



# Cessation treatment adherence and smoking abstinence in patients after acute myocardial infarction

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**Background** Previous trials examining the use of bupropion for smoking cessation therapy after myocardial infarction (MI) have been inconclusive. To understand better the observed lack of effectiveness of bupropion in this population, we examined abstinence rates by level of adherence across treatment groups.

**Methods** We used data from a randomized, double-blind, placebo-controlled trial of bupropion in smokers ( $n = 388$ ) hospitalized with MI to study the association of interest. Patients were classified as being fully adherent if they reported taking 2 pills/d; partially adherent if they reported 0, 1, and/or 2 pills/d; and nonadherent if they reported 0 and/or 1 pill/d throughout the 9-week treatment period. Abstinence was assessed by 7-day biochemically validated self-report at 4 and 9 weeks and 6 and 12 months.

**Results** A total of 156 patients were fully adherent to the study medication (66 bupropion and 90 placebo), 149 were partially adherent (76 and 73, respectively), and 83 were nonadherent (46 and 37, respectively). Regardless of treatment group, patients who were fully or partially adherent reported greater abstinence than did nonadherent patients. Among partially adherent patients, bupropion conferred an important benefit at 12 months (% difference 13.3, 95% CI 1.3-25.3). At 12 months, patients who were fully adherent were more likely to be abstinent compared with those who were nonadherent (adjusted odds ratio 7.6, 95% CI 3.2-17.6).

**Conclusions** Adherence to study medication, regardless of assigned treatment, is associated with a substantial increase in abstinence. Patients who are motivated to quit smoking should be targeted for smoking cessation treatment after MI. (*Am Heart J* 2016;173:35-40.)

Although the benefit of smoking cessation on clinical outcomes in myocardial infarction (MI) patients surpasses that of other evidence-based post-MI therapies,<sup>1,2</sup> more than 50% of patients relapse within the first year after MI.<sup>3</sup> The use

of pharmacotherapy, including varenicline, bupropion, and nicotine replacement therapy, doubles abstinence rates in healthy individuals as well as in patients with a history of cardiovascular disease.<sup>4-7</sup> However, trials investigating bupropion as a smoking cessation therapy in patients with acute cardiovascular disease have been inconclusive.<sup>8-10</sup> A possible explanation for these discordant findings is that adherence to study medication may be different in this patient population.

Two previous studies examining adherence to smoking cessation therapies and abstinence found that adherence improved the likelihood of remaining abstinent.<sup>11,12</sup> However, these studies were limited by their small samples, heterogeneous study populations, and lack of assessment of long-term abstinence. In order to investigate this issue, we examined abstinence rates at 12 months by level of adherence to cessation pharmacotherapy in post-MI patients randomly assigned to bupropion or placebo.

## Methods

Data were available in a multicenter, randomized, double-blind, placebo-controlled trial investigating the

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efficacy of bupropion for smoking cessation in MI patients ( $n = 388$ ). The full details of the trial have been described elsewhere.<sup>10</sup> Briefly, inclusion criteria included that the patient smoked a minimum of 10 cigarettes per day, was  $\geq 18$  years of age, had suffered an enzyme-positive MI, and was motivated to quit. Patients were randomized to bupropion (150 mg/d) or placebo treatment for 9 weeks and returned for clinic visits at 4 and 9 weeks and at 6 and 12 months. All patients received motivational support from either a research nurse or a trained smoking cessation counselor at baseline and follow-up visits. Patients who died or withdrew during the treatment period ( $n = 7$ ) were excluded from the analysis, and those who died during follow-up ( $n = 8$ ) were censored at the time of death.

Adherence was assessed by self-report by telephone calls at weeks 1 and 2 and in clinical visits at weeks 4 and 9, where a pill count was undertaken in addition to self-report. Adherence was categorized using a summary score based on the total number of pills/d reported at each of the 4 follow-up visits during the 9-week treatment period. Based on this scoring system, individuals were classified as (1) fully adherent, a total score of 8, including individuals who reported taking 2 pills/d at each of the 4 follow-up visits; (2) partially adherent, a summary score of 4 to 7, including individuals who reported taking a combination of 0, 1, and/or 2 pills/d during the treatment period; and (3) nonadherent, total score of  $\leq 3$ , including individuals who reported a combination of 0 and/or 1 pill/d.

Abstinence was assessed at all clinic visits by self-report and validated by expired carbon monoxide. Smoking abstinence in the current study refers to abstinence from cigarette smoking in the week prior to the follow-up visit. Point prevalence abstinence was defined as reporting no cigarettes smoked in the last 7 days with an expired carbon monoxide  $\leq 10$  ppm at the 4- and 9-week and 6- and 12-month clinic visits. Patients lost to follow-up during the treatment period were considered to be nonadherent, and patients lost to follow-up at any time during the 12-month follow-up were considered to have returned to smoking.

### Data analysis

Baseline demographic, smoking, and clinical characteristics are reported as means with standard deviation (SD) or percentages, as appropriate. The association between adherence and abstinence is presented as differences in proportions with corresponding 95% CIs between treatment and adherence groups. The independent association between adherence to medication and abstinence was assessed using multivariable logistic regression. Covariates were selected based on clinical judgment and substantive knowledge regarding the potential association between adherence and smoking cessation and included age, sex, other smokers at home (yes, no), number of previous quit attempts (0-10), number

of cigarettes smoked per day at baseline, the Fagerstrom Tolerance Questionnaire score at baseline (as a continuous variable), the Beck Depression Inventory II score at baseline (0-13 [no depressive symptoms], Beck Depression Inventory II  $\geq 14$  [any depressive symptoms]), number of years smoked, percutaneous coronary intervention (yes/no), and ST-segment elevation MI (yes/no). Statistical analyses were performed using the SAS statistical software (Version 9.2; SAS, Cary, NC) and R (Version 3.1.2 <http://www.r-project.org/>).

### Results

The sample included 388 MI patients. Most participants (83.3%) were male, and the mean (SD) age at baseline was 53.8 (10.4) years. Patients had smoked for 3 decades on average, and they smoked an average of 23 cigarettes per day prior to their MI. A total of 156 patients were fully adherent to the study medication (66 in the bupropion group and 90 in the placebo group), 149 were partially adherent (76 and 73, respectively), and 83 were nonadherent (46 and 37, respectively; [Table D](#)). Nonadherent patients in the bupropion group were more likely to report living with other smokers and to have hypertension compared with the fully and partially adherent group. Nonadherent patients in the placebo group were more likely to have a history of diabetes mellitus but less likely to have hypertension compared with patients who were partially and fully adherent. Overall, baseline characteristics were similar between treatment and adherence groups.

Approximately 42% of patients experienced an adverse effect over the 9-week treatment period ([Table II](#)). The most common adverse effects were insomnia (19.7%) and dry mouth (10.4%). Among patients in the bupropion group, patients who were partially adherent were more likely to report any adverse effect compared with patients who were nonadherent (between-adherence group difference 18.6%, 95% CI 1.2%-35.9%). Patients in the bupropion group who were partially adherent were also more likely to report dry mouth compared with nonadherent patients (between-adherence group difference 10.8%, 95% CI 0.0%-21.5%). In the placebo group, a higher proportion of fully and partially adherent patients reported a bad taste in mouth compared with nonadherent patients (between-adherence group difference 8.9% [95% CI 3.0%-14.8%] and 6.9% [95% CI 1.1%-12.6%], respectively). Among patients who discontinued study medication ( $n = 123$ ), 10.7% reported adverse effects as the primary reason. Among patients who discontinued,  $<1.0\%$  discontinued study medication due to a serious adverse event.

Regardless of treatment group, patients who were fully or partially adherent reported greater abstinence than did nonadherent patients ([Table III](#)). The most notable differences were found during the treatment period,

**Table I.** Baseline demographic, smoking, and clinical characteristics of patients by level of adherence in each treatment group

	Bupropion			Placebo		
	Fully adherent* (n = 66)	Partially adherent* (n = 76)	Nonadherent* (n = 46)	Fully adherent* (n = 90)	Partially adherent* (n = 73)	Nonadherent* (n = 37)
Male (%)	87.9	85.7	72.9	78.9	87.7	88.6
Age (y), mean (SD)	53.6 (10.3)	54.0 (10.0)	56.6 (10.9)	54.0 (11.3)	52.6 (10.4)	53.3 (7.1)
No. of years smoked, mean (SD)	32.8 (12.4)	31.8 (12.7)	35.9 (14.0)	33.1 (13.0)	32.1 (11.7)	32.3 (9.6)
No. cigarettes/d, mean (SD)	22.5 (10.4)	23.9 (10.5)	23.1 (12.0)	23.0 (9.8)	23.7 (11.5)	22.5 (9.9)
Other smokers at home (%)	25.8	34.2	42.6	41.1	37.0	34.3
No. of previous quit attempts, mean (SD)	2.3 (6.1)	2.4 (6.0)	1.8 (2.7)	2.4 (3.1)	1.8 (2.7)	2.1 (2.6)
FTQ nicotine dependence, mean (SD)†	5.3 (2.3)	5.5 (2.2)	5.7 (2.3)	5.6 (2.1)	5.7 (2.2)	5.8 (2.2)
Beck Depression Inventory II score ≥14 (%)‡	13.6	24.7	21.3	15.6	26.0	20.0
Hyperlipidemia (%)	54.6	54.6	42.6	48.9	46.6	45.7
Hypertension (%)	39.4	37.7	53.2	41.1	35.6	28.6
Diabetes mellitus (%)	25.8	20.8	21.3	6.7	16.4	14.3
Prior MI (%)	21.2	16.9	21.3	20.0	23.3	25.7
Prior revascularization (%)	12.1	14.3	12.8	13.3	9.6	8.6
STEMI (%)	72.7	58.4	57.5	66.7	64.4	71.4
PCI (%)	57.6	40.3	48.9	58.9	42.5	54.3
CABG (%)	4.6	3.9	8.5	6.7	8.2	8.6

Abbreviations: FTQ, Fagerstrom Tolerance Questionnaire; STEMI, ST-segment elevation MI; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.  
\* Adherence was defined as follows: (1) fully adherent, a score of 8; (2) partially adherent, a score of 4 to 7; and (3) nonadherent, a score of ≤3.

† Score ranges from 0 to 63.

‡ A score of ≥14 is indicative of depressive symptoms.

**Table II.** Adverse effects by level of adherence in each treatment group

	Bupropion			Placebo		
	Fully adherent* (n = 66)	Partially adherent* (n = 76)	Nonadherent* (n = 46)	Fully adherent* (n = 90)	Partially adherent* (n = 73)	Nonadherent* (n = 37)
Any adverse effect (%)	42.4	53.3	34.7	41.1	42.5	37.8
No. of adverse effects (%)						
0	57.6	46.8	65.3	58.9	57.5	62.2
1	24.2	23.4	20.4	21.1	19.2	21.6
2	3.0	16.9	-	8.9	5.5	10.8
≥3	15.2	13.0	14.3	11.1	17.8	5.4
Adverse effects (%)						
Insomnia	13.6	26.0	26.5	17.8	20.6	13.5
Dry mouth	13.6	16.9	6.1	7.8	12.3	5.4
Bad taste in mouth	6.1	11.7	6.1	8.9	6.9	-
Constipation	9.1	5.2	8.2	2.2	8.2	10.8
Nausea	6.1	7.8	4.1	2.2	2.7	-

\* Adherence was defined as follows: (1) fully adherent, a score of 8; (2) partially adherent, a score of 4 to 7; and (3) nonadherent, a score of ≤3.

but important differences persisted until 12 months. Differences in abstinence between treatment groups were seen for the partially adherent and nonadherent groups at 6 months. This trend was found to persist in the partially adherent group at 12 months. No important differences between the treatment groups among fully adherent patients were noted due to high rates of abstinence in the placebo group. The  $\beta$  coefficients for the test of interaction between treatment group and adherence were inconclusive due to wide CIs, likely related to the modest sample size (data not shown). However, at 12 months, patients who reported being fully adherent were more likely to be abstinent compared with patients who

reported being partially adherent and nonadherent (adjusted odds ratio [OR] 3.5 [95% CI 2.0-6.0] and adjusted odds ratio 7.6 [95% CI 3.2-17.6], respectively). Although the point estimate suggests increased abstinence among individuals who were partially adherent to study medication compared with those who were nonadherent (adjusted OR 2.2, 95% CI 0.9-5.3), the wide CI makes it difficult to draw strong conclusions.

## Discussion

This analysis examined abstinence at 12 months and level of adherence to study medication in post-MI patients

**Table III.** Prevalence of biochemically validated smoking abstinence by treatment group

		Fully adherent* (%)	Partially adherent* (%)	Nonadherent* (%)	Difference in abstinence (fully adherent – nonadherent), % (95% CI)	Difference in abstinence (partially adherent – nonadherent), % (95% CI)
4 wk†	Bupropion	77.3	56.6	19.6	57.7 (42.4 to 73.0)	37.0 (21.0 to 53.0)
	Placebo	67.8	41.1	8.1	59.7 (46.6 to 72.7)	33.0 (18.7 to 47.3)
	Difference (bupropion-placebo) (95% CI)	9.5 (–4.5 to 23.5)	15.5 (–0.4 to 31.3)	11.5 (–3.0 to 25.9)	–	–
9 wk†	Bupropion	72.7	39.5	17.4	55.3 (40.0 to 70.7)	22.1 (6.6 to 37.6)
	Placebo	63.3	29.2	5.6	57.8 (45.3 to 70.2)	23.6 (10.7 to 36.5)
	Difference (bupropion-placebo), % (95% CI)	9.4 (–5.3 to 24.0)	10.3 (–4.9 to 25.5)	11.8 (–1.4 to 25.1)	–	–
6 mo†	Bupropion	47.0	28.8	15.2	31.8 (15.9 to 47.7)	13.6 (–1.1 to 28.2)
	Placebo	43.8	14.3	2.8	41.0 (29.4 to 52.7)	11.5 (1.7 to 21.3)
	Difference (bupropion-placebo), % (95% CI)	3.2 (–12.7 to 19.0)	14.5 (1.3 to 27.7)	12.4 (0.8 to 24.1)	–	–
12 mo†	Bupropion	40.0	23.3	13.3	26.7 (11.2 to 42.2)	10.0 (–3.9 to 23.8)
	Placebo	39.8	10.0	2.8	37.0 (25.5 to 48.5)	7.2 (–1.62 to 16.1)
	Difference (bupropion-placebo), % (95% CI)	0.2 (–15.5 to 15.9)	13.3 (1.3 to 25.3)	10.7 (–0.7 to 21.9)	–	–

A total of 388, 386, 380, and 377 patients were included at 4 and 9 weeks and 6 and 12 months (as patients who died during follow-up were censored at the time of the event).

\*Adherence was defined as follows: (1) fully adherent, a score of 8; (2) partially adherent, a score of 4 to 7; and (3) nonadherent, a score of  $\leq 3$ .

†The 95% CIs for the interaction term between adherence and treatment group at 4 and 9 weeks and at 6 and 12 months were too wide to provide a meaningful conclusion.

across treatment groups. We found that regardless of treatment, patients who were fully adherent were more likely to be abstinent at 12 months. Bupropion was efficacious for smoking cessation in patients who were partially adherent to study medication, with no observed benefit among those who were fully adherent or not adherent. Moreover, the lack of effectiveness of bupropion among fully adherent patients suggests that adherence may be a marker for motivation to quit smoking post-MI.

Previous studies in the general population have identified nonadherence to medication as an important predictor of smoking relapse.<sup>13</sup> Determinants of nonadherence suggested to influence relapse include (1) newly acquired medical conditions, (2) occurrence of adverse effects, and (3) perceived lack of treatment efficacy.<sup>13–17</sup> Nonadherence to treatment due to adverse effects may partially explain our findings because approximately 11% of patients discontinued their medication as a result of adverse effects. However, whether the adverse effects reported by patients are a result of the study medication or a combination of other therapies given to post-MI patients is unclear. Moreover, because of the relatively small number of patients, it would be difficult to provide any meaningful conclusions regarding the timing of adverse effects and subsequent adherence. Despite this, patients who are taking smoking cessation therapies should be carefully monitored in order to reduce the potential for adverse effects and discontinuation as a result of adverse effects.

Studies in the general population suggest that adherence to smoking cessation therapy is generally low, particularly among individuals using over-the-counter pharmacotherapies such as nicotine replacement therapy.<sup>18,19</sup> Moreover, adherence may be a proxy for level of motivation to quit.<sup>20,21</sup> Although a quarter of patients were nonadherent in this study, the proportion was substantially lower than in the general population.<sup>15,22</sup> This may be a result of the inclusion criteria for the trial, which required that patients be motivated to quit smoking. Alternatively, our study was conducted in patients hospitalized for an MI, a “teachable moment” during which patients are more likely to adopt lifestyle changes as a result of their recent cardiac event.<sup>23</sup> A higher level of motivation among post-MI patients may also explain the large differences in abstinence rates at 6 and 12 months between nonadherent and fully adherent patients in both treatment groups.

Successful cessation typically requires multiple attempts. Although patients in this trial had smoked 3 decades on average and had moderate levels of nicotine dependence, the range in number of previous quit attempts was wide (0–10). Patients who have never tried to quit may be less likely to adhere to treatment and more likely to relapse than those with a history of unsuccessful attempts.<sup>24–26</sup> Although we considered the number of previous quit attempts as a candidate variable in our regression models, it ultimately was not an important confounder in our study. Nonetheless, there remains a need to better understand the relationship between the number of previous quit attempts, treatment adherence, and smoking cessation.

Our study has some potential limitations. First, adherence was based primarily on self-report and misclassification is possible. However, it is unlikely that this would be differential across treatment and adherence groups given the double-blind study design, and self-report was supplemented by pill counts during clinic visits. Second, as it is conventional in smoking cessation trials,<sup>6-8</sup> patients lost-to-follow-up during the treatment period were considered to be nonadherent and patients lost to follow-up at any time during follow-up were considered to have returned to smoking. Despite this limitation, the loss-to-follow-up is nondifferential across treatment groups and much lower than in most smoking cessation trials.<sup>6-8</sup> Third, our sample size was insufficient to provide meaningful estimates of the interaction between adherence to cessation treatment and smoking abstinence. Consequently, although we were able to examine treatment effects within each subgroup, we were unable to conclusively determine if treatment effects differ by adherence group. Finally, because the inclusion criteria included being motivated to quit, generalizability of the findings to all post-MI patients attempting to quit may be limited.

## Conclusion

Adherence to study medication, regardless of assigned treatment, is associated with increased abstinence. Among patients who are partially adherent, there is some evidence of a benefit of bupropion for smoking cessation. The observed overall lack of effectiveness of bupropion for smoking cessation post-MI appears to be driven, at least in part, by a higher than expected prevalence of abstinence among patients who were adherent to placebo. Moreover, adherence to treatment may be a marker for motivation to quit smoking, with some patients being sufficiently motivated to quit without the use of bupropion and others deriving some benefit from its use.

## Authors' contributions

Dr Filion had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mrs Grandi was responsible for interpretation and drafting of the manuscript. All other authors contributed equally to the interpretation of data and critical revision of the manuscript.

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