February 28, 1989, during evening sessions that lasted 2.5 hours on the initial visit and 30–45 minutes on subsequent visits. At the final visit, patients were asked to rate the overall effectiveness of the bupirone in relieving their withdrawal symptoms on a four-point Likert scale. They were also asked to compare their recent withdrawal symptoms with previous attempts to quit smoking using a similar four-point Likert scale. All patients received behavioral counselling consisting of a review of reasons for smoking, coping methods, and verbal encouragement and support at the abstinence visits. The initial meeting was the only session with the entire group. Patients were seen individually or in groups of two or three for the brief follow-up visits.

Study Instruments

The tobacco withdrawal questionnaire² lists each of the *DSM-III-R* withdrawal symptoms, as well as insomnia, drowsiness, headache, gastrointestinal disturbances, and somatic symptoms of anxiety, such as tremor, sweating, and palpitations. Patients rated each symptom from 0 = not present to 1 = mild, 2 = moderate, and 3 = severe. At each

visit, they were asked to rate their symptoms for the previous 24 hours.

The Spielberger state-anxiety scale¹⁸ consists of 20 statements that measure the anxiety the respondent feels "right now, at this moment." The trait-anxiety scale consists of 20 statements that assess how generally anxious the respondent feels. Both tests are well validated and reliable. The state-anxiety scale was used for repeated measures of anxiety, whereas the trait scale was administered only once at the initial visit.

The Fagerstrom tolerance questionnaire (FTQ) is a widely used paper-and-pencil test of nicotine dependence.¹⁹ The FTQ was administered at baseline and correlates with carbon monoxide, nicotine, and cotinine levels, which are biochemical markers of nicotine dependence. The mean score for those smokers seeking treatment is usually between 6 and 7. Scores greater than or equal to 7 are indicative of dependence.

Data Analysis

The self-reported ratings for each withdrawal symptom were summed to produce a daily withdrawal discomfort score as previously described by Hughes.⁴ For repeated measures, analysis of variance (ANOVA) was used to analyze the serial withdrawal symptom ratings, daily withdrawal discomfort, and Spielberger anxiety scores. The Dunnett *t*-test²⁰ was used to compare serial scores with baseline scores. The Fisher Protected Least Significant Differences (PLSD) procedure was used to compare abstinence scores with quit date scores. Two patients had missing data for the 48-hour visit. The missing scores for daily withdrawal and Spielberger state-anxiety were substituted by regressing the 48-hour score on the scores from the other visits to compute predicted values for the two patients with missing data. The independent samples *t*-test was used to compare baseline measures of smoking, nicotine dependence, anxiety, and cotinine-creatinine ratios between abstaining and relapsing smokers.

Results

Thirteen smokers were entered into the protocol. There were 5 women and 8 men; their average age was 38.8 years (range 28–57). Seven were active-duty soldiers, and the remainder were military dependents or retirees. Their smoking his-

Table 1. Smoking History (n = 13).

History	Mean	Range
Cigarettes smoked per day	30.2	10–50
Years of smoking	22.9	14–41
Quit attempts	7.8	1–36
FTQ score	7.7	5–10

tory is summarized in Table 1. The mean score for the baseline Spielberger trait-anxiety scale was 32.4 (range 24–43), which is normal. Two patients were unable to tolerate the buspirone and did not complete the protocol. One of these complained of palpitations, shortness of breath, and light-headedness and stopped the medication after 3 days. The second complained of a "spacey" feeling with the first dose and was unable to tolerate further therapy. This patient was subsequently diagnosed to have lung cancer with brain metastases.

Effect on Nicotine Withdrawal

At the final visit, all 11 patients who completed the study (100 percent) reported some relief from withdrawal symptoms using buspirone therapy. Three (27 percent) reported very definite relief, 6 (55 percent) had moderate relief, 2 (18 percent), slight relief, and none reported no relief.

Figure 1 shows mean daily withdrawal discomfort scores for each study visit. Mean withdrawal scores increased slightly but not significantly from baseline to the quit date. When compared with baseline (day 1), the 24-hour (day 16) and the 48-hour (day 17) scores are significantly elevated from baseline (Dunnett *t*-test $P < 0.05$). When abstinence scores were compared with the quit

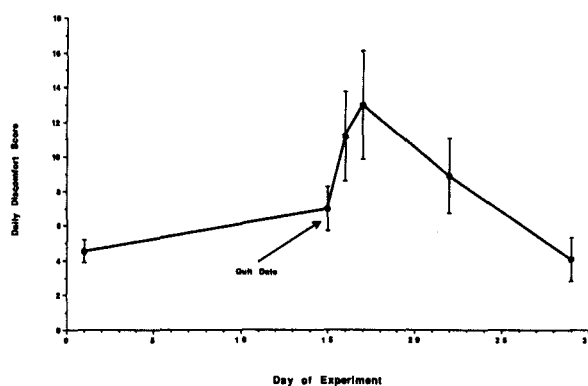


Figure 1. Daily discomfort score versus time (means with S.E.M. bars).

Table 2. Comparison of Buspirone Therapy with Earlier Withdrawal Attempts.

Symptom	Patients' Ratings			
	Much Better No. (Percent)	Slightly Better No. (Percent)	No Difference No. (Percent)	Worse No. (Percent)
Craving	7 (63.6)	3 (27.3)	1 (9.1)	0
Irritability	2 (18.2)	4 (36.4)	3 (27.3)	2 (18.2)
Anxiety	4 (36.4)	4 (36.4)	2 (18.2)	1 (9.1)
Difficulty concentrating	8 (72.2)	0	2 (18.2)	1 (9.1)
Restlessness	5 (45.5)	4 (36.4)	1 (9.1)	1 (9.1)

date, only the 48-hour score was significantly elevated (Fisher PLSD $P < 0.05$).

Figure 2 shows the Spielberger state-anxiety scores. The curve is similar in shape to the withdrawal discomfort curve. Mean state-anxiety scores decreased slightly from baseline to the quit date, but this was not statistically significant. The 24- and 48-hour scores were significantly elevated compared with the quit date (Fisher PLSD $P < 0.05$) but not with baseline (day 1).

The repeated measures ANOVA on the individual withdrawal symptoms showed that, despite buspirone therapy, there were still significant increases during the test period in craving, difficulty concentrating, restlessness, and eating (ANOVA all values $P < 0.05$). With the exception of the hunger and eating scores, there were no significant differences in withdrawal symptoms between smokers who achieved abstinence and those unable to abstain completely during the study. As expected, the hunger and eating scores were higher in the abstinent group (ANOVA $P < 0.01$). Smokers who achieved abstinence reported smoking fewer cigarettes at baseline (22.2 ± 14.3)

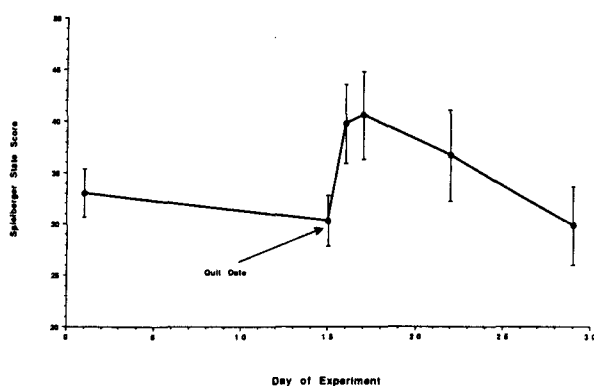


Figure 2. Spielberger state-anxiety score versus time (means with S.E.M. bars).

than those who relapsed (37.0 ± 9.7), but this was not significant (t-test $P = 0.07$). There were no significant differences between abstaining and relapsing smokers in any of the following baseline variables: years smoked, number of quit attempts, Fagerstrom tolerance scores, Spielberger state- and trait-anxiety scores, and initial cotinine-creatinine ratios.

Compared with earlier tobacco withdrawal attempts, difficulty concentrating, craving, restlessness, and anxiety were rated as improved with buspirone therapy by more than two-thirds of the patients. Ratings of the degree of improvement are given in Table 2.

Eight patients (73 percent) reported that the taste of cigarettes was less appealing during buspirone therapy. Five (46 percent) reported a decreased urge to smoke for the 2-week precessation period despite instructions not to change their smoking patterns before their quit date.

Self-reports of abstinence or relapse were confirmed by the urine cotinine measurements without any evidence of deception. The mean cotinine-creatinine ratio decreased rapidly in the first 48 hours of abstinence then increased slightly over subsequent visits (Figure 3). All patients abstained for the first 48 hours except for 3 who smoked 1 or 2 cigarettes per day (Table 3). Two did not attend the 48-hour visit and had relapsed. At the 2-week visit, 6 patients (55 percent) were confirmed abstinent with minimal lapses (mean cigarettes smoked 0.14/day). Three (27 percent) did not smoke a single cigarette after the quit date.

Subjects were contacted by telephone 3 months after the quit date. Despite no further follow-up treatment, 4 (36 percent) reported abstinence, 6 had resumed smoking, and one who had relapsed during the study could not be contacted.

No urine cotinine was performed to confirm abstinence at this time.

Side Effects

Four patients reported side effects during the study: 3 (27 percent) had transient dizziness and 1 (9 percent) noted mild headache. One of the patients with dizziness required dosage reduction for nausea, dizziness, and sweating; the symptoms were controlled after decreasing the buspirone to 20 mg/day. By the third week of therapy, only 1 patient (9 percent) still reported mild side effects. Side effects were decreased when patients took the medication with meals.

Discussion

This pilot study suggests that buspirone may be helpful in treating nicotine withdrawal. Nearly two-thirds of the smokers rated their craving as much less when compared with previous attempts to quit smoking. Nearly one-half (46 percent) reported a decreased urge to smoke during the premedication period despite instructions to smoke as usual. These findings support Gawin's¹⁵ finding of decreased smoking and craving with buspirone therapy. Glassman⁹ cites craving as the most severe and consistent symptom of cigarette withdrawal. Any agent with proven efficacy in the relief of craving will have ready clinical application in the treatment of addictive disorders. Our finding that 8 of 11 (73 percent) noted the taste of cigarettes to be less appealing could have implications in relapse prevention if confirmed by controlled clinical trials.

Despite buspirone therapy, tobacco withdrawal symptoms still occurred, and without a placebo comparison group, our study cannot evaluate drug efficacy. These relatively heavy smokers (mean 30 cigarettes/day for 22.9 years) would be expected to experience some tobacco withdrawal even with nicotine gum therapy. The shape of the withdrawal discomfort curve (Figure 1) is similar to previously reported studies that compare nicotine gum with a placebo.^{4,5}

Our 30-mg/day dosage is conservative, because the maximum recommended dosage of buspirone for anxiety is 60 mg/day. An added titration, as was done for 1 patient in this study, may further relieve withdrawal symptoms. A longer course of drug therapy before cessation may also prove helpful, because peak anxiolytic effects of

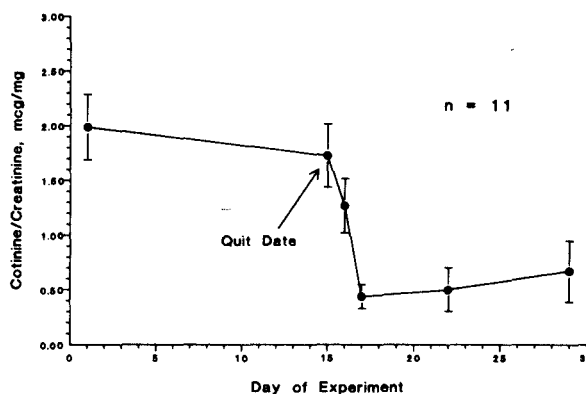


Figure 3. Cotinine/creatinine versus time (means with S.E.M. bars).

buspirone may require 3 weeks of therapy.¹⁰ An intentional effort by the smoker to decrease nicotine intake during the precessation period (unlike this protocol) might further ease withdrawal severity.

We are unaware of any other studies that used the Spielberger state-anxiety scale serially during 2 weeks of tobacco withdrawal. Figure 2 (anxiety versus time) has a shape similar to the withdrawal discomfort curve (Figure 1). We found the test very quick and simple to administer with excellent subject acceptance.

Results from this pilot study should be interpreted with caution. It is limited because of small sample size, open design, and lack of a placebo control group. Placebo and expectancy effects²¹ may account for the findings. Personal contact with a physician in a family practice setting may have provided therapeutic effects on tobacco withdrawal that may have been falsely attributed to drug effect. The validity and accuracy of the retrospective withdrawal comparisons are questionable. However, tobacco withdrawal symptoms have been shown to change little among repeated periods of abstinence.²²

Because of these limitations, clinicians treating tobacco withdrawal should await the results of controlled clinical trials before using buspirone for this condition. Even if buspirone therapy alle-

Table 3. Smoking Cessation Status by Time Periods.

Status	48 Hours No. (Percent)	2 Weeks No. (Percent)	3 Months* No. (Percent)
Abstinent	9 (82)	6 (55)	4 (36)
Relapsed	2 (18)	5 (45)	7 (64)

*Three-month cessation rates by self report only.

viates tobacco withdrawal, it may not promote abstinence. Long-term, placebo-controlled clinical trials are needed to assess whether buspirone improves cessation rates compared with existing methods.

As the rate of smoking in the United States decreases, the proportion of smokers with nicotine dependence will increase because of a selection process noted by Hughes, et al.²³ New agents and approaches are needed to treat this difficult addiction. Results of this pilot study have encouraged us to test buspirone's effect on nicotine withdrawal in a randomized, double-blind, placebo-controlled clinical trial.

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