

Original Investigation

# Should All Smokers Use Combination Smoking Cessation Pharmacotherapy? Using Novel Analytic Methods to Detect Differential Treatment Effects Over 8 Weeks of Pharmacotherapy

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## Abstract

**Introduction:** Combination pharmacotherapy for smoking cessation has been shown to be more effective than monotherapy in meta-analyses. We address the question of whether combination pharmacotherapy should be used routinely with smokers or if some types of smokers show little or no benefit from combination pharmacotherapy versus monotherapy.

**Methods:** Two smoking cessation trials were conducted using the same assessments and medications (bupropion, nicotine lozenge, nicotine patch, bupropion + lozenge, and patch + lozenge). Participants were smokers presenting either to primary care clinics in southeastern Wisconsin for medical treatment (Effectiveness trial,  $N = 1,346$ ) or volunteering for smoking cessation treatment at smoking cessation clinics in Madison and Milwaukee, WI (Efficacy trial,  $N = 1,504$ ). For each trial, decision tree analyses identified variables predicting outcome from combination pharmacotherapy versus monotherapy at the end of treatment (smoking 8 weeks after the target quit day).

**Results:** All smokers tended to benefit from combination pharmacotherapy except those low in nicotine dependence (longer latency to smoke in the morning as per item 1 of the Fagerström Test of Nicotine Dependence) who also lived with a spouse or partner who smoked.

**Conclusions:** Combination pharmacotherapy was generally more effective than monotherapy among smokers, but one group of smokers, those who were low in nicotine dependence and who lived with a smoking spouse, did not show greater

benefit from using combination pharmacotherapy. Use of monotherapy with these smokers might be justified considering the expense and side effects of combination pharmacotherapy.

## Introduction

Recent research shows that combinations of smoking cessation medications tend to produce higher cessation rates than do single agents (monotherapies: e.g., Fiore et al., 2008; Piper et al., 2009; Smith et al., 2009; Stead, Perera, Bullen, Mant, & Lancaster, 2008). Such findings have led to suggestions for greater use of combination pharmacotherapy (e.g., Rigotti, 2009; also see Ebbert, Hays, & Hurt, 2010). This raises the question of whether there are any groups of smokers for whom combination pharmacotherapies are not significantly effective (i.e., relatively ineffective). If such a group could be identified easily, it might be appropriate to provide them monotherapy (single-agent smoking cessation pharmacotherapy) since combination pharmacotherapy is more expensive than monotherapy and can produce somewhat higher levels of side effects (typically not serious ones: Piper et al., 2009).

The first goal of the present research is to identify particular variables (*outcome discriminators*) that most efficiently separate patients who succeed versus fail in quitting smoking when using different types of smoking cessation medications (e.g., monotherapies vs. combination therapies). Outcome discriminators will be identified in the present work using a novel analytic method — *importance scores* derived from decision tree analyses

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(Loh, in press). These scores reveal which individuals benefit most and least from a particular treatment. Thus, such scores can be used to identify types of individuals for whom combination therapy may be less effective.

An appraisal of outcome discriminators should reveal whether different *types* or classes of variables (e.g., nicotine dependence) discriminate success and failure for different types of treatments. Identification of these classes of outcome discriminators could provide insights into how different treatments work. For instance, if nicotine dependence is unrelated to outcome in individuals who get combination pharmacotherapy, but is related in smokers getting monotherapy, it is possible that combination medication works by neutralizing the effect of severe dependence (i.e., the medication “treats” the effects of severe dependence such as withdrawal).

The second and chief aim of the present research is to separate smokers into those who significantly benefit from combination pharmacotherapy, versus monotherapy, and those who do not. In the present research, two types of combination pharmacotherapies were used: the nicotine patch + the nicotine lozenge, and bupropion + the nicotine lozenge. Three types of monotherapy were used: the nicotine patch, the nicotine lozenge, and bupropion. Optimal assignment to combination versus monotherapies seems important since they differ in cost and side effect incidence, as well as in efficacy and effectiveness (Bittoun, 2006; Fiore et al., 2004, 2008; Piper et al., 2009; Smith et al., 2009).

The current research used a decision tree method called GUIDE to identify strength of predictive relations (see Loh, 2002, 2008, 2009; also Kim & Loh, 2001; Loh & Shih, 1997). A decision tree is a statistical model for predicting an outcome variable from the values of one or more predictor variables. A novel feature of GUIDE is that it can produce an “importance score” for each variable that measures that variable’s ability to discriminate between outcomes at all nodes of a decision tree (Loh, in press; Mueckstein, Lepar, Posekany, Hofacker, & Kreil, 2010). In this research, the importance scores were used to identify the variables that accounted for success versus failure for combination pharmacotherapies and, separately, to identify the variables that accounted for success versus failure for the monotherapies. These importance scores were then used to suggest variables that predicted differential response to monotherapy versus combination therapy.

This research used data from two large clinical trials in analyses which: used the same combination and monotherapies, comprised large samples ( $N = 1,346$  and  $1,504$ ), and used a common set of brief assessments designed to efficiently predict differential response to treatment (an *a priori* aim of the research). Finally, the trials were sufficiently different to allow a meaningful test of the generalizability of the outcome discriminators: (a) an Effectiveness trial (Gartlehner, Hanson, Nissman, Lohr, & Carey, 2006) that entailed little patient contact with recruitment occurring at primary health care visits and (b) an Efficacy trial with more intensive treatment and assessment methods that recruited motivated volunteers from the community. Consistency of findings across the two trials would suggest good generalizability of obtained results. This research focused on smoking at the end of treatment (EOT; 8

weeks after the target quit day [TQD]) as the main outcome measure since intratreatment outcomes are often more sensitive to treatment differences than are later outcomes (Baker et al., 2011; Piasecki, Fiore, McCarthy, & Baker, 2002). Intending to match patient characteristics with treatment effects, we chose to use an outcome that was sensitive to the latter.

## Methods

For the Efficacy and Effectiveness trials (see below), full Consort diagrams and subject recruitment/selection procedures are provided in Piper et al. (2009) and Smith et al. (2009), respectively. Demographics for the Effectiveness and Efficacy studies are, respectively, female: 55.9%, 58.2%; white: 87.2%, 83.9%;  $\leq$ high school education: 57.2%, 29.1%; married: 54%, 44.5%; mean age (*SD*): 44.3 (12.1), 44.7 (11.1); mean number of prior quit attempts (*SD*): 5.7 (9.3), 5.7 (9.7); mean number cigarettes per day (*SD*): 20.3 (8.8), 21.4 (8.9); and mean score on Fagerström Test for Nicotine Dependence (*SD*): 5.1 (2.1), 5.4 (2.1).

### Effectiveness Trial

This was a randomized trial in which 1,346 primary care patients attending routine appointments were recruited by medical assistants in 12 Wisconsin primary care clinics (see Smith et al., 2009). Patients were randomly assigned to one of five open-label active pharmacotherapies, the same used in the Efficacy Trial: three monotherapies (nicotine patch, nicotine lozenge, and bupropion SR) and two combination therapies (patch + lozenge and bupropion + lozenge). There was no placebo control condition in this Effectiveness trial. Pharmacotherapies for the 5 conditions were: (a) bupropion SR (uptitrated to 150 mg twice daily for 9 weeks total: 1-week pre-TQD and 8-week post-TQD); (b) nicotine lozenge (2 or 4 mg based on appropriate dose-for-dependence level per package instructions for 12-week post-TQD); (c) nicotine patch (24-hr patch; 21 mg for 4 weeks after the TQD then 14 and 7 mg for 2 weeks each); (d) nicotine patch (24-hr patch; 21 mg for 4 weeks after the TQD then 14 and 7 mg for 2 weeks each) plus nicotine lozenge (2 or 4 mg based on appropriate dose-for-dependence level per package instructions for 12-week post-TQD) combination therapy; and (e) bupropion SR (uptitrated to 150 mg twice daily for 9 weeks total: 1-week pre-TQD and 8-week post-TQD) plus nicotine lozenge (2 or 4 mg based on appropriate dose-for-dependence level per package instructions for 12-week post-TQD) combination therapy. Varenicline was not included as a pharmacotherapy because when this research began it had not yet earned FDA approval for clinical use.

Participants were referred to a telephone quitline for cessation counseling. Results showed that 40.5% had a least one quitline counseling contact and contact did not vary across experimental (medication) conditions. Primary outcomes included 7-day point prevalence abstinence at 1-week, 8-week, and 6-month post-quit and number of days to relapse. Eight-week abstinence rates obtained were: bupropion = 27.7%; lozenge = 28%; patch = 28.4%; patch + lozenge = 44.8%; and bupropion + lozenge = 45.5%. At 8-week post-TQD, combination pharmacotherapies differed significantly from the monotherapies ( $p$ 's < .05).

Because the trial conformed to many criteria of an Effectiveness trial (e.g., primary care population, assessment of adherence, tracking health-relevant outcomes, targeted assessment of adverse events; Gartlehner et al., 2006), abstinence reports were not biochemically confirmed (they were in the Efficacy trial).

## Efficacy Trial

This was a randomized double-blind, placebo-controlled clinical trial that recruited smokers from the community at two urban research sites in Wisconsin (see Piper et al., 2009). Participants were 1,504 adult smokers smoking >9 cigarettes/day over the prior 6 months and reporting being motivated to quit smoking.

All participants received six individual counseling sessions. Participants were randomized to the same active pharmacotherapy conditions and dosing as in the Effectiveness trial (plus a placebo condition). While no medication adherence data were available for the Effectiveness trial, in the Efficacy trial, participants were asked to return any unused medication at each study visit through 8-week post-TQD and then they were given medication for the next phase of the study. On the basis of such "pill count" evidence, we determined that, on average, participants used approximately 77% of the medication given during the 1-week pre-TQD and 8-week post-TQD over the course of the study (placebo, 75%; patch, 86%; bupropion, 85%; lozenge, 67%; bupropion + lozenge, 77%; and patch + lozenge, 74%).

Results yielded the following biochemically confirmed abstinence rates at 8-week post-TQD: bupropion = 40.2%; lozenge = 40.4%; patch = 44.7%; patch + lozenge = 53.6%; and bupropion + lozenge = 50.4%. At 8-week post-TQD, the combination pharmacotherapies differed significantly from the monotherapies ( $p$ 's < .05). The 8-week post-TQD abstinence rate for the Placebo condition was 30.2%.

## Measures

Appendix 1 presents measures used as outcome predictors. These variables were selected on empiric and substantive grounds. They were ones that theory suggested might moderate the impacts of the different treatments (e.g., dependence measures) or were ones that previous research has shown predict cessation outcomes (e.g., Bolt et al., 2009; J. A. Ferguson et al., 2003). Many of these measures were derived from the University of Wisconsin Center for Tobacco Research and Intervention Smoking History Questionnaire which was designed for routine clinical use: that is, items are brief and can be scored easily. The items selected from the Smoking History Questionnaire were those related to treatment efficacy or quitting likelihood in prior research (e.g., Bolt et al., 2009). In addition, we used Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989) items because of their relations with treatment outcome and their ease of use in treatment settings (Baker et al., 2007; Fiore et al., 2008; Shiffman et al., 2002). All analyses used smoking at the EOT, defined as not providing biochemically confirmed point prevalence abstinence at 8-week post-TQD, as the measure of treatment outcome.

## Analytic Methods

A two-step procedure was used to analyze the data for each trial. First, calculation of importance scores allowed an ordering of the variables in terms of the strength of their association with the outcome. This was performed for each pharmacotherapy condition as well as for combinations of conditions (i.e., monotherapies vs. combination therapies). The method used to produce the importance scores was GUIDE, an algorithm for fitting decision tree prediction models to data (Loh, 2002, 2008, 2009). GUIDE recursively partitions the data, at each stage using the variable most highly associated with the outcome variable to form the partition. Strength of association is measured by a chi-square test statistic. For a nominal predictor variable, such as marital status, a contingency table chi-square test of independence between the predictor variable and the outcome variable is computed. For an ordered predictor variable, such as age, values are grouped into a small number of levels before application of the chi-square test. The predictor variable having the most significant  $p$  value is selected to partition the data into two subsets, with the splitting value chosen to maximize a function of the difference in outcome rates (at the 8-week follow-up mark) in the two subsets. The process is repeated recursively on each subset of data until either the number of observations is less than 30 or the outcome is the same for all observations. To prevent overfitting the data, the nodes are pruned to yield a tree with the best cross validation estimate of prediction accuracy using the CART method described in Breiman, Friedman, Olshen, and Stone (1984). The result can be represented as a decision tree, with each node of the tree representing a split of the data. Predicting the probability of smoking for a specific person is simply a matter of dropping the person down the tree to see in which terminal node she/he falls. The predicted probability is the proportion of smoking cases in the terminal node.

The set of the chi-square statistics for a predictor variable over all the nodes of the decision tree gives a measure of the overall importance of a predictor variable. Taking a weighted sum of these statistics (with weight proportional to the square root of the sample size in each node) yields a single importance score for the variable (Loh, *in press*). Additionally, a threshold score is given that can be used to identify the predictor variables likely to influence the outcome variable. Although there are many decision tree methods, only GUIDE computes importance scores and the necessary thresholds. Further, unlike CART and other older methods, such as C4.5 (Quinlan, 1993), the GUIDE splitting method has no selection bias (Loh, 2009).

After an importance score for each predictor variable was obtained for the monotherapy and combination therapy conditions, the variables whose scores differed substantially between the monotherapy and combination therapy conditions were identified. For each pair of these variables, a  $2 \times 2$  table was formed for each therapy condition and the 8-week smoking rates in the cells were analyzed. We also examined the performance of the two-predictor model in predicting the effects of the mono- and combination nicotine replacement therapy (NRT) per se (i.e., excluding arms that used bupropion), to examine performance regarding this combination pharmacotherapy that enjoys especially strong empirical support (Fiore et al., 2008; Stead et al., 2008).

## Results

### Sample Comparability

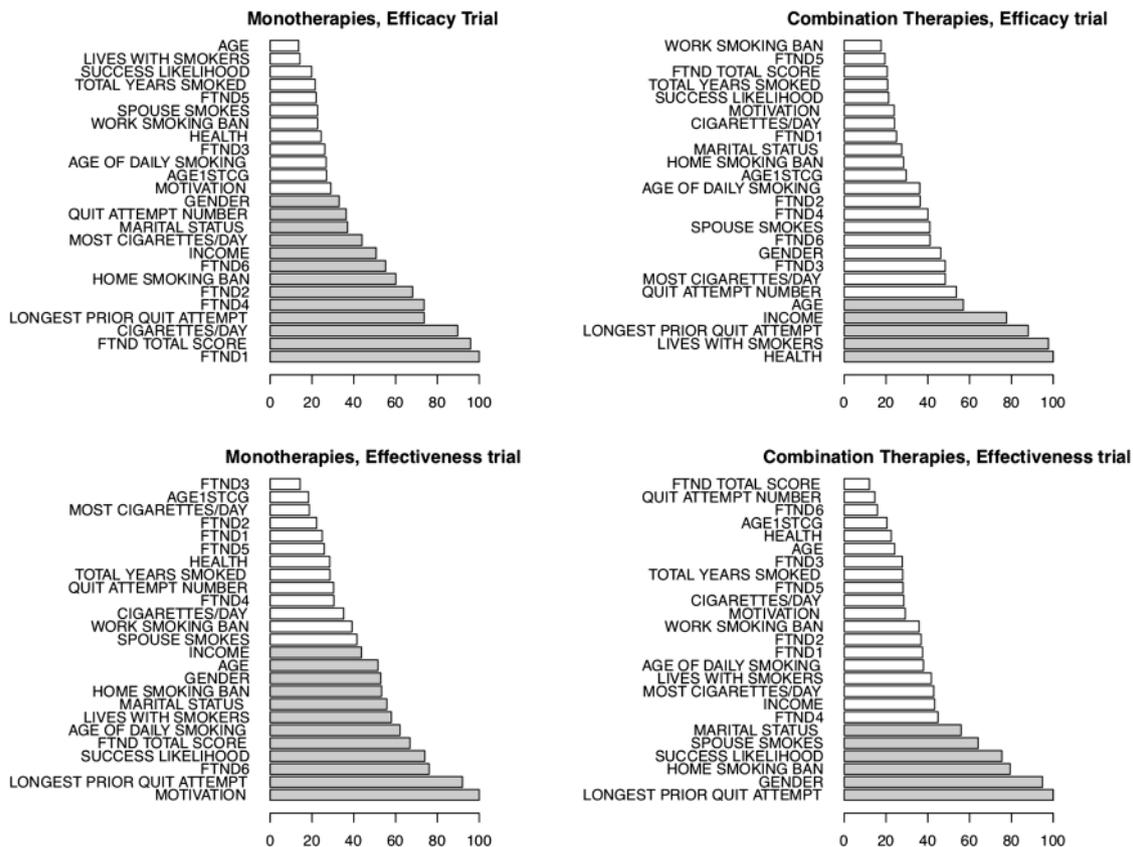
To see how the two trials differ in terms of the predictor variables (Appendix 1), two-sample *t*-tests (for ordinal variables) and chi-square tests (for nominal variables) were performed. In all, 15 of the 25 variables differed significantly across the two samples at the 0.01 level. For instance, three variables (MOTIVATION, SPOUSE SMOKES, and FTND4; Table 2) had *p* values  $< 2 \times 10^{-16}$ . Differences between predictor values in the two samples and in the recruitment and methods in the two trials argued against merging participants across the trials.

### Importance Scores

Figure 1 presents the importance scores for the combined mono and combination therapies for the Effectiveness and Efficacy trials. These plots rank order the variables in terms of their importance in the prediction of outcomes (i.e., smoking vs. abstinence at 8-week post-TQD) for each treatment; this is reflected by the length of its value along the horizontal axis. The plots were very similar when individual treatments were examined within the monotherapies and within the combination pharmacotherapies. However, different variables assumed predictive importance across the monotherapy and combination therapy conditions.

For instance, for all monotherapy conditions in the Effectiveness trial, the important predictors (statistically significant, indicated by gray bars) included FTND6 and the FTND TOTAL SCORE. In the Efficacy Trial, the important predictors for the monotherapy conditions included FTND1, FTND TOTAL SCORE, CIGARETTES/DAY, FTND4, FTND2, FTND6, and MOST CIGARETTES/DAY (see Table 2 for item definitions). Similar results were obtained for the NRT monotherapy conditions (i.e., lozenge alone, patch alone) in both the Effectiveness and Efficacy trials (Figure 2). This led to the prediction that smokers who were low versus high in dependence might be better aided by monotherapy.

For the combination therapy conditions, the dependence variables were less predictive of outcomes than they were for the monotherapy conditions. In neither the Effectiveness nor the Efficacy Trial did any dependence variable significantly predict outcomes in the combination conditions (Figure 1). Instead, in these conditions, outcomes were most consistently predicted by life context and demographic factors such as smokers in the person's life, marital status, income, and smoking restrictions. A similar pattern was seen in both trials when only combination NRT was examined (Figure 2). However, life context and demographic variables were not as consistently predictive of outcomes in the combination NRT condition in the Effectiveness trial as in the Efficacy trial. This whole pattern of findings led to



**Figure 1.** Importance scores for the all monotherapies and all combination treatment groups in the Effectiveness and Efficacy trials. Gray bars indicate that the importance scores of the variables are statistically significant in predicting follow-up smoking 8 weeks after the quit day. (See Table 2 for predictor variable definitions.)



**Table 2. Sample Sizes, Follow-up Smoking Rates (SEs in parentheses), and Relative Risks for Monotherapy and Combination Pharmacotherapies in the Efficacy Trial**

		Monotherapy		Combination therapies	
		FTND1		FTND1	
		High	Low	High	Low
		Sample sizes			
SPOUSE SMOKES	High	78	149	49	90
	Low	147	403	114	268
		Smoking rates (SE)			
	High	.68 (.05)	.58 (.04) <sup>a</sup>	.47 (.07)	.56 (.05) <sup>a</sup>
	Low	.68 (.04)	.53 (.02)	.54 (.05)	.42 (.03)
		Risk of smoking for combination therapies relative to monotherapies			
	High			.69	.96
	(95% CI)			(.49, .97)	(.76, 1.21)
	Low			.80	.80
	(95% CI)			(.65, .98)	(.67, .94)

Note. FTND1 risk is high if smoking within 5 min of waking. SPOUSE SMOKES risk is high if living with spouse or partner who smokes and is low otherwise.

<sup>a</sup>Cells that DO NOT differ across the monotherapy and combination pharmacotherapy conditions.

(FTND TOTAL SCORE, FTND1, FTND2, and MOST CIGARETTES/DAY as measures of nicotine dependence, and SPOUSE SMOKES and LONGEST PRIOR QUIT ATTEMPT as measures of other risk). Comparisons of the leading candidate predictors over the two trials implicated two variables as the strongest predictors: FTND1 and SPOUSE SMOKES. Tables 1 and 2 show how these variables predict smoking at 8-week post-TQD for the different treatment conditions in both trials.

Table 1 shows sample sizes, 8-week smoking outcomes, and the relative risks of smoking at 8 weeks in the Effectiveness trial when using FTND1 and the SPOUSE SMOKES (context exposure) variables to categorize relapse risk. The relative risk of smoking is the smoking rate observed in the combination therapy cell divided by the smoking rate in the corresponding monotherapy cell. The dichotomous measurement of the SPOUSE SMOKES item makes its scoring straightforward. FTND1 has four response options (Table 1); the decision tree analytic strategy identified a cutscore of smoking within the first 5 min of waking versus a longer smoking latency, as providing the most efficient prediction of 8-week smoking outcomes. Therefore, all analyses involving FTND1 used this cutscore (i.e., response option 1 vs. 2–4). Table 1 shows that risk of 8-week smoking generally is lower among all individuals receiving combination therapy: ranging from 68% to 80% in the monotherapy conditions and between 50% and 60% in the combination pharmacotherapy conditions, across the four cells yielded by crossing FTND1 and SPOUSE SMOKES. The rate of smoking was significantly lower in the combination pharmacotherapy condition than in the monotherapy conditions in three of the four cells. In fact, smoking rates were about 20 percentage points higher in the monotherapy cells with one exception—the cell constituted by smokers with low-dependence (low FTND1 score) and high-context exposure (a spouse who smokes), which produced a nonsignificant difference between the smoking rates for the monotherapy condition (71%) and the combination conditions (60%).

Table 1 also displays *relative* risk of 8-week smoking between the monotherapy and combination therapy conditions for the four cells constituted by the crossing of SPOUSE SMOKES and FTND1. Table 1 shows that in the Effectiveness trial, 8-week smoking rates among those using combination therapy were only about 72%–75% of what they were among those getting monotherapy, except for individuals with low FTND1 scores and high-context exposure: the combination therapy smoking rates were 85% of those produced by monotherapy. Thus, there was some benefit to receiving combination therapy in all cells, but the effect was smaller and nonsignificant among individuals with low FTND1 scores and high-context exposure.

The same analyses were conducted using only the NRT treatments and produced results essentially the same as when all treatment conditions were used in analyses (i.e., Table 1). Again, combination therapy produced generally lower 8-week smoking rates than monotherapy. Further, as is the case in the All Mono and All Combo comparisons, the discrepancy in smoking rates between monotherapy and combination NRT conditions is significant in all cells except that of the combination of high-context exposure and low FTND1 scores. The relative 8-week smoking risk was 86% in individuals receiving combination NRT versus monotherapy NRT in this cell and ranged from 72% to 77% in the other three cells.

The Effectiveness Trial data showed that combination pharmacotherapy produced significantly better results in most smokers, except those who were low in nicotine dependence and who lived with a spouse who smokes.

For the Efficacy Trial, Table 2 shows the sample sizes, 8-week smoking rates, and relative risks of smoking when using dependence (FTND1) and the context exposure (SPOUSE SMOKES) variables to categorize smoking risk. Table 2 shows that, as in the Effectiveness analyses, the rate of smoking was significantly lower in the All Combo condition versus the All

Mono condition in only three of the four cells constituted by the crossing of the FTND1 and context exposure variables. For instance, when subjects had a low FTND1 score and low-context exposure, 53% were smoking by 8 weeks among those receiving one of the monotherapies compared with only 42% in comparable cells in the combination therapy condition. However, among subjects who had low FTND1 scores and high-context exposure, 58% were smoking if given monotherapy and 56% were smoking if given combination therapy. Relative risk data also showed that combination pharmacotherapy benefitted all groups except those with low FTND1 scores and high-context exposure. The Efficacy trial also comprised a placebo control group. This group was smaller in size than the pharmacotherapy conditions by design ( $n = 188$ ), conferring little power for statistical comparisons. However, this group showed a risk pattern similar to that of the monotherapy participants, with high FTND1 scores predicting a greater risk of 8-week smoking than was found in the low-dependence group (78% vs. 66%).

The same analyses were conducted in the Efficacy sample using only the NRT treatments. These analyses showed that combination therapy generally produced lower 8-week smoking rates than did monotherapy. However, in the Efficacy trial, the smoking rate was *higher* in individuals with low FTND1 scores and high-context exposure who received combination NRT versus monotherapy NRT (i.e., 61% vs. 55%); thus, the relative risk of smoking was 111% in the combination NRT subjects versus the monotherapy NRT subjects in the low-dependence/high-context exposure cell.

The decision utility of the dependence (FTND1) and life context (SPOUSE SMOKES) variables for treatment assignment involved comparing 8-week smoking rates in the Effectiveness trial (where prediction effects were weaker than in the Efficacy trial) under conditions of equal selection ratios (equal assignment rates to the monotherapy and combination therapy conditions) with the rates of 8-week smoking obtained when smokers high in context and low in dependence were assigned to monotherapy. The smoking rate under a condition of random assignment would be about 54% across the total sample; the rate would be about 49% using the algorithm. Finally, the pattern of data in the two studies implies an interaction between combination therapy responder group (nonresponders being those low in dependence and having a smoking spouse) and combination versus monotherapy condition. This interaction was significant via logistic regression when the trials were merged (Wald = 4.13;  $p = .04$ ) and in the Efficacy trial (Wald = 4.3;  $p = .03$ ) but not in the Effectiveness trial (Wald = .98;  $p = .30$ ).

## Discussion

This research shows that most smokers derive significant benefit from combination pharmacotherapy. A large group of variables was tested to determine their ability to predict differential response to treatment. Analyses using the strongest predictors among these variables, each modeled with an optimal cutscore, yielded no evidence that any group of smokers would do worse (based on smoking outcomes) using combination pharmacotherapy than monotherapy, and most smokers would do substantially better. However, one group of smokers did not

show significant added benefit from combination pharmacotherapy. Across two fairly large clinical trials, smokers who had relatively low levels of nicotine dependence (smoked later than 5 min after awakening) and who had high levels of environmental risk (lived with a spouse who smokes) did not attain significant benefit from combination pharmacotherapy relative to monotherapy. One study sample showed essentially no benefit by this group (Table 2), while the other study sample showed evidence of moderate benefit (Table 1), but only half the benefit that other smokers obtained. The similarity of the findings across two clinical trials with different levels of research contact further supports the validity of these findings. Thus, if concern about costs (see [Campaign for Tobacco Free Kids, 2010](#)), treatment compliance, or side effects argue for some restriction on use of combination pharmacotherapy, then use of the two predictors identified in this research would produce outcomes superior to those of a random selection strategy.

Moreover, if data from the two studies are merged (acknowledging that differences in importance score patterns suggests some sample specificity), the smoking rates that would be obtained by giving all patients combination pharmacotherapy (49%) are essentially identical those to those obtained if medication were restricted according to the proposed algorithm (48%). In other words, due to the validity of the predictors, withholding combination pharmacotherapy from the low-dependence + high environmental risk group, and giving all others combination pharmacotherapy, will produce about the same likelihood of abstinence/smoking as would be obtained if all individuals were given combination pharmacotherapy (to the extent that our results are generalizable).

This research demonstrates the potential of a relatively new statistical index, importance scores, for screening large numbers of predictors of differential treatment benefit. These scores allow researchers to screen simultaneously large numbers of variables and then identify the predictive validity of variables across all possible nodes of a decision tree and across thousands of iterations (Mueckstein et al., 2010; Wei et al., 2008). The use of importance scores may be superior to regression-based approaches in that importance scores are less dependent upon model specification. For example, if a linear regression model is assumed and the true model is nonlinear, each coefficient represents an average slope, at best. The importance score, on the other hand, quantifies the overall prediction power of the variable without any prior assumptions about the exact form of the model because the complexity of the decision tree model automatically adapts itself to the information content and the complexity of the data.

Second, the results of these importance score analyses appear to have substantive value in that they suggest risk factors that are, and are not, addressed by treatments. In this case, they suggest that combination therapy ameliorates the risk posed by tobacco dependence but does not address the risk posed by environmental challenges (Figures 1 and 2). This information can help to focus formal mediation analyses (e.g., McCarthy et al., 2010; Piper et al., 2008). For instance, it suggests that combination pharmacotherapy may work by suppressing such risks as withdrawal-related craving, while counseling might poten-

tially mitigate environmental risk. Finally, this research adds to prior research that characterizes factors that index relapse proneness (Baker et al., 2007; Bolt et al., 2009; J. A. Ferguson et al., 2003; Kozlowski, Porter, Orleans, Pope, & Heatherton, 1994; Levy, Romano, & Mumford, 2005; Nides et al., 1995; Osler & Prescott, 1998), and this offers potential for treatment tailoring.

The results do not strongly implicate particular mechanisms for the observed effects. However, recent data show that combination therapy appears to produce higher abstinence rates than monotherapy because it reduces the risk posed by tobacco dependence (Japuntich et al., 2011), apparently because of its greater suppression of craving (Bolt, Piper, Theobald, & Baker, 2011). The results also suggest that the ready availability of cigarettes and density of smoking cues, due to spousal/partner smoking, increases risk of smoking, but that this environmental threat is not mitigated by combination pharmacotherapy. Thus, it may be that pharmacotherapy is more effective at reducing craving and other withdrawal symptoms that arise from dependence but less effective at mitigating episodic, environmental threats. This conjecture is consistent with recent work suggesting that high-dose pharmacotherapy does not affect the environmental precipitants of lapses (although it may affect the affective threshold for lapsing in response to environmental events: S. G. Ferguson & Shiffman, 2010), that lapse-associated distress is not strongly related to withdrawal (S. G. Ferguson & Shiffman, 2010) and that dependence does not modulate the relation between situational risk and smoking (Shiffman & Rathbun, 2011). This theoretical account must be viewed as speculative and post hoc, however.

Limitations of this research include the possibility that the items available for identifying smokers unresponsive to combination therapy were not optimal. Similarly, the predictor item cutscores identified by the GUIDE method may not be optimal for all samples. Also, while the results of the importance scores suggest mechanisms via which treatments work (e.g., suppression of dependence processes), the evidence remains merely suggestive. In addition, the two studies in this research used only a limited set of pharmacotherapy conditions and a limited, but representative, set of dosing parameters. It is possible that different findings would be obtained with different treatments and dosing. Further, the effects of the pharmacotherapies might have been different, and therefore, the magnitudes of predictive relations different, if participants had used the pharmacotherapies more adherently. However, significant nonadherence appears to be common in real-world use (Lam, Abdullah, Chan, & Hedley, 2005). Finally, this research does not prove the null hypothesis (that combination pharmacotherapy is inert in the identified subpopulation of smokers); rather, it merely yields evidence of differential effect sizes and calls for replication in different populations.

## Conclusions

Recent reports suggest that combination pharmacotherapy be used more extensively with smokers making quit attempts. This research showed that when numerous subpopulations of smokers were examined with decision tree analysis, the majority were greatly aided by combination pharmacotherapy, but a subgroup of smokers received modest or no benefit. Those smokers receiving less benefit, 25%–30% of all smokers, were those low in nicotine dependence (smoked 5 min or later after arising) and who faced environmental risk (a smoking spouse). In the face of concerns about costs or side effects that argue for limiting the use or provision of combination pharmacotherapy, the current results suggest a strategy for doing so that would not lower overall abstinence rates.

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## Declaration of Interests

*The authors report the following potential conflicts of interest for the last 5 years: M.C.F. has served as an investigator on research studies at the University of Wisconsin that were funded by Pfizer, GlaxoSmithKline, and Nabi Biopharmaceuticals. In 1998, the University of Wisconsin (UW) appointed him to a named Chair funded by a gift to UW from Glaxo Wellcome. S.S.S. has received research support from Elan Corporation. D.E.J. has received research support from Pfizer Inc., Sanofi-Synthelabo, and Nabi Biopharmaceuticals. He has received consulting fees from Nabi Biopharmaceuticals. T.B.B. has served as an investigator on research projects for which drug was supplied by GlaxoSmithKline. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.*

## Appendix: Predictor Variable Names, Definitions, and Values

Name	Definition and values
Age	Current age (18–84)
Age of first cigarette	Age when first tried a cigarette (3–52)
Age of daily smoking	Age started daily smoking (6–60)
Cigarettes/day	Baseline cigarettes per day (1–80)
FTND1*	How soon after you wake up do you smoke? (1 = “≤5 min,” 2 = “6–30 min,” 3 = “31–60 min,” 4 = “>60 min”)
FTND2*	Hard to refrain from smoking in forbidden places (yes, no)
FTND3*	Which cigarette you hate most to give up? (first one in morning, any other)
FTND4*	How many cigarettes/day do you smoke? (1 = “1–10,” 2 = “11–20,” 3 = “21–30,” 4 = “>30”)
FTND5*	Smoke more frequently in 1st hours after waking? (yes, no)
FTND6*	Smoke when so ill you are in bed most of day? (yes, no)
FTND total score	FTND total score (0–10)
Gender	Gender (male, female)
Health	What would you say your health in general is? (excellent, very good, good, fair, poor, not sure)
Income	Annual household income (1 = “<10K,” 2 = “10–20K,” 3 = “20–25K,” 4 = “25–35K,” 5 = “35–50K,” 6 = “50–75K,” 7 = “≥75K”)
SPOUSE SMOKES	Do you live with a spouse or partner who smokes? (yes, no)
Lives with smokers	Do you live with others who smoke? (yes, no, NA)
Marital status	Marital status (married, living with partner, separated, divorced, widowed, never married)
Most cigarettes/day	When smoking the most, how many cigarettes/day? (1–99)
Motivation	How motivated are you to stop smoking at this time? (0 = <i>not at all</i> through 10 = <i>extremely motivated</i> )
Quit attempt number	How many times have you tried to quit smoking? (0–99)
Home smoking ban	Must go outside to smoke? (yes, no)
Success likelihood	If quit in next 30 days, how likely successful? (0 = <i>not at all likely</i> through 7 = <i>very likely</i> )
Work smoking ban	Workplace smoking policy (allowed all areas, allowed some areas, not allowed any work area, NA)
Longest prior quit attempt	Longest period without smoking? (1 = “<1 day,” 2 = “1–7 days,” 3 = “8–14 days,” 4 = “15 days–1 month,” 5 = “1–3 months,” 6 = “3–6 months,” 7 = “6–12 months,” 8 = “>1 year”)
Total years smoked	Total number of years smoked (0–80)

Note. NA = not applicable. \*FTND1–6 represent individual FTND items.

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