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A randomized controlled pilot study of standardized counselling and cost-free pharmacotherapy for smoking cessation among stroke and TIA patients

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ABSTRACT

BACKGROUND: Tobacco use is a major risk factor for recurrent stroke. Very few studies have been performed to support smoking cessation among patients who have experienced a stroke or TIA. The purpose of this pilot study was to assess the feasibility and obtain preliminary data on the effectiveness of providing cost-free quit smoking pharmacotherapy and counselling to smokers identified in a stroke prevention clinic.

DESIGN: Randomized controlled trial.

METHODS: All patients seen at the Ottawa Hospital Stroke Prevention Clinic were screened for smoking status, advised to quit smoking and treated using a standardized protocol including counselling and pharmacotherapy. Eligible smokers were randomly assigned to either a prescription only usual care group, or, the experimental group who received a 4-week supply of cost-free quit smoking medications and prescription for medication renewal. All patients received follow-up counselling 7-days prior to and 5, 14, 30, 60, 90, 180 days following their quit attempt. The primary outcome was bio-chemically validated quit rates at 26-weeks.

RESULTS: Of 219 smokers screened, 73 were eligible, 28 consented and were randomized, and 25 completed the study. The bio-chemically validated 7-day point prevalence abstinence rate in the experimental group compared to usual care group was 26.6% vs. 15.4%, adjusted Odds Ratio (OR) 2.00, 95% CI 0.33, 13.26, p=.20.

CONCLUSIONS: This pilot study provides preliminary data which suggests the provision of 4-weeks of cost-free quit smoking medications may improve quitting success in smokers with TIA and stroke. The study was underpowered to achieve statistically significant results. It would be feasible to definitively evaluate this intervention in a large multi-site trial.

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ARTICLE SUMMARY

Providing stroke and TIA patients with cost-free quit smoking medications accompanied with counselling may improve quitting success in smokers with TIA and stroke. It would be feasible to definitively evaluate this intervention in a large multi-site trial.

Article Focus:

- Limited information is available regarding interventions to support cessation among patients who experience a stroke or TIA.
- The purpose of this pilot study was to assess the feasibility and obtain preliminary data on the effectiveness of providing cost-free quit smoking pharmacotherapy and counselling to smokers identified in a speciality stroke prevention clinic.

Key Messages:

- Cost-free quit smoking medications may improve quitting success in smokers with TIA and stroke.
- It would be feasible to definitively evaluate this intervention in a large multi-site trial.
- To our knowledge this is the first study to evaluate the efficacy of the provision of cost-free pharmacotherapy among patients at high risk of stroke.

Strengths and Limitations:

- This study used a randomized controlled trial design.
- While a positive intervention effect was documentged the limited sample size of this pilot study meant it was not able to document a significant intervention effect over control.

- The study involved the recruitment of patients from a single stroke prevention clinic results may not be generalizable to the broader population of stroke and TIA patients in other settings.

INTRODUCTION

Cigarette smoking is a major independent risk factor for recurrent stroke and has been identified as an important treatment target for all patients at high risk of future stroke.[1-4] Stroke and transient ischemic attack (TIA) patients who quit smoking reduce their relative risk of stroke recurrence by 50%.[5] Smoking cessation is also associated with a reduction in stroke related hospitalizations.[6,7] Unfortunately most smokers with cerebrovascular disease have difficulty quitting on their own. Previous research has documented that approximately 80 to 90% of stroke and TIA patients identified as smokers at the time of their event continued to use tobacco six to 12-months later.[8-10]

Evidence from placebo-controlled clinical trials consistently demonstrates that cessation medications such as nicotine replacement therapy, bupropion and varenicline combined with counselling, can double or triple long-term smoking abstinence in smokers.[11-13] Consequently stroke prevention guidelines recommend that healthcare providers strongly advise every smoker who is at high risk for a stroke or TIA to quit, and provide specific assistance with quitting including counselling and pharmacotherapy.[14, 15]

Despite the evidence supporting the importance of smoking cessation, there is a well documented practice gap in the rates at which smoking cessation is addressed by healthcare professionals, even for high-risk groups such as TIA patients and/or stroke survivors.[8-10] The absence of a coordinated approach to screening and counselling smokers has been identified as a potential barrier to successful cessation.[11] In addition, the cost of quit smoking medications has been identified as a barrier to the use of cessation pharmacotherapies.[16] The provision of cost-free

medications has been shown to improve motivation to quit and increase quit attempts and smoking abstinence in the general population; no study, however, has examined the efficacy of providing cost-free cessation pharmacotherapy to patients who have recently experienced a TIA or stroke or are at high risk for stroke.[17-20] The purpose of this pilot study was to assess the feasibility and obtain preliminary data on the effectiveness of providing cost-free quit smoking pharmacotherapy and counselling to smokers identified in a speciality stroke prevention clinic compared to the provision of a conventional prescription for pharmacotherapy.

METHODS

Design

This pilot study was a two-group, open label, experimental feasibility study with random assignment to either the prescription-only usual care group (PO Group) or the cost-free quit smoking medications group (CF Group). Pilot studies are designed specifically to test the feasibility of a proposed intervention and study protocol, as well as obtain effect estimates to inform the design of a larger study.[21] The primary outcome was bio-chemically validated quit rates at 26 weeks. Secondary outcome measures included patient quit attempts at 26 weeks and adherence to quit smoking counselling and pharmacotherapy protocols. Levels of eligibility, consent, adherence and retention were used as indicators of study feasibility. The study protocol was approved by the University of Ottawa Heart Institute Human Research Ethics Board.

Setting and Patient Population

Patients were recruited from The Ottawa Hospital Stroke Prevention Clinic, Ottawa, Ontario, Canada. The clinic provides assessment and secondary prevention services to patients who have

recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event.

Standardized Smoking Cessation Protocol

As part of the study a systematic approach to the identification and treatment of patients who smoke was introduced into routine clinic practice at the Stroke Prevention Clinic; the protocol was based on the Ottawa Model for Smoking Cessation.[22,23] The nurse specialists and neurologists providing care in this setting were provided with training session in evidence-based smoking cessation interventions. Patient and provider tools and resources, adapted from the Ottawa Model for Smoking Cessation, were introduced in the Stroke Clinic to facilitate and support the standardized delivery of tobacco treatment. This included a waiting room screener, consult form to support clinicians in the delivery of cessation interventions, and a quit plan for patients ready to quit smoking.

The waiting room screener which assessed current smoking status was distributed to all patients upon registration at the clinic. Patients were instructed to return the waiting room screener to the clerk when completed. The screening nurse used the results obtained in the screening process to flag all patient charts indicating whether the patient was a smoker or non-smoker. A smoking cessation consult form was placed on the chart of each patient identified as a smoker by the clerk and served as a prompt to the neurologist for delivering evidence-based smoking cessation interventions. The neurologist then provided strong, unambiguous, non-judgemental advice to quit to all smokers along with an offer of support with making a cessation attempt. The neurologist also assessed patient readiness to quit in the next 30 days, documented patient response on the consult form.

Eligibility Screening

Patients were eligible to participate in the study if they reported smoking an average of 5 or more cigarettes per day in past 3 months; were 18 years of age or older; were willing to set a quit date in the next 30 days; and were willing to use a quit smoking medication. Patients who were unable to read and understand English or French or who had contraindications to all approved smoking cessation medications (nicotine replacement therapy, bupropion, and varenicline) were excluded from the study. Eligible patients were invited by the neurologist or the stroke prevention nurse-specialist to take part in the study. Eligible patients interested in participating in the study had the study procedures explained to them by the research study coordinator. All participants provided informed consent.

Allocation to Treatment

Patients were randomly assigned to one of two intervention groups. The research coordinator or clinic nurse specialist opened a sealed envelope which contained the treatment group allocation. Randomization envelopes were prepared by a third party using a random numbers table blocked in groups of four and sealed until treatment allocation. Due to the nature of the intervention, participants and clinicians were not blinded to their intervention assignment.

Comparison Groups

Cost-Free Pharmacotherapy Experimental Group (CF Group)

Participants assigned to the CF group received a starter kit (4-week supply) of cost-free quit smoking medication (nicotine replacement therapy, bupropion, or varenicline) and a pre-printed prescription to be filled by the patient at the end of the 4-weeks.

Prescription Only Usual Care Group (PO Group)

Participants assigned to the prescription only usual care group received a prescription for smoking cessation pharmacotherapy to be filled at their own cost at their local community pharmacy.

Patient Quit Plan Consultation and Telephone Follow-up Support

The stroke prevention nurse specialist conducted a 10 to 20 minute consultation with all study participants using a standardized consult form and patient education materials. During the consult the nurse specialist addressed patient concerns about quitting, set a target quit date (TQD) with the patient in the next 30 days, developed strategies for addressing cravings and withdrawal, and identified strategies for relapse prevention and management. Patients were then prescribed a first-line quit smoking pharmacotherapy. The choice of the pharmacotherapy was based on patient preference and smoking history. All study participants were contacted by phone by a trained smoking cessation counsellor 7 days before their TQD, and 5, 14, 30, 90, and 180 days after to discuss the patient's quit smoking progress, address potential concerns, and assist with relapse prevention strategies and management. During the call, the smoking cessation nurse specialist posed a series of questions concerning: current smoking status; confidence in staying smoke-free until the next planned call; and the use of pharmacotherapy, self-help materials, and other forms of cessation support.

Post-assessment and follow-up data collection

All participants were contacted by telephone 26 weeks (+/-2 weeks) after their TQD to assess outcome measures. All patients reporting smoking abstinence had an end-expired carbon monoxide (CO) sample collected in order to validate smoking abstinence.

Outcome Measures

The dependent variables of primary interest were measured at 26 weeks and included: (1) bio-chemically confirmed 7-day point prevalence abstinence; and (2) continuous abstinence since TQD. Participants who were not available for follow-up were considered smokers. At the 26 week follow-up, all patients who reported being abstinent from smoking had their smoking status confirmed by measurement of a CO sample. If any CO was >10 ppm, the subject was considered a smoker. At the 26 week follow-up assessments patient quit attempts in the previous six months of 24 hours or longer were documented. During the 26-week telephone follow-up assessment patient adherence with pharmacotherapy was assessed by evaluating the number of doses of pharmacotherapy consumed within the prescribed study interval. The telephone counsellor recorded the completion of all seven counselling sessions in order to assess patient adherence.

Analysis

Descriptive characteristics were assessed for all smokers screened at the stroke prevention clinic during the recruitment period. Baseline characteristics of study participants assigned to each of the intervention groups were compared using independent t-tests for continuous variables and chi-square tests for categorical variables to assess any chance imbalances that may have occurred. A logistic regression model was 'fitted' to 26-week abstinence status (smoker or non-smoker) and treatment group included as the independent variable. Adjusted analyses were conducted to account for baseline differences between groups. Treatment adherence and patient quit attempts were also compared between treatment groups. All patients were included in the intention to treat analysis. Missing data was categorized as active smoking (smoking

abstinence), not having made a quit attempt (quit attempts), or non-compliant with medications (adherence).

RESULTS

Participant recruitment and data collection

Figure 1 presents the CONSORT diagram for data collection flow. A total of 2182 patient visits occurred at the Stroke Prevention Clinic between August 2008 and December 2009 and 219 unique patients were identified as having used tobacco in the last seven days. Table 1 provides a summary of the characteristics of all patients screened at the Stroke Prevention Clinic who reported active smoking during the study recruitment period. At the initial screening seventy four percent of smokers reported they were planning on quitting smoking within the next 6-months and thirty-six percent were planning on quitting in the next 30 days. One hundred and forty-seven patients who smoked did not meet eligibility criteria. The primary reason for exclusion was the patient not being willing to quit smoking in the next 30 days and smoking less than an average of five cigarettes per day. An additional fourteen patients were not willing to use pharmacotherapy. Among eligible patients 29/73 (40%) agreed to participate in the study. Study participants were more likely than non-participants to be younger, smoke a greater number of cigarettes per day, more likely to be concerned about withdrawal and stress, and less concerned about boredom. Two study participants withdrew from the study. Twenty-six week follow-up data was completed for 25/28 (89%) of study participants. There were no significant differences in the loss to follow-up between intervention groups.

Participant Characteristics

A total of 28 eligible smokers (mean age 54.5±10.5 years, 70% male) were enrolled in the pilot study. The characteristics of study participants are presented in table 1. CF participants reported smoking significantly more cigarettes per day as well as significantly greater self-efficacy (confidence) with quitting compared to participants randomized to the PO group.

Smoking Abstinence

Table 2 presents the effect estimates for smoking abstinence. Quit rates were 33.3% in CF group versus 15.4% in the PO group for 7-day point prevalence abstinence and 23.1% versus 15.4% for continuous abstinence at 26 weeks. Effect estimates were adjusted to account for the observed differences between groups. The adjusted odds ratio for self-reported continuous abstinence was 5.51; 95% CI 0.44, 69.3; p=.186 and 7-day point prevalence abstinence was 2.25; 95% CI 0.25. 20.4; p=.470. While a positive trend favouring CF group was observed differences between groups were not statistically significant.

Bio-chemical validation of self-reported smoking abstinence was completed with 75% of patients who reported a smoke-free status at the end of 26 weeks. No differences were noted in the rate of completion of the bio-chemical validation at the pre- and post-intervention assessments nor were differences noted between CF and PO intervention groups (26.6% vs. 15.4%). The adjusted odds ratio for bio-chemically validated 7-day point prevalence abstinence was 5.95 (95% CI 0.40. 88.7; p=.195) however the observed differences between groups were not significant.

Table 1. Characteristics of smokers screened and study participants

Parameter	Smokers Screened (n=219)	Eligible Non Participants (n=44)	Study Participants (n=28)	PO Group (n=13)	CF Group (n=15)	*p*-value*
Age, mean (SD)	55.4(12.8)	59.4(9.8)	54.5(10.5)	53.5(8.1)	55.4(12.4)	.65
% Male	48.8	61.4	60.7	69.2	53.3	.39
Years of education, mean (SD)	12.1(3.1)	11.6(4.2)	11.7(3.4)	12.9(2.3)	10.6(4.0)	.08
Cigarettes/day, mean (SD)	15.1(10.4)	16.9(10.6)	17.5(8.0)	20.7(8.8)	14.8(6.2)	**.05**
Years smoking cigarettes, mean (SD)	33.3(15.0)	34.7(13.6)	34.6(14.5)	32.5(15.1)	36.4(14.1)	.49
Time to first cigarette						
% Within 30 minutes of waking	67.3	72.2	78.5	77.0	80.0	.87
% more than 30 minutes after waking	32.7	27.8	21.5	23.0	20.0	
Confidence (SD)[*]	5.4(3.3)	6.1(3.4)	6.2(3.1)	5.0(3.2)	7.3(2.6)	**.05**
Importance of quitting (SD)[†]	7.2(3.3)	7.5(3.2)	8.3(2.4)	8.6(2.7)	7.9(2.3)	.47
Quit Attempts						
None	41.3	53.2	35.7	30.8	40.0	.78
1 to 2	36.0	18.4	39.3	46.2	33.3	
3 or more	22.7	26.3	25.0	23.1	26.7	
Readiness to quit at initial screening[‡]						
Next 30 days	40.4	54.5	70.4	84.6	57.1	.12
Next 6-months	59.6	45.5	29.6	15.4	42.9	
Other smoker in the home	45.3	51.3	46.4	53.8	40.0	.35
Medication coverage						
Yes	18.2	15.9	32.1	38.5	26.7	.62
No	49.4	45.4	32.1	23.1	40.0	
Don't know	32.4	38.7	35.7	38.5	33.3	
HADS Score[‡‡]						
Anxiety, mean (SD)	-	-	7.0(3.8)	6.8(3.8)	7.1(3.9)	.88
Depression, mean (SD)	-	-	5.1(4.1)	5.5(2.8)	4.7(4.9)	.64
Reasons for quitting						
Health reasons	81.9	77.8	93.1	92.3	93.8	.88
Family	20.6	16.7	34.5	38.5	31.3	.68
Financial	20.5	19.4	20.7	23.1	18.8	.78
Social	11.9	11.4	13.8	15.4	12.5	.82
Concerns about quitting						
Stress	53.3	43.2	62.1	46.2	75.0	.11
Withdrawal	35.3	38.6	48.3	53.8	43.8	.59
Weight	29.4	25.0	37.9	38.5	37.5	.96
Boredom	18.2	13.6	24.1	23.1	25.0	.90
Social	9.6	9.1	3.4	0.0	6.3	.36

PO, Prescription only; CF, Cost-Free Pharmacotherapy; HADS, Hospital Anxiety and Depression Scale

**Comparisons are based on the Pearson chi-square test for categorical variables and Student's t-test for continuous variables between intervention groups.*

[**] *On a scale of 1 to 10 how confident are you that you would be able to quit smoking at this time? (1=not at all confident, 10=extremely confident)*

[†] *On a scale of 1 to 10 how important is it to you to quit smoking at this time? (1=not important at all, 10=*extremely important)

[‡]Response provide on the waiting room screener to the question "Which of the following best describes your feelings about smoking right now?" Patients readiness to quit was reassessed following neurologists strong personalized advice to quit.

[‡‡]HADS scores: 0-7 = normal; 8-10 = borderline abnormal; 11-21 = abnormal[24]

Table 2. 26-week Smoking Abstinence

6-month abstinence measure	PO Group n/N (%)	Cost-Free Group n/N (%)	Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI) [†]	*p*-value[†]
Continuous abstinence	2/13 (15.4)	5/15 (33.3)	2.75 (0.43, 17.5)	.26	5.51 (0.44, 69.3)	.19
7-day point prevalence abstinence	3/13 (23.1)	5/15 (33.3)	1.67 (0.31, 8.9)	.43	2.25 (.25, 20.4)	.47
Bio-chemically validated 7-day point prevalence abstinence	2/13 (15.4)	4/15 (26.6)	2.00 (0.33, 13.3)	.40	5.95 (0.40, 88.7)	.20

PO, Prescription only; CF, Cost-Free Pharmacotherapy; CI, Confidence Interval

[†]Adjusted for number of cigarettes smoked per day and self-efficacy

Secondary outcomes

At the 26-week follow-up assessment a greater number of patients in the PO group reported making a quit attempt compared to the CF group (62% vs. 53%). Patients in the CF group were more likely to report use of the quit smoking medication prescribed and had greater overall compliance with the full course of the quit smoking pharmacotherapy. Observed differences were not statistically significant. More patients in the CF group completed at least 80% of the seven scheduled telephone based counselling session with the quit smoking nurse specialist compared to the PO group. Participants in the CF group completed a mean of 6.3/7 (91%) sessions compared to 5.5/7 (78%) of sessions in the PO group. See table 3.

Table 3. Compliance with Medications and Quit Attempts

6-month abstinence measure	PO Group n/N (%)	Cost-free Group n/N (%)	Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI) †	*p*-value†
Quit Attempts	8/13 (61.5)	8/15 (53.3)	.71 (.16, 3.2)	.66	.72 (.12, 4.5)	.72
Began using medication prescribed	8/13 (61.5)	11/15 (73.3)	1.7 (.35, 8.5)	.51	.44 (.03, 5.9)	.54
Compliance with Medication, >90%	4/13 (30.7)	7/15 (46.7)	2.0 (.42, 9.3)	.39	2.2 (.35, 14.5)	.40
Compliance with Telephone Counselling, >80%	8/13 (61.5)	14/15 (93.3)	8.7 (0.9, 88.7)	.07	4.2 (.32, 58.9)	.28

PO, Prescription only; CF, Cost-Free Pharmacotherapy; CI, Confidence Interval

†Adjusted for number of cigarettes smoked per day and self-efficacy

DISCUSSION

This feasibility study found the provision of a 4-week starter-kit of cost-free pharmacotherapy to be associated with a positive effect on medication compliance and smoking abstinence measured at the 26-week follow-up, however observed differences were not statistically significant. A larger trial would be required to validate these preliminary observations. Given that only 40% of eligible smokers enrolled in the study suggesting considerations must be given to interventions to increase patient enrolment in future investigations.

To our knowledge this is the first study to evaluate the efficacy of the provision of cost-free pharmacotherapy among patients at high risk of stroke. While there have been no trials to evaluate the efficacy of providing cost-free quit smoking medications to stroke or TIA patients, studies in the general population have found that the provision of a cost-free smoking cessation medications increases patient motivation to quit, quit attempts, and smoking abstinence.[17-20] A systematic review including three trials examining the benefit of covering the cost of smoking cessation treatment (primarily the cost of pharmacotherapy) found that cost-free treatment increased the odds of achieving abstinence by 60% (OR = 1.6; 95% CI 1.2 to 2.2) compared to having smokers pay for their own treatment.[11,25] One additional trial, completed after the meta-analysis described above was published, found that providing cost-free effective smoking cessation pharmacotherapies to smokers in primary care increased the odds of quitting 12 months after recruitment almost 5-fold (OR = 4.77; 95% CI 2.0 to 11.2)[20]. Our study provides preliminary support that similar effects many be observed among TIA and stroke patients. Given the significant acute health benefits derived from smoking cessation among TIA and stroke

patients it would appear that this intervention program may be of particular significance to reducing disease burden and improving stroke outcomes.

Our investigation identified that a large proportion of smokers screened as part of the present study were not ready to quit smoking in the thirty days following their visit to the Stroke Prevention Clinic. The reported rates are lower than that observed in the general population despite the presence of a teachable moment resulting from their health event.[11, 26] This would suggest the possibility that smokers identified in the stroke prevention setting represent a "hardened" population of smokers i.e. those with higher levels of nicotine addiction and lack of interest in cessation[27]. This is reflected by the proportion of high risk patients who were not interested in embarking upon a quit attempt in the next 30 days following strong clinician advice, and the fact that more than 65% of patients sampled reported time to first cigarette in the morning to be within 30 minutes of waking. Interestingly, thirty percent of the study sample had indicated on the waiting room screener that they were not ready to quit in the next 30 days. Following standardized counselling from the clinic physician, however, these patients decided to quit smoking and were randomized to the trial. Additional research is required to better understand the lack of intentions among stroke and TIA patients to make a quit attempt and how best to motivate and/or support increased patient motivation to quit and/or harm reduction interventions such as reduce to quit (RTQ) approaches.

Participants in the CF group reported greater adherence with the telephone-based counselling intervention compared with PO participants. A larger trial would be required to further examine this relationship.

There has been very limited research published regarding smoking cessation interventions among patients with stroke or TIA. An uncontrolled prospective study examining the effects of a specific smoking cessation education intervention after stroke found that at 3 months post-event 43% of smokers had quit smoking compared with the 28% of smokers previously reported in the literature as achieving cessation post event.[28] In another study, which involved in-hospital initiation of secondary stroke prevention therapies including smoking cessation, 83% of those identified as smokers at the time of the event remained smoke free at 3-month follow up.[3] In contrast, there was no improvement in smoking quit rates of patients with stroke or TIA at 3-month follow-up after a multiple risk factor modification intervention led by a stroke nurse specialist in a single-blind randomized controlled trial.[29] Given the paucity of smoking cessation trials in stroke and TIA patients, it was particularly important for study authors to investigate interventions to motivate and support cessation in this high risk population of smokers. Further research is critical to inform the design of policy and programs to address tobacco use for this population of high risk smokers.

There are several limitations to the present study which should be considered in any interpretation of the findings. Despite positive trends the pilot study was small and included only 28 participants and was not able to document a significant intervention effect over control. As such a larger trial would be required to further explore the favourable trend documented in the present study. In the present study all patients received access to: 1) standardized counselling; 2) a prescription for quit smoking medications while in clinic; 3) follow-up support for 26-weeks following their scheduled quit attempt. This may be considered an enhancement over the current

'real world' standard of care experienced by stroke and TIA patients. The inclusion of the standardized counselling supports and pharmacotherapy may have increased quit rates observed in both intervention groups. The study involved the recruitment of patients from a single stroke prevention clinic results may not be generalizable to the broader population of stroke and TIA patients in other settings. Only 40% of eligible patients screened consented to participate. Finally this pilot study provided patients in the CF group with a 4-week supply of pharmacotherapy free of cost. A full course of treatment is typically 10 to 12 weeks. Extending the availability of the cost-free pharmacotherapy might have further enhanced study outcomes.

Contributorship statement: S. Papadakis, D. Aitken, S. Gocan, R. Reid have provided substantial contributed to the conception, design, acquisition of data, analysis, and interpretation of data and drafting of article. A. Pipe, M. Sharma contributed to the conception, design, and interpretation of data and drafting of article. D. Riley, M. Laplante, A. Bhatnagar-Bost, D. Cousineau, D. Simpson, R. Edjoc contributed to the acquisition of data, interpretation of results and drafting of the article. All authors have approved the final version of the manuscript to be published.

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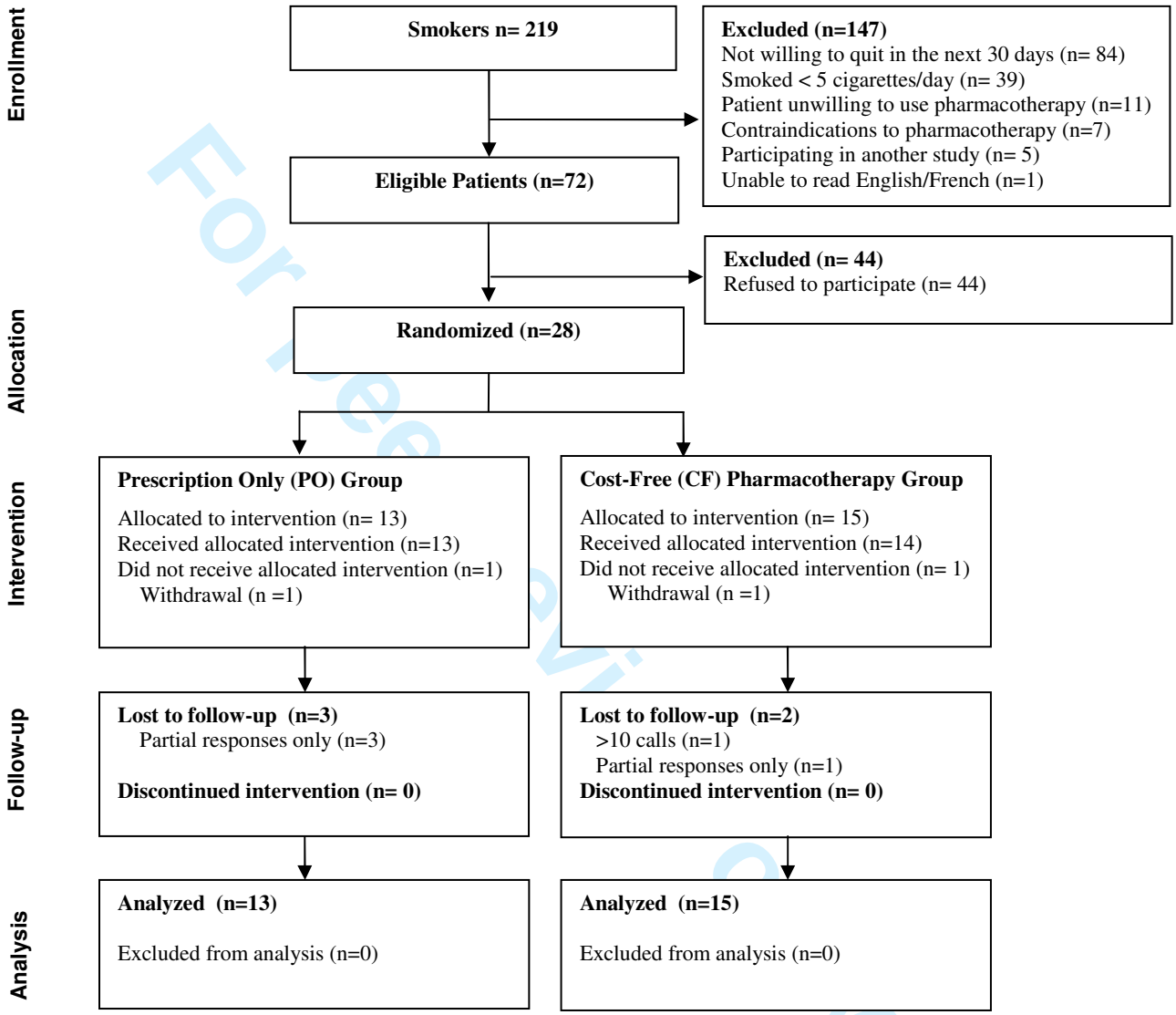
Figure 1. CONSORT (Consolidated Standards of Reporting Trials) Diagram



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	n/a – pilot study
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	5 and 6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8 and 9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17 and 18
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	18
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	19 and 20
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	23
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	UOHI2010-1 Clinicaltrials.gov
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	No funder

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ open

A randomized controlled pilot study of standardized counselling and cost-free pharmacotherapy for smoking cessation among stroke and TIA patients

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A randomized controlled pilot study of standardized counselling and cost-free pharmacotherapy for smoking cessation among stroke and TIA patients

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Word Count: 3905 (main body and tables)

ABSTRACT

BACKGROUND: Tobacco use is a major risk factor for recurrent stroke. The provision of cost-free quit smoking medications has been shown to be efficacious in increasing smoking abstinence in the general population. Very few studies have been performed to support smoking cessation among patients who have experienced a stroke or TIA.

OBJECTIVE: The objective of this pilot study was to assess the feasibility and obtain preliminary data on the effectiveness of providing cost-free quit smoking pharmacotherapy and counselling to smokers identified in a stroke prevention clinic.

TRIAL DESIGN: Cluster randomized controlled trial.

METHODS: All patients seen at the Ottawa Hospital Stroke Prevention Clinic who smoked more five or more cigarettes per day, were ready to quit smoking in the next 30 days, and willing to use pharmacotherapy were invited to participate in the study. All participants were advised to quit smoking and treated using a standardized protocol including counselling and pharmacotherapy. Participants were randomly assigned to either a prescription only usual care group, or, the experimental group who received a 4-week supply of cost-free quit smoking medications and prescription for medication renewal. All patients received follow-up counselling 7-days prior to and 5, 14, 30, 60, 90, 180 days following their quit attempt. The primary outcome was bio-chemically validated quit rates at 26-weeks. Secondary outcomes included compliance with the intervention including adherence to the medication and participation in telephone follow-up counselling. The research coordinator conducting outcome assessment was blind to group allocation.

RESULTS: Of 219 smokers screened, 73 were eligible, 28 consented and were randomized, and 25 completed the 26-week follow-up assessment. All 28 patients randomized were included in

the analysis. The bio-chemically validated 7-day point prevalence abstinence rate in the experimental group compared to usual care group was 26.6% vs. 15.4%, adjusted Odds Ratio (OR) 2.00, 95% CI 0.33, 13.26, p=.20.

CONCLUSIONS: This pilot study provides preliminary data to inform the design of larger study to assess the efficacy of providing cost-free quit smoking medications to smokers with TIA and stroke. The study was underpowered to achieve statistically significant results. It would be feasible to definitively evaluate this intervention in a large multi-site trial.

Source of funding: No external funding. In-kind support from academic institutions.

Trial Registration: ClinicalTrials.gov # UOHI2010-1~~UOHI-01~~

Word Count: 350

ARTICLE SUMMARY

Providing stroke and TIA patients with cost-free quit smoking medications accompanied with counselling resulted in 26.6% of participants reporting a bio-chemically validated 7-day point prevalence abstinence rate compared to 15.4% in the control group, adjusted odds ratio (OR) 2.00, 95% CI 0.33, 13.26, p=.20. This pilot study was not powered to detect significant differences between groups. The results of this pilot study suggest it would be feasible to definitively evaluate this intervention in a large multi-site trial.

INTRODUCTION

Cigarette smoking is a major independent risk factor for recurrent stroke and has been identified as an important treatment target for all patients at high risk of future stroke.[1-4] Stroke and transient ischemic attack (TIA) patients who quit smoking reduce their relative risk of stroke recurrence by 50%.[5] Smoking cessation is also associated with a reduction in stroke related hospitalizations.[6,7] Unfortunately most smokers with cerebrovascular disease have difficulty quitting on their own. Previous research has documented that approximately 80 to 90% of stroke and TIA patients identified as smokers at the time of their event continued to use tobacco six to 12-months later.[8-10]

Evidence from placebo-controlled clinical trials consistently demonstrates that cessation medications such as nicotine replacement therapy, bupropion and varenicline combined with counselling, can double or triple long-term smoking abstinence in smokers.[11-13] Consequently stroke prevention guidelines recommend that healthcare providers strongly advise every smoker who is at high risk for a stroke or TIA to quit, and provide specific assistance with quitting including counselling and pharmacotherapy.[14,15] Despite the evidence supporting the importance of smoking cessation, there is a well documented practice gap in the rates at which smoking cessation is addressed by healthcare professionals, even for high-risk groups such as TIA patients and/or stroke survivors.[8-10]

Sub-optimal use of evidence-based quit smoking medications and pre-mature discontinuation of pharmacotherapy has been linked to poorer rates of smoking abstinence.[16,17] Although reasons for poor adherence are varied financial barriers are a major determinant on non use and

non-adherence.[18,19] The provision of cost-free medications has been shown to improve motivation to quit and increase quit attempts and smoking abstinence in the general population; no study, however, has examined the efficacy of providing cost-free cessation pharmacotherapy to patients who have recently experienced a TIA or stroke or are at high risk for stroke.[20-23]

Given that high incidence of stroke has been reported among lower socioeconomic groups, it is hypothesized that making cost-free medications available to patients who receive standardized smoking cessation intervention will enhance patient quit attempts, remove barriers related to cost of pharmacotherapy, and enhance compliance with the full course of pharmacotherapy among patients and lead to increased success with quitting.[24,25] The low quit rates documented among patients who experience TIA or stroke, supports the need to understand the efficacy of interventions which may enhance cessation in this high risk group of smokers.[8-10] Moreover, the high risk of a recurrent event among stroke patients who continue to smoke suggests the cost-benefit of providing cost free pharmacotherapy may be realized in a relatively short time frame which may justify providing coverage to this group of high risk smokers.[6] As such the purpose of this pilot study was to test the feasibility and obtain effect estimates to inform the design of a larger definitive study on the effectiveness of providing cost-free quit smoking pharmacotherapy and counselling to smokers identified in a speciality stroke prevention clinic compared to the provision of a conventional prescription for pharmacotherapy.[26]

METHODS

Design

This pilot study was a two-group, open label, experimental feasibility study with random assignment to either the prescription-only usual care group (PO Group) or the cost-free quit smoking medications group (CF Group). The primary outcome was bio-chemically validated quit rates at 26 weeks. Secondary outcome measures included patient quit attempts at 26 weeks and adherence to quit smoking counselling and pharmacotherapy protocols. Levels of eligibility, consent, adherence and retention were used as indicators of study feasibility. The study protocol was approved by the University of Ottawa Heart Institute Human Research Ethics Board.

Setting and Patient Population

Patients were recruited from The Ottawa Hospital Stroke Prevention Clinic, Ottawa, Ontario, Canada over an 18-month period. The clinic provides assessment and secondary prevention services to patients who have recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event.

Sample Size

It was estimated that a total of 70 patients would be enrolled over the 18 month recruitment period based on the assumption that 200 smokers were seen at the clinic in the previous year and 25% were estimated to be eligible and willing to participate. It was hypothesized that a 5 to 10% increase in smoking abstinence would be documented in the CF group compared to the PS group based on trials in the general population.[20-23] It was understood that the trial would not be powered to detect significant differences between groups.

Standardized Smoking Cessation Protocol

As part of the study a systematic approach to the identification and treatment of patients who smoke was introduced into routine clinic practice at the Stroke Prevention Clinic; the protocol was based on the Ottawa Model for Smoking Cessation.[27,28] The nurse specialists and neurologists providing care in this setting were provided with training session in evidence-based smoking cessation interventions. Patient and provider tools and resources, adapted from the Ottawa Model for Smoking Cessation, were introduced in the Stroke Clinic to facilitate and support the standardized delivery of tobacco treatment. This included a waiting room screener, consult form to support clinicians in the delivery of cessation interventions, and a quit plan for patients ready to quit smoking.

The waiting room screener which assessed current smoking status was distributed to all patients upon registration at the clinic. Patients were instructed to return the waiting room screener to the clerk when completed. The screening nurse used the results obtained in the screening process to flag all patient charts indicating whether the patient was a smoker or non-smoker. A smoking cessation consult form was placed on the chart of each patient identified as a smoker by the clerk and served as a prompt to the neurologist for delivering evidence-based smoking cessation interventions. The neurologist then provided strong, unambiguous, non-judgemental advice to quit to all smokers along with an offer of support with making a cessation attempt. The neurologist also assessed patient readiness to quit in the next 30 days, documented patient response on the consult form.

Eligibility Screening

Patients were eligible to participate in the study if they reported smoking an average of 5 or more cigarettes per day in past 3 months; were 18 years of age or older; were willing to set a quit date in the next 30 days; and were willing to use a quit smoking medication. Patients who were unable to read and understand English or French or who had contraindications to all approved smoking cessation medications (nicotine replacement therapy, bupropion, and varenicline) were excluded from the study. Eligible patients were invited by the neurologist or the stroke prevention nurse-specialist to take part in the study. Eligible patients interested in participating in the study had the study procedures explained to them by the research study coordinator. All participants provided informed consent.

Allocation to Treatment

Patients were randomly assigned to one of two intervention groups. The research coordinator or clinic nurse specialist opened a sealed envelope which contained the treatment group allocation. Randomization envelopes were prepared by a third party using a random numbers table blocked in groups of four and sealed until treatment allocation. Due to the nature of the intervention, participants and clinicians were not blinded to their intervention assignment.

Comparison Groups

Cost-Free Pharmacotherapy Experimental Group (CF Group)

Participants assigned to the CF group received a starter kit (4-week supply) of cost-free quit smoking medication (nicotine replacement therapy, bupropion, or varenicline) and a pre-printed prescription to be filled by the patient at the end of the 4-weeks.

Prescription Only Usual Care Group (PO Group)

Participants assigned to the prescription only usual care group received a prescription for smoking cessation pharmacotherapy to be filled at their own cost at their local community pharmacy.

Patient Quit Plan Consultation and Telephone Follow-up Support

The stroke prevention nurse specialist conducted a 10 to 20 minute consultation with all study participants using a standardized consult form and patient education materials. During the consult the nurse specialist addressed patient concerns about quitting, set a target quit date (TQD) with the patient in the next 30 days, developed strategies for addressing cravings and withdrawal, and identified strategies for relapse prevention and management. Patients were then prescribed a first-line quit smoking pharmacotherapy. The choice of the pharmacotherapy was based on patient preference and smoking history. All study participants were contacted by phone by a trained smoking cessation counsellor 7 days before their TQD, and 5, 14, 30, 90, and 180 days after to discuss the patient's quit smoking progress, address potential concerns, and assist with relapse prevention strategies and management. During the call, the smoking cessation nurse specialist posed a series of questions concerning: current smoking status; confidence in staying smoke-free until the next planned call; and the use of pharmacotherapy, self-help materials, and other forms of cessation support.

Post-assessment and follow-up data collection

All participants were contacted by telephone 26 weeks (+/-2 weeks) after their TQD to assess outcome measures. All patients reporting smoking abstinence had an end-expired carbon monoxide (CO) sample collected in order to validate smoking abstinence.

Outcome Measures

The dependent variables of primary interest were measured at 26 weeks and included: (1) bio-chemically confirmed 7-day point prevalence abstinence; and (2) continuous abstinence since TQD. Participants who were not available for follow-up were considered smokers. At the 26 week follow-up, all patients who reported being abstinent from smoking had their smoking status confirmed by measurement of a CO sample. If any CO was >10 ppm, the subject was considered a smoker. At the 26 week follow-up assessments patient quit attempts in the previous six months of 24 hours or longer were documented. During the 26-week telephone follow-up assessment patient adherence with pharmacotherapy was assessed by evaluating the number of doses of pharmacotherapy consumed within the prescribed study interval. The telephone counsellor recorded the completion of all seven counselling sessions in order to assess patient adherence.

Analysis

Descriptive characteristics were assessed for all smokers screened at the stroke prevention clinic during the recruitment period. Baseline characteristics of study participants assigned to each of the intervention groups were compared using independent t-tests for continuous variables and chi-square tests for categorical variables to assess any chance imbalances that may have occurred. A logistic regression model was 'fitted' to 26-week abstinence status (smoker or non-smoker) and treatment group included as the independent variable. Adjusted analyses were conducted to account for baseline differences between groups. Treatment adherence and patient quit attempts were also compared between treatment groups. All patients were included in the intention to treat analysis. Missing data was categorized as active smoking (smoking

abstinence), not having made a quit attempt (quit attempts), or non-compliant with medications (adherence).

RESULTS

Participant recruitment and data collection

Figure 1 presents the CONSORT diagram for data collection flow. A total of 2182 patient visits occurred at the Stroke Prevention Clinic between August 2008 and December 2009 and 219 unique patients were identified as having used tobacco in the last seven days. Table 1 provides a summary of the characteristics of all patients screened at the Stroke Prevention Clinic who reported active smoking during the study recruitment period. At the initial screening seventy four percent of smokers reported they were planning on quitting smoking within the next 6-months and thirty-six percent were planning on quitting in the next 30 days. One hundred and forty-seven patients who smoked did not meet eligibility criteria. The primary reason for exclusion was the patient not being willing to quit smoking in the next 30 days and smoking less than an average of five cigarettes per day. An additional fourteen patients were not willing to use pharmacotherapy. Among eligible patients 29/73 (40%) agreed to participate in the study. Study participants were more likely than non-participants to be younger, smoke a greater number of cigarettes per day, more likely to be concerned about withdrawal and stress, and less concerned about boredom. Two study participants withdrew from the study. Twenty-six week follow-up data was completed for 25/28 (89%) of study participants. There were no significant differences in the loss to follow-up between intervention groups.

Participant Characteristics

A total of 28 eligible smokers (mean age 54.5±10.5 years, 70% male) were enrolled in the pilot study. The characteristics of study participants are presented in table 1. CF participants reported smoking significantly more cigarettes per day as well as significantly greater self-efficacy (confidence) with quitting compared to participants randomized to the PO group.

Smoking Abstinence

Table 2 presents the effect estimates for smoking abstinence. Quit rates were 33.3% in CF group versus 15.4% in the PO group for 7-day point prevalence abstinence and 23.1% versus 15.4% for continuous abstinence at 26 weeks. Effect estimates were adjusted to account for the observed differences between groups. The adjusted odds ratio for self-reported continuous abstinence was 5.51; 95% CI 0.44, 69.3; p=.186 and 7-day point prevalence abstinence was 2.25; 95% CI 0.25. 20.4; p=.470. Observed differences between groups were not statistically significant.

Bio-chemical validation of self-reported smoking abstinence was completed with 75% of patients who reported a smoke-free status at the end of 26 weeks. No differences were noted in the rate of completion of the bio-chemical validation at the pre- and post-intervention assessments nor were differences noted between CF and PO intervention groups (26.6% vs. 15.4%). The adjusted odds ratio for bio-chemically validated 7-day point prevalence abstinence was 5.95 (95% CI 0.40. 88.7; p=.195), the observed differences between groups were not significant.

Table 1. Characteristics of smokers screened and study participants

Parameter	Smokers Screened (n=219)	Eligible Non Participants (n=44)	Study Participants (n=28)	PO Group (n=13)	CF Group (n=15)	*p*-value*
Age, mean (SD)	55.4(12.8)	59.4(9.8)	54.5(10.5)	53.5(8.1)	55.4(12.4)	.65
% Male	48.8	61.4	60.7	69.2	53.3	.39
Years of education, mean (SD)	12.1(3.1)	11.6(4.2)	11.7(3.4)	12.9(2.3)	10.6(4.0)	.08
Cigarettes/day, mean (SD)	15.1(10.4)	16.9(10.6)	17.5(8.0)	20.7(8.8)	14.8(6.2)	**.05**
Years smoking cigarettes, mean (SD)	33.3(15.0)	34.7(13.6)	34.6(14.5)	32.5(15.1)	36.4(14.1)	.49
Time to first cigarette						
% Within 30 minutes of waking	67.3	72.2	78.5	77.0	80.0	.87
% more than 30 minutes after waking	32.7	27.8	21.5	23.0	20.0	
Confidence (SD)[*]	5.4(3.3)	6.1(3.4)	6.2(3.1)	5.0(3.2)	7.3(2.6)	**.05**
Importance of quitting (SD)[†]	7.2(3.3)	7.5(3.2)	8.3(2.4)	8.6(2.7)	7.9(2.3)	.47
Quit Attempts						
None	41.3	53.2	35.7	30.8	40.0	.78
1 to 2	36.0	18.4	39.3	46.2	33.3	
3 or more	22.7	26.3	25.0	23.1	26.7	
Readiness to quit at initial screening[‡]						
Next 30 days	40.4	54.5	70.4	84.6	57.1	.12
Next 6-months	59.6	45.5	29.6	15.4	42.9	
Other smoker in the home	45.3	51.3	46.4	53.8	40.0	.35
Medication coverage						
Yes	18.2	15.9	32.1	38.5	26.7	.62
No	49.4	45.4	32.1	23.1	40.0	
Don't know	32.4	38.7	35.7	38.5	33.3	
HADS Score[‡‡]						
Anxiety, mean (SD)	-	-	7.0(3.8)	6.8(3.8)	7.1(3.9)	.88
Depression, mean (SD)	-	-	5.1(4.1)	5.5(2.8)	4.7(4.9)	.64
Reasons for quitting						
Health reasons	81.9	77.8	93.1	92.3	93.8	.88
Family	20.6	16.7	34.5	38.5	31.3	.68
Financial	20.5	19.4	20.7	23.1	18.8	.78
Social	11.9	11.4	13.8	15.4	12.5	.82
Concerns about quitting						
Stress	53.3	43.2	62.1	46.2	75.0	.11
Withdrawal	35.3	38.6	48.3	53.8	43.8	.59
Weight	29.4	25.0	37.9	38.5	37.5	.96
Boredom	18.2	13.6	24.1	23.1	25.0	.90
Social	9.6	9.1	3.4	0.0	6.3	.36

PO, Prescription only; CF, Cost-Free Pharmacotherapy; HADS, Hospital Anxiety and Depression Scale

**Comparisons are based on the Pearson chi-square test for categorical variables and Student's t-test for continuous variables between intervention groups.*

[**] *On a scale of 1 to 10 how confident are you that you would be able to quit smoking at this time? (1=not at all confident, 10=extremely confident)*

[†] *On a scale of 1 to 10 how important is it to you to quit smoking at this time? (1=not important at all, 10=*extremely important)

[‡]Response provide on the waiting room screener to the question "Which of the following best describes your feelings about smoking right now?" Patients readiness to quit was reassessed following neurologists strong personalized advice to quit.

[‡‡]HADS scores: 0-7 = normal; 8-10 = borderline abnormal; 11-21 = abnormal[29]

Table 2. 26-week Smoking Abstinence

6-month abstinence measure	PO Group n/N (%)	Cost-Free Group n/N (%)	Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI) †	*p*-value†
Continuous abstinence	2/13 (15.4)	5/15 (33.3)	2.75 (0.43, 17.5)	.26	5.51 (0.44, 69.3)	.19
7-day point prevalence abstinence	3/13 (23.1)	5/15 (33.3)	1.67 (0.31, 8.9)	.43	2.25 (.25, 20.4)	.47
Bio-chemically validated 7-day point prevalence abstinence	2/13 (15.4)	4/15 (26.6)	2.00 (0.33, 13.3)	.40	5.95 (0.40, 88.7)	.20

PO, Prescription only; CF, Cost-Free Pharmacotherapy; CI, Confidence Interval

†Adjusted for number of cigarettes smoked per day and self-efficacy

Secondary outcomes

At the 26-week follow-up assessment 62% of participants in the PO group reported making a quit attempt compared to 53% in the CF group. . Observed differences between groups for both use of quit smoking medications and compliance with the full course of medication were not statistically significant. Participants in the CF group completed a mean of 6.3/7 (91%) sessions compared to 5.5/7 (78%) of sessions in the PO group. See table 3.

Table 3. Compliance with Medications and Quit Attempts

6-month abstinence measure	PO Group n/N (%)	Cost-free Group n/N (%)	Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI) †	*p*-value†
Quit Attempts	8/13 (61.5)	8/15 (53.3)	.71 (.16, 3.2)	.66	.72 (.12, 4.5)	.72
Began using medication prescribed	8/13 (61.5)	11/15 (73.3)	1.7 (.35, 8.5)	.51	.44 (.03, 5.9)	.54
Compliance with Medication, >90%	4/13 (30.7)	7/15 (46.7)	2.0 (.42, 9.3)	.39	2.2 (.35, 14.5)	.40
Compliance with Telephone Counselling, >80%	8/13 (61.5)	14/15 (93.3)	8.7 (0.9, 88.7)	.07	4.2 (.32, 58.9)	.28

PO, Prescription only; CF, Cost-Free Pharmacotherapy; CI, Confidence Interval

†Adjusted for number of cigarettes smoked per day and self-efficacy

DISCUSSION

To our knowledge this is the first study to evaluate the efficacy of providing a starter kit of cost-free pharmacotherapy to patients at high risk of stroke who are ready to quit smoking. Observed differences between intervention groups for both the primary and secondary study outcomes were non-significant, as such, a larger trial would be required to assess intervention efficacy. This pilot study found the study methods to be feasible and has provided previously unavailable data which will be used to inform sample size estimates for the design of a larger definitive trial. The study documented a much lower eligibility and participation rate than was originally hypothesized. Given that only 40% of eligible smokers enrolled in the study suggests considerations must be given to interventions to increase patient enrolment in future investigations.

While there have been no trials to evaluate the efficacy of providing cost-free quit smoking medications to stroke or TIA patients, studies in the general population have found that the provision of a cost-free smoking cessation medications increases patient motivation to quit, quit attempts, and smoking abstinence.[20-23] A systematic review including three trials examining the benefit of covering the cost of smoking cessation treatment (primarily the cost of pharmacotherapy) found that cost-free treatment increased the odds of achieving abstinence (OR = 1.6; 95% CI 1.2 to 2.2) compared to having smokers pay for their own treatment.[11,30] One additional trial, completed after the meta-analysis described above was published, found that providing cost-free effective smoking cessation pharmacotherapies to smokers in primary care increased the odds of quitting 12 months after recruitment almost 5-fold (OR = 4.77; 95% CI 2.0 to 11.2).[23] In the present study fifteen percent of smokers screened had completed a university

degree compared to 25.5% of smokers in the general population.[31] Moreover, only eighteen percent of smokers screened had insurance coverage for quit smoking medications. This data supports the hypothesis that financial barriers may influence decisions to use pharmacotherapy among patients who have experienced TIA or stroke. Given the significant acute health benefits derived from smoking cessation among TIA and stroke patients it would appear that this intervention program may be of particular significance to reducing disease burden and improving stroke outcomes.

Our investigation identified that a large proportion of smokers screened as part of the present study were not ready to quit smoking in the thirty days following their visit to the Stroke Prevention Clinic. The reported rates are lower than that observed in the general population despite the presence of a teachable moment resulting from their health event.[11, 16] This would suggest the possibility that smokers identified in the stroke prevention setting represent a "hardened" population of smokers i.e. those with higher levels of nicotine addiction and lack of interest in cessation.[32] This is reflected by the proportion of high risk patients who were not interested in embarking upon a quit attempt in the next 30 days following strong clinician advice, and the fact that more than 65% of patients sampled reported time to first cigarette in the morning to be within 30 minutes of waking. Interestingly, thirty percent of the study sample had indicated on the waiting room screener that they were not ready to quit in the next 30 days. Following standardized counselling from the clinic physician, however, these patients decided to quit smoking and were randomized to the trial. Additional research is required to better understand the lack of intentions among stroke and TIA patients to make a quit attempt and how

best to motivate and/or support increased patient motivation to quit and/or harm reduction interventions such as reduce to quit (RTQ) approaches.

There has been very limited research published regarding smoking cessation interventions among patients with stroke or TIA. An uncontrolled prospective study examining the effects of a specific smoking cessation education intervention after stroke found that at 3 months post-event 43% of smokers had quit smoking compared with the 28% of smokers previously reported in the literature as achieving cessation post event.[33] In another study, which involved in-hospital initiation of secondary stroke prevention therapies including smoking cessation, 83% of those identified as smokers at the time of the event remained smoke free at 3-month follow up.[3] In contrast, there was no improvement in smoking quit rates of patients with stroke or TIA at 3-month follow-up after a multiple risk factor modification intervention led by a stroke nurse specialist in a single-blind randomized controlled trial.[34] Given the paucity of smoking cessation trials in stroke and TIA patients, it was particularly important for study authors to investigate interventions to motivate and support cessation in this high risk population of smokers.

There are several limitations to the present study which should be considered in any interpretation of the findings. Despite positive trends the pilot study was small and included only 28 participants and was not able to document a significant intervention effect over control. As such a larger trial would be required to further explore the favourable trend documented in the present study. In the present study all patients received access to: 1) standardized counselling; 2) a prescription for quit smoking medications while in clinic; 3) follow-up support for 26-weeks

following their scheduled quit attempt. This may be considered an enhancement over the current 'real world' standard of care experienced by stroke and TIA patients. The inclusion of the standardized counselling supports and pharmacotherapy may have increased quit rates observed in both intervention groups. The study involved the recruitment of patients from a single stroke prevention clinic, as such, study findings may not be generalizable to the broader population of stroke and TIA patients in other settings. Only 40% of eligible patients screened consented to participate. Finally this pilot study provided patients in the CF group with a 4-week supply of pharmacotherapy free of cost. A full course of treatment is typically 10 to 12 weeks. Extending the availability of the cost-free pharmacotherapy might have further enhanced study outcomes.

Contributorship statement: SP, DA, SG, RR have provided substantial contributed to the conception, design, acquisition of data, analysis, and interpretation of data and drafting of article. AP, MS contributed to the conception, design, and interpretation of data and drafting of article. DR, ML, AB, DC, DS, RE contributed to the acquisition of data, interpretation of results and drafting of the article. All authors have approved the final version of the manuscript to be published.

Competing Interests: The institutions and study authors at no time received payment or services from a third party for any aspect of the work submitted. The UOHI has received research and education grant support from Pfizer Canada, Johnson and Johnson, and Glaxo Smith Kline. AP: consultant and received speaker honoraria from Pfizer, Johnson and Johnson, and Glaxo Smith Kline; RR: speaker honoraria from Pfizer; DA: speaker honoraria from Pfizer; DR: has served as consultant to Pfizer.

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Data sharing statement: The study database including participant characteristics and outcomes has been uploaded to the Dryad Digital Repository. doi:10.5061/dryad.p67jf576

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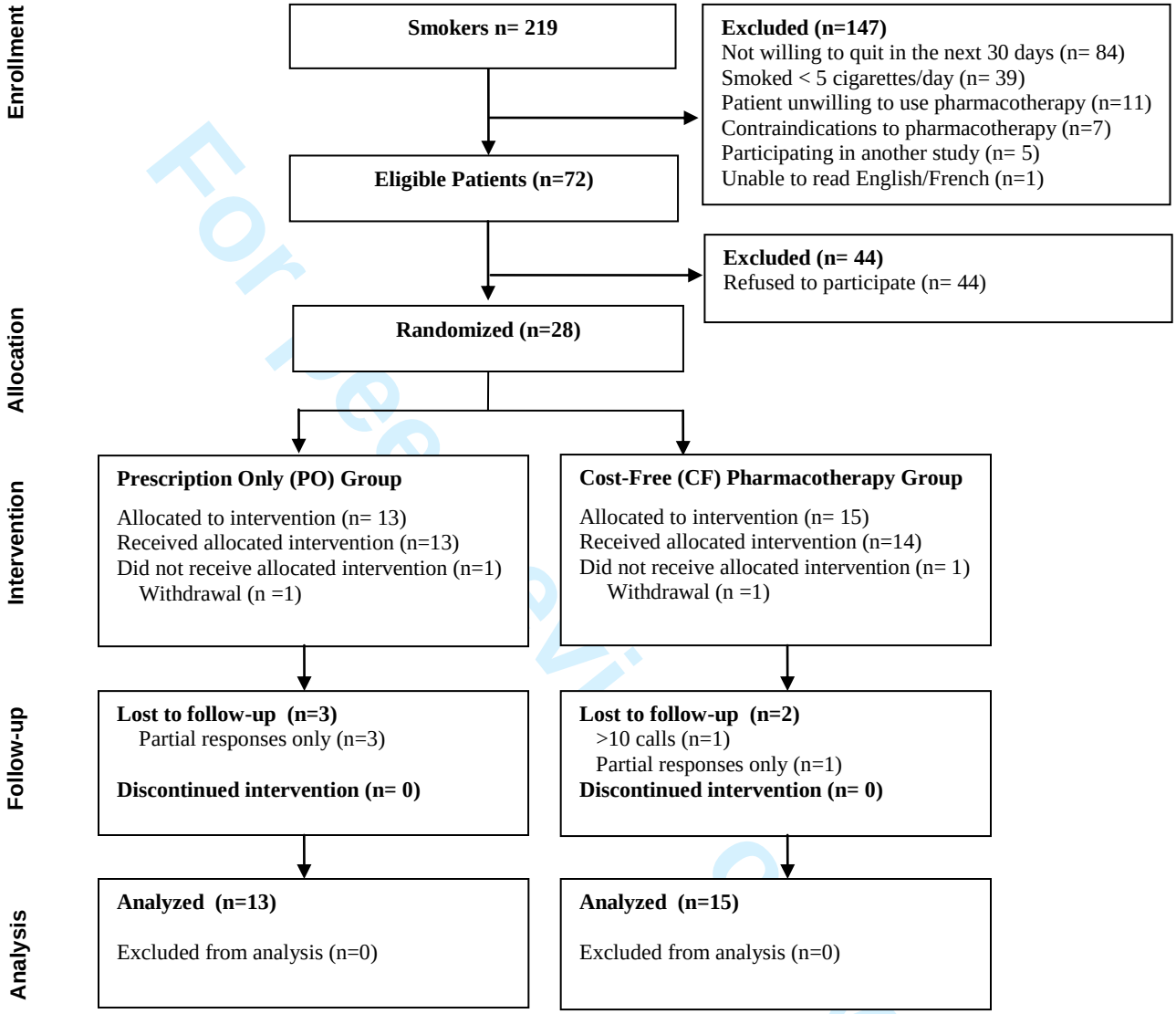
Figure 1. CONSORT (Consolidated Standards of Reporting Trials) Diagram



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	n/a – pilot study
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	5 and 6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8 and 9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17 and 18
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	18
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	19 and 20
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	23
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	UOHI2010-1 Clinicaltrials.gov
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	No funder

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.