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Effectiveness of pharmacotherapy for smoking cessation in the general population: Duration of use matters

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ABSTRACT

Aim: To investigate the association of the duration of use of prescription medications and nicotine replacement therapy (NRT) with smoking cessation using a national sample of the general population in the United States, controlling for nicotine dependence and sociodemographic variables.

Methods: We used data from the 2010-2011 Tobacco Use Supplement to the US Current Population Survey. We limited the analysis to current daily smokers who made a quit attempt in the past year and former smokers who were a daily smoker one year prior to the survey (n = 8 263). Respondents were asked about duration of use of prescription medication (Varenicline, Bupropion, other) and NRT (nicotine patch, gum/lozenges, nasal spray, and inhaler) for smoking cessation.

Results: After adjusting for daily cigarette consumption and sociodemographic covariates, we found overwhelming evidence ($p < 0.001$) for an association between duration of pharmacotherapy use and smoking cessation. Adjusted cessation rates for those who used prescription medication or NRT for 5+ weeks were 28.8% and 27.8%, respectively. Adjusted cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Adjusted cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

Conclusion: Pharmacotherapies for smoking cessation can be effective in the general population if used for at least five weeks. Encouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation.

ARTICLE SUMMARY

Strengths and limitations of the study:

- This was the first population-based study to examine the duration of use of prescription medication as well as NRT for smoking cessation as a predictor of successful smoking cessation, controlling for nicotine dependence and sociodemographic variables.
- A strength of this study was that it used a large nationally representative sample with a relatively high response rate.
- Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids could also be effective in the general population if they are used for at least five weeks.
- Recall bias, especially related to the smokers previous quit attempts and the observational nature of the study precluding the establishment of a causal link were between the duration of pharmacotherapy use and successful smoking cessation, were the major limitations of this study.

INTRODUCTION

Clinical trials provide strong evidence that pharmacotherapy for smoking cessation including various forms of nicotine replacement therapies (NRT), Bupropion, or Varenicline greatly increase the chances of a successful smoking cessation attempt.[1, 2] However, observational population-based studies have shown mixed results. While some have shown that pharmacotherapy increases smoking cessation rates,[3-6] others have concluded the opposite.[7-11] Yet, other population-based studies have shown no difference in cessation rates between those who use and those who do not use pharmacotherapy.[12, 13] The population-based reports that have found no favorable effect of pharmacotherapy have been criticized for not controlling for nicotine dependence,[14-16] which is a predictor of abstinence and is usually higher among smokers who choose to use pharmacotherapy for smoking cessation.[4, 14, 17, 18] Some of the analyses that have controlled for nicotine dependence have found a favorable effect of pharmacotherapy on smoking cessation[3, 4, 19] but others have not.[7]

An additional confounder that rarely is taken into account in population-based studies is duration of use of pharmacotherapy, which has been found to be associated with treatment success in clinical trials.[20-22] We know of one population-based study which examined the association of duration of use of pharmacotherapy with smoking cessation and found no association.[12] This study was conducted in the US where NRT can be purchased over the counter and medications such as Bupropion and Varenicline can only be obtained as prescription drugs.

While clinical trials have high internal validity and can provide evidence for the efficacy of pharmacotherapy, observational population-based studies can address effectiveness of these

therapies under conditions that they are intended to be used.[14] Furthermore, while clinical trials provide confidence in causal associations, population-based studies are strong in representativeness and external validity. Thus, both are needed to advance the science of smoking cessation.[19]

There is no literature on population-based studies that examine the association of duration of NRT and prescription medication use with smoking cessation. Our aim was to use a large representative sample of the general population in the United States and investigate the association of the duration of use of prescription medications and NRT with smoking cessation, controlling for nicotine dependence and sociodemographic variables.

METHODS

Data

We used data from the 2010-2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), sponsored by the National Cancer Institute and administered by the US Census Bureau in May 2010, August 2010, and January 2011.[23] The TUS-CPS is administered as a part of the CPS, which is a monthly national survey of representative households by the US Census Bureau and the Bureau of Labor Statistics.[24] The TUS-CPS utilizes a multistage probability sampling of individuals 15 years and older, from a sample of approximately 56,000 housing units, in turn selected from 792 primary sampling units. The average response rate for CPS for the 3 months of surveys used in this study was 93%, whereas for the TUS it was 63%.

Measures

Successful smoking cessation:

Individuals who reported to have smoked at least 100 cigarettes in their entire life but were not smoking at all at the time of the interview were considered to have successfully quit

smoking (n = 1 769). Those who reported to have quit within the last four weeks were excluded from the analysis (n = 322). Individuals who reported to have smoked at least 100 cigarettes in their entire life, were smoking every day at the time of the interview and had made a quit attempt in the past year were considered to have failed in their quit attempt (n = 7 304). Individuals who reported to have used both prescription medication and NRT for smoking cessation were excluded from the analysis (n = 488) because after subdividing this group by categories of duration of use for prescription medication and NRT, some of the subgroup sample sizes were extremely small. The total sample size for the study was 8 263 respondents, consisting of 1 379 who successfully quit smoking and 6 884 whose quit attempt was not successful.

Assisted quit attempt and duration of pharmacotherapy use:

Both daily and former smokers were asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used a prescription pill called (a) Chantix or Varenicline, (b) Zyban, Bupropion, or Wellbutrin, or (b) other prescription pills. They were also asked in three separate questions to indicate whether, in their last quit attempt, they used (a) a nicotine patch, (b) nicotine gum or nicotine lozenge, or (c) nicotine nasal spray or nicotine inhaler. They were also asked to indicate how many days, weeks or months they used these prescription and/or NRT medications. Furthermore, both daily and former smokers were asked three separate questions about use of behavioral counseling in their last quit attempt in the past year. They were asked if they used a (a) telephone helpline or quitline, (b) one-on-one counseling or (c) stop smoking clinic, class or support group. Based on the questions about use of prescription medication, NRT and behavioral counseling, we created the following two categorical variables:

Method of quit attempt

- Prescription medication only
- Prescription medication and behavioral counseling
- NRT only
- NRT and behavioral counseling
- Behavioral counseling only
- Unassisted

Duration of use of pharmacotherapy

- Prescription medication: 5+ weeks
- Prescription medication: 3-4 weeks
- Prescription medication: 1-2 weeks1
- NRT: 5+ weeks
- NRT: 3-4 weeks
- NRT: 1-2 weeks
- Behavioral counseling only
- Unassisted

We categorized duration of use of pharmacotherapy based on a systematic review of studies assessing adherence to smoking cessation medication.[20] In categorizing duration of use, we made no distinction between whether or not the medication was combined with behavioral counseling as this distinction was inconsequential in the analysis.

Statistical analysis

We used multivariable logistic regression models to compute adjusted odds ratios for the association of the method of quit attempt and duration of use of pharmacotherapy with

successful smoking cessation. Sampling weights were taken into account in the computation of parameter estimates. We computed *p*-values using the jackknife, which is an unbiased estimator for a statistic and a data-dependent method to calculate standard errors.[25] All models controlled for daily cigarette consumption (current daily consumption among daily smokers, and daily consumption 12 months ago among former smokers), age, race/ethnicity, education, occupation, and family income. In order to account for the missing income data, CPS uses one of the three imputation methods, relational imputation, longitudinal edits, or hot deck allocation. Details of these methods are described elsewhere.[26] In multivariable logistic regression models, we omitted observations that had a missing value for any of the covariates. This constituted 1.7% of the full sample in the analysis pertaining to the method of quit attempt (n = 142) and 6.3% of the full sample in the analysis pertaining to duration of pharmacotherapy use (n = 491). We used the logistic regression results to compute adjusted cessation rates by method of quit attempt and duration of use of pharmacotherapy. These adjusted rates were computed by fixing covariates at their means in the fitted models.[27]

RESULTS

Sample characteristics and bivariate associations

Table 1. Weighted sample characteristics and unadjusted smoking cessation rates across categories of each covariate

Variable	% in sample	% quit	*p*- value
Method of quit attempt			0.074
Prescription only	10.01	18.54	
Prescription plus behavioral support	1.14	23.8	
NRT only	18.26	14.32	
NRT plus behavioral support	2.54	18.98	
Behavioral only	1.36	18.59	
Unassisted	66.68	17.16	
Duration of pharmacotherapy use			<0.001
Prescription: 5+ weeks	4.9	34.38	
Prescription: 3-4 weeks	1.43	16.82	
Prescription: 1-2 weeks	1.89	15.28	
NRT: 5+ weeks	6.04	30.65	
NRT: 3-4 weeks	1.48	19.9	
NRT: 1-2 weeks	13.48	7.36	
Behavioral only	1.42	18.59	
Unassisted	69.36	17.16	
Cigarettes per day			<0.001
0-9	24.48	15.08	
10-14	30.04	12.58	
15-19	10.31	12.58	
20-29	29.23	21.83	
30+	5.93	29.59	
Sex			0.975
Female	50.12	16.99	
Male	49.88	17.02	
Age			< 0.001
18-24	11.79	15.32	
25-39	33.08	18.17	
40-54	32.33	14.49	
55+	22.8	19.77	
Race/Ethnicity			0.003
Non-Hispanic White	76.17	17.99	
Non-Hispanic Black	11.34	12.98	
Hispanic	7.39	15.73	
Other	5.09	13.15	
Education			<0.001
Less than high school	15.25	13.15	
High school diploma	73.34	16.74	
Bachelor's degree	11.41	23.91	
Occupation			<0.001
Professional	14.33	20.99	
Service	12.31	13.96	
Sales	14.5	18.45	
Farming/construction/production	17.28	13.08	
Unemployed	12.01	13.81	
Not in labor force	29.57	19.24	
Family income			<0.001
<$25,000	36.27	13.94	
$25,000-$49,000	31.65	17.21	
$50,000-$99,000	23.86	19.63	
$100,000+	8.23	22.17	
Full sample		17.01	

Note: Sample size for each covariate varies from 7 820 to 8 263 depending on the number of missing values for that covariate.

Weighted sample characteristics are shown in Table 1. About 66.7% of the sample reported to have made an unassisted quit attempt; 10% used only prescription medication; 1.1% used prescription medication plus behavioral counseling; 18.2% used only NRT; 2.5% used NRT plus behavioral therapy; and 1.3% used only behavioral counseling. When broken down by duration of use, while most of those who used prescription medication did so for five or more weeks, the great majority of those who used NRT did so for 2 weeks or less. The reported number of cigarettes smoked per day was 14 or less for about 54.5% of the sample. Age was distributed with 11.8% of the sample under 25 years of age, 33% between 25-39 years, 32.3% between 40-54 years, and 22.8% 55 years or older. The sample was 76% non-Hispanic white, 11.3% non-Hispanic Black, 7.4% Hispanic, and 5% of other race/ethnicity. About 15.2% of the sample did not have a high school diploma, 73.3% had high school diploma, and 11.4% had at least a bachelor's degree. The distribution of family income was skewed such that over a third of the sample had an income of less than $25 000 and less than a tenth of the sample had an income of $100 000 or greater.

Table 1 also provides smoking cessation rates across categories of each covariate, indicating bivariate (unadjusted) associations between the covariates and quitting. Cessation rate was 17% in the whole sample. There was very little evidence that method of quit attempt was associated with cessation rate ($p < 0.074$). However, there was overwhelming evidence that duration of pharmacotherapy use was associated with quitting ($p < 0.001$) such that the use of prescription medication or NRT for 5+ weeks was associated with remarkably higher cessation rates compared to the use of these products for shorter durations, behavioral counseling or unassisted quit attempts. Number of cigarettes smoked per day had a curvilinear relationship with cessation such that those who smoked 0-9 cigarettes and those who smoked 20+ cigarettes per day had a higher cessation rate than others ($P < 0.001$). Age had a curvilinear relationship with cessation in that individuals in the 25-39 and 55+ age categories had notably higher cessation rates than others ($p < 0.001$). Race/ethnicity was associated with quitting such that Non-Hispanic Whites had the highest and non-Hispanic Blacks had the lowest cessation rates ($p = 0.003$). Higher socioeconomic status as measured by education, occupation, and income was associated with a higher cessation rate ($p < 0.001$ for all three indicators of socioeconomic status). Sex had no association with cessation.

Adjusted results from multivariable logistic regression models

Table 2. Adjusted[a] odds ratios and 95% confidence intervals (CI) for the association of method of quit attempt and duration of pharmacotherapy use with the probability of successful smoking cessation

	OR (95% CI)	*p*-value
Method of quit attempt (n = 8 121)		0.025
Prescription only	1.00	
Prescription plus behavioral support	1.42 (0.76-2.66)	
NRT only	0.78 (0.59-1.02)	
NRT plus behavioral support	1.17 (0.73-1.86)	
Behavioral only	1.06 (0.57-1.97)	
Unassisted	1.09 (0.87-1.37)	
Duration of pharmacotherapy use (n = 7 772)		< 0.001
Prescription: 5+ weeks	1.00	
Prescription: 3-4 weeks	0.42 (0.21-0.84)	
Prescription: 1-2 weeks	0.38 (0.22-0.66)	
NRT: 5+ weeks	0.95 (0.67-1.36)	
NRT: 3-4 weeks	0.53 (0.29-0.97)	
NRT: 1-2 weeks	0.16 (0.11-0.24)	
Behavioral only	0.47 (0.25-0.90)	
Unassisted	0.48 (0.37-0.64)	

[a] Adjusted for the effect of number of cigarettes smoked per day, sex, age, race/ethnicity, education, occupation, and family income.

Figure 1 here……

Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence of an association between quitting method and successful cessation, the adjusted results revealed some evidence of an association ($p = 0.025$). The highest cessation rate was among those who used prescription medication and behavioral counseling (20.4%) followed by those who used NRT and behavioral counseling (17.4%), attempted to quit unassisted (16.4%), used behavioral counseling only (16.1%), and those who used prescription medication only (15.3%). The lowest cessation rate was among those who only used NRT as a quitting method (12.3%).

Figure 2 here……

Table 2 also provides adjusted odds ratios for the association of duration of pharmacotherapy use with the probability of smoking cessation. Figure 2 shows the adjusted cessation rates for various durations of pharmacotherapy use. Consistent with the unadjusted results in Table 1, the adjusted results provide strong evidence ($p < 0.001$) of an association between duration of pharmacotherapy use and successful cessation. Those who used prescription medication for 5+ weeks or NRT for 5+ weeks had higher cessation rates, 28.8%

and 27.8% respectively, than others. Cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

The results pertaining to the association of other covariates with successful cessation were very similar in the multivariable regression models for method of quit attempt and duration of pharmacotherapy use. These results were consistent with bivariate associations reported above, except for the fact that there was very little evidence for an association of race/ethnicity and smoking cessation in multivariable analyses.

DISCUSSION

This is the first population-based study to examine the duration of use of prescription medication as well as NRT for smoking cessation as a predictor of successful smoking cessation. We found that using pharmacotherapy for five weeks or longer is associated with a remarkably higher probability of cessation compared to using pharmacotherapy for shorter durations, only using behavioral counseling or trying to quit unassisted.

Our findings are consistent with the results of a study of a hospital-based cessation program where participants who used NRT for 5 weeks or longer were found to have a higher cessation rate at 6-month follow-up.[28] However, our findings are not consistent with those of a population-based study which did not find any evidence that using NRT for more than 6 weeks versus not using NRT at all was associated with smoking cessation.[12] In that study, the survey response rate was low, the sample size was small and prescription medications were not examined. These factors could explain the discrepant findings.

While we found that smokers who used pharmacotherapy for at least 5 weeks have a far more favorable outcome than others, only 11% of the sample was in this group and notably about 70% of the sample did not use any pharmacotherapy for smoking cessation. Previous research indicates that barriers to the use of these cessation aids include concerns with their addictiveness, cost and side effects, as well as the belief that a treatment of any kind is not needed to quit smoking.[29-31]

A weakness of the study relates to the fact that smokers forget many quit attempts [7, 32] and they are more prone to recall attempts that used pharmacotherapy than those that did

not.[14, 17] Such recall bias can underestimate the success rate of attempts at quitting with the aid of pharmacotherapy.[17] Another limitation of the study is that because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race, education, occupation, and income, it is possible that there is residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation. Moreover, there is a possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use Varenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse.

A strength of this study was that it used a large nationally representative sample with a relatively high response rate. This was the first time that questions about the duration of pharmacotherapy use were included in the TUS-CPS. We know of no other national data on the general population that provide information on this variable. Many population-based studies of pharmacotherapies for smoking cessation have found these aids to be ineffective. It is likely that if these studies were able to account for duration of use, their findings would have been different. However, data on duration of use is not routinely collected and it would require a large sample size to provide a reliable estimate of the effect of using these medications for duration of a few weeks. Nonetheless, it would likely be an important area for further research to establish the relationship between duration of use of pharmacotherapy and successful quitting in the general population.

Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids also be effective in the general population if they are used for at least five weeks. Smokers who intend to quit should be encouraged to use pharmacotherapy and adhere to their recommended duration of use.

CONTRIBUTORSHIP STATEMENT

We assure that all authors included on a paper fulfill the criteria of authorship. All have contributed in the conception and design, analysis and interpretation of data, drafting of the article and revising it critically for important intellectual content, and final approval of the version to be published. In addition we also assure that there is no one else who fulfills the criteria but has not been included as an author. Dr. Mohammad Siahpush was instrumental in conceptualization of research study, data analysis, and writing of the initial draft of the manuscript. Raees Shaikh and Molly McCarthy contributed in the development of study, data analysis, and preparation of the results section. They also helped with writing the manuscript and editing it for final submission. Dr. Asia Sikora helped with literature review, provided inputs for the materials and method section, and contributed to writing and editing the manuscript. Dr. Melissa Tibbits was involved with literature review and data analysis and provided her inputs to the entire manuscript. Dr. Gopal Singh was involved with formulation of research study and helped in the data analysis and contributed in the writing and editing of the final manuscript.

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This work did not require or receive funding.

CONFLICT OF INTEREST STATEMENT

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) declare that no support was received from any organization for the submitted work and that there was no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, neither did we have other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL STATEMENT

No ethical approval was required for this work.

DATA SHARING STATEMENT

No additional data used or available.

FIGURE LEGENDS

Figure1: Adjusted Cessation Rate by Method of Quit Attempt

Figure2: Adjusted Cessation Rate by Duration of Pharmacotherapy Use

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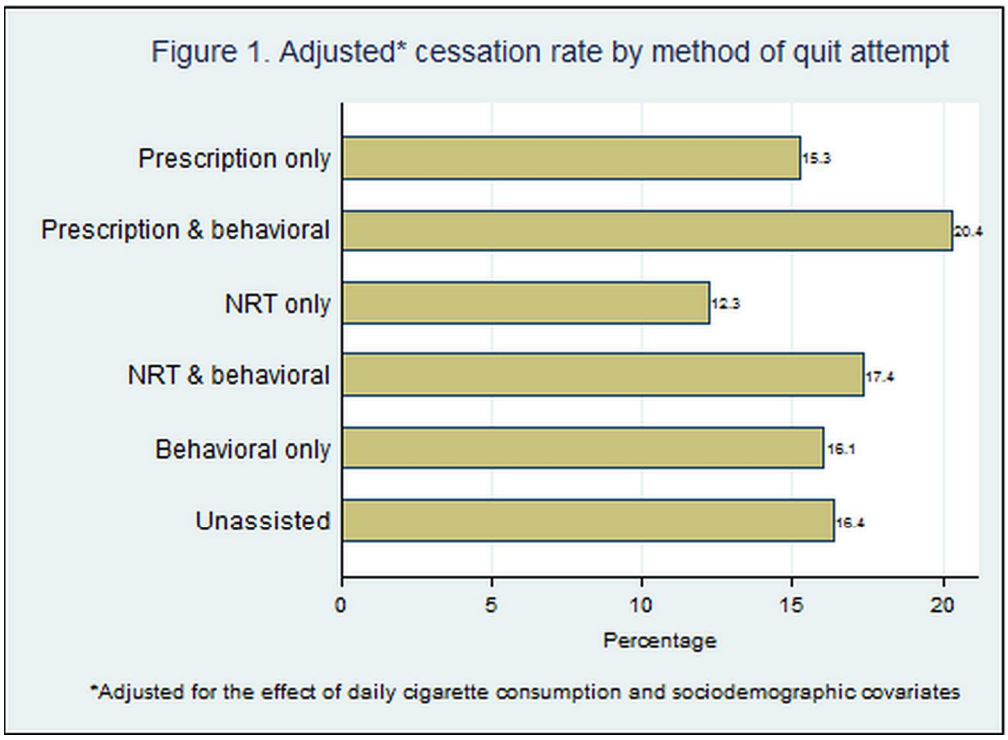

Figure1: Adjusted Cessation Rate by Method of Quit Attempt.

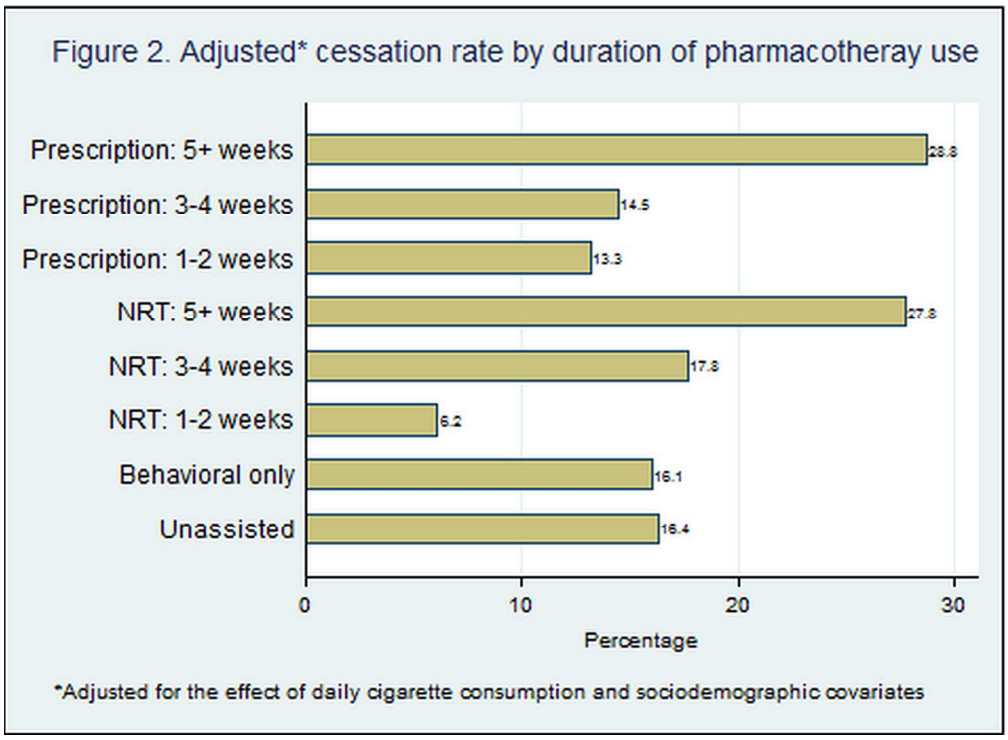

Figure 2: Adjusted Cessation Rate by Duration of Pharmacotherapy Use

STROBE Statement Checklist

	Checklist
Title and abstract	Yes
Introduction	
Background/rationale	Yes
Objectives/Aims	Yes
Methods	
Data sources	Yes
Measurement	Yes
Statistical methods	Yes
Results	
Descriptive data	Yes
Main results	Yes
Discussion	
Key results	Yes
Interpretation	Yes
Generalizability/Strengths	Yes
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Effectiveness of pharmacotherapy for smoking cessation in the general population: Duration of use matters

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Association between duration of use and success of pharmacotherapy for smoking cessation: Findings from a national survey

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ABSTRACT

Objective: To investigate the association of the duration of use of prescription medications and nicotine replacement therapy (NRT) with smoking cessation using a national sample of the general population in the United States, controlling for nicotine dependence and sociodemographic variables.

Setting: United States

Participants: We used data from the 2010-2011 Tobacco Use Supplement to the US Current Population Survey. We limited the analysis to current daily smokers who made a quit attempt in the past year and former smokers who were a daily smoker one year prior to the survey (n = 8 263). Respondents were asked about duration of use of prescription medication (varenicline, bupropion, other) and NRT (nicotine patch, gum/lozenges, nasal spray, and inhaler) for smoking cessation.

Primary Outcome Measure: Successful Smoking Cessation

Results: After adjusting for daily cigarette consumption and sociodemographic covariates, we found evidence for an association ($p<0.001$) between duration of pharmacotherapy use and smoking cessation. Adjusted cessation rates for those who used prescription medication or NRT for 5+ weeks were 28.8% and 27.8%, respectively. Adjusted cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Adjusted cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

Conclusion: Pharmacotherapies for smoking cessation can be effective in the general population if used for at least five weeks. Results suggest that encouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation.

ARTICLE SUMMARY

Strengths and limitations of the study:

- This was the first population-based study to examine the association between the duration of use of prescription medication as well as NRT for smoking cessation and successful smoking cessation, controlling for nicotine dependence and sociodemographic variables.
- A strength of this study was that it used a large nationally representative sample with a relatively high response rate.
- Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids might also be successful in the general population if they are used for at least five weeks.
- A strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa, was a major limitation of this study. Recall bias, especially related to the smokers previous quit attempts and the observational nature of the study precluding the establishment of a causal link were between the duration of pharmacotherapy use and successful smoking cessation, were the other limitations.

INTRODUCTION

Clinical trials provide strong evidence that pharmacotherapy for smoking cessation including various forms of nicotine replacement therapies (NRT), bupropion, or varenicline greatly increase the chances of a successful smoking cessation attempt.[1, 2] However, observational population-based studies have shown mixed results. While some have shown that pharmacotherapy increases smoking cessation rates,[3-6] others have concluded the opposite.[7-11] Yet, other population-based studies have shown no difference in cessation rates between those who use and those who do not use pharmacotherapy.[12, 13] The population-based reports that have found no favorable effect of pharmacotherapy have been criticized for not controlling for nicotine dependence,[14-16] which is a predictor of abstinence and is usually higher among smokers who choose to use pharmacotherapy for smoking cessation.[4, 14, 17, 18] Some of the analyses that have controlled for nicotine dependence have found a favorable effect of pharmacotherapy on smoking cessation[3, 4, 19] but others have not.[7]

An additional confounder that rarely is taken into account in population-based studies is duration of use of pharmacotherapy, which has been found to be associated with treatment success in clinical trials.[20-22] We know of one population-based study which examined the association of duration of use of pharmacotherapy with smoking cessation and found no association.[12] This study was conducted in the US where NRT can be purchased over the counter and medications such as bupropion and varenicline can only be obtained as prescription drugs.

While clinical trials have high internal validity and can provide evidence for the efficacy of pharmacotherapy, observational population-based studies can address effectiveness of these

therapies under conditions that they are intended to be used.[14] Furthermore, while clinical trials provide confidence in causal associations, population-based studies are strong in representativeness and external validity. Thus, both are needed to advance the science of smoking cessation.[19]

There is no literature on population-based studies that examine the association of duration of NRT and prescription medication use with smoking cessation. Our aim was to use a large representative sample of the general population in the United States and investigate the association of the duration of use of prescription medications and NRT with smoking cessation, controlling for nicotine dependence and sociodemographic variables.

METHODS

Data

We used data from the 2010-2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), sponsored by the National Cancer Institute and administered by the US Census Bureau in May 2010, August 2010, and January 2011.[23] The TUS-CPS is administered as a part of the CPS, which is a monthly national survey of representative households by the US Census Bureau and the Bureau of Labor Statistics.[24] The TUS-CPS utilizes a multistage probability sampling of individuals 15 years and older, from a sample of approximately 56,000 housing units, in turn selected from 792 primary sampling units. The average response rate for CPS for the 3 months of surveys used in this study was 93%, whereas for the TUS it was 63%.

Measurement

Successful smoking cessation:

Individuals who reported to have smoked at least 100 cigarettes in their entire life but were not smoking at all at the time of the interview and were a daily smoker one year prior to

the interview ("Around this time 12 months ago were you smoking everyday …?") were considered to have successfully quit smoking (n = 1 769). Those who reported to have quit within the last four weeks were excluded from the analysis (n = 322). Individuals who reported to have smoked at least 100 cigarettes in their entire life, were smoking every day at the time of the interview and had made a quit attempt in the past year were considered to have failed in their quit attempt (n = 7 304). Individuals who reported to have used both prescription medication and NRT for smoking cessation were excluded from the analysis (n = 488) because after subdividing this group by categories of duration of use for prescription medication and NRT, some of the subgroup sample sizes were extremely small. The total sample size for the study was 8 263 respondents, consisting of 1 379 who successfully quit smoking and 6 884 whose quit attempt was not successful.

Assisted quit attempt and duration of pharmacotherapy use:

Both daily and former smokers were asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used a prescription pill called (a) Chantix or varenicline, (b) zyban, bupropion, or wellbutrin, or (b) other prescription pills. They were also asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used (a) a nicotine patch, (b) nicotine gum or nicotine lozenge, or (c) nicotine nasal spray or nicotine inhaler. They were also asked to indicate how many days, weeks or months they used these prescription and/or NRT medications. Furthermore, both daily and former smokers were asked three separate questions about use of behavioral counseling in their last quit attempt in the past year. They were asked if they used a (a) telephone helpline or quitline, (b) one-on-one counseling or (c) stop smoking clinic, class or

support group. Based on the questions about use of prescription medication, NRT and behavioral counseling, we created the following two categorical variables:

Method of quit attempt

- Prescription medication only
- Prescription medication and behavioral counseling
- NRT only
- NRT and behavioral counseling
- Behavioral counseling only
- Unassisted

Duration of use of pharmacotherapy

- Prescription medication: 5+ weeks
- Prescription medication: 3-4 weeks
- Prescription medication: 1-2 weeks1
- NRT: 5+ weeks
- NRT: 3-4 weeks
- NRT: 1-2 weeks
- Behavioral counseling only
- Unassisted

We categorized duration of use of pharmacotherapy based on a systematic review of studies assessing adherence to smoking cessation medication.[20] In categorizing duration of use, we made no distinction between whether or not the medication was combined with behavioral counseling as this distinction was inconsequential in the analysis.

Statistical analysis

We used multivariable logistic regression models to compute adjusted odds ratios for the association of the method of quit attempt and duration of use of pharmacotherapy with successful smoking cessation. Sampling weights were taken into account in the computation of parameter estimates. We computed *p*-values using the jackknife, which is an unbiased estimator for a statistic and a data-dependent method to calculate standard errors.[25] All models controlled for daily cigarette consumption (current daily consumption among daily smokers, and daily consumption 12 months ago among former smokers), age, race/ethnicity, education, occupation, and family income. In order to account for the missing income data, CPS uses one of the three imputation methods, relational imputation, longitudinal edits, or hot deck allocation. Details of these methods are described elsewhere.[26] In multivariable logistic regression models, we omitted observations that had a missing value for any of the covariates. This constituted 1.7% of the full sample in the analysis pertaining to the method of quit attempt (n = 142) and 6.3% of the full sample in the analysis pertaining to duration of pharmacotherapy use (n = 491). We used the logistic regression results to compute adjusted cessation rates by method of quit attempt and duration of use of pharmacotherapy. These adjusted rates were computed by fixing covariates at their means in the fitted models.[27]

RESULTS

Sample characteristics and bivariate associations

Table 1. Weighted sample characteristics and unadjusted smoking cessation rates across categories of each covariate

Variable	% in sample	% quit	*p*- value
Method of quit attempt			0.074
Prescription only	10.01	18.54	
Prescription plus behavioral support	1.14	23.8	
NRT only	18.26	14.32	
NRT plus behavioral support	2.54	18.98	
Behavioral only	1.36	18.59	
Unassisted	66.68	17.16	
Duration of pharmacotherapy use			<0.001
Prescription: 5+ weeks	4.9	34.38	
Prescription: 3-4 weeks	1.43	16.82	
Prescription: 1-2 weeks	1.89	15.28	
NRT: 5+ weeks	6.04	30.65	
NRT: 3-4 weeks	1.48	19.9	
NRT: 1-2 weeks	13.48	7.36	
Behavioral only	1.42	18.59	
Unassisted	69.36	17.16	
Cigarettes per day			<0.001
0-9	24.48	15.08	
10-14	30.04	12.58	
15-19	10.31	12.58	
20-29	29.23	21.83	
30+	5.93	29.59	
Sex			0.975
Female	50.12	16.99	
Male	49.88	17.02	
Age			< 0.001
18-24	11.79	15.32	
25-39	33.08	18.17	
40-54	32.33	14.49	
55+	22.8	19.77	
Race/Ethnicity			0.003
Non-Hispanic White	76.17	17.99	
Non-Hispanic Black	11.34	12.98	
Hispanic	7.39	15.73	
Other	5.09	13.15	
Education			<0.001
Less than high school	15.25	13.15	
High school diploma	73.34	16.74	
Bachelor's degree	11.41	23.91	
Occupation			<0.001
Professional	14.33	20.99	
Service	12.31	13.96	
Sales	14.5	18.45	
Farming/construction/production	17.28	13.08	
Unemployed	12.01	13.81	
Not in labor force	29.57	19.24	
Family income			<0.001
<$25,000	36.27	13.94	
$25,000-$49,000	31.65	17.21	
$50,000-$99,000	23.86	19.63	
$100,000+	8.23	22.17	
Full sample		17.01	

Note: Sample size for each covariate varies from 7 820 to 8 263 depending on the number of missing values for that covariate. *P*-values are based on chi-square tests.

Weighted sample characteristics are shown in Table 1. About 66.7% of the sample reported to have made an unassisted quit attempt; 10% used only prescription medication; 1.1% used prescription medication plus behavioral counseling; 18.2% used only NRT; 2.5% used NRT plus behavioral therapy; and 1.3% used only behavioral counseling. When broken down by duration of use, while most of those who used prescription medication did so for five or more weeks, the great majority of those who used NRT did so for 2 weeks or less. The reported number of cigarettes smoked per day was 14 or less for about 54.5% of the sample. Age was distributed with 11.8% of the sample under 25 years of age, 33% between 25-39 years, 32.3% between 40-54 years, and 22.8% 55 years or older. The sample was 76% non-Hispanic white, 11.3% non-Hispanic Black, 7.4% Hispanic, and 5% of other race/ethnicity. About 15.2% of the sample did not have a high school diploma, 73.3% had high school diploma, and 11.4% had at least a bachelor's degree. The distribution of family income was skewed such that over a third of the sample had an income of less than $25 000 and less than a tenth of the sample had an income of $100 000 or greater.

Table 1 also provides smoking cessation rates across categories of each covariate, indicating bivariate (unadjusted) associations between the covariates and quitting. Cessation rate was 17% in the whole sample. There was very little evidence that method of quit attempt was associated with cessation rate ($p < 0.074$). However, the duration of pharmacotherapy use ($p < 0.001$), number of cigarettes smoked per day ($p < 0.001$), age ($p < 0.001$), and race/ethnicity ($p = 0.003$) were all associated with quitting. Higher socioeconomic status as measured by education, occupation, and income was associated with a higher cessation rate ($p < 0.001$ for all three indicators of socioeconomic status). Sex had no association with cessation.

Adjusted results from multivariable logistic regression models

Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence of an association between quitting method and successful cessation, the adjusted results

Table 2. Adjusted[a] odds ratios and 95% confidence intervals (CI) for the association of method of quit attempt and duration of pharmacotherapy use with the probability of successful smoking cessation

	OR (95% CI)	*p*-value
Method of quit attempt (n = 8 121)		0.025
Prescription only	1.00	
Prescription plus behavioral support	1.42 (0.76-2.66)	0.277
NRT only	0.78 (0.59-1.02)	0.072
NRT plus behavioral support	1.17 (0.73-1.86)	0.513
Behavioral only	1.06 (0.57-1.97)	0.844
Unassisted	1.09 (0.87-1.37)	0.464
Duration of pharmacotherapy use (n = 7 772)		< 0.001
Prescription: 5+ weeks	1.00	
Prescription: 3-4 weeks	0.42 (0.21-0.84)	0.014
Prescription: 1-2 weeks	0.38 (0.22-0.66)	0.001
NRT: 5+ weeks	0.95 (0.67-1.36)	0.786
NRT: 3-4 weeks	0.53 (0.29-0.97)	0.040
NRT: 1-2 weeks	0.16 (0.11-0.24)	<0.001
Behavioral only	0.47 (0.25-0.90)	0.022
Unassisted	0.48 (0.37-0.64)	<0.001

[a] Adjusted for the effect of number of cigarettes smoked per day, sex, age, race/ethnicity, education, occupation, and family income.

Figure 1 here……

revealed some evidence of an association ($p = 0.025$). The highest cessation rate was among those who used prescription medication and behavioral counseling (20.4%) followed by those who used NRT and behavioral counseling (17.4%), attempted to quit unassisted (16.4%), used behavioral counseling only (16.1%), and those who used prescription medication only (15.3%). The lowest cessation rate was among those who only used NRT as a quitting method (12.3%).

Figure 2 here……

Table 2 also provides adjusted odds ratios for the association of duration of pharmacotherapy use with the probability of smoking cessation. Figure 2 shows the adjusted cessation rates for various durations of pharmacotherapy use. Consistent with the unadjusted results in Table 1, the adjusted results in Table 2 also provide evidence ($p < 0.001$) of an association between duration of pharmacotherapy use and successful cessation. As shown in Figure 2, cessation rates were highest among those who used prescription medication for 5+ weeks (28.8%) and those who used NRT for 5+ weeks (27.8%). Cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%.

Cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

The results pertaining to the association of other covariates with successful cessation were very similar in the multivariable regression models for method of quit attempt and duration of pharmacotherapy use. These results were consistent with bivariate associations reported above, except for the fact that there was very little evidence for an association of race/ethnicity and smoking cessation in multivariable analyses.

DISCUSSION

This is the first population-based study to examine the association of successful smoking cessation and duration of use of prescription medication as well as NRT for smoking cessation. We found that using pharmacotherapy for five weeks or longer is associated with a higher probability of cessation compared to using pharmacotherapy for shorter durations, only using behavioral counseling or trying to quit unassisted.

Our findings are consistent with the results of a study of a hospital-based cessation program where participants who used NRT for 5 weeks or longer were found to have a higher cessation rate at 6-month follow-up.[28] However, our findings are not consistent with those of a population-based study which did not find any evidence that using NRT for more than 6 weeks versus not using NRT at all was associated with smoking cessation.[12] In that study, the survey response rate was low, the sample size was small and prescription medications were not examined. These factors could explain the discrepant findings.

While we found that smokers who used pharmacotherapy for at least 5 weeks have a far more favorable outcome than others, only 11% of the sample was in this group and notably about 70% of the sample did not use any pharmacotherapy for smoking cessation. Previous research indicates that barriers to the use of these cessation aids include concerns with their addictiveness, cost and side effects, as well as the belief that a treatment of any kind is not needed to quit smoking.[29-31]

A major limitation of the study is that there is a strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use varenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a

short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse. Furthermore, because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race, education, occupation, and income, it is possible that there might be residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation.

Another weakness of the study relates to the fact that smokers forget many quit attempts [7, 32] and they are more prone to recall attempts that used pharmacotherapy than those that did not.[14, 17] Such recall bias can underestimate the success rate of attempts at quitting with the aid of pharmacotherapy.[17]

A strength of this study was that it used a large nationally representative sample with a relatively high response rate. This was the first time that questions about the duration of pharmacotherapy use were included in the TUS-CPS. We know of no other national data on the general population that provide information on this variable. Many population-based studies of pharmacotherapies for smoking cessation have found these aids to be ineffective. It is likely that if these studies were able to account for duration of use, their findings would have been different. However, data on duration of use is not routinely collected and it would require a large sample size to provide a reliable estimate of the effect of using these medications for duration of a few weeks. Nonetheless, it would likely be an important area for further research to establish the relationship between duration of use of pharmacotherapy and successful quitting in the general population.

Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids might also be successful in the general population if they are used for at least five weeks.

CONTRIBUTORSHIP STATEMENT

We assure that all authors included on a paper fulfill the criteria of authorship. All have contributed in the conception and design, analysis and interpretation of data, drafting of the article and revising it critically for important intellectual content, and final approval of the version to be published. In addition we also assure that there is no one else who fulfills the criteria but has not been included as an author. Dr. Mohammad Siahpush was instrumental in conceptualization of research study, data analysis, and writing of the initial draft of the manuscript. Raees Shaikh and Molly McCarthy contributed in the development of study, data analysis, and preparation of the results section. They also helped with writing the manuscript and editing it for final submission. Dr. Asia Sikora helped with literature review, provided inputs for the materials and method section, and contributed to writing and editing the manuscript. Dr. Melissa Tibbits was involved with literature review and data analysis and provided her inputs to the entire manuscript. Dr. Gopal Singh was involved with formulation of research study and helped in the data analysis and contributed in the writing and editing of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) declare that no support was received from any organization for the submitted work and that there was no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, neither did we have other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL STATEMENT

No ethical approval was required for this work.

DATA SHARING STATEMENT

No additional data used or available.

FIGURE LEGENDS

Figure1: Adjusted Cessation Rate by Method of Quit Attempt

Figure2: Adjusted Cessation Rate by Duration of Pharmacotherapy Use

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Association between duration of use and success ~~Effectiveness~~ of pharmacotherapy for smoking cessation: Findings from a national survey ~~in the general population: Duration of use matters~~

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ABSTRACT

~~Aim~~**Objective:** To investigate the association of the duration of use of prescription medications and nicotine replacement therapy (NRT) with smoking cessation using a national sample of the general population in the United States, controlling for nicotine dependence and sociodemographic variables.

Setting: United States

Participants:

~~**Methods:**~~ We used data from the 2010-2011 Tobacco Use Supplement to the US Current Population Survey. We limited the analysis to current daily smokers who made a quit attempt in the past year and former smokers who were a daily smoker one year prior to the survey (n = 8 263). Respondents were asked about duration of use of prescription medication (v~~V~~arenicline, b~~B~~upropion, other) and NRT (nicotine patch, gum/lozenges, nasal spray, and inhaler) for smoking cessation.

Primary Outcome Measure: Successful Smoking Cessation

Results: After adjusting for daily cigarette consumption and sociodemographic covariates, we found ~~overwhelming~~ evidence ~~(p < 0.001)~~ for ~~a~~an~~n~~ association (p<0.001) between duration of pharmacotherapy use and smoking cessation. Adjusted cessation rates for those who used prescription medication or NRT for 5+ weeks were 28.8% and 27.8%, respectively. Adjusted cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Adjusted cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

Conclusion: Pharmacotherapies for smoking cessation can be effective in the general population if used for at least five weeks. Results suggest that e~~E~~ncouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation.

ARTICLE SUMMARY

Strengths and limitations of the study:

- This was the first population-based study to examine the association between the duration of use of prescription medication as well as NRT for smoking cessation ~~as a predictor of~~and successful smoking cessation, controlling for nicotine dependence and sociodemographic variables.
- A strength of this study was that it used a large nationally representative sample with a relatively high response rate.
- Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids ~~could~~ might also be ~~effective~~ successful in the general population if they are used for at least five weeks.
- A strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa, was a major limitation of this study. Recall bias, especially related to the smokers previous quit attempts and the observational nature of the study precluding the establishment of a causal link were between the duration of pharmacotherapy use and successful smoking cessation, were the ~~major~~ other limitations. ~~of this study.~~

INTRODUCTION

Clinical trials provide strong evidence that pharmacotherapy for smoking cessation including various forms of nicotine replacement therapies (NRT), bBupropion, or vVarenicline greatly increase the chances of a successful smoking cessation attempt.[1, 2] However, observational population-based studies have shown mixed results. While some have shown that pharmacotherapy increases smoking cessation rates,[3-6] others have concluded the opposite.[7-11] Yet, other population-based studies have shown no difference in cessation rates between those who use and those who do not use pharmacotherapy.[12, 13] The population-based reports that have found no favorable effect of pharmacotherapy have been criticized for not controlling for nicotine dependence,[14-16] which is a predictor of abstinence and is usually higher among smokers who choose to use pharmacotherapy for smoking cessation.[4, 14, 17, 18] Some of the analyses that have controlled for nicotine dependence have found a favorable effect of pharmacotherapy on smoking cessation[3, 4, 19] but others have not.[7]

An additional confounder that rarely is taken into account in population-based studies is duration of use of pharmacotherapy, which has been found to be associated with treatment success in clinical trials.[20-22] We know of one population-based study which examined the association of duration of use of pharmacotherapy with smoking cessation and found no association.[12] This study was conducted in the US where NRT can be purchased over the counter and medications such as bBupropion and vVarenicline can only be obtained as prescription drugs.

While clinical trials have high internal validity and can provide evidence for the efficacy of pharmacotherapy, observational population-based studies can address effectiveness of these

therapies under conditions that they are intended to be used.[14] Furthermore, while clinical trials provide confidence in causal associations, population-based studies are strong in representativeness and external validity. Thus, both are needed to advance the science of smoking cessation.[19]

There is no literature on population-based studies that examine the association of duration of NRT and prescription medication use with smoking cessation. Our aim was to use a large representative sample of the general population in the United States and investigate the association of the duration of use of prescription medications and NRT with smoking cessation, controlling for nicotine dependence and sociodemographic variables.

METHODS

Data

We used data from the 2010-2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), sponsored by the National Cancer Institute and administered by the US Census Bureau in May 2010, August 2010, and January 2011.[23] The TUS-CPS is administered as a part of the CPS, which is a monthly national survey of representative households by the US Census Bureau and the Bureau of Labor Statistics.[24] The TUS-CPS utilizes a multistage probability sampling of individuals 15 years and older, from a sample of approximately 56,000 housing units, in turn selected from 792 primary sampling units. The average response rate for CPS for the 3 months of surveys used in this study was 93%, whereas for the TUS it was 63%.

Measurement

Successful smoking cessation:

Individuals who reported to have smoked at least 100 cigarettes in their entire life but were not smoking at all at the time of the interview and were a daily smoker one year prior to

the interview ("Around this time 12 months ago were you smoking everyday …?") were considered to have successfully quit smoking (n = 1 769). Those who reported to have quit within the last four weeks were excluded from the analysis (n = 322). Individuals who reported to have smoked at least 100 cigarettes in their entire life, were smoking every day at the time of the interview and had made a quit attempt in the past year were considered to have failed in their quit attempt (n = 7 304). Individuals who reported to have used both prescription medication and NRT for smoking cessation were excluded from the analysis (n = 488) because after subdividing this group by categories of duration of use for prescription medication and NRT, some of the subgroup sample sizes were extremely small. The total sample size for the study was 8 263 respondents, consisting of 1 379 who successfully quit smoking and 6 884 whose quit attempt was not successful.

Assisted quit attempt and duration of pharmacotherapy use:

Both daily and former smokers were asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used a prescription pill called (a) Chantix or ~~Varenicline~~varenicline, (b) z~~Z~~yban, b~~B~~upropion, or w~~W~~ellbutrin, or (b) other prescription pills. They were also asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used (a) a nicotine patch, (b) nicotine gum or nicotine lozenge, or (c) nicotine nasal spray or nicotine inhaler. They were also asked to indicate how many days, weeks or months they used these prescription and/or NRT medications. Furthermore, both daily and former smokers were asked three separate questions about use of behavioral counseling in their last quit attempt in the past year. They were asked if they used a (a) telephone helpline or quitline, (b) one-on-one counseling or (c) stop smoking clinic, class or

support group. Based on the questions about use of prescription medication, NRT and behavioral counseling, we created the following two categorical variables:

Method of quit attempt

- Prescription medication only
- Prescription medication and behavioral counseling
- NRT only
- NRT and behavioral counseling
- Behavioral counseling only
- Unassisted

Duration of use of pharmacotherapy

- Prescription medication: 5+ weeks
- Prescription medication: 3-4 weeks
- Prescription medication: 1-2 weeks1
- NRT: 5+ weeks
- NRT: 3-4 weeks
- NRT: 1-2 weeks
- Behavioral counseling only
- Unassisted

We categorized duration of use of pharmacotherapy based on a systematic review of studies assessing adherence to smoking cessation medication.[20] In categorizing duration of use, we made no distinction between whether or not the medication was combined with behavioral counseling as this distinction was inconsequential in the analysis.

Statistical analysis

We used multivariable logistic regression models to compute adjusted odds ratios for the association of the method of quit attempt and duration of use of pharmacotherapy with successful smoking cessation. Sampling weights were taken into account in the computation of parameter estimates. We computed *p*-values using the jackknife, which is an unbiased estimator for a statistic and a data-dependent method to calculate standard errors.[25] All models controlled for daily cigarette consumption (current daily consumption among daily smokers, and daily consumption 12 months ago among former smokers), age, race/ethnicity, education, occupation, and family income. In order to account for the missing income data, CPS uses one of the three imputation methods, relational imputation, longitudinal edits, or hot deck allocation. Details of these methods are described elsewhere.[26] In multivariable logistic regression models, we omitted observations that had a missing value for any of the covariates. This constituted 1.7% of the full sample in the analysis pertaining to the method of quit attempt (n = 142) and 6.3% of the full sample in the analysis pertaining to duration of pharmacotherapy use (n = 491). We used the logistic regression results to compute adjusted cessation rates by method of quit attempt and duration of use of pharmacotherapy. These adjusted rates were computed by fixing covariates at their means in the fitted models.[27]

RESULTS

Sample characteristics and bivariate associations

Table 1. Weighted sample characteristics and unadjusted smoking cessation rates across categories of each covariate

Variable	% in sample	% quit	*p*- value
Method of quit attempt			0.074
Prescription only	10.01	18.54	
Prescription plus behavioral support	1.14	23.8	
NRT only	18.26	14.32	
NRT plus behavioral support	2.54	18.98	
Behavioral only	1.36	18.59	
Unassisted	66.68	17.16	
Duration of pharmacotherapy use			<0.001
Prescription: 5+ weeks	4.9	34.38	
Prescription: 3-4 weeks	1.43	16.82	
Prescription: 1-2 weeks	1.89	15.28	
NRT: 5+ weeks	6.04	30.65	
NRT: 3-4 weeks	1.48	19.9	
NRT: 1-2 weeks	13.48	7.36	
Behavioral only	1.42	18.59	
Unassisted	69.36	17.16	
Cigarettes per day			<0.001
0-9	24.48	15.08	
10-14	30.04	12.58	
15-19	10.31	12.58	
20-29	29.23	21.83	
30+	5.93	29.59	
Sex			0.975
Female	50.12	16.99	
Male	49.88	17.02	
Age			< 0.001
18-24	11.79	15.32	
25-39	33.08	18.17	
40-54	32.33	14.49	
55+	22.8	19.77	
Race/Ethnicity			0.003
Non-Hispanic White	76.17	17.99	
Non-Hispanic Black	11.34	12.98	
Hispanic	7.39	15.73	
Other	5.09	13.15	
Education			<0.001
Less than high school	15.25	13.15	
High school diploma	73.34	16.74	
Bachelor's degree	11.41	23.91	
Occupation			<0.001
Professional	14.33	20.99	
Service	12.31	13.96	
Sales	14.5	18.45	
Farming/construction/production	17.28	13.08	
Unemployed	12.01	13.81	
Not in labor force	29.57	19.24	
Family income			<0.001
<$25,000	36.27	13.94	
$25,000-$49,000	31.65	17.21	
$50,000-$99,000	23.86	19.63	
$100,000+	8.23	22.17	
Full sample		17.01	

Note: Sample size for each covariate varies from 7 820 to 8 263 depending on the number of missing values for that covariate. *P*-values are based on chi-square tests.

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Weighted sample characteristics are shown in Table 1. About 66.7% of the sample reported to have made an unassisted quit attempt; 10% used only prescription medication; 1.1% used prescription medication plus behavioral counseling; 18.2% used only NRT; 2.5% used NRT plus behavioral therapy; and 1.3% used only behavioral counseling. When broken down by duration of use, while most of those who used prescription medication did so for five or more weeks, the great majority of those who used NRT did so for 2 weeks or less. The reported number of cigarettes smoked per day was 14 or less for about 54.5% of the sample. Age was distributed with 11.8% of the sample under 25 years of age, 33% between 25-39 years, 32.3% between 40-54 years, and 22.8% 55 years or older. The sample was 76% non-Hispanic white, 11.3% non-Hispanic Black, 7.4% Hispanic, and 5% of other race/ethnicity. About 15.2% of the sample did not have a high school diploma, 73.3% had high school diploma, and 11.4% had at least a bachelor's degree. The distribution of family income was skewed such that over a third of the sample had an income of less than $25 000 and less than a tenth of the sample had an income of $100 000 or greater.

Table 1 also provides smoking cessation rates across categories of each covariate, indicating bivariate (unadjusted) associations between the covariates and quitting. Cessation rate was 17% in the whole sample. There was very little evidence that method of quit attempt was associated with cessation rate ($p < 0.074$). However, ~~there was overwhelming evidence that~~ the duration of pharmacotherapy use ~~was associated with quitting~~ ($p < 0.001$), ~~such that the use of prescription medication or NRT for 5+ weeks was associated with remarkably higher cessation rates compared to the use of these products for shorter durations, behavioral counseling or unassisted quit attempts.~~ n~~-~~Number of cigarettes smoked per day ~~had a curvilinear relationship with cessation such that those who smoked 0-9 cigarettes and those who smoked 20+ cigarettes per day had a higher cessation rate than others~~ (p~~P~~ < 0.001), a~~.~~ Age ~~had a curvilinear relationship with cessation in that individuals in the 25-39 and 55+ age categories had notably higher cessation rates than others~~ ($p < 0.001$), and ra~~.~~ Race/ethnicity ($p = 0.003$) were~~was~~ all associated with quitting~~.~~ ~~such that Non-Hispanic Whites had the highest and non-Hispanic Blacks had the lowest cessation rates ($p = 0.003$).~~ H~~H~~igher socioeconomic status as measured by education, occupation, and income was associated with a higher cessation rate ($p < 0.001$ for all three indicators of socioeconomic status). Sex had no association with cessation.

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Adjusted results from multivariable logistic regression models

Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence of an association between quitting method and successful cessation, the adjusted results

Table 2. Adjusted[a] odds ratios and 95% confidence intervals (CI) for the association of method of quit attempt and duration of pharmacotherapy use with the probability of successful smoking cessation

	OR (95% CI)	*p*-value
Method of quit attempt (n = 8 121)		0.025
Prescription only	1.00	
Prescription plus behavioral support	1.42 (0.76-2.66)	0.277
NRT only	0.78 (0.59-1.02)	0.072
NRT plus behavioral support	1.17 (0.73-1.86)	0.513
Behavioral only	1.06 (0.57-1.97)	0.844
Unassisted	1.09 (0.87-1.37)	0.464
Duration of pharmacotherapy use (n = 7 772)		< 0.001
Prescription: 5+ weeks	1.00	
Prescription: 3-4 weeks	0.42 (0.21-0.84)	0.014
Prescription: 1-2 weeks	0.38 (0.22-0.66)	0.001
NRT: 5+ weeks	0.95 (0.67-1.36)	0.786
NRT: 3-4 weeks	0.53 (0.29-0.97)	0.040
NRT: 1-2 weeks	0.16 (0.11-0.24)	<0.001
Behavioral only	0.47 (0.25-0.90)	0.022
Unassisted	0.48 (0.37-0.64)	<0.001

[a] Adjusted for the effect of number of cigarettes smoked per day, sex, age, race/ethnicity, education, occupation, and family income.

Figure 1 here……

~~Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence of an association between quitting method and successful cessation, the adjusted results~~ revealed some evidence of an association (p = 0.025). The highest cessation rate was among those who used prescription medication and behavioral counseling (20.4%) followed by those who used NRT and behavioral counseling (17.4%), attempted to quit unassisted (16.4%), used

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behavioral counseling only (16.1%), and those who used prescription medication only (15.3%). The lowest cessation rate was among those who only used NRT as a quitting method (12.3%).

Figure 2 here……

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Table 2 also provides adjusted odds ratios for the association of duration of pharmacotherapy use with the probability of smoking cessation. Figure 2 shows the adjusted cessation rates for various durations of pharmacotherapy use. Consistent with the unadjusted results in Table 1, the adjusted results in Table 2 also provide ~~strong~~ evidence ($p < 0.001$) of an association between duration of pharmacotherapy use and successful cessation. As shown in Figure 2, cessation rates were highest among t~~T~~hose who used prescription medication for 5+ weeks (28.8%) and those who used~~or~~ NRT for 5+ weeks (27.8%)~~had higher cessation rates, 28.8% and 27.8% respectively, than others~~. Cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

The results pertaining to the association of other covariates with successful cessation were very similar in the multivariable regression models for method of quit attempt and duration of pharmacotherapy use. These results were consistent with bivariate associations reported above, except for the fact that there was very little evidence for an association of race/ethnicity and smoking cessation in multivariable analyses.

DISCUSSION

This is the first population-based study to examine the association of successful smoking cessation and duration of use of prescription medication as well as NRT for smoking cessation ~~as a predictor of successful smoking cessation~~. We found that using pharmacotherapy for five weeks or longer is associated with a ~~remarkably~~ higher probability of cessation compared to using pharmacotherapy for shorter durations, only using behavioral counseling or trying to quit unassisted.

Our findings are consistent with the results of a study of a hospital-based cessation program where participants who used NRT for 5 weeks or longer were found to have a higher

cessation rate at 6-month follow-up.[28] However, our findings are not consistent with those of a population-based study which did not find any evidence that using NRT for more than 6 weeks versus not using NRT at all was associated with smoking cessation.[12] In that study, the survey response rate was low, the sample size was small and prescription medications were not examined. These factors could explain the discrepant findings.

While we found that smokers who used pharmacotherapy for at least 5 weeks have a far more favorable outcome than others, only 11% of the sample was in this group and notably about 70% of the sample did not use any pharmacotherapy for smoking cessation. Previous research indicates that barriers to the use of these cessation aids include concerns with their addictiveness, cost and side effects, as well as the belief that a treatment of any kind is not needed to quit smoking.[29-31]

A major ~~weakness~~limitation of the study is that there is a strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use v~~V~~arenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse. Furthermore, because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race, education, occupation, and income, it is possible that there might be residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation.

Another -weakness of the study relates to the fact that smokers forget many quit attempts [7, 32] and they are more prone to recall attempts that used pharmacotherapy than those that did not.[14, 17] Such recall bias can underestimate the success rate of attempts at quitting with the aid of pharmacotherapy.[17] ~~Another limitation of the study is that because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race,~~

~~education, occupation, and income, it is possible that there is residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation. Moreover, there is a possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use Varenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse.~~

A strength of this study was that it used a large nationally representative sample with a relatively high response rate. This was the first time that questions about the duration of pharmacotherapy use were included in the TUS-CPS. We know of no other national data on the general population that provide information on this variable. Many population-based studies of pharmacotherapies for smoking cessation have found these aids to be ineffective. It is likely that if these studies were able to account for duration of use, their findings would have been different. However, data on duration of use is not routinely collected and it would require a large sample size to provide a reliable estimate of the effect of using these medications for duration of a few weeks. Nonetheless, it would likely be an important area for further research to establish the relationship between duration of use of pharmacotherapy and successful quitting in the general population.

Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids ~~can~~might also be ~~effective~~ successful in the general population if they are used for at least five weeks. ~~Smokers who intend to quit should be encouraged to use pharmacotherapy and adhere to their recommended duration of use.~~

CONTRIBUTORSHIP STATEMENT

We assure that all authors included on a paper fulfill the criteria of authorship. All have contributed in the conception and design, analysis and interpretation of data, drafting of the article and revising it critically for important intellectual content, and final approval of the version to be published. In addition we also assure that there is no one else who fulfills the criteria but has not been included as an author. Dr. Mohammad Siahpush was instrumental in conceptualization of research study, data analysis, and writing of the initial draft of the manuscript. Raees Shaikh and Molly McCarthy contributed in the development of study, data analysis, and preparation of the results section. They also helped with writing the manuscript and editing it for final submission. Dr. Asia Sikora helped with literature review, provided inputs for the materials and method section, and contributed to writing and editing the manuscript. Dr. Melissa Tibbits was involved with literature review and data analysis and provided her inputs to the entire manuscript. Dr. Gopal Singh was involved with formulation of research study and helped in the data analysis and contributed in the writing and editing of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) declare that no support was received from any organization for the submitted work and that there was no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, neither did we have other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL STATEMENT

No ethical approval was required for this work.

DATA SHARING STATEMENT

No additional data used or available.

FIGURE LEGENDS

Figure1: Adjusted Cessation Rate by Method of Quit Attempt

Figure2: Adjusted Cessation Rate by Duration of Pharmacotherapy Use

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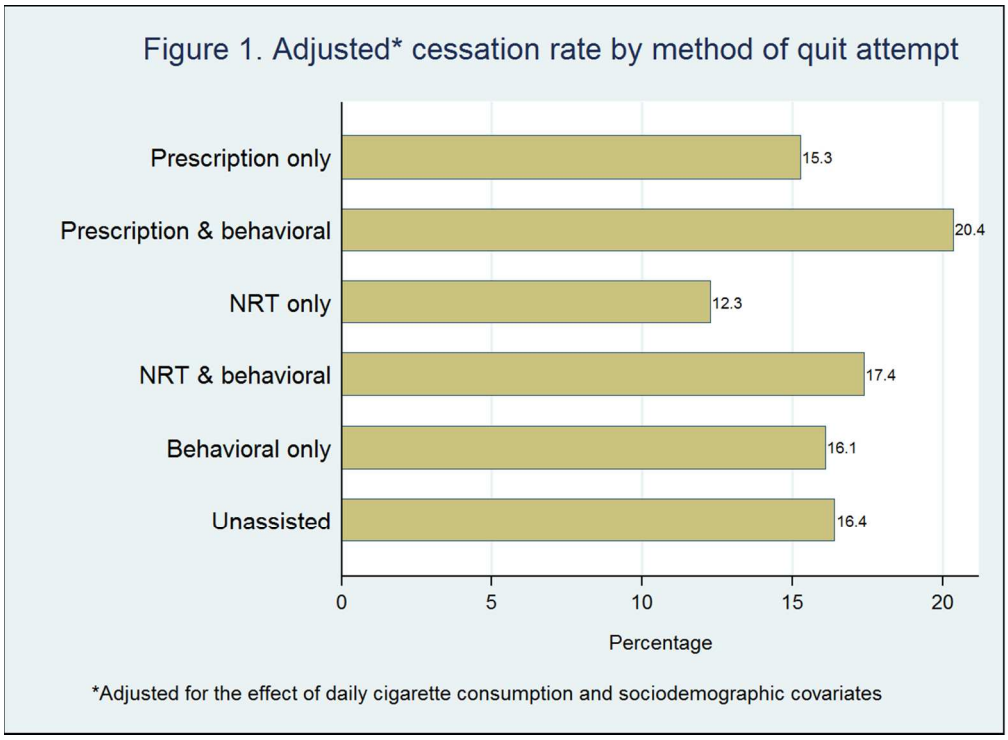

Figure1- Adjusted Cessation Rate by Method of Quit Attempt
105x76mm (300 x 300 DPI)

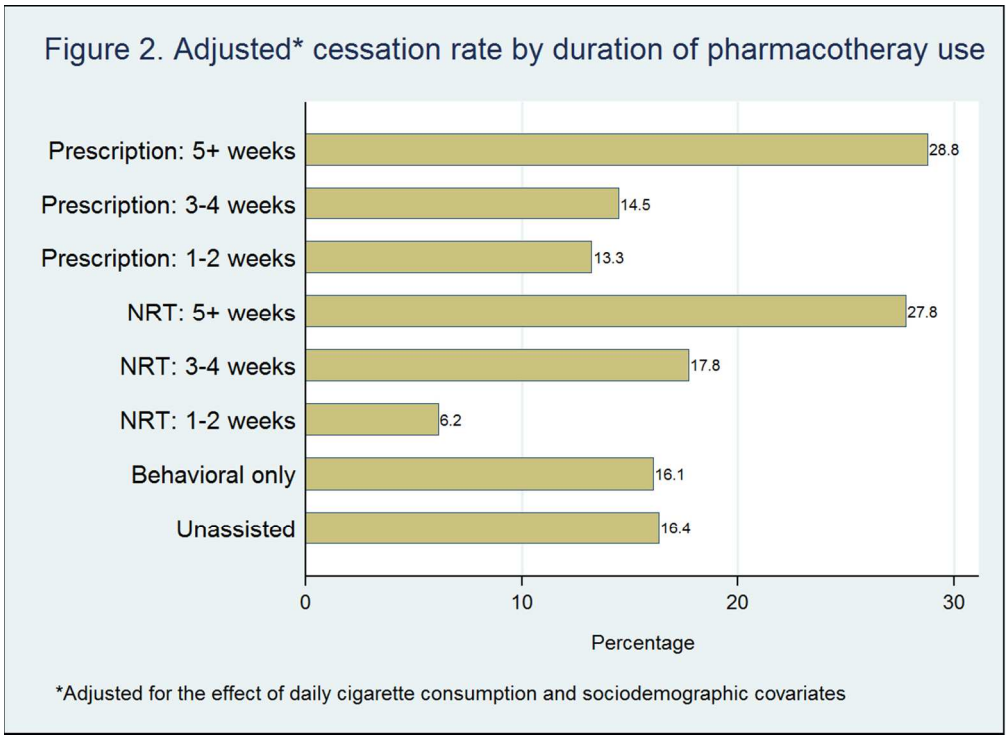

Figure2- Adjusted Cessation Rate by Duration of Pharmacotherapy Use
105x76mm (300 x 300 DPI)

STROBE Statement Checklist

	Checklist
Title and abstract	Yes
Introduction	
Background/rationale	Yes
Objectives/Aims	Yes
Methods	
Data sources	Yes
Measurement	Yes
Statistical methods	Yes
Results	
Descriptive data	Yes
Main results	Yes
Discussion	
Key results	Yes
Interpretation	Yes
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Association between duration of use of pharmacotherapy and smoking cessation: Findings from a national survey

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Association between duration of use of pharmacotherapy and smoking cessation: Findings from a national survey

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ABSTRACT

Objective: To investigate the association of the duration of use of prescription medications and nicotine replacement therapy (NRT) with smoking cessation using a national sample of the general population in the United States, controlling for nicotine dependence and sociodemographic variables.

Setting: United States

Participants: We used data from the 2010-2011 Tobacco Use Supplement to the US Current Population Survey. We limited the analysis to current daily smokers who made a quit attempt in the past year and former smokers who were a daily smoker one year prior to the survey (n = 8 263). Respondents were asked about duration of use of prescription medication (varenicline, bupropion, other) and NRT (nicotine patch, gum/lozenges, nasal spray, and inhaler) for smoking cessation.

Primary Outcome Measure: Successful Smoking Cessation. Individuals who reported to have smoked at least 100 cigarettes in their lifetime but were not smoking at all at the time of the interview and were a daily smoker one year prior to the interview were considered to have successfully quit smoking.

Results: After adjusting for daily cigarette consumption and sociodemographic covariates, we found evidence for an association between duration of pharmacotherapy use and smoking cessation ($p<0.001$). Adjusted cessation rates for those who used prescription medication or NRT for 5+ weeks were 28.8% and 27.8%, respectively. Adjusted cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Adjusted cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

Conclusion: Use of pharmacotherapy for at least five weeks is associated with increased likelihood of successful smoking cessation. Results suggest that encouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation.

ARTICLE SUMMARY

Strengths and limitations of the study:

- This was the first population-based study to examine the association between the duration of use of prescription medication as well as NRT for smoking cessation and successful smoking cessation, controlling for nicotine dependence and sociodemographic variables.
- A strength of this study was that it used a large nationally representative sample with a relatively high response rate.
- Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids might also be successful in the general population if they are used for at least five weeks.
- A strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa, was a major limitation of this study. Recall bias, especially related to the smokers previous quit attempts and the observational nature of the study precluding the establishment of a causal link were between the duration of pharmacotherapy use and successful smoking cessation, were the other limitations.

INTRODUCTION

Clinical trials provide strong evidence that pharmacotherapy for smoking cessation including various forms of nicotine replacement therapies (NRT), bupropion, or varenicline greatly increase the chances of a successful smoking cessation attempt.[1, 2] However, observational population-based studies have shown mixed results. While some have shown that pharmacotherapy increases smoking cessation rates,[3-6] others have concluded the opposite.[7-11] Yet, other population-based studies have shown no difference in cessation rates between those who use and those who do not use pharmacotherapy.[12, 13] The population-based reports that have found no favorable effect of pharmacotherapy have been criticized for not controlling for nicotine dependence,[14-16] which is a predictor of abstinence and is usually higher among smokers who choose to use pharmacotherapy for smoking cessation.[4, 14, 17, 18] Some of the analyses that have controlled for nicotine dependence have found a favorable effect of pharmacotherapy on smoking cessation[3, 4, 19] but others have not.[7]

An additional confounder that rarely is taken into account in population-based studies is duration of use of pharmacotherapy, which has been found to be associated with treatment success in clinical trials.[20-22] We know of one population-based study which examined the association of duration of use of pharmacotherapy with smoking cessation and found no association.[12] This study was conducted in the US where NRT can be purchased over the counter and medications such as bupropion and varenicline can only be obtained as prescription drugs.

While clinical trials have high internal validity and can provide evidence for the efficacy of pharmacotherapy, observational population-based studies can address effectiveness of these

therapies under conditions that they are intended to be used.[14] Furthermore, while clinical trials provide confidence in causal associations, population-based studies are strong in representativeness and external validity. Thus, both are needed to advance the science of smoking cessation.[19]

There is no literature on population-based studies that examine the association of duration of NRT and prescription medication use with smoking cessation. Our aim was to use a large representative sample of the general population in the United States and investigate the association of the duration of use of prescription medications and NRT with smoking cessation, controlling for nicotine dependence and sociodemographic variables.

METHODS

Data

We used data from the 2010-2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), sponsored by the National Cancer Institute and administered by the US Census Bureau in May 2010, August 2010, and January 2011.[23] The TUS-CPS is administered as a part of the CPS, which is a monthly national survey of representative households by the US Census Bureau and the Bureau of Labor Statistics.[24] The TUS-CPS utilizes a multistage probability sampling of individuals 15 years and older, from a sample of approximately 56,000 housing units, in turn selected from 792 primary sampling units. The average response rate for CPS for the 3 months of surveys used in this study was 93%, whereas for the TUS it was 63%.

Measurement

Successful smoking cessation:

Individuals who reported to have smoked at least 100 cigarettes in their entire life but were not smoking at all at the time of the interview and were a daily smoker one year prior to

the interview ("Around this time 12 months ago were you smoking everyday …?") were considered to have successfully quit smoking (n = 1 769). Those who reported to have quit within the last four weeks were excluded from the analysis (n = 322). Individuals who reported to have smoked at least 100 cigarettes in their entire life, were smoking every day at the time of the interview and had made a quit attempt in the past year were considered to have failed in their quit attempt (n = 7 304). Individuals who reported to have used both prescription medication and NRT for smoking cessation were excluded from the analysis (n = 488) because after subdividing this group by categories of duration of use for prescription medication and NRT, some of the subgroup sample sizes were extremely small. The total sample size for the study was 8 263 respondents, consisting of 1 379 who successfully quit smoking and 6 884 whose quit attempt was not successful.

Assisted quit attempt and duration of pharmacotherapy use:

Both daily and former smokers were asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used a prescription pill called (a) Chantix or varenicline, (b) zyban, bupropion, or wellbutrin, or (b) other prescription pills. They were also asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used (a) a nicotine patch, (b) nicotine gum or nicotine lozenge, or (c) nicotine nasal spray or nicotine inhaler. They were also asked to indicate how many days, weeks or months they used these prescription and/or NRT medications. Furthermore, both daily and former smokers were asked three separate questions about use of behavioral counseling in their last quit attempt in the past year. They were asked if they used a (a) telephone helpline or quitline, (b) one-on-one counseling or (c) stop smoking clinic, class or

support group. Based on the questions about use of prescription medication, NRT and behavioral counseling, we created the following two categorical variables:

Method of quit attempt

- Prescription medication only
- Prescription medication and behavioral counseling
- NRT only
- NRT and behavioral counseling
- Behavioral counseling only
- Unassisted

Duration of use of pharmacotherapy

- Prescription medication: 5+ weeks
- Prescription medication: 3-4 weeks
- Prescription medication: 1-2 weeks1
- NRT: 5+ weeks
- NRT: 3-4 weeks
- NRT: 1-2 weeks
- Behavioral counseling only
- Unassisted

We categorized duration of use of pharmacotherapy based on a systematic review of studies assessing adherence to smoking cessation medication.[20] In categorizing duration of use, we made no distinction between whether or not the medication was combined with behavioral counseling as this distinction was inconsequential in the analysis.

Statistical analysis

We used multivariable logistic regression models to compute adjusted odds ratios for the association of the method of quit attempt and duration of use of pharmacotherapy with successful smoking cessation. Sampling weights were taken into account in the computation of parameter estimates. We computed *p*-values using the jackknife, which is an unbiased estimator for a statistic and a data-dependent method to calculate standard errors.[25] All models controlled for daily cigarette consumption (current daily consumption among daily smokers, and daily consumption 12 months ago among former smokers), age, race/ethnicity, education, occupation, and family income. In order to account for the missing income data, CPS uses one of the three imputation methods, relational imputation, longitudinal edits, or hot deck allocation. Details of these methods are described elsewhere.[26] In multivariable logistic regression models, we omitted observations that had a missing value for any of the covariates. This constituted 1.7% of the full sample in the analysis pertaining to the method of quit attempt (n = 142) and 6.3% of the full sample in the analysis pertaining to duration of pharmacotherapy use (n = 491). We used the logistic regression results to compute adjusted cessation rates by method of quit attempt and duration of use of pharmacotherapy. These adjusted rates were computed by fixing covariates at their means in the fitted models.[27]

RESULTS

Sample characteristics and bivariate associations

Table 1. Weighted sample characteristics and unadjusted smoking cessation rates across categories of each covariate

Variable	% in sample	% quit	*p*- value
Method of quit attempt			0.074
Prescription only	10.01	18.54	
Prescription plus behavioral support	1.14	23.8	
NRT only	18.26	14.32	
NRT plus behavioral support	2.54	18.98	
Behavioral only	1.36	18.59	
Unassisted	66.68	17.16	
Duration of pharmacotherapy use			<0.001
Prescription: 5+ weeks	4.9	34.38	
Prescription: 3-4 weeks	1.43	16.82	
Prescription: 1-2 weeks	1.89	15.28	
NRT: 5+ weeks	6.04	30.65	
NRT: 3-4 weeks	1.48	19.9	
NRT: 1-2 weeks	13.48	7.36	
Behavioral only	1.42	18.59	
Unassisted	69.36	17.16	
Cigarettes per day			<0.001
0-9	24.48	15.08	
10-14	30.04	12.58	
15-19	10.31	12.58	
20-29	29.23	21.83	
30+	5.93	29.59	
Sex			0.975
Female	50.12	16.99	
Male	49.88	17.02	
Age			< 0.001
18-24	11.79	15.32	
25-39	33.08	18.17	
40-54	32.33	14.49	
55+	22.8	19.77	
Race/Ethnicity			0.003
Non-Hispanic White	76.17	17.99	
Non-Hispanic Black	11.34	12.98	
Hispanic	7.39	15.73	
Other	5.09	13.15	
Education			<0.001
Less than high school	15.25	13.15	
High school diploma	73.34	16.74	
Bachelor's degree	11.41	23.91	
Occupation			<0.001
Professional	14.33	20.99	
Service	12.31	13.96	
Sales	14.5	18.45	
Farming/construction/production	17.28	13.08	
Unemployed	12.01	13.81	
Not in labor force	29.57	19.24	
Family income			<0.001
<$25,000	36.27	13.94	
$25,000-$49,000	31.65	17.21	
$50,000-$99,000	23.86	19.63	
$100,000+	8.23	22.17	
Full sample		17.01	

Note: Sample size for each covariate varies from 7 820 to 8 263 depending on the number of missing values for that covariate. *P*-values are based on chi-square tests.

Weighted sample characteristics are shown in Table 1. About 66.7% of the sample reported to have made an unassisted quit attempt; 10% used only prescription medication; 1.1% used prescription medication plus behavioral counseling; 18.2% used only NRT; 2.5% used NRT plus behavioral therapy; and 1.3% used only behavioral counseling. When broken down by duration of use, while most of those who used prescription medication did so for five or more weeks, the great majority of those who used NRT did so for 2 weeks or less. The reported number of cigarettes smoked per day was 14 or less for about 54.5% of the sample. Age was distributed with 11.8% of the sample under 25 years of age, 33% between 25-39 years, 32.3% between 40-54 years, and 22.8% 55 years or older. The sample was 76% non-Hispanic white, 11.3% non-Hispanic Black, 7.4% Hispanic, and 5% of other race/ethnicity. About 15.2% of the sample did not have a high school diploma, 73.3% had high school diploma, and 11.4% had at least a bachelor's degree. The distribution of family income was skewed such that over a third of the sample had an income of less than $25 000 and less than a tenth of the sample had an income of $100 000 or greater.

Table 1 also provides smoking cessation rates across categories of each covariate, indicating bivariate (unadjusted) associations between the covariates and quitting. Cessation rate was 17% in the whole sample. There was very little evidence that method of quit attempt was associated with cessation rate ($p < 0.074$). However, the duration of pharmacotherapy use ($p < 0.001$), number of cigarettes smoked per day ($p < 0.001$), age ($p < 0.001$), and race/ethnicity ($p = 0.003$) were all associated with quitting. Higher socioeconomic status as measured by education, occupation, and income was associated with a higher cessation rate ($p < 0.001$ for all three indicators of socioeconomic status). Sex had no association with cessation.

Adjusted results from multivariable logistic regression models

Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence of an association between quitting method and successful cessation, the adjusted results

Table 2. Adjusted[a] odds ratios and 95% confidence intervals (CI) for the association of method of quit attempt and duration of pharmacotherapy use with the probability of successful smoking cessation

	OR (95% CI)	*p*-value
Method of quit attempt (n = 8 121)		0.025
Prescription only	1.00	
Prescription plus behavioral support	1.42 (0.76-2.66)	
NRT only	0.78 (0.59-1.02)	
NRT plus behavioral support	1.17 (0.73-1.86)	
Behavioral only	1.06 (0.57-1.97)	
Unassisted	1.09 (0.87-1.37)	
Duration of pharmacotherapy use (n = 7 772)		< 0.001
Prescription: 5+ weeks	1.00	
Prescription: 3-4 weeks	0.42 (0.21-0.84)	
Prescription: 1-2 weeks	0.38 (0.22-0.66)	
NRT: 5+ weeks	0.95 (0.67-1.36)	
NRT: 3-4 weeks	0.53 (0.29-0.97)	
NRT: 1-2 weeks	0.16 (0.11-0.24)	
Behavioral only	0.47 (0.25-0.90)	
Unassisted	0.48 (0.37-0.64)	

[a] Adjusted for the effect of number of cigarettes smoked per day, sex, age, race/ethnicity, education, occupation, and family income.

Figure 1 here……

revealed some evidence of an association ($p = 0.025$). The highest cessation rate was among those who used prescription medication and behavioral counseling (20.4%) followed by those who used NRT and behavioral counseling (17.4%), attempted to quit unassisted (16.4%), used behavioral counseling only (16.1%), and those who used prescription medication only (15.3%). The lowest cessation rate was among those who only used NRT as a quitting method (12.3%).

Figure 2 here……

Table 2 also provides adjusted odds ratios for the association of duration of pharmacotherapy use with the probability of smoking cessation. Figure 2 shows the adjusted cessation rates for various durations of pharmacotherapy use. Consistent with the unadjusted results in Table 1, the adjusted results in Table 2 also provide evidence ($p < 0.001$) of an association between duration of pharmacotherapy use and successful cessation. As shown in Figure 2, cessation rates were highest among those who used prescription medication for 5+ weeks (28.8%) and those who used NRT for 5+ weeks (27.8%). Cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%.

Cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

The results pertaining to the association of other covariates with successful cessation were very similar in the multivariable regression models for method of quit attempt and duration of pharmacotherapy use. These results were consistent with bivariate associations reported above, except for the fact that there was very little evidence for an association of race/ethnicity and smoking cessation in multivariable analyses.

DISCUSSION

This is the first population-based study to examine the association of successful smoking cessation and duration of use of prescription medication as well as NRT for smoking cessation. We found that using pharmacotherapy for five weeks or longer is associated with a higher probability of cessation compared to using pharmacotherapy for shorter durations, only using behavioral counseling or trying to quit unassisted.

Our findings are consistent with the results of a study of a hospital-based cessation program where participants who used NRT for 5 weeks or longer were found to have a higher cessation rate at 6-month follow-up.[28] However, our findings are not consistent with those of a population-based study which did not find any evidence that using NRT for more than 6 weeks versus not using NRT at all was associated with smoking cessation.[12] In that study, the survey response rate was low, the sample size was small and prescription medications were not examined. These factors could explain the discrepant findings.

While we found that smokers who used pharmacotherapy for at least 5 weeks have a far more favorable outcome than others, only 11% of the sample was in this group and notably about 70% of the sample did not use any pharmacotherapy for smoking cessation. Previous research indicates that barriers to the use of these cessation aids include concerns with their addictiveness, cost and side effects, as well as the belief that a treatment of any kind is not needed to quit smoking.[29-31]

A major limitation of the study is that there is a strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use varenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a

short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse. Furthermore, because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race, education, occupation, and income, it is possible that there might be residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation.

Another weakness of the study relates to the fact that smokers forget many quit attempts [7, 32] and they are more prone to recall attempts that used pharmacotherapy than those that did not.[14, 17] Such recall bias can underestimate the success rate of attempts at quitting with the aid of pharmacotherapy.[17]

A strength of this study was that it used a large nationally representative sample with a relatively high response rate. This was the first time that questions about the duration of pharmacotherapy use were included in the TUS-CPS. We know of no other national data on the general population that provide information on this variable. Many population-based studies of pharmacotherapies for smoking cessation have found these aids to be ineffective. It is likely that if these studies were able to account for duration of use, their findings would have been different. However, data on duration of use is not routinely collected and it would require a large sample size to provide a reliable estimate of the effect of using these medications for duration of a few weeks. Nonetheless, it would likely be an important area for further research to establish the relationship between duration of use of pharmacotherapy and successful quitting in the general population.

Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids might also be successful in the general population if they are used for at least five weeks.

CONTRIBUTORSHIP STATEMENT

We assure that all authors included on a paper fulfill the criteria of authorship. All have contributed in the conception and design, analysis and interpretation of data, drafting of the article and revising it critically for important intellectual content, and final approval of the version to be published. In addition we also assure that there is no one else who fulfills the criteria but has not been included as an author. Dr. Mohammad Siahpush was instrumental in conceptualization of research study, data analysis, and writing of the initial draft of the manuscript. Raees Shaikh and Molly McCarthy contributed in the development of study, data analysis, and preparation of the results section. They also helped with writing the manuscript and editing it for final submission. Dr. Asia Sikora helped with literature review, provided inputs for the materials and method section, and contributed to writing and editing the manuscript. Dr. Melissa Tibbits was involved with literature review and data analysis and provided her inputs to the entire manuscript. Dr. Gopal Singh was involved with formulation of research study and helped in the data analysis and contributed in the writing and editing of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) declare that no support was received from any organization for the submitted work and that there was no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, neither did we have other relationships or activities that could appear to have influenced the submitted work. No competing interests to declare.

ETHICAL APPROVAL STATEMENT

No ethical approval was required for this work.

DATA SHARING STATEMENT

No additional data used or available.

FIGURE LEGENDS

Figure1: Adjusted Cessation Rate by Method of Quit Attempt

Figure2: Adjusted Cessation Rate by Duration of Pharmacotherapy Use

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Association between duration of use of pharmacotherapy and smoking cessation: Findings from a national survey~~Effectiveness of pharmacotherapy for smoking cessation in the general population: Duration of use matters~~

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ABSTRACT

~~Aim~~Objective: To investigate the association of the duration of use of prescription medications and nicotine replacement therapy (NRT) with smoking cessation using a national sample of the general population in the United States, controlling for nicotine dependence and sociodemographic variables.

Setting: United States

Participants:

~~Methods:~~ We used data from the 2010-2011 Tobacco Use Supplement to the US Current Population Survey. We limited the analysis to current daily smokers who made a quit attempt in the past year and former smokers who were a daily smoker one year prior to the survey (n = 8 263). Respondents were asked about duration of use of prescription medication (v~~V~~arenicline, b~~B~~upropion, other) and NRT (nicotine patch, gum/lozenges, nasal spray, and inhaler) for smoking cessation.

Primary Outcome Measure: Successful Smoking Cessation. Individuals who reported to have smoked at least 100 cigarettes in their lifetime but were not smoking at all at the time of the interview and were a daily smoker one year prior to the interview were considered to have successfully quit smoking.

Results: After adjusting for daily cigarette consumption and sociodemographic covariates, we found ~~overwhelming~~ evidence ~~(p < 0.001)~~ for ~~a~~an~~n~~ ~~association between~~association between duration of pharmacotherapy use and smoking cessation (p<0.001). Adjusted cessation rates for those who used prescription medication or NRT for 5+ weeks were 28.8% and 27.8%, respectively. Adjusted cessation rates for those who used prescription medication or NRT for

less than five weeks varied from 6.2% to 14.5%. Adjusted cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

Conclusion: Use of ~~P~~pharmacotherapy ~~ies for smoking cessation~~ for at least five weeks is associated with increased likelihood of successful smoking cessation. ~~can be effective in the general population if used for at least five weeks.~~ Results suggest that e~~E~~ncouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation.

ARTICLE SUMMARY

Strengths and limitations of the study:

- This was the first population-based study to examine the association between the duration of use of prescription medication as well as NRT for smoking cessation ~~as a predictor of~~and successful smoking cessation, controlling for nicotine dependence and sociodemographic variables.
- A strength of this study was that it used a large nationally representative sample with a relatively high response rate.
- Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids ~~could~~ might also be ~~effective~~ successful in the general population if they are used for at least five weeks.
- A strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa, was a major limitation of this study. Recall bias, especially related to the smokers previous quit attempts and the observational nature of the study precluding the establishment of a causal link were between the

duration of pharmacotherapy use and successful smoking cessation, were the ~~major~~ other limitations. ~~of this study.~~

INTRODUCTION

Clinical trials provide strong evidence that pharmacotherapy for smoking cessation including various forms of nicotine replacement therapies (NRT), b~~B~~upropion, or v~~V~~arenicline greatly increase the chances of a successful smoking cessation attempt.[1, 2] However, observational population-based studies have shown mixed results. While some have shown that pharmacotherapy increases smoking cessation rates,[3-6] others have concluded the opposite.[7-11] Yet, other population-based studies have shown no difference in cessation rates between those who use and those who do not use pharmacotherapy.[12, 13] The population-based reports that have found no favorable effect of pharmacotherapy have been criticized for not controlling for nicotine dependence,[14-16] which is a predictor of abstinence and is usually higher among smokers who choose to use pharmacotherapy for smoking cessation.[4, 14, 17, 18] Some of the analyses that have controlled for nicotine dependence have found a favorable effect of pharmacotherapy on smoking cessation[3, 4, 19] but others have not.[7]

An additional confounder that rarely is taken into account in population-based studies is duration of use of pharmacotherapy, which has been found to be associated with treatment success in clinical trials.[20-22] We know of one population-based study which examined the association of duration of use of pharmacotherapy with smoking cessation and found no association.[12] This study was conducted in the US where NRT can be purchased over the

counter and medications such as bBupropion and vVarenicline can only be obtained as prescription drugs.

While clinical trials have high internal validity and can provide evidence for the efficacy of pharmacotherapy, observational population-based studies can address effectiveness of these therapies under conditions that they are intended to be used.[14] Furthermore, while clinical trials provide confidence in causal associations, population-based studies are strong in representativeness and external validity. Thus, both are needed to advance the science of smoking cessation.[19]

There is no literature on population-based studies that examine the association of duration of NRT and prescription medication use with smoking cessation. Our aim was to use a large representative sample of the general population in the United States and investigate the association of the duration of use of prescription medications and NRT with smoking cessation, controlling for nicotine dependence and sociodemographic variables.

METHODS

Data

We used data from the 2010-2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), sponsored by the National Cancer Institute and administered by the US Census Bureau in May 2010, August 2010, and January 2011.[23] The TUS-CPS is administered as a part of the CPS, which is a monthly national survey of representative households by the US Census Bureau and the Bureau of Labor Statistics.[24] The TUS-CPS utilizes a multistage probability sampling of individuals 15 years and older, from a sample of approximately 56,000 housing units, in turn selected from 792 primary sampling units. The average response rate for CPS for the 3 months of surveys used in this study was 93%, whereas for the TUS it was 63%.

Measuremen~~s~~t

Successful smoking cessation:

Individuals who reported to have smoked at least 100 cigarettes in their entire life but were not smoking at all at the time of the interview and were a daily smoker one year prior to the interview ("Around this time 12 months ago were you smoking everyday …?") were considered to have successfully quit smoking (n = 1 769). Those who reported to have quit within the last four weeks were excluded from the analysis (n = 322). Individuals who reported to have smoked at least 100 cigarettes in their entire life, were smoking every day at the time of the interview and had made a quit attempt in the past year were considered to have failed in their quit attempt (n = 7 304). Individuals who reported to have used both prescription medication and NRT for smoking cessation were excluded from the analysis (n = 488) because after subdividing this group by categories of duration of use for prescription medication and NRT, some of the subgroup sample sizes were extremely small. The total sample size for the study was 8 263 respondents, consisting of 1 379 who successfully quit smoking and 6 884 whose quit attempt was not successful.

Assisted quit attempt and duration of pharmacotherapy use:

Both daily and former smokers were asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used a prescription pill called (a) Chantix or ~~Varenicline~~varenicline, (b) z~~Z~~yban, b~~B~~upropion, or w~~W~~ellbutrin, or (b) other prescription pills. They were also asked in three separate questions to indicate whether, in their last quit attempt in the past year, they used (a) a nicotine patch, (b) nicotine gum or nicotine lozenge, or (c) nicotine nasal spray or nicotine inhaler. They were also asked to indicate how many days, weeks or months they used these prescription and/or NRT medications.

Furthermore, both daily and former smokers were asked three separate questions about use of behavioral counseling in their last quit attempt in the past year. They were asked if they used a (a) telephone helpline or quitline, (b) one-on-one counseling or (c) stop smoking clinic, class or support group. Based on the questions about use of prescription medication, NRT and behavioral counseling, we created the following two categorical variables:

Method of quit attempt

- Prescription medication only
- Prescription medication and behavioral counseling
- NRT only
- NRT and behavioral counseling
- Behavioral counseling only
- Unassisted

Duration of use of pharmacotherapy

- Prescription medication: 5+ weeks
- Prescription medication: 3-4 weeks
- Prescription medication: 1-2 weeks1
- NRT: 5+ weeks
- NRT: 3-4 weeks
- NRT: 1-2 weeks
- Behavioral counseling only
- Unassisted

We categorized duration of use of pharmacotherapy based on a systematic review of studies assessing adherence to smoking cessation medication.[20] In categorizing duration of

use, we made no distinction between whether or not the medication was combined with behavioral counseling as this distinction was inconsequential in the analysis.

Statistical analysis

We used multivariable logistic regression models to compute adjusted odds ratios for the association of the method of quit attempt and duration of use of pharmacotherapy with successful smoking cessation. Sampling weights were taken into account in the computation of parameter estimates. We computed *p*-values using the jackknife, which is an unbiased estimator for a statistic and a data-dependent method to calculate standard errors.[25] All models controlled for daily cigarette consumption (current daily consumption among daily smokers, and daily consumption 12 months ago among former smokers), age, race/ethnicity, education, occupation, and family income. In order to account for the missing income data, CPS uses one of the three imputation methods, relational imputation, longitudinal edits, or hot deck allocation. Details of these methods are described elsewhere.[26] In multivariable logistic regression models, we omitted observations that had a missing value for any of the covariates. This constituted 1.7% of the full sample in the analysis pertaining to the method of quit attempt (n = 142) and 6.3% of the full sample in the analysis pertaining to duration of pharmacotherapy use (n = 491). We used the logistic regression results to compute adjusted cessation rates by method of quit attempt and duration of use of pharmacotherapy. These adjusted rates were computed by fixing covariates at their means in the fitted models.[27]

RESULTS

Sample characteristics and bivariate associations

Table 1. Weighted sample characteristics and unadjusted smoking cessation rates across categories of each covariate

Variable	% in sample	% quit	*p*- value
Method of quit attempt			0.074
Prescription only	10.01	18.54	
Prescription plus behavioral support	1.14	23.8	
NRT only	18.26	14.32	
NRT plus behavioral support	2.54	18.98	
Behavioral only	1.36	18.59	
Unassisted	66.68	17.16	
Duration of pharmacotherapy use			<0.001
Prescription: 5+ weeks	4.9	34.38	
Prescription: 3-4 weeks	1.43	16.82	
Prescription: 1-2 weeks	1.89	15.28	
NRT: 5+ weeks	6.04	30.65	
NRT: 3-4 weeks	1.48	19.9	
NRT: 1-2 weeks	13.48	7.36	
Behavioral only	1.42	18.59	
Unassisted	69.36	17.16	
Cigarettes per day			<0.001
0-9	24.48	15.08	
10-14	30.04	12.58	
15-19	10.31	12.58	
20-29	29.23	21.83	
30+	5.93	29.59	
Sex			0.975
Female	50.12	16.99	
Male	49.88	17.02	
Age			< 0.001
18-24	11.79	15.32	
25-39	33.08	18.17	
40-54	32.33	14.49	
55+	22.8	19.77	
Race/Ethnicity			0.003
Non-Hispanic White	76.17	17.99	
Non-Hispanic Black	11.34	12.98	
Hispanic	7.39	15.73	
Other	5.09	13.15	
Education			<0.001
Less than high school	15.25	13.15	
High school diploma	73.34	16.74	
Bachelor's degree	11.41	23.91	
Occupation			<0.001
Professional	14.33	20.99	
Service	12.31	13.96	
Sales	14.5	18.45	
Farming/construction/production	17.28	13.08	
Unemployed	12.01	13.81	
Not in labor force	29.57	19.24	
Family income			<0.001

<$25,000	36.27	13.94
$25,000-$49,000	31.65	17.21
$50,000-$99,000	23.86	19.63
$100,000+	8.23	22.17
Full sample		17.01

Note: Sample size for each covariate varies from 7 820 to 8 263 depending on the number of missing values for that covariate. *P*-values are based on chi-square tests.

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Weighted sample characteristics are shown in Table 1. About 66.7% of the sample reported to have made an unassisted quit attempt; 10% used only prescription medication; 1.1% used prescription medication plus behavioral counseling; 18.2% used only NRT; 2.5% used NRT plus behavioral therapy; and 1.3% used only behavioral counseling. When broken down by duration of use, while most of those who used prescription medication did so for five or more weeks, the great majority of those who used NRT did so for 2 weeks or less. The reported number of cigarettes smoked per day was 14 or less for about 54.5% of the sample. Age was distributed with 11.8% of the sample under 25 years of age, 33% between 25-39 years, 32.3% between 40-54 years, and 22.8% 55 years or older. The sample was 76% non-Hispanic white, 11.3% non-Hispanic Black, 7.4% Hispanic, and 5% of other race/ethnicity. About 15.2% of the sample did not have a high school diploma, 73.3% had high school diploma, and 11.4% had at least a bachelor's degree. The distribution of family income was skewed such that over a third of the sample had an income of less than $25 000 and less than a tenth of the sample had an income of $100 000 or greater.

Table 1 also provides smoking cessation rates across categories of each covariate, indicating bivariate (unadjusted) associations between the covariates and quitting. Cessation rate was 17% in the whole sample. There was very little evidence that method of quit attempt was associated with cessation rate ($p < 0.074$). However, ~~there was overwhelming evidence that~~ the duration of pharmacotherapy use ~~was associated with quitting~~ ($p < 0.001$), ~~such that the use of prescription medication or NRT for 5+ weeks was associated with remarkably higher cessation rates compared to the use of these products for shorter durations, behavioral counseling or unassisted quit attempts.~~ n~~-~~Number of cigarettes smoked per day ~~had a curvilinear relationship with cessation such that those who smoked 0-9 cigarettes and those who smoked 20+ cigarettes per day had a higher cessation rate than others~~ (p~~P~~ < 0.001), a~~.~~ Age ~~had a curvilinear relationship with cessation in that individuals in the 25-39 and 55+ age categories had notably higher cessation rates than others~~ ($p < 0.001$), and ra~~.~~ Race/ethnicity ($p = 0.003$) were~~was~~ all associated with quitting~~.~~ ~~such that Non-Hispanic Whites had the highest~~

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~~and non-Hispanic Blacks had the lowest cessation rates (p = 0.003).~~ HHigher socioeconomic status as measured by education, occupation, and income was associated with a higher cessation rate (p < 0.001 for all three indicators of socioeconomic status). Sex had no association with cessation.

Adjusted results from multivariable logistic regression models

Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence of an association between quitting method and successful cessation, the adjusted results

Table 2. Adjusted[a] odds ratios and 95% confidence intervals (CI) for the association of method of quit attempt and duration of pharmacotherapy use with the probability of successful smoking cessation

	OR (95% CI)	*p*-value
Method of quit attempt (n = 8 121)		0.025
Prescription only	1.00	
Prescription plus behavioral support	1.42 (0.76-2.66)	~~0.277~~
NRT only	0.78 (0.59-1.02)	~~0.072~~
NRT plus behavioral support	1.17 (0.73-1.86)	~~0.513~~
Behavioral only	1.06 (0.57-1.97)	~~0.844~~
Unassisted	1.09 (0.87-1.37)	~~0.464~~
Duration of pharmacotherapy use (n = 7 772)		< 0.001
Prescription: 5+ weeks	1.00	
Prescription: 3-4 weeks	0.42 (0.21-0.84)	~~0.014~~
Prescription: 1-2 weeks	0.38 (0.22-0.66)	~~0.001~~
NRT: 5+ weeks	0.95 (0.67-1.36)	~~0.786~~
NRT: 3-4 weeks	0.53 (0.29-0.97)	~~0.040~~
NRT: 1-2 weeks	0.16 (0.11-0.24)	~~<0.001~~
Behavioral only	0.47 (0.25-0.90)	~~0.022~~
Unassisted	0.48 (0.37-0.64)	~~<0.001~~

[a] Adjusted for the effect of number of cigarettes smoked per day, sex, age, race/ethnicity, education, occupation, and family income.

Figure 1 here……

~~Table 2 provides adjusted odds ratios for the association of method of quit attempt with the probability of smoking cessation. Figure 1 shows the adjusted cessation rates for various quitting methods. Unlike the unadjusted results in Table 1 which provided very little evidence~~

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~~of an association between quitting method and successful cessation, the adjusted results~~ revealed some evidence of an association (p = 0.025). The highest cessation rate was among those who used prescription medication and behavioral counseling (20.4%) followed by those who used NRT and behavioral counseling (17.4%), attempted to quit unassisted (16.4%), used behavioral counseling only (16.1%), and those who used prescription medication only (15.3%). The lowest cessation rate was among those who only used NRT as a quitting method (12.3%).

Figure 2 here……

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Table 2 also provides adjusted odds ratios for the association of duration of pharmacotherapy use with the probability of smoking cessation. Figure 2 shows the adjusted cessation rates for various durations of pharmacotherapy use. Consistent with the unadjusted results in Table 1, the adjusted results in Table 2 also provide ~~strong~~ evidence (p < 0.001) of an association between duration of pharmacotherapy use and successful cessation. As shown in Figure 2, cessation rates were highest among t~~T~~hose who used prescription medication for 5+ weeks (28.8%) and those who used~~or~~ NRT for 5+ weeks (27.8%)~~had higher cessation rates, 28.8% and 27.8% respectively, than others~~. Cessation rates for those who used prescription medication or NRT for less than five weeks varied from 6.2% to 14.5%. Cessation rates for those who used only behavioral counseling and those who attempted to quit smoking unassisted were 16.1% and 16.4%, respectively.

The results pertaining to the association of other covariates with successful cessation were very similar in the multivariable regression models for method of quit attempt and duration of pharmacotherapy use. These results were consistent with bivariate associations reported above, except for the fact that there was very little evidence for an association of race/ethnicity and smoking cessation in multivariable analyses.

DISCUSSION

This is the first population-based study to examine the association of successful smoking cessation and duration of use of prescription medication as well as NRT for smoking cessation ~~as a predictor of successful smoking cessation~~. We found that using pharmacotherapy for five weeks or longer is associated with a ~~remarkably~~ higher probability of cessation compared to

using pharmacotherapy for shorter durations, only using behavioral counseling or trying to quit unassisted.

Our findings are consistent with the results of a study of a hospital-based cessation program where participants who used NRT for 5 weeks or longer were found to have a higher cessation rate at 6-month follow-up.[28] However, our findings are not consistent with those of a population-based study which did not find any evidence that using NRT for more than 6 weeks versus not using NRT at all was associated with smoking cessation.[12] In that study, the survey response rate was low, the sample size was small and prescription medications were not examined. These factors could explain the discrepant findings.

While we found that smokers who used pharmacotherapy for at least 5 weeks have a far more favorable outcome than others, only 11% of the sample was in this group and notably about 70% of the sample did not use any pharmacotherapy for smoking cessation. Previous research indicates that barriers to the use of these cessation aids include concerns with their addictiveness, cost and side effects, as well as the belief that a treatment of any kind is not needed to quit smoking.[29-31]

A major ~~weakness~~limitation of the study is that there is a strong possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use v~~V~~arenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse. Furthermore, because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race, education, occupation, and income, it is possible that there might be residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation.

Another ~~-~~weakness of the study relates to the fact that smokers forget many quit attempts [7, 32] and they are more prone to recall attempts that used pharmacotherapy than those that did not.[14, 17] Such recall bias can underestimate the success rate of attempts at

quitting with the aid of pharmacotherapy.[17] ~~Another limitation of the study is that because of its observational nature, our study cannot establish a causal link between the duration of pharmacotherapy use and successful smoking cessation. While our analyses controlled for several important predictors of cessation including daily cigarette consumption, age, race, education, occupation, and income, it is possible that there is residual confounding related to variables such as depression, anxiety, alcohol use, and financial stress.[33, 34] Such confounding would further weaken the ability of the study to imply causation. Moreover, there is a possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] Smokers who use Varenicline to quit smoking are asked to completely stop smoking one week after their quit date.[36] Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse.~~

A strength of this study was that it used a large nationally representative sample with a relatively high response rate. This was the first time that questions about the duration of pharmacotherapy use were included in the TUS-CPS. We know of no other national data on the general population that provide information on this variable. Many population-based studies of pharmacotherapies for smoking cessation have found these aids to be ineffective. It is likely that if these studies were able to account for duration of use, their findings would have been different. However, data on duration of use is not routinely collected and it would require a large sample size to provide a reliable estimate of the effect of using these medications for duration of a few weeks. Nonetheless, it would likely be an important area for further research to establish the relationship between duration of use of pharmacotherapy and successful quitting in the general population.

Our results strengthen the findings of clinical trials about the efficacy of pharmacotherapy for smoking cessation and indicate that these aids ~~can~~might also be ~~effective~~ successful in the general population if they are used for at least five weeks. ~~Smokers who intend to quit should be encouraged to use pharmacotherapy and adhere to their recommended duration of use.~~

CONTRIBUTORSHIP STATEMENT

We assure that all authors included on a paper fulfill the criteria of authorship. All have contributed in the conception and design, analysis and interpretation of data, drafting of the article and revising it critically for important intellectual content, and final approval of the version to be published. In addition we also assure that there is no one else who fulfills the criteria but has not been included as an author. Dr. Mohammad Siahpush was instrumental in conceptualization of research study, data analysis, and writing of the initial draft of the manuscript. Raees Shaikh and Molly McCarthy contributed in the development of study, data analysis, and preparation of the results section. They also helped with writing the manuscript and editing it for final submission. Dr. Asia Sikora helped with literature review, provided inputs for the materials and method section, and contributed to writing and editing the manuscript. Dr. Melissa Tibbits was involved with literature review and data analysis and provided her inputs to the entire manuscript. Dr. Gopal Singh was involved with formulation of research study and helped in the data analysis and contributed in the writing and editing of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) declare that no support was received from any organization for the submitted work and that there was no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, neither did we have other relationships or activities that could appear to have influenced the submitted work. No competing interests to declare.

ETHICAL APPROVAL STATEMENT

No ethical approval was required for this work.

DATA SHARING STATEMENT

No additional data used or available.

FIGURE LEGENDS

Figure1: Adjusted Cessation Rate by Method of Quit Attempt

Figure2: Adjusted Cessation Rate by Duration of Pharmacotherapy Use

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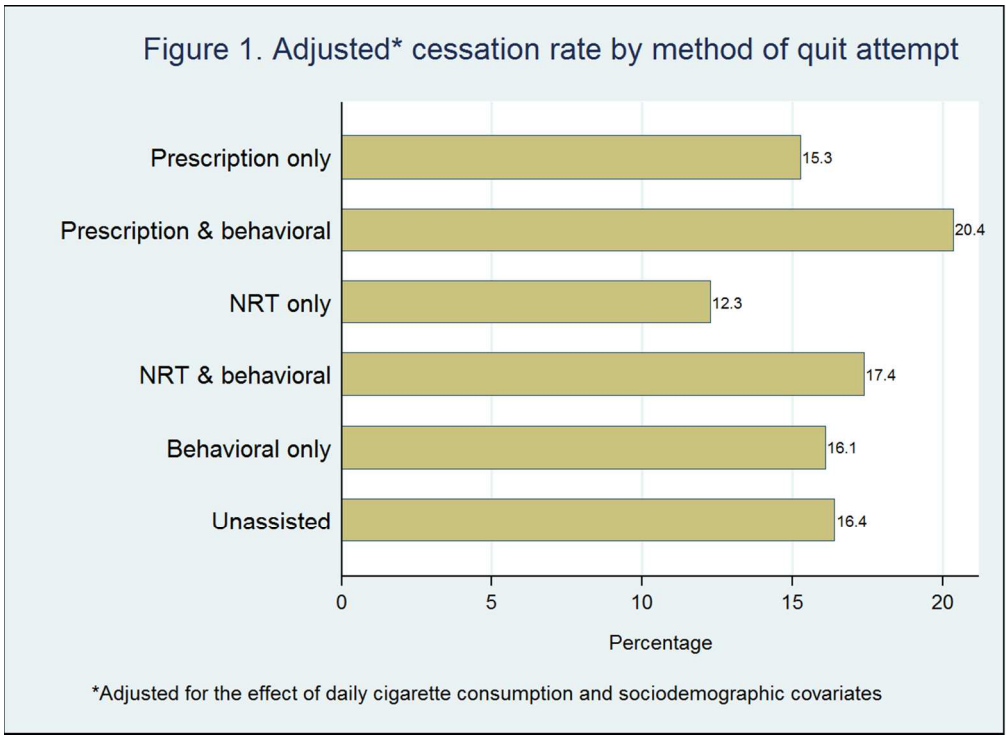

Figure1- Adjusted Cessation Rate by Method of Quit Attempt
105x76mm (300 x 300 DPI)

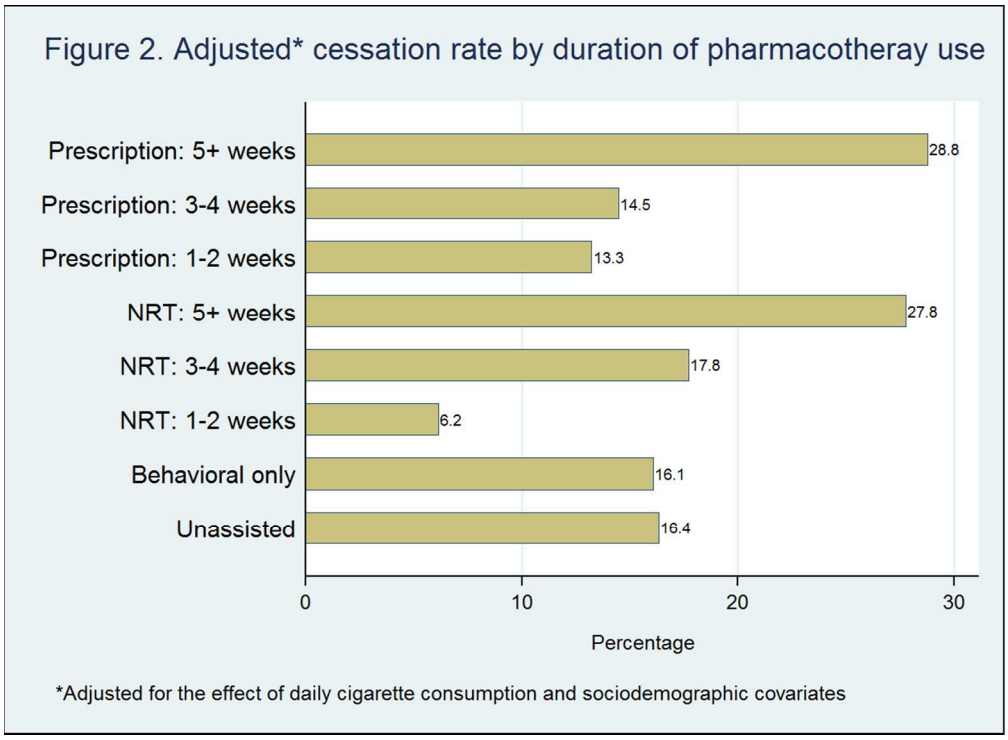

Figure2- Adjusted Cessation Rate by Duration of Pharmacotherapy Use
105x76mm (300 x 300 DPI)

STROBE Statement Checklist

	Checklist
Title and abstract	Yes
Introduction	
Background/rationale	Yes
Objectives/Aims	Yes
Methods	
Data sources	Yes
Measurement	Yes
Statistical methods	Yes
Results	
Descriptive data	Yes
Main results	Yes
Discussion	
Key results	Yes
Interpretation	Yes
Generalizability/Strengths	Yes
Limitations	Yes
Other information	
Funding	Yes
Competing Interest Statement:	Yes
Ethical Approval Statement	Yes
Contributorship Statement	Yes