A Perioperative Smoking Cessation Intervention with Varenicline

A Double-blind, Randomized, Placebo-controlled Trial

Jean Wong, M.D., F.R.C.P.C.,* Amir Abrishami, M.D.,† Yiliang Yang, M.D.,‡ Amna Zaki, M.B.B.S.,‡
Zeev Friedman, M.D., F.R.C.P.C.,§ Peter Selby, M.B.B.S., C.C.F.P., F.C.F.P.,‖
Kenneth R. Chapman, M.D., M.Sc., F.R.C.P.C.,# Frances Chung, M.B.B.S., F.R.C.P.C.**

ABSTRACT

Background: The efficacy of perioperative tobacco interventions on long-term abstinence and the safety of smoking cessation less than 4 weeks before surgery is unclear. Our objective was to determine the efficacy and safety of a perioperative smoking cessation intervention with varenicline to reduce smoking in elective surgical patients.

Methods: In a prospective, multicenter, double-blind, placebo-controlled trial, 286 patients were randomized to receive varenicline or placebo. Both groups received in-hospital and telephone counseling during 12 months. The primary outcome was the 7-day point prevalence abstinence rate 12

What We Already Know about This Topic

- The efficacy of perioperative smoking cessation interventions remains unclear
- Varenicline administration may facilitate smoking cessation
- Varenicline administration may facilitate perioperative smoking cessation

What This Article Tells Us That Is New

- In a double-blind randomized trial, varenicline improved abstinence a year after surgery from 36% to 25% (relative risk 1.45, 95% CI: 1.01–2.05, $P = 0.04$)
- Varenicline appears to be a useful smoking cessation intervention

* Assistant Professor, † Anesthesia Resident, ‡ Research Fellow, ** Professor, Department of Anesthesia, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada. § Associate Professor, Department of Anesthesia, Mt. Sinai Hospital, University of Toronto, Toronto, Ontario, Canada. ‖ Associate Professor, Departments of Family and Community Medicine and Psychiatry, Dalla Lana School of Public Health, University of Toronto, and Addictions Program and Ontario Tobacco Research Unit, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada. # Professor, Department of Medicine, Division of Respirology, Toronto Western Hospital, University Health Network, University of Toronto.

Address correspondence to Dr. Chung: Department of Anesthesia, Toronto Western Hospital, University Health Network, 2-405 McLaughlin Wing, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. frances.chung@uhn.ca. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

months after surgery. Secondary outcomes included abstinence at 3 and 6 months after surgery. Multivariable logistic regression was used to identify independent variables related to abstinence.

Results: The 7-day point prevalence abstinence at 12 months for varenicline *versus* placebo was 36.4% *versus* 25.2% (relative risk: 1.45; 95%: CI: 1.01–2.07; $P = 0.04$). At 3 and 6 months, the 7-day point prevalence abstinence was 43.7% *versus* 31.9% (relative risk: 1.37; 95% CI: 1.01 to 1.86; $P = 0.04$), and 35.8% *versus* 25.9% (relative risk: 1.43; 95%: CI 1.01–2.04; $P = 0.04$) for varenicline *versus* placebo, respectively. Treatment with varenicline (odds ratio: 1.76; 95% CI: 1.03–3.01; $P = 0.04$), and preoperative nicotine dependence (odds ratio: 0.82, 95% CI: 0.68 to 0.98; $P = 0.03$) predicted abstinence at 12 months. The adverse events profile in both groups was similar except for nausea, which occurred more frequently for varenicline *versus* placebo (13.3% *vs.* 3.7%, $P = 0.004$).

Conclusions: A perioperative smoking cessation intervention with varenicline increased abstinence from smoking 3, 6, and 12 months after elective noncardiac surgery with no increase in serious adverse events.

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

WORLDWIDE, tobacco use is the leading cause of preventable death. It is estimated that nearly 6 million people die each year from tobacco-related diseases.[1] Smoking is also associated with increased odds of perioperative death and serious postoperative complications.[2] Smoking is a modifiable risk factor for reducing the risks for postoperative complications, and cessation has long-term health benefits.

Patients facing surgery are more likely to be receptive to advice offered by healthcare professionals.[3,4] Therefore, the preoperative clinic visit may represent an opportunity for a "teachable moment" for tobacco-cessation interventions. A "teachable moment" describes a health experience likely to motivate an individual to adopt risk-reducing behaviors.[3] The preoperative clinic visit, combined with the forced abstinence during hospital stay, can be used to design a perioperative tobacco-cessation intervention to promote long-term abstinence from smoking.

A systematic review of perioperative smoking interventions, including counseling and pharmacotherapy with nicotine replacement therapy or bupropion, showed that these interventions can increase abstinence at 3- to 6-month follow-up.[5] However, the efficacy of perioperative smoking interventions on long-term abstinence at 12 months is still unclear.[6,7] Only intensive interventions reduced smoking rates after 1 yr.[8]

There are multiple nicotinic acetylcholine receptor subtypes involved in producing nicotine dependence. Varenicline is a partial agonist and antagonist at the $\alpha4\beta2$ subtype of the nicotinic acetylcholine receptor.[9] Therefore, varenicline partially mimics the effect of nicotine by occupying the receptor site, effectively reducing withdrawal. Varenicline also blocks the reinforcing effects of continued nicotine use through its antagonist action.[10] This may be responsible for reduced cravings over time. Hence, it may be an effective agent for maintaining abstinence from smoking.[11] Varenicline has been shown to be more efficacious than the other available therapies when used in nonsurgical populations.[12–14] To our knowledge, there are no studies examining the use of varenicline in the perioperative period for surgical patients.

We hypothesized that a perioperative smoking intervention with varenicline would improve both short-term (3- and 6-month) and long-term (12-month) abstinence compared with placebo in surgical patients. Our objective was to determine the effectiveness and safety of a perioperative smoking cessation intervention including varenicline and counseling *versus* placebo and counseling to increase short- and long-term abstinence in surgical patients.

Materials and Methods

This randomized, multi-center, double-blind, placebo-controlled study was registered in the public registry ClinicalTrials.gov (No. NCT01320462). Approval was obtained from the Research Ethics Boards of the partici-

pating institutions and written informed consent was obtained from all participants.

All adult patients (18 yr or older) at the preoperative clinics of the Toronto Western Hospital and Mt. Sinai Hospital, Toronto, Ontario, Canada, who were scheduled for elective ambulatory or inpatient general surgical, orthopedic, urologic, plastic, gynecologic, ophthalmologic, or neurosurgical procedures were screened for eligibility. Patients who were scheduled for surgery within 8–30 days, smoked a minimum of 10 cigarettes per day during the previous year, and had no period of smoking abstinence longer than 3 months in the past year were recruited.

Exclusion criteria included: surgery within 7 days; current pregnancy or breastfeeding; major depression, panic disorder, psychosis, or bipolar disorder within the previous year; use of nicotine replacement therapy or bupropion within the previous 3 months; cardiovascular disease within the past 6 months; drug or alcohol abuse or dependence within the past year; use of tobacco products other than cigarettes or marijuana use within the previous month; participation in other studies; language barrier; and any form of cognitive impairment.

Demographic data and smoking habits of the patients, including the number of cigarettes smoked per day, were recorded. The Fagerström Test for Nicotine Dependence was administered. This test consists of six items, with a maximum score of 10. Higher scores indicate greater nicotine dependence.[15] Patients also completed an adapted Prochaska and DiClemente's Stages of Change questionnaire to determine their readiness to stop smoking.[16] Patients were asked whether they were considering quitting smoking, and if they were planning to quit within the next month.

To establish the baseline smoking status, urinary cotinine (a metabolite of nicotine) using NicAlert urine strips (the Accutest; Jant Pharmacal Corp., Encino, CA),[17] and expired-air carbon monoxide were measured using Smokerlyzer (the Bedfont EC50; Bedfont Scientific Ltd., Harrietsham, England) in all patients at the preoperative clinic. Patients who had expired-air carbon monoxide readings of 10 or more than 10 parts per million and NicAlert levels exceeding 100 ng/ml (indicative of smoking in the previous 48 h) were classified as smokers.

Smokers were randomly assigned to receive varenicline (Pfizer Inc., Kirkland, Quebec, Canada) or matching placebo using a computer-generated randomization list at each center. A stratified randomization with blocks of 40, based on the smoker's stage of change, was employed because the stage of change may predict successful abstinence from smoking. The patient assignments were placed into sequentially numbered, opaque sealed envelopes, and were kept by an independent research pharmacist at each center who was not involved with patient care or outcome assessments. For each patient, the research pharmacist opened the envelope and provided the research coordinator with the medication or placebo (lactose, identical in appearance) according to the

randomization schedule. The patients, healthcare personnel, and research staff were blinded to the randomization throughout the study period.

All patients received two 15-min standardized counseling sessions by the research coordinators. The counseling was based on the smoking cessation guidelines endorsed by the Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada. The research coordinators and investigators were certified with a 3-day training course on smoking cessation counseling.[18] The first counseling session occurred in the preoperative clinic. Counseling included the benefits of short-term and long-term abstinence and information regarding smoking behavior and skill building to prevent relapse, supplemented with standard printed materials.

The target quit date for all patients was 24 h before surgery, because surgical patients are routinely asked to be abstinent at the time of surgery. The patients were instructed to initiate the study medication (or placebo) exactly 1 week before the target quit date. The patients received the study medication or placebo for a total of 12 weeks, including a 1-week titration as follows: days 1–3: 0.5 mg once daily; days 4–7: 0.5 mg twice daily; and days 8–12 weeks: 1 mg twice daily.

If surgery was delayed or cancelled, the target quit date did not change and the patients continued the treatment according to the established schedule. On the day of surgery, the patients took the study medication before surgery and resumed taking the medication as soon as possible after surgery, according to the treatment schedule.

The second counseling session occurred before discharge for ambulatory surgical patients. The second counseling session for inpatients was given 24 h after surgery to allow patients to recover from the amnestic effects of anesthesia. The expired-air carbon monoxide and urinary cotinine was measured in all patients to verify self-reported abstinence. For each patient, the research coordinator who interviewed the patient at the preoperative clinic was the same during the whole treatment and follow-up period.

Long-term Follow-up and Telephone Counseling after Discharge

Participants in both groups received weekly phone calls from the research coordinator for the first 4 weeks, and at the end of 8 weeks. For the remainder of the follow-up period from 3 months until 12 months, patients received telephone calls every 4 weeks to ascertain smoking status, nicotine dependence, stage of change, number of cigarettes smoked per day for those who had not quit smoking, and for brief (fewer than 5 min) counseling to encourage maintenance of abstinence.

Patients were asked to come to the hospital at 3, 6, and 12 months. At each visit, patients were asked about their smoking status, stage of change, nicotine dependence, or number of cigarettes smoked per day for those who had not stopped smoking. In addition, the expired-air carbon monoxide

and urinary cotinine were measured to verify self-reported abstinence. If there was a discrepancy between the urinary cotinine and expired-air carbon monoxide, the patient was considered a smoker if either of the tests was positive. If the patients were unable to come to hospital for their follow-up visits at 3, 6, and 12 months, the patients were telephoned and asked to self-administer the urine cotinine test at home. The patients read and informed the research assistant of the result by telephone, and returned the NicAlert urine cotinine strips by mail using prepaid return envelopes. The patients were not told what a positive or negative test result on the test strip would be. The mailed-in test results were read by the research coordinator to confirm the test result reported by the patients.

Outcome Measures

The primary outcome was the 7-day point prevalence (PP) abstinence rate at 12 months after the start of treatment; PP represents those who had not smoked cigarettes for the previous 7 days. The secondary outcomes were abstinence on the target quit day and 7-day PP of abstinence at 3 and 6 months after the target quit date. Other secondary outcome measures included the self-reported changes in the number of cigarettes consumed per day and stage of change at 3, 6, and 12 months. Abstinence was defined as a biochemically confirmed self-report of no smoking or use of any nicotine-containing products. The research coordinator recorded all perioperative complications documented in the hospital charts and all adverse events at each follow-up visit or telephone follow-up.

Statistical Analysis

An intention-to-treat analysis was performed. Patients who discontinued treatment or discontinued follow-up were considered smokers. Differences in the primary and secondary outcomes between the two groups at each time point were assessed by comparing abstinence between the groups using chi-square test or Fisher exact test (for categorical variables) and independent sample Student t tests (for continuous variables). The demographic data are presented with descriptive statistics. Continuous data are presented as mean $\pm$ SD or median and range; categorical data are presented as frequency and percentage with 95% CI.

Multivariable logistic regression was used to identify independent variables related to the outcome of smoking cessation. The independent variables included in the analyses were demographic characteristics such as age, gender, body mass index, ambulatory or inpatient surgery, type of surgery (*i.e.*, orthopedic/plastic surgery *versus* other types of surgery), and American Society of Anesthesiologists classification, as well as baseline information including Fagerström score, age the patient started smoking, previous quit attempts, stage of change, expired-air carbon monoxide, and number of cigarettes per day. The initial model included independent variables based on univariate logistic regression analysis
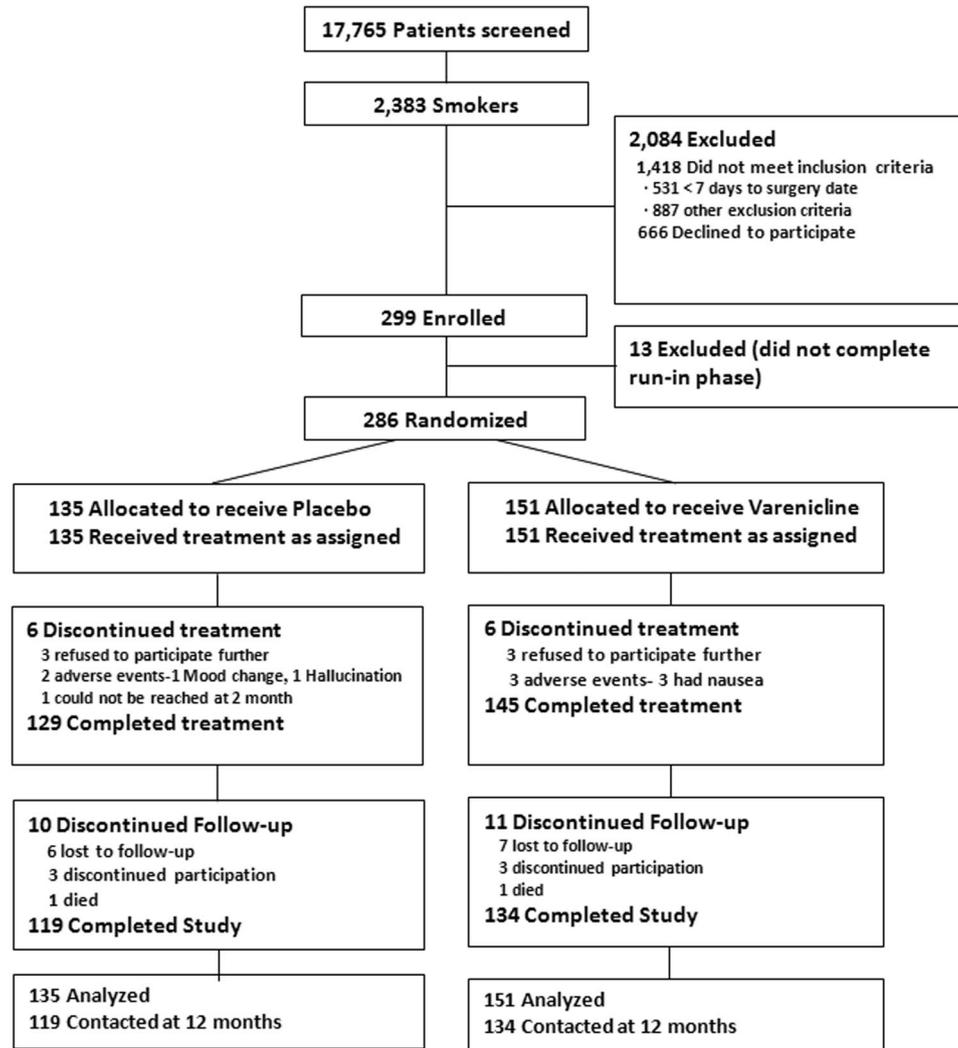
Fig. 1. Flow diagram of participants included in the study.

and clinical variables. Then, a backward elimination procedure was used to remove variables with $P > 0.20$ from the model step by step according to their P value. Odds ratio and relative risk (RR) with 95% CI for prediction of quitting were calculated using logistic regression. All statistical tests were two-tailed ($\alpha = 0.05$). For all comparisons, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Sample Size

The sample-size estimate was based on the difference in the primary outcome (7-day PP abstinence at 12 months) between the two study groups. The calculation was based on information from several randomized controlled trials that have shown that varenicline can increase the prevalence of abstinence at 12-month follow-up by 4–10% to 17–28% compared with placebo.[11,13,14] Based on this information and assuming that varenicline has the same efficacy in surgical patients, we assumed the average effect size would be 15% (risk difference). The required sample size was estimated as

145 patients per group (Student t test, two-tailed, $\alpha = 0.05$ and power $= 0.8$). Therefore, a total of 290 patients (145 patients per group) were needed to detect differences in long-term abstinence.

Results

From June 2008 to November 2010, 17,765 patients were screened in the two preoperative clinics. Of the 2,383 (13.4%) patients who were smokers, 2,084 were excluded for various reasons including not meeting inclusion criteria (1,418) or declining to participate (666) (fig. 1). A total of 299 patients (12.5% of the smokers) were enrolled. However, 13 patients did not complete the run-in phase (12 patients changed their mind about participating in the study, one patient had a myocardial infarction). Therefore, 286 patients were randomly assigned to receive placebo (n = 135) or varenicline (n = 151) (fig. 1). Two patients who received placebo discontinued treatment because of adverse events: one patient experienced mood changes, and the other

patient experienced hallucinations. Three patients who received varenicline discontinued treatment because of nausea. Six patients had their surgery delayed, but all of the patients took the study medication as planned and were included in the study. Overall study completion rates at the 12-month follow-up for varenicline *versus* placebo was 134 (88.7%) *versus* 119 (88.8%) patients.

The demographic variables and baseline smoking characteristics of the two groups were similar (table 1).

Some patients did not return to the hospital for their follow-up visits. Therefore, expired-air carbon monoxide and in-person urinary cotinine results were available for 174 patients (60.8%) at 3 months, 121 patients (42.3%) at 6 months, and 118 patients (41.2%) at 12 months. However, mailed-in urinary cotinine results for confirming self-reported abstinence were available for all patients at all time-points with the exception of missing results for 33 patients at 6 months. In both groups, the self-reported abstinence correlated well with urine cotinine results. The ϕ correlation coefficients for the correlation between self-reported abstinence and urine cotinine results were 0.92 *versus* 0.87 at 3 months, 0.98 *versus* 0.91 at 6 months, and 0.95 *versus* 0.91 at 12 months for varenicline *versus* placebo, respectively.

Efficacy

Using an intention to treat analysis, the 7-day PP of abstinence at 12 months was higher for varenicline *versus* placebo, 36.4% *versus* 25.2% (RR: 1.45; 95% CI: 1.01–2.07; $P = 0.04$). At admission to hospital, there was no difference in the abstinence rate between varenicline *versus* placebo, 29.6% *versus* 20%, $P = 0.10$. Varenicline produced higher 7-day PP abstinence rates than placebo at 2 weeks, and most follow-up intervals between 3 and 12 months (fig. 2). During the second week, the PP for abstinence was highest for both varenicline and placebo, 49.7% *versus* 35.6% (RR: 1.37; 95% CI: 1.04 to1.81; $P = 0.02$). At 3 months, *i.e.*, the end of treatment, the 7-day PP of abstinence was higher for varenicline *versus* placebo, 43.7% *versus* 31.9% (RR: 1.37; 95% CI: 1.01 to 1.86; $P = 0.04$). Similarly, at 6 months, the 7-day PP abstinence was higher for varenicline *versus* placebo, 35.8% *versus* 25.9% (RR: 1.43; 95% CI: 1.01–2.04; $P = 0.04$).

Predictors of Smoking Cessation

The age, gender, American Society of Anesthesiologists classification, body mass index, stage of change, preoperative expired-air carbon monoxide, number of previous quit attempts, and number of cigarettes smoked per day did not predict smoking abstinence at any time-point.

Multivariable logistic regression analysis for factors associated with smoking cessation outcomes are shown in table 2. At 12 months, treatment with varenicline was associated with higher abstinence (odds ratio: 1.76; 95% CI: 1.03–3.01; $P = 0.04$), whereas lower Fagerström nicotine dependence test scores were associated with higher abstinence (odds ratio: 0.82, 95% CI: 0.68 to 0.98; $P = 0.03$) at 12

months. These associations were also significant at earlier time points. At 3- and 6-month follow-up analyses, inpatient *versus* ambulatory surgery and orthopedic/plastic *versus* other surgery were positively associated with abstinence, but these associations were nonsignificant at 1 yr.

Of the patients who continued to smoke, the number of cigarettes smoked per day was reduced for both groups from the start of the study to the end of the study (12 months). The number of cigarettes smoked per day for the varenicline group decreased from 18 ± 8 to 12 ± 5, $P < 0.0001$ at 12 months. For the placebo group, the number of cigarettes smoked per day decreased from 17 ± 8 to 11 ± 6, $P < 0.0001$ at 12 months (fig. 3). There was no difference in the number of cigarettes smoked per day at 12 months for varenicline *versus* placebo, 12 ± 5 *versus* 11 ± 6, $P = 0.30$.

The incidence of surgical complications was similar for varenicline *versus* placebo, 19 (12.6%) *versus* 18 (13.3%), $P = 0.85$. There was no difference in wound, pulmonary, cardiovascular, infectious, gastrointestinal, or urinary tract complications between the two groups (table 3).

Nausea was the most common adverse event reported by patients in both groups. At least one adverse event was experienced by 38 (25%) in the varenicline group *versus* 15 (11%) in the placebo group, $P = 0.0023$. This difference was because of nausea, which was reported more frequently for varenicline *versus* placebo, 20 (13.3%) *versus* 5 (3.7%), $P = 0.004$ (table 4). For varenicline, the nausea was mild in 11 patients, moderate in eight patients, and unclassified for one patient. For placebo, four patients had mild nausea and one patient had moderate nausea. There was no difference in other adverse events between the two groups (table 4).

Discussion

In the present study, a perioperative smoking intervention including varenicline, 30 min of counseling, brief follow-up, and monitoring of outcomes significantly increased both short- and long-term abstinence in patients having elective noncardiac surgery. At 12 months, 36.4% of subjects in the varenicline group were abstinent from smoking compared with 25.2% in the placebo group. Patients receiving varenicline were 45% more likely to be abstinent at 12 months than patients receiving placebo. The reduction in smoking prevalence with varenicline *versus* placebo was sustained from the end of treatment, *i.e.*, 3 months, until 12 months after surgery. At 12 months, only treatment with varenicline and lower preoperative level of nicotine dependence were predictive of abstinence.

To our knowledge, our study is the first to report the efficacy of a perioperative smoking intervention with varenicline for short- and long-term abstinence in surgical patients. Our abstinence rates are comparable with two previous randomized controlled trials of varenicline with 12 months of counseling in the general population.[13,14] In these studies, the 7-day PP of abstinence at 12 months for varenicline *versus* placebo was 30.5% *versus* 17.3%,[13] and 28.1% *versus*

Table 1. Baseline Demographic and Smoking Characteristics of the Study Participants

	Placebo (No. = 135)	Varenicline (No. = 151)	P Value
Age, years	—	—	0.29
Mean (SD)	53.3 (11.4)	51.9 (11.8)	—
Median (range)	54 (24–86)	53 (22–79)	—
Gender, n (%)	—	—	0.44
Female	67 (49.6)	68 (45.0)	—
Male	68 (50.4)	83 (55.0)	—
BMI, kg/m^2	—	—	—
Mean (SD)	28.3 (5.8)	28.8 (6.6)	0.53
Median (range)	27.8 (17.2–53.9)	27.5 (17.6–57.2)	—
Procedure, n (%)	—	—	0.44
Ambulatory surgery	46 (34.1)	45 (29.8)	—
Inpatient	89 (65.9)	106 (70.2)	—
ASA status, n (%)	—	—	0.13
I	0	3 (2.0)	—
II	114 (84.4)	117 (77.5)	—
III	21 (15.6)	31 (20.5)	—
Surgery type, n (%)	—	—	0.42
Orthopedic	46 (34.1)	49 (32.5)	—
General	43 (31.9)	36 (23.8)	—
Spine	15 (11.1)	19 (12.6)	—
Ophthalmology	9 (6.7)	13 (8.6)	—
Plastic	8 (5.9)	6 (4.0)	—
Urology	3 (2.2)	7 (4.6)	—
Others	11 (8.2)	21 (13.9)	—
Fagerström Test score	—	—	0.95
Mean (SD)	4.9 (1.5)	4.8 (1.5)	—
Median (range)	5 (1–9)	5 (1–9)	—
Age when started smoking (years)	—	—	0.79
Mean (SD)	17.9 (5.8)	17.8 (5.2)	—
Median (range)	16 (7–48)	17 (8–40)	—
Number of previous quit attempts	—	—	0.06
Mean (SD)	2.7 (2.7)	2.2 (1.9)	—
Median (range)	2 (0–20)	2 (0–10)	—
Number of cigarettes per day	—	—	0.36
Mean (SD)	17.0 (7.5)	17.8 (8.2)	—
Median (range)	15 (4–70)	15 (3–75)	—
Expired-air carbon monoxide (ppm)	—	—	0.47
Mean (SD)	15.7 (6.3)	16.3 (7.0)	—
Median (range)	15 (6–40)	15 (3–38)	—
Nicotine dependence, n (%)	—	—	0.99
Very low (0–2)	3 (2.2)	3 (2.0)	—
Low (3 or 4)	58 (43.0)	65 (43.1)	—
Medium (5)	33 (24.4)	39 (25.8)	—
High (6 or 7)	32 (23.7)	36 (23.8)	—
Very high (8–10)	9 (6.7)	8 (5.3)	—
Stage of change, n (%)	—	—	0.40
Precontemplation	10 (7.4)	18 (11.9)	—
Contemplation	35 (25.9)	37 (24.5)	—
Preparation	84 (62.2)	85 (56.3)	—
Action stage	6 (4.5)	11 (7.3)	—
Maintenance	0	0	—
Termination	0	0	—
Number of previous quit attempts, n (%)	—	0.88	—
0	29 (14.1)	29 (19.2)	—
1	30 (22.2)	37 (24.5)	—
2	31 (23.0)	32 (21.2)	—
3	23 (17.0)	26 (17.2)	—
4	10 (7.4)	7 (4.6)	—
5	10 (7.4)	11 (7.3)	—
≥6	12 (8.9)	9 (6.0)	—

ASA = American Society of Anesthesiologists; BMI = body mass index; SD = standard deviation.
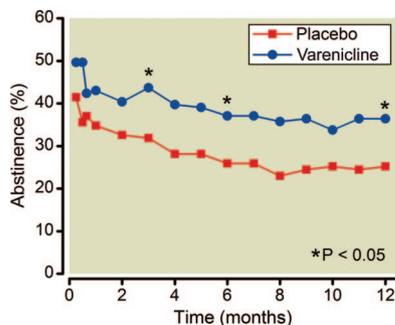
Fig. 2. Seven-day point prevalence of biochemically confirmed abstinence for varenicline *versus* placebo using intention to treat analysis. The 7-day point prevalence of abstinence at 3, 6, and 12 months was higher for varenicline *versus* placebo. *$P < 0.05$.
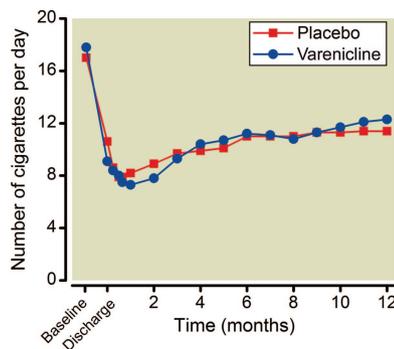

Fig. 3. The number of cigarettes smoked per day of patients without abstinence was significantly reduced for both varenicline and placebo at 12 months *versus* the start of the study, $P < 0.0001$. There was no difference in the number of cigarettes smoked per day between varenicline *versus* placebo at any time, $P > 0.05$.

14%,[14] respectively. The 7-day PP of abstinence at 12 months appears to be higher for both varenicline and placebo than the 7-day PP of abstinence at 12 months in previous studies in the literature. Our results likely reflect the "teachable moment" of the perioperative period and the high motivation of the surgical patients to quit smoking.

For those who continued to smoke, there was a reduction in the number of cigarettes smoked per day at the end of the study compared with the beginning of the study. Although the health benefit of smoking reduction compared with abstinence is controversial,[19] these patients also had a decrease in the level of nicotine dependence. In our study, lower nicotine dependence predicted abstinence at 12 months, therefore, future cessation attempts may be more successful in these patients. This is likely given that lower levels of nicotine dependence predict quit-attempt success[20,21] and additional interventions are likely to be successful. Multiple quit attempts are usually required for permanent cessation. Moreover, the higher relapse once the medication is stopped indicates that the optimal duration of treatment for all smokers is unknown. There is some evidence that 26 weeks of vareni-

cline further delays relapse and increases the proportion of nonsmokers at 52 weeks compared with placebo.[22]

Our study confirms that surgical patients are a suitable target for smoking cessation interventions. The preoperative visit and perioperative period offers a unique opportunity to be used as a "teachable moment" to counsel smokers and promote long-term abstinence. Indeed, our data shows that inpatient surgery is a predictor of short-term (up to 6 months) abstinence. This may be partially attributed to the forced abstinence while patients are in the nonsmoking environment of the hospital. Abstinence rates have been shown to be three times higher in hospitalized than non-hospitalized patients.[23] Our findings confirm the results from a previous study that undergoing surgery, particularly major surgery, was associated with an increased likelihood of quitting smoking.[24]

Another predictor of short-term abstinence was orthopedic and plastic surgery. This may be because of our intervention and the standard practice of the orthopedic and plastic

Table 2. Multivariate Logistic Regression Analysis for Predicting Abstinence

Period of Follow-up	Covariate	Odds Ratio (95% CI)	P Value
3 month	Varenicline *vs.* placebo	1.73 (1.03–2.88)	0.04
	Inpatient *vs.* ambulatory surgery	2.12 (1.18–3.80)	0.01
	Orthopedic/Plastic *vs.* other surgery	1.82 (1.08–3.07)	0.02
	Preop Fagerström Test score (increase of 1)	0.85 (0.72 to 1.01)	0.07
	Age for starting smoking (increase of 1 y)	1.04 (0.99 to 1.09)	0.11
6 month	Varenicline *vs.* placebo	1.72 (1.00–2.97)	0.05
	Inpatient *vs.* ambulatory surgery	2.22 (1.1–4.17)	0.01
	Orthopedic/Plastic *vs.* other surgery	1.72 (0.99–2.98)	0.05
	ASA III *vs.* ASA I and ASA II	0.59 (0.29 to 1.23)	0.16
	Preop Fagerström Test score (increase of 1)	0.78 (0.65 to 0.95)	0.01
	Age for starting smoking (increase of 1 yr)	1.05 (1.00 to 1.10)	0.04
12 month	Varenicline *vs.* placebo	1.76 (1.03–3.01)	0.04
	Inpatient *vs.* ambulatory surgery	1.56 (0.86–2.81)	0.14
	ASA III *vs.* ASA I and ASA II	0.57 (0.27 to 1.20)	0.14
	Preop Fagerström Test score (increase of 1)	0.82 (0.68 to 0.98)	0.03

ASA = American Society of Anesthesiologists; preop = preoperative.

Table 3. Postoperative Complications

	No. (%) of Complication		
	Placebo	Varenicline	P Value
Patients (n)	135	151	—
Total complications (case)*	18 (13.3)	19 (12.6)	0.85
Wound complication (case)†	7 (5.2)	7 (4.6)	0.83
Infection	2 (1.5)	3 (2.0)	—
Seroma	1 (0.7)	1 (0.7)	—
Erythema	1 (0.7)	2 (1.3)	—
Dehiscence, abrasion	3 (2.2)	0	—
Hematoma	0	1 (0.7)	—
Pulmonary complication (case)†	1 (0.7)	0	0.47
Postoperative fever diagnosed as atelectasis	1 (0.7)	0	—
Cardiovascular complication (case)†	4 (3.0)	2 (1.3)	0.43
Bradycardia	1 (0.7)	0	—
Myocardial infarction	1 (0.7)	0	—
Ischemia	1 (0.7)	1 (0.7)	—
Mild stroke	1 (0.7)	0	—
Inguinal deep vein thrombosis	0	1 (0.7)	—
Infectious complication (case)†	1 (0.7)	1 (0.7)	1
Clostridium difficile colitis	1 (0.7)	0	—
Vaginal infection	0	1 (0.7)	—
Urinary tract complication (case)	7 (5.2)	9 (6.0)	0.78
Urinary retention	5 (3.7)	8 (5.3)	—
Minimal urinary symptoms	0	1 (0.7)	—
Hematuria	1 (0.7)	0	—
Deterioration of bladder function	1 (0.7)	0	—
Gastrointestinal complication (case)†	1 (0.7)	1 (0.7)	1
Prolonged ileus	1 (0.7)	0	—
Abdominal pain and distension	0	1 (0.7)	—

* The number of patients with at least one postoperative complication. † The number of patients with at least one event for each type of postoperative complication.

Table 4. Adverse Events

	Number (%)		
Adverse Event	Placebo (No. = 135)	Varenicline (No. = 151)	P Value
Nausea	5 (3.7)	20 (13.3)	0.004
Dyspepsia	0	2 (1.3)	0.50
Vomiting	0	2 (1.3)	0.50
Headache	0	5 (3.3)	0.06
Sleep disturbance	1 (0.7)	2 (1.3)	1
Abnormal dream	0	3 (2.0)	0.25
Mood change	1 (0.7)	2 (1.3)	1
Depression	2 (1.5)	2 (1.3)	1
Anxiety	2 (1.5)	1 (0.7)	0.60
Agitation	2 (1.5)	2 (1.3)	1
Hallucination	1 (0.7)	1 (0.7)	1
Other adverse events (dry mouth, erythema, acidity, weight gain, itchy, rash, bad taste)	4 (3.0)	4 (2.7)	1

surgeons at the participating institutions to advise patients to abstain from smoking to improve surgical outcomes of bone and wound healing.

The safety of smoking cessation shortly before surgery has been questioned.[24] Our findings support the safety of short-term abstinence before surgery as our patients were enrolled 8 days to 3 weeks before surgery. Our results are consistent with a recent meta-analysis that found no adverse effects of stopping smoking shortly before surgery on surgery outcomes.[25] In our study, varenicline was generally well tolerated and there was no increase in perioperative cardiovascular, respiratory, or other complications compared with placebo. Nausea was more common with varenicline than placebo, but the severity was mild or moderate, and only three patients discontinued treatment because of nausea. Our study was not powered to detect differences in perioperative complications and wound healing to demonstrate the benefit or harm of varenicline to these outcomes or to detect a difference in serious adverse complications related to varenicline use. The heterogeneity of the surgical procedures included in our study further reduces power for detecting a difference in adverse events.

In the United States, clinical practice guidelines from 2008 recommend that every physician address tobacco use at each patient visit.[26] The American Society of Anesthesiologists†† and the Canadian Anesthesiologists' Society‡‡ also recommend that anesthesiologists promote abstinence before surgery. However, few surgical patients receive preoperative tobacco interventions.[27] In addition to long-term health benefits, even brief periods of preoperative smoking abstinence can be beneficial. A period of 12–18 h abstinence (3 carboxyhemoglobin half-lives) reduces carboxyhemoglobin concentrations significantly,[28] and the oxygen dissociation curve returns to the normal position.[29] Postoperative abstinence is also critical for orthopedic surgery, because patients who continue to smoke after surgery have significantly higher rates of nonunion compared with nonsmokers.[30,31]

Our findings of increased 12-month abstinence are consistent with a previous randomized controlled trial with individual counseling and nicotine replacement therapy for 6–8 weeks before surgery, and weekly consultations until 10

†† www.asahq.org. Accessed November 12, 2011.
‡‡ www.cas.ca. Accessed November 13, 2011.

days after surgery.[20] This study reported 12-month absti-nence rates of 22% *versus* 3% for treatment *versus* placebo.[20] Our findings confirm a previous systematic review conclud-ing that intensive interventions increase abstinence 12 months after surgery.[32] We counseled patients for 12 months after surgery; it is possible that the efficacy of varenicline without prolonged counseling may be lower. Our findings suggest that anesthesiologists have a valuable opportunity as perioperative physicians to make a significant impact on the long-term health of surgical patients. Our intervention was intensive, and included prescribing medication to preopera-tive patients. This is not a standard practice of anesthesiolo-gists, and extends beyond an "Ask, Advise, and Refer" strat-egy[33] to include "Assisting" those who are willing to quit and "Arranging" for follow-up.[26] We have shown this is benefi-cial and successfully increased long-term abstinence.

All pharmacological therapies including nicotine replace-ment therapy, bupropion, and varenicline are effective in helping smokers to quit, but can have adverse effects. In June 2011, the Food and Drug Administration issued a warning that varenicline may be associated with a small increased risk of certain cardiovascular adverse events, including myocar-dial infarction in patients with cardiovascular disease.§§ In 2009, the Food and Drug Administration issued a warning about postmarketing reports of exacerbation of preexisting psychiatric disorders and reports of psychiatric symptoms, such as depression and suicidal ideation, in patients without preexisting psychiatric disorders with varenicline. We did not find an increase in cardiovascular events or psychiatric adverse effects in patients receiving varenicline, but we ex-cluded patients with known cardiovascular disease within the previous 6 months, and psychiatric disorders.

The present study has several limitations. More patients were randomized to receive varenicline because of the limited number of patients in the first and fourth stages of change, and large block numbers in the stratified randomization. We also did not measure continuous abstinence, but the 7-day point prevalence confirmed by biochemical means is a more pragmatic outcome that more closely mimics real-world out-come measures of smoking cessation. We included a variety of surgical procedures, but the generalizability of our find-ings is limited to elective, noncardiac surgical patients with-out a history of cardiovascular or psychiatric illnesses. These findings may not be applicable to patients undergoing emer-gency surgery where acute nicotine withdrawal may be more clinically relevant.

In conclusion, our perioperative smoking cessation inter-vention with varenicline and counseling significantly in-creased both short- and long-term abstinence 12 months after elective noncardiac surgery compared with placebo and counseling. Anesthesiologists should take the opportunity to use the perioperative period as a "teachable moment" to ad-vise patients to stop smoking. Our perioperative smoking

cessation intervention effectively and safely improved long-term abstinence from smoking. Further research is required to explore the feasibility of intensive perioperative smoking cessation interventions to achieve the public health goal to reduce smoking and improve both short-term surgical out-comes and the long-term health of surgical patients who smoke.

References

1. WHO report on the global tobacco epidemic, 2011: Warning about the dangers of tobacco. World Health Organization 2011; 8

2. Turan A, Mascha EJ, Roberman D, Turner PL, You J, Kurz A, Sessler DI, Saager L: Smoking and perioperative outcomes. ANESTHESIOLOGY 2011; 114:837–46

3. McBride CM, Emmons KM, Lipkus IM: Understanding the potential of teachable moments: The case of smoking cessa-tion. Health Educ Res 2003; 18:156–70

4. Shi Y, Warner DO: Surgery as a teachable moment for smok-ing cessation. ANESTHESIOLOGY 2010; 112:102–7

5. Zaki A, Abrishami A, Wong J, Chung FF: Interventions in the preoperative clinic for long term smoking cessation: A quan-titative systematic review. Can J Anesth 2008; 55:11–21

6. Ratner PA, Johnson JL, Richardson CG, Bottorff JL, Moffat B, Mackay M, Fofonoff D, Kingsbury K, Miller C, Budz B: Effi-cacy of a smoking-cessation intervention for elective-surgical patients. Res Nurs Health 2004; 27:148–61

7. Thomsen T, Tønnesen H, Møller AM: Effect of preoperative smoking cessation interventions on postoperative complica-tions and smoking cessation. Br J Surg 2009; 96:451–61

8. Tønnesen H, Thomsen T: Review: Long-term effect of peri-operative smoking cessation programmes. Clin Health P 2011; 1:22–6

9. Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, Labarca C, Whiteaker P, Marks MJ, Collins AC, Lester HA: Nicotine activation of alpha4* receptors: Sufficient for re-ward, tolerance, and sensitization. Science 2004; 306: 1029–32

10. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML: Phar-macotherapy for nicotine dependence. CA Cancer J Clin 2005; 55:281–99

11. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR, Varenicline Phase 3 Study Group: Effect of main-tenance therapy with varenicline on smoking cessation: A randomized controlled trial. JAMA 2006; 296:64–71

12. Wu P, Wilson K, Dimoulas P, Mills EJ: Effectiveness of smok-ing cessation therapies: A systematic review and meta-anal-ysis. BMC Public Health 2006; 6:300

13. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR, Varenicline Phase 3 Study Group: Efficacy of varenicline, an α4β2 nico-tinic acetylcholine receptor partial agonist, *versus* placebo or sustained-release bupropion for smoking cessation: A ran-domized controlled trial. JAMA 2006; 296:56–63

14. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR, Varenicline Phase 3 Study Group: Varenicline, an α4β2 nic-otinic acetylcholine receptor partial agonist, *versus* sus-

§§ http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm. Ac-cessed November 10, 2011.

tained-release bupropion and placebo for smoking cessation: A randomized controlled trial. JAMA 2006; 296:47–55

15. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO: The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991; 86:1119–27

16. DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS: The processes of smoking cessation: An analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991; 59:295–304

17. Marrone GF, Shakleya DM, Scheidweiler KB, Singleton EG, Huestis MA, Heishman SJ: Relative performance of common biochemical indicators in detecting cigarette smoking. Addiction 2011; 106:1325–34

18. Herie M, Connolly H, Voci S, Dragonetti R, Selby P: Changing practitioner behavior and building capacity in tobacco cessation treatment: The TEACH project. Patient Educ Couns 2012; 86:49–56

19. Hughes JR, Carpenter MJ: The feasibility of smoking reduction: An update. Addiction 2005; 100:1074–89

20. Villebro NM, Pedersen T, Møller AM, Tønnesen H: Long-term effects of a preoperative smoking cessation programme. Clin Respir J 2008; 2:175–82

21. Vangeli E, Stapleton J, Smit ES, Borland R, West R: Predictors of attempts to stop smoking and their success in adult general population samples: A systematic review. Addiction 2011; 106:2110–21

22. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR, Varenicline Phase 3 Study Group: Effect of maintenance therapy with varenicline on smoking cessation: A randomized controlled trial. JAMA 2006; 296:64–71

23. Rigotti NA, Munafo MR, Stead LF: Interventions for smoking cessation in hospitalised patients. Cochrane Database Syst Rev 2007; CD001837

24. Shi Y, Warner DO: Brief preoperative smoking abstinence: Is there a dilemma? Anesth Analg 2011; 113:1348–51

25. Myers K, Hajek P, Hinds C, McRobbie H: Stopping smoking shortly before surgery and postoperative complications: A systematic review and meta-analysis. Arch Intern Med 2011; 171:983–9

26. Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Healton CG, Henderson PN, Heyman RB, Koh HK, Kottke TE, Lando HA, Mecklenburg RE, Mermelstein RJ, Mullen PD, Orleans CT, Robinson L, Stitzer ML, Tommasello AC, Villejo L, Wewers ME: Clinical practice guideline: Treating tobacco use and dependence: 2008 update. Public Health Service 2008; 1–92

27. Warner DO, Sarr MG, Offord KP, Dale LC: Anesthesiologists, general surgeons, and tobacco interventions in the perioperative period. Anesth Analg 2004; 99:1766–73

28. Pearce AC, Jones RM: Smoking and anesthesia: Preoperative abstinence and perioperative morbidity. Anesthesiology 1984; 61:576–84

29. Kambam JR, Chen LH, Hyman SA: Effect of short-term smoking halt on carboxyhemoglobin levels and P50 values. Anesth Analg 1986; 65:1186–8

30. Nåsell H, Adami J, Samnegård E, Tønnesen H, Ponzer S: Effect of smoking cessation intervention on results of acute fracture surgery: A randomized controlled trial. J Bone Joint Surg Am 2010; 92:1335–42

31. Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR: The effect of cigarette smoking and smoking cessation on spinal fusion. Spine 2000; 25:2608–15

32. Thomsen T, Tønnesen H, Møller AM: Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg 2009; 96:451–61

33. Warner DO, American Society of Anesthesiologists Smoking Cessation Initiative Task Force: Feasibility of tobacco interventions in anesthesiology practices. A pilot study. Anesthesiology 2009; 110:1223–8