EFFICACY OF BUPROPION SR ON REDUCING CRAVING IN SMOKING CESSATION

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INTRODUCTION: Bupropion HCl sustained release (Bup SR, Zyban™) is the first non-nicotine treatment proven to be safe and effective for smoking cessation. Clinical studies have demonstrated that when used in combination with a behavioral support program, Bup SR produces increases in smoking cessation rates relative to placebo, and that the efficacy of Bup SR is greater than that seen with the Habitrol® nicotine patch. Hurt, et al., reported the results of a dose-response study showing a clear dose response for smoking cessation. In the same report, an analysis of composite withdrawal symptoms, including craving, failed to demonstrate a treatment effect.(1)

OBJECTIVES: The purpose of this analysis was to use the individual daily craving scores to develop a comprehensive model evaluating the effect of Bup SR on the time course of craving alone.

METHODS:

Study Design

The study was a parallel, randomized, double-blind, placebo-controlled trial conducted in chronic cigarette smoking outpatients aged 18+ years at three clinical centers with brief individual smoking cessation and relapse prevention counseling provided. There were four treatment groups, including: 50 mg b.i.d. (100 mg/day), 150 mg q.d. (150 mg/day), 150 mg b.i.d. (300 mg/day), and placebo. Following at least seven days of treatment (screen/baseline phase), patients chose a target quit date (TQD), which was followed by 7 weeks of treatment and a 45-week follow-up phase. Each evening before bed, patients recorded in diaries their 'craving for a cigarette now' using the following 5-point scale: 0 = absent (none), 1 = slight, 2 = mild, 3 = moderate, 4 = severe.

Model

The probability of a score (Y_t) less than or equal to *m* was modeled using a proportional-odds model(2) as shown below:

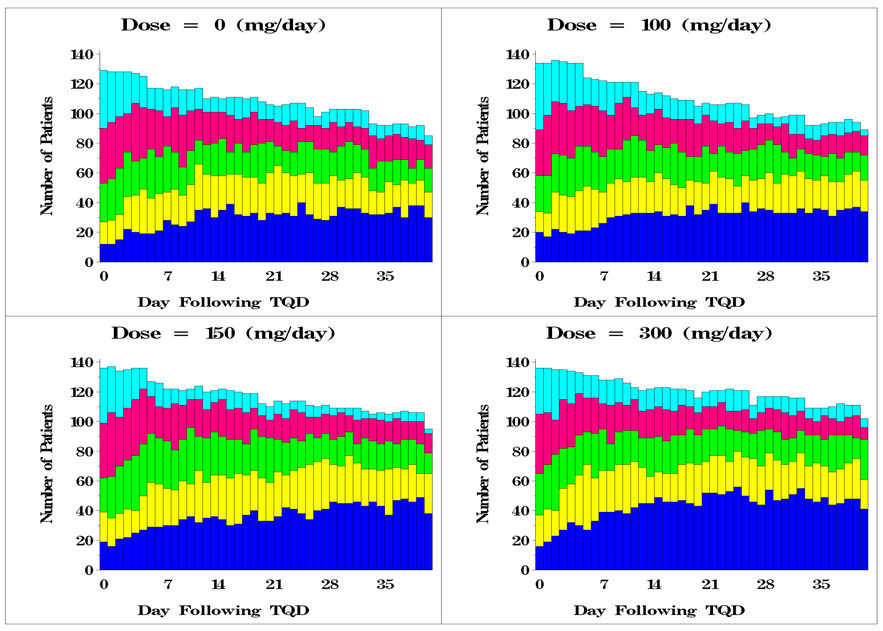
$$logit\{P(Y_t<=m|\eta)\} = f(m,t) + \eta, \quad \text{where: } f(m,t) = \sum_{m=0}^{3} b_m + \frac{Max \times t}{ET_{50} + t}$$

This function describes the increase over time in the cumulative probability of craving score ≤ *m*. The logit transform of the function is used to ensure probability values between 0 and 1. Parameters of the Emax function (*Baseline [b_m], Max, ET_{50}*) were modeled as functions of bupropion dose and covariates. The η are random individual-specific effects assumed to have mean 0 and variance ω^2.

The influences of treatment versus placebo and number of cigarettes per day (>1 pack vs. ≤1 pack) were explored on the Baseline parameter. The influences of treatment versus placebo, number of cigarettes per day (>1 pack vs. ≤1 pack), age, gender, Fagerström score ≥7 at baseline versus <7, and history of depression were explored on the *Max* and *ET_{50}* parameters.

Model parameters were estimated using the NONMEM program, version V (β) with the Laplacian estimation method.(3) To determine the goodness of fit of a particular model, the expected values of the cumulative probabilities at each day were estimated using NONMEM and compared to the data-derived calculated values. Differences between the data-derived estimates and the model-based estimates at each day were calculated and a sum of squared residuals was calculated for each model by squaring and summing these differences. This statistic was also compared across models.

Distribution of Craving Scores by Day for Each Treatment Group



RESULTS:

A total of 19,154 post-quit craving scores observed during the treatment phase in 548 patients were included in the analysis. On average, 35 observations were recorded per individual during this time period with a range of 1 to 42 measurements. Approximately 50% of patients recorded craving scores every day throughout the treatment phase. Looking across the study days of the post-quit treatment phase, the first day post-quit had the most observed craving scores (n=535 patients) and the last day of the treatment phase had the least observations (n=371 patients). This translates into a range of 2 - 32% censoring across study days.

RESULTS (cont'd.):

The population was 54% female, primarily caucasian (95.8% caucasian, 2.6% black and 1.6% other races), with a mean (SD) age of 44.1 (11.2) years and a mean (SD) weight of 76.3 (16.2) kg. Eighteen percent (18%) of patients had a history of depression. On average (±1 SD), subjects smoked 27 (±10) cigarettes per day at baseline and forty-four percent (44%) of patients had a Fagerström score ≥ 7 at baseline. Overall, 27.2% of patients achieved the four-week quit.

Predicted Probabilities of Craving (±1 SD) Using the Final Model

Craving Level	at Baseline	at End of Treatment Phase
absent	3.1% (0.2%, 32.7%)	29.5% (2.7%, 86.4%)
slight or absent	16.7% (1.3%, 75.2%)	72.3% (14.7%, 97.5%)
mild, slight, or absent	51.7% (6.6%, 94.2%)	93.3% (48.0%, 99.5%)
moderate, mild, slight, or absent	90.1% (37.5%, 99.3%)	99.2% (88.7%, 99.9%)

Severe craving has a 9.9% probability at baseline and a 0.8% probability at the end of the treatment phase.

Covariate Analysis Results

Bup SR versus placebo:
- larger reduction in craving

Heavy versus light smokers at baseline:
- greater degree of baseline craving
- larger reduction in craving

Patient age:
- reduction in craving decreases with age

History of depression versus none:
- smaller reduction in craving

Females versus males:
- no significant effect

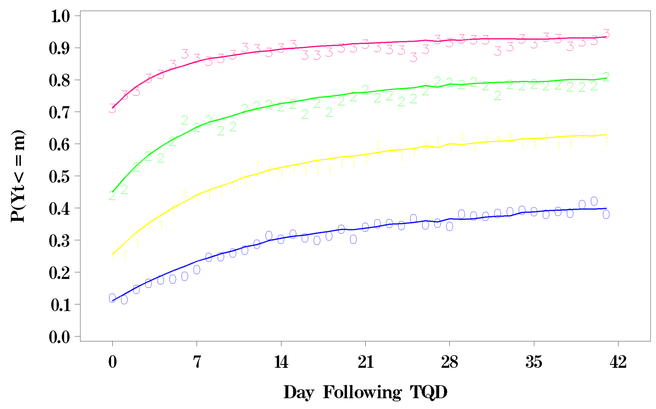
Fagerström score ≥7 versus <7 at baseline:
- no significant effect

The model predicts the following odds of experiencing no craving for various patient groups:

Odds of Experiencing No Craving for Various Significant Covariates

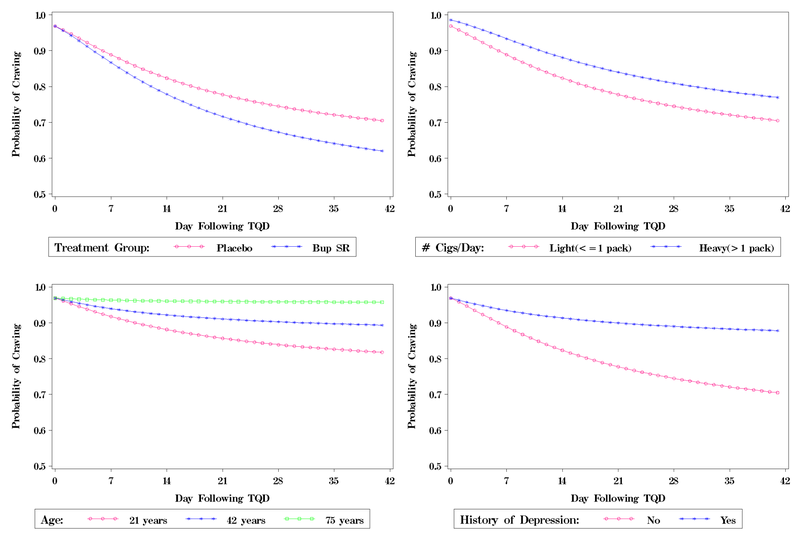
Covariate Comparison	Odds at one week following TQD	Odds at end of treatment phase
Heavy versus light smoker at baseline	0.57	0.72
Treatment versus placebo	1.22	1.46
Elderly (75 years) versus middle aged (42 years)	0.59	0.37
Young (21 years) versus middle aged (42 years)	1.40	1.88
History of depression versus none	0.56	0.33

Goodness of Fit for Final Model
Illustrating the Increase in the Probability of Not Craving Over Time



The symbols represent the data–derived estimates for probabilities of craving <= the corresponding level.
The lines represent the model–based estimates for the probability of craving <= each level.

Time Course of Craving Probability for Covariate Subgroups



CONCLUSIONS:

- Patients receiving treatment with bupropion SR exhibited a larger reduction in craving as compared to patients receiving placebo.
- The time course of craving following the target quit date is described by a proportional odds model using an Emax function across time in this population.
- The model predicts the following probabilities of craving at baseline: none - 3.1%, slight or less than slight - 16.7%, mild or less than mild - 51.7%, moderate or less than moderate - 90.1%.
- Craving is reduced following the target quit date to the following probabilities at the end of the treatment phase: none - 29.5%, slight or less than slight - 72.3%, mild or less than mild - 93.3%, moderate or less than moderate - 99.2%.
- The estimated time to achieve 50% of the maximum reduction in craving was approximately 9 days after the target quit date.
- The predicted odds of no craving for age 42, light smokers with no history of depression who are receiving treatment with bupropion as compared to patients with the same characteristics receiving placebo is 1.46 after 7 weeks of treatment with Bup SR.

REFERENCES:

1 Hurt, R.D., Sachs, D.P.L., Glover, E.D., et al. A Comparison of Sustained-Release Bupropion and Placebo for Smoking Cessation. N Engl J Med 1997; 337; 1195-1202.
2 McCullagh, P. (1980) Regression models for ordinal data (with Discussion), J.R. Statistical Society B, 42, 109-142.
3 NONMEM User's Guides, 1992, Version V Beta, Beal, S.L. and Sheiner, L.B. (Eds.) NONMEM Project Group, University of California at San Francisco, San Francisco.