Original Investigation

Effect of Mailing Nicotine Patches on Tobacco Cessation Among Adult Smokers
A Randomized Clinical Trial

John A. Cunningham, PhD; Vladyslav Kushnir, MSc; Peter Selby, MD; Rachel F. Tyndale, PhD; Laurie Zawertailo, PhD; Scott T. Leatherdale, PhD

IMPORTANCE The efficacy of nicotine replacement therapy (NRT) is well demonstrated in clinical trials in which NRT is accompanied by behavioral support. Epidemiologic data, however, indicate that people using NRT are no more likely to successfully quit smoking than those who do not use NRT.

OBJECTIVE To evaluate the effect of mailing nicotine patches to smokers without behavioral support on quit success rates.

DESIGN, SETTING, AND PARTICIPANTS A single-blinded, 2-group randomized clinical trial of adult smokers recruited across Canada by random-digit dialing of home and cell telephone numbers from June 4, 2012, through June 26, 2014. Follow-up was completed on January 5, 2015, and data were analyzed from May 24, 2015, through July 6, 2015. A total of 2093 individuals who smoked more than 10 cigarettes per day were interviewed at baseline and asked if they would be hypothetically interested in receiving nicotine patches by mail to quit smoking. Those who were interested and deemed eligible to participate (no contraindications to NRT) were randomized to the experimental group to be mailed a 5-week supply of nicotine patches or to a control group. Telephone follow-ups were conducted at 8 weeks and 6 months.

INTERVENTIONS Participants in the experimental group were sent a 5-week course of nicotine patches by expedited postal mail (3 weeks of step 1 [21 mg of nicotine], 1 week of step 2 [14 mg of nicotine], 1 week of step 3 [7 mg of nicotine], no behavioral support provided). Participants randomized to the control group were not offered the nicotine patches or any other intervention.

MAIN OUTCOMES AND MEASURES The primary outcome was 30-day smoking abstinence at 6 months.

RESULTS Of the 2093 participants who were interviewed as part of the baseline survey (76.5% response rate), 1000 were found eligible for the trial and randomized to a group. Analyses were conducted on 500 participants in the experimental group (mean [SD] age, 48.0 [12.8] years; 255 female [51.0%]) and 499 in the control group (mean [SD] age, 49.7 [12.7] years; 256 female [51.3%]). Self-reported abstinence rates were significantly higher among participants who were sent nicotine patches compared with the control group (30-day abstinence: 38 [7.6%] of 500 vs 15 [3.0%] of 499; odds ratio, 2.65; 95% CI, 1.44-4.89; $P = .002$). Usable saliva samples were returned by only 50.9% of the participants. Biochemically validated abstinence at 6 months was found in 14 (2.8%) of 500 participants in the experimental group vs 5 (1.0%) of 499 in the control group (odds ratio, 2.85; 95% CI, 1.02-7.96; $P = .046$).

CONCLUSIONS AND RELEVANCE The trial provides evidence of the effectiveness of mailed nicotine patches without behavioral support to promote tobacco cessation. The strength of these findings is tempered by the lack of biochemical validation for all participants.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01429129

JAMA Intern Med. doi:10.1001/jamainternmed.2015.7792
Published online January 25, 2016.

Supplemental content at jamainternalmedicine.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: John A. Cunningham, PhD, Centre for Addiction and Mental Health, 33 Russell St, Toronto, ON, M5S 2S1, Canada (john.cunningham@camh.ca).

Smoking remains a leading cause of preventable disease worldwide.[1] There are numerous ongoing tobacco control initiatives, of which some have had success, particularly in countries where there is support for these initiatives.[2] However, more scalable, evidence-based interventions are needed to further reduce the prevalence of tobacco smoking.

Provision of nicotine replacement therapy (NRT) is one option that has a considerable evidence base, at least in clinical trials. In a meta-analysis of 150 trials, NRT has demonstrated efficacy, with NRT increasing the rate of quitting smoking by 50% to 70%, irrespective of the clinical setting in which the smoker is treated.[3] However, concern over the effectiveness of NRT in real-world settings has emerged. Population survey data comparing those who used NRT (obtained over the counter) during a quit attempt and those who did not use NRT has found no association between use of NRT and an increase in success rates.[4,5] Although causal statements regarding the effect of NRT cannot be made based on these population survey data, because participants were not randomized and thus other factors could be systematically different between those who used NRT and those who did not, these findings are troubling. They point specifically to the need for randomized clinical trials of the effectiveness of NRT in naturalistic settings where there is no additional behavioral support (such as that provided in clinical trials) to evaluate the effectiveness of NRT as it is likely used by most people trying to quit smoking.[6] A meta-analysis[7] revealed that earlier trials investigating the efficacy of over-the-counter NRT incorporated methods that entailed between 3 and 10 visits with researchers or pharmacists, making it unrealistic to describe these studies as research testing the efficacy of NRT without behavioral support.

Another compelling reason for the conduct of such randomized clinical trials is the ongoing public health initiatives in which NRT has been distributed free of charge by mail to those who call in to receive them. These mass distribution initiatives have been ongoing in a number of countries, with considerable resources allocated to their implementation.[8,9] There are promising results supporting these mass distribution efforts in the number of current smokers responding to the initiatives and the proportion of smokers who are reporting abstinence at follow-up.[9-13] Furthermore, there is evidence that the distribution of free NRT is cost-effective, with a cost of Can$1720 per quit participant in the Canadian mass distribution initiative.[9] However, data collected before and after the implementation of these initiatives cannot allow causal statements as to their effectiveness because there is no randomization to condition.

The current trial was designed to evaluate the efficacy of providing free NRT (in the form of the nicotine patch) by expedited postal mail without behavioral assistance to smokers interested in receiving it. The design allowed for a randomized clinical trial comparing participants who were interested in receiving nicotine patches and received them with participants who were interested in receiving nicotine patches but did not receive them. Those who did not receive nicotine patches were unaware that the nicotine patches were being offered to others, allowing for a strong test of the hypothesis. The primary hypothesis was that participants who were sent free nicotine patches by mail would have a higher proportion of 30-day abstinence at 6-month follow-up compared with participants who were not sent nicotine patches. The secondary hypothesis tested the effect of receiving free nicotine patches on 7-day abstinence at 8-week follow-up.

Methods

Trial Design

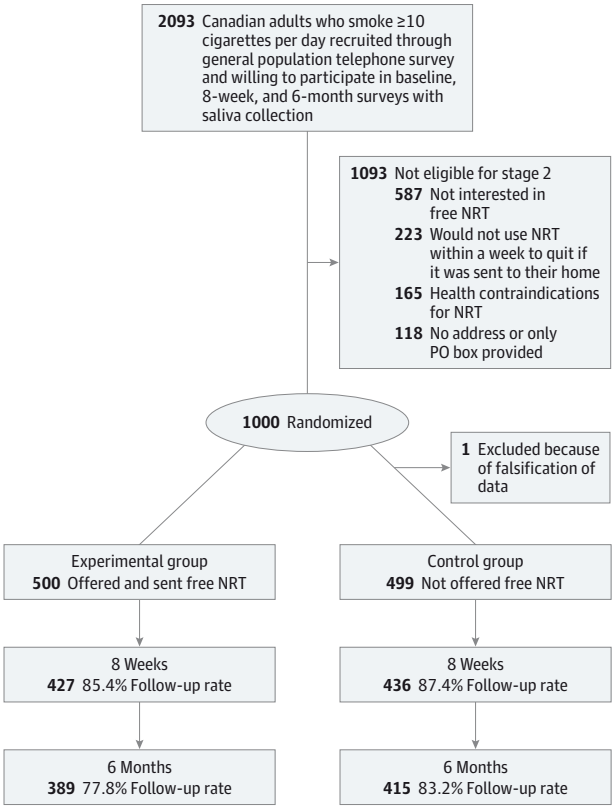
We conducted a single-blinded, 2-group randomized clinical trial comparing a control group with an experimental group receiving nicotine patches by mail. The trial protocol can be found in the Supplement. The research was approved by the institutional review board at the Centre for Addiction and Mental Health. The published protocol[14] was approved by the institutional review board at the Centre for Addiction and Mental Health before trial initiation.

Study Population and Recruitment

Participants were recruited using a general population telephone survey of Canadian households, conducted from June 4, 2012, through June 26, 2014. Follow-up was completed on January 5, 2015, and data were analyzed from May 24, 2015, through July 6, 2015. Interviews and recruitment were conducted by trained interviewers at the Survey Research Centre, University of Waterloo, using computer-assisted telephone interview technology. With the use of random-digit dialing of home and cell telephone numbers, an initial screening interview identified adult (aged ≥18 years) smokers who smoked 10 or more cigarettes per day. Respondents were selected based on the next birthday randomization method, whereby individuals answering the telephone were asked for an adult smoker in the household with the next birthday. Individuals contacted on their cell phone were considered as individual households, and this next birthday random selection method was not used. Verbal consent to participate in the study was obtained via telephone because this was the primary method of recruitment. All participants were informed at baseline that they would be taking part in a longitudinal survey on smoking and consented to submit a saliva sample at each time point (baseline, 8 weeks, and 6 months) to examine changes in nicotine metabolism over time. No mention was made to participants at any time that they were taking part in a randomized clinical trial. We wished to reduce any potential differential rates of saliva sample return by condition and smoking status and diminish the possibility that receiving a saliva sample kit would encourage participants to provide biased responses. Therefore, saliva sample kits were sent to all participants at each survey time point, regardless of whether they reported abstinence.

As part of the telephone survey and nested within a series of questions inquiring about use of, or interest in, other tobacco cessation aids, participants were asked, "The Ministry of Health is considering different ways to help people stop smoking. One option would be to provide interested smokers

Figure. Trial CONSORT Flowchart



NRT indicates nicotine replacement therapy.

with free nicotine patches. If nicotine patches were offered for free, would you be interested in receiving them?" Those who stated that they were interested were then asked if they would use the patches to quit smoking, would use them within 1 week of receiving them, and were willing to have the patches sent to their home. Participants who said yes to all these questions, had no contraindications to using nicotine patches (being pregnant, intending to become pregnant, breastfeeding, or having a serious heart or circulation problem, not including high blood pressure), and had a valid home address that was not a post office box (for timely expedited postal delivery of nicotine patches and saliva sample kits) were randomized. Participants who did not answer yes to these questions were ineligible for the randomized clinical trial and were thanked for their participation in the survey but were not recontacted for the follow-up surveys.

Randomization, Masking, and Interventions

Participants eligible for the trial were randomized to the experimental or control group (**Figure**) using a random number generator contained in the computer-assisted telephone interview program. Randomization was conducted in blocks of 10 with a 1:1 allocation to the experimental group within each block and with no stratification. Those in the experimental group were told, "As part of a pilot trial, the Centre for Addiction and Mental Health has a supply of nicotine patches to distribute to interested smokers. You told us that you would be interested in receiving a free supply of nicotine patches. Do we have your permission to mail them directly to your home?" All who were offered the nicotine patches also consented to have them sent to their home. They were sent a 5-week course of nicotine patches by expedited postal mail along with a cover letter instructing them on the use of the patches and advising them to talk to their physician or pharmacist if they had any further questions (no other behavioral support was provided; 3 weeks of step 1 [21 mg of nicotine], 1 week of step 2 [14 mg of nicotine], 1 week of step 3 [7 mg of nicotine]). The 5-week course was chosen because it mimicked the quantity of nicotine patches sent in the Ontario-based mass distribution initiative and is in line with the amount of nicotine patches mailed in other reports of mass distributions initiatives.[8,9] Participants randomized to the control group were told that they would be recontacted at the next follow-up survey, but no mention of nicotine patches was made. All participants were followed up at 8 weeks and 6 months by telephone. Interviewers were masked to the experimental group at the time the primary outcome measures were assessed at each follow-up (ensured through use of the computer-assisted telephone interview program). The Salivette saliva sample collection kit (Sarstedt AG & Co) was mailed with the $20 payment after the baseline interview. One week before the 8-week and 6-month follow-ups, participants were sent the $20 payment for the respective telephone survey and the saliva sample kit. As an added incentive for the return of saliva samples, participants were also informed that they would receive an additional $10 on the submission of each sample.

Outcomes and Statistical Analyses

Full details of the sample size calculations and statistical analyses can be found in the trial protocol in the Supplement.[14] In brief, based on data from the 2008 Canadian Tobacco Use Monitoring Survey,[15] we estimated that a baseline smoking cessation rate of 3.7% would be observed in the control group at 6 months. This estimate was consistent with another report[16] of successful unassisted long-term abstinence rates of 3% to 5%. Quit rates for the experimental group were estimated based on systematic reviews,[17,18] which indicated an approximately 10% increase in tobacco cessation rates with the use of nicotine patches at 6-month follow-up compared with placebo. We recognized that this estimate was probably too large for a pragmatic randomized clinical trial of this nature; therefore, we chose to power our trial based on the assumption that our quit rate would be half as large (ie, a 5% increase in quit rates in the experimental group vs the control group at 6-month follow-up). Given these assumptions, we predicted that participants in the experimental group would have an 8.7% quit rate at 6-month follow-up. It was determined that a sample size of 1000 participants would be needed to take part in the trial to detect a 5% difference in quit rates between groups at 6 months, at a significance level of .05 and a power of 80% (taking into account a 20% attrition rate at the 6-month follow-up).

Separate logistic regression analyses were conducted to compare the proportion of participants who had reported stopping smoking at 6 months (primary outcome: 30-day absti-

nence from tobacco cigarettes, even a puff) and 8 weeks (secondary outcome: 7-day abstinence from tobacco cigarettes, even a puff). Following the analysis plan specified in the protocol, an intent-to-treat approach was used, and participants lost to follow-up were considered active smokers. A complete case analysis is also reported, including only participants who provided follow-up data at each time point. The protocol for this study called for abstinence to be confirmed by biochemical validation. Despite following the postal mail saliva collection protocol used in other research,[19,20] a large proportion of participants did not return usable saliva samples. For example, 69.8% of participants reporting 30-day abstinence at the 6-month follow-up returned their saliva samples, and 27.0% of these samples had evaporated, allowing biochemical validation of only 50.9% of participants who claimed abstinence (no significant difference; $P > .05$ between groups on these factors). Furthermore, the fact that so many saliva samples evaporated calls into question the validity of the remaining samples because some may have partially evaporated, thus increasing the cotinine concentration in the sample. Given these limitations, both self-reported and biochemically validated outcome results are reported here. Biochemical validation of abstinence was defined as the participant having a returned saliva sample with a cotinine concentration of less than 15 µg/L (to convert to nanomoles per liter, multiply by 5.675).[21] All statistical analyses were conducted using SPSS statistical software, version 20.0 (SPSS Inc).

Results

A total of 43 785 Canadian households (including cell phones) were contacted from June 4, 2012, through June 26, 2014, using random-digit dialing methods and screened for initial eligibility, of which 2737 were identified as having at least 1 adult who smoked 10 or more cigarettes per day. A total of 2093 participants consented and were interviewed as part of the baseline survey (76.5% response rate). Of these, 1000 were found eligible for the trial and randomized to a group. One individual in the control group had reported at follow-up that her responses throughout the study had been falsely provided by someone else in the household; therefore, after this individual's exclusion, analyses had been conducted on 500 participants in the experimental group and 499 participants in the control group. Follow-up rates were not significantly different (Fisher exact test, $P = .41$) between groups at 8 weeks but were significant at 6 months ($P = .04$). However, because participants lost to follow-up were counted as current smokers and because the follow-up rate in the experimental group was lower than in the control group (77.8% vs 83.2%), the differential rates do not increase the chances of finding a significant difference in cessation rates owing to the provision of NRT. The Figure provides a CONSORT flow diagram for the trial.

Bivariate comparisons were made between participants in the experimental and control groups on demographic and smoking characteristics. With the exception of age (mean age, 48.0 years for the experimental group and 49.7 years for the control group; $P = .046$), no significant differences were observed between groups on any of the demographic or smoking characteristics ($P > .05$; **Table**). Because the difference in age was marginal and only significant because of the large sample size, we chose not to control for age in the outcome analyses. Separate logistic regressions were conducted to assess differences in the proportion of participants reporting 30-day abstinence at the 6-month follow-up and 7-day abstinence at the 8-week follow-up, using an intent-to-treat approach.

Table. Demographic and Smoking Characteristics

Characteristic	Group[a] Experimental (n = 500)	Control (n = 499)
Age, mean (SD), y	48.0 (12.8)	49.7 (12.7)[b]
Female sex	255 (51.0)	256 (51.3)
Married or common-law spouse	266 (53.2)	284 (56.9)
Employed full or part time	318 (63.6)	296 (59.3)
Educational level		
Less than high school diploma	116 (23.2)	97 (19.5)
High school diploma	200 (40.1)	226 (45.4)
Postsecondary	183 (36.7)	175 (35.1)
Household income, $		
<60 000	297 (63.2)	311 (65.6)
≥60 000	173 (36.8)	163 (34.4)
Cigarettes, mean (SD), d	18.5 (8.5)	18.2 (7.1)
FTND score, mean (SD)	5.0 (2.0)	4.9 (2.0)
Level of nicotine dependence[c]		
Low	56 (11.6)	58 (11.9)
Low to moderate	131 (27.2)	148 (30.5)
Moderate	244 (50.7)	236 (48.6)
High	50 (10.4)	44 (9.1)
Age at first smoking, mean (SD), y	14.5 (4.1)	15.0 (4.1)
Time as smoker, mean (SD), y	24.5 (13.6)	25.6 (14.4)
No. of previous quit attempts		
0	37 (7.4)	34 (6.8)
1-5	338 (67.6)	337 (67.5)
>6	125 (25.0)	128 (25.7)
Previously used NRT (patch, gum, inhaler) in a quit attempt	277 (59.8)	290 (62.4)

Abbreviations: FTND, Fagerström Test for Nicotine Dependence; NRT, nicotine replacement therapy.

[a] Data are presented as number (percentage) of participants unless otherwise indicated. Sample sizes vary because of missing data on some variables.

[b] $P < .05$.

[c] Level of nicotine dependence is based on the FTND scores. Scores range from 1 to 10, with higher scores indicating a more intense physical dependence on nicotine. Low dependence corresponds to a score of 1 or 2, low to moderate dependence a score of 3 or 4, moderate dependence a score of 5 to 7, and high dependence a score of 8 to 10.

Biochemically Validated Abstinence

Half (50.9%) of the participants had useable saliva samples for biochemical validation. Saliva sample return rates among self-reported abstainers did not differ significantly by group at either the 8-week ($P = .36$) or 6-month ($P > .99$) follow-up. Participants receiving nicotine patches were significantly more likely to have verified abstinence at 6-month follow-up (14

[2.8%] of 500 in the experimental group vs 5 [1.0%] of 499 in the control group; odds ratio [OR], 2.85; 95% CI, 1.02-7.96; $P = .046$). At 8 weeks, rates of biochemically confirmed cessation were not significant (12 [2.4%] of 500 in the experimental group vs 4 [0.8%] of 499 in the control group; OR, 3.04; 95% CI, 0.98-9.50; $P = .06$). The number needed to treat to achieve cessation was 56 (95% CI, 29-922) for the 6-month follow-up. Complete case analyses at 6 months similarly revealed greater odds of cessation in the experimental group (14 [3.6%] of 389) vs the control group (5 [1.2%] of 415) (OR, 3.06; 95% CI, 1.09-8.58; $P = .03$). At 8 weeks, 12 (2.8%) of 427 participants in the experimental group and 4 (0.9%) of 436 in the control group had stopped smoking (OR, 3.12; 95% CI, 1.00-9.76; $P = .05$)

Self-reported Abstinence

Participants receiving nicotine patches were significantly more likely to report abstinence at 6 months (38 [7.6%] of 500 vs 15 [3.0%] of 499; OR, 2.65; 95% CI, 1.44-4.89; $P = .002$) and 8 weeks (37 [7.4%] of 500 vs 11 [2.2%] of 499; OR, 3.55; 95% CI, 1.79-7.03; $P < .001$) compared with the control group. The numbers needed to treat to achieve cessation were 22 (95% CI, 14-55) and 20 (95% CI, 13-39) for the 6-month and 8-week end points, respectively. Complete case analyses revealed similar findings, with self-reported abstinence rates significantly higher among participants who were sent nicotine patches by mail compared with the control group at 6-month (38 [9.8%] of 389 vs 15 [3.6%] of 415; OR, 2.89; 95% CI, 1.56-5.34; $P = .001$) and 8-week (37 [8.7%] of 427 vs 11 [2.5%] of 436; OR, 3.67; 95% CI, 1.84-7.29; $P < .001$) follow-ups.

Use of Nicotine Patches

In the experimental group, 421 (98.6%) of all 427 participants surveyed at 8 weeks reported to have received the nicotine patches they were sent, and 246 (58.4%) of those 421 reported to have used the nicotine patches. A total of 200 (81.3%) of all 246 nicotine patch users reported using only some of the nicotine patches they received by 8 weeks, whereas 46 (18.7%) of 246 had used all that were provided. Of participants followed up at 8 weeks, 13 (3.0%) of 427 of those in the experimental group had purchased additional nicotine patches, compared with 30 (6.9%) of 436 in the control group ($P = .01$). At the 6-month follow-up, however, no differences between groups were observed, such that 25 (6.4%) of 389 of those in the experimental group and 31 (7.5%) of 415 in the control group had purchased nicotine patches ($P = .58$). Purchase of any other smoking cessation aids (ie, nicotine gum, inhaler, bupropion, or varenicline) similarly did not differ between groups ($P = .19$).

Discussion

Providing a 5-week supply of nicotine patches via mail resulted in more than a doubling of 30-day abstinence quit rates at the 6-month follow-up. Because the provision of NRT was without behavioral assistance, the results of this trial provide evidence of the effectiveness of nicotine patches as a tobacco cessation aid in real-world settings.

Although a random-digit dialing method was used, the sample should not be taken as representative of the general population because of the multiple inclusion steps taken to recruit the sample. Rather, the sample is best regarded as a diverse one from rural and urban settings across Canada. Furthermore, the findings of the trial do not provide direct evidence of the efficacy of mass distribution initiatives because the recruitment method for this trial was different from that used in mass distribution initiatives (random-digit dialing rather than interested participants calling a toll-free number). However, the results of the trial provide general support for direct-to-smoker programs with free mailed nicotine patches.

In efficacy trials of smoking cessation medications, biochemical validation using exhaled carbon dioxide or cotinine in saliva, urine, or blood is considered the criterion standard. However, in population-based studies, given the large sample sizes, differential reporting biases between groups are unlikely to invalidate the findings. Although consensus statements indicate that biochemical validation of tobacco cessation is not required in the present study,[21] the protocol for the current trial stated that biochemical validation would be conducted. Thus, the poor response rate and the questionable reliability of the saliva samples because of evaporation are limitations of the results and reduce confidence in the validity of the findings. Although the study design has several strengths in allowing for a test of the effect of nicotine patches without behavioral support and without participants in the control group being aware that other participants were even offered nicotine patches (or participants even being aware they were in a randomized trial), the recruitment method and study rationale provided to the participants likely resulted in a study population that was not aware of the importance of returning the saliva samples. Perhaps a larger incentive would have resulted in a better return rate. However, this approach would not have addressed the additional issue of evaporated saliva samples. To partially counteract this limitation, we also provided self-reported abstinence as an outcome measure. We suspect that the self-reported abstinence rate is closer to the actual abstinence rate in this study because the self-reported abstinence rate in the control group was similar to that reported in other general population samples[15,16] and because the rates reported in the experimental group were similar to that reported based on before-after data from a mass distribution initiative in the same country.[9] However, there is no way to confirm this hypothesis. Perhaps this is a limitation that needs to be accepted in a pragmatic trial, such as the one described here, because the participant sample was widely dispersed (across all of Canada) and the procedures called for no physical contact with the participants. We conclude that, although biochemical validation would increase confidence in the results, there is sufficient evidence of the reliability of self-reported tobacco cessation[22-25] to warrant the statement that the provision of nicotine patches by expedited postal mail, and without behavioral support, promotes tobacco cessation in the short term. Further research is merited to systematically replicate these findings and to estab-

lish any long-term effect of providing NRT without behavioral assistance.

The absolute level of increase in 30-day abstinence rates (3.0% in the control group to 7.6% in the experimental group) represents a smaller increase than that observed in clinical trials that involve nicotine patches.[17,18] We believe this is a result of recruiting a general population sample of smokers who were not seeking tobacco cessation assistance. Furthermore, we note that the 30-day abstinence rate in the control group was lower than the estimate in our sample size calculation (3.0% vs 3.7%). This outcome resulted in a significant finding in this trial even though the absolute difference between groups was 4.6% rather than the estimated 5%. The choice of 5% for the sample size calculation did not represent a cutoff below which the utility of mailed NRT is diminished. Rather, it was a simple estimate of the anticipated effect of the intervention in the general population. The ORs reported in this trial are larger than those observed in clinical trials of the efficacy of NRT[3] because the low cessation rates seen in the control group of this general population sample (3.0%) allowed for a significant increase in cessation rates, whereas the actual increase in cessation rates was small (4.6%).

Conclusions

Meta-analyses and population-based studies[3,26] suggest that NRT should be used for approximately 8 weeks; however, a shorter duration as used in our study indicated an effect. Also encouraging was that the 6-month quit rates were similar to those observed in other NRT mass distribution initiatives that used 5 weeks of NRT.[9] Although some smokers may benefit from receiving more NRT, mass distribution initiatives providing less NRT allow for more people to access the program at the same cost. Research is needed to determine the optimum amount of NRT to be distributed to have the greatest effect at the population level.

ARTICLE INFORMATION

Accepted for Publication: November 24, 2015.

Published Online: January 25, 2016. doi:10.1001/jamainternmed.2015.7792.

Author Affiliations: Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Cunningham, Kushnir, Selby, Tyndale, Zawertailo); National Institute for Mental Health Research, Research School of Population Health, the Australian National University, Canberra (Cunningham); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Cunningham, Selby, Tyndale); Department of Pharmaceutical Sciences, University of Toronto, Toronto, Ontario, Canada (Kushnir); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Selby); Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada (Selby); Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada (Tyndale, Zawertailo); School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario, Canada (Leatherdale).

Author Contributions: Dr Cunningham and Mr Kushnir had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cunningham, Selby, Tyndale, Zawertailo.
Acquisition, analysis, or interpretation of data: Cunningham, Kushnir, Selby, Tyndale, Leatherdale.
Drafting of the manuscript: Cunningham, Kushnir.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kushnir, Leatherdale.
Obtained funding: Cunningham, Selby, Zawertailo, Leatherdale.
Administrative, technical, or material support: Kushnir, Tyndale.
Study supervision: Cunningham.

Conflict of Interest Disclosures: Dr Tyndale reported, in the past 3 years, that she has consulted with Apotex on topics unrelated to smoking cessation. Dr Selby reported receiving grant or research funding from Pfizer Inc, Pfizer Canada Inc, and Shoppers Drug Mart; speakers' bureau fees from Pfizer Inc, Canada, Pfizer Global, and ABBVie; and consulting fees from Pfizer Inc, Pfizer Canada Inc, Pfizer Global, NABI Pharmaceuticals, and V-CC Systems Inc. No other disclosures were reported.

Funding/Support: This research was funded by grant 230448 from the Canadian Institutes of Health Research (Dr Cunningham). We acknowledge the support of the Centre for Addiction and Mental Health, the Centre for Addiction and Mental Health Foundation, grants 20289 and 16014 from the Canada Foundation for Innovation, the Ontario Ministry of Research and Innovation, and the Endowed Chair in Addictions for the Department of Psychiatry (Dr Tyndale). Dr Leatherdale is a chair in applied public health funded by the Public Health Agency of Canada in partnership with Canadian Institutes of Health Research Institute of Neurosciences, Mental Health and Addiction and Institute of Population and Public Health. Support to CAMH for salary of scientists and infrastructure has been provided by the Ontario Ministry of Health and Long Term Care.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article do not necessarily reflect those of the Ministry of Health and Long Term Care.

REFERENCES

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2224-2260.

2. Shibuya K, Ciecierski C, Guindon E, Bettcher DW, Evans DB, Murray CJ; WHO Framework Convention on Tobacco Control. WHO Framework Convention on Tobacco Control: development of an evidence based global public health treaty. *BMJ*. 2003;327(7407):154-157.

3. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;11:CD000146.

4. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. *Addiction*. 2013;89(10):1360-1367.

5. Kotz D, Brown J, West R. Prospective cohort study of the effectiveness of smoking cessation treatments used in the "real world." *Mayo Clin Proc*. 2014;89(10):1360-1367.

6. Kasza KA, Hyland AJ, Borland R, et al. Effectiveness of stop-smoking medications: findings from the International Tobacco Control (ITC) Four Country Survey. *Addiction*. 2013;108(1):193-202.

7. Hughes JR, Shiffman S, Callas P, Zhang J. A meta-analysis of the efficacy of over-the-counter nicotine replacement. *Tob Control*. 2003;12(1):21-27.

8. Cummings KM, Fix B, Celestino P, Carlin-Menter S, O'Connor R, Hyland A. Reach, efficacy, and cost-effectiveness of free nicotine medication giveaway programs. *J Public Health Manag Pract*. 2006;12(1):37-43.

9. Zawertailo L, Dragonetti R, Bondy SJ, Victor JC, Selby P. Reach and effectiveness of mailed nicotine replacement therapy for smokers: 6-month outcomes in a naturalistic exploratory study. *Tob Control*. 2013;22(3):e4.

10. Miller N, Frieden TR, Liu SY, et al. Effectiveness of a large-scale distribution programme of free nicotine patches: a prospective evaluation. *Lancet*. 2005;365(9474):1849-1854.

11. Swartz SH, Cowan TM, Klayman JE, Welton MT, Leonard BA. Use and effectiveness of tobacco telephone counseling and nicotine therapy in Maine. *Am J Prev Med*. 2005;29(4):288-294.

12. Tinkelman D, Wilson SM, Willett J, Sweeney CT. Offering free NRT through a tobacco quitline: impact on utilisation and quit rates. *Tob Control*. 2007;16(suppl 1):i42-i46.

13. Bush TM, McAfee T, Deprey M, et al. The impact of a free nicotine patch starter kit on quit rates in a state quit line. *Nicotine Tob Res*. 2008;10(9):1511-1516.

14. Cunningham JA, Leatherdale ST, Selby PL, Tyndale RF, Zawertailo L, Kushnir V. Randomized controlled trial of mailed nicotine replacement therapy to Canadian smokers: study protocol. *BMC Public Health*. 2011;11(1):741.

15. Statistics Canada. Canadian Tobacco Use Monitoring Survey. 2008. http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2008-eng.php. Accessed July 29, 2009.

16. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction*. 2004;99(1):29-38.

17. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2008;(1):CD000146.

18. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update US Public Health Service Clinical Practice Guideline executive summary. *Respir Care*. 2008;53(9):1217-1222.

19. Binnie V, McHugh S, Macpherson L, Borland B, Moir K, Malik K. The validation of self-reported smoking status by analysing cotinine levels in stimulated and unstimulated saliva, serum and urine. *Oral Dis*. 2004;10(5):287-293.

20. Etter JF, Neidhart E, Bertrand S, Malafosse A, Bertrand D. Collecting saliva by mail for genetic and cotinine analyses in participants recruited through the Internet. *Eur J Epidemiol*. 2005;20(10):833-838.

21. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. 2002;4(2):149-159.

22. Vartiainen E, Seppälä T, Lillsunde P, Puska P. Validation of self reported smoking by serum cotinine measurement in a community-based study. *J Epidemiol Community Health*. 2002;56(3):167-170.

23. Wong SL, Shields M, Leatherdale S, Malaison E, Hammond D. Assessment of validity of self-reported smoking status. *Health Rep*. 2012;23(1):47-53.

24. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health*. 1994;84(7):1086-1093.

25. Pierce JP, Dwyer T, DiGiusto E, et al. Cotinine validation of self-reported smoking in commercially run community surveys. *J Chronic Dis*. 1987;40(7):689-695.

26. Zhang B, Cohen JE, Bondy SJ, Selby P. Duration of nicotine replacement therapy use and smoking cessation: a population-based longitudinal study. *Am J Epidemiol*. 2015;181(7):513-520.