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Quitting Smoking Before and After Varenicline: A Population Study Based on Two Representative Samples of U.S. Smokers

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Abstract

Background—Varenicline is known to have greater efficacy than other pharmacotherapy for treating nicotine dependence and has gained popularity since its introduction in 2006. This study examines if adding varenicline to existing pharmacotherapies increased the population cessation rate.

Methods—Data are from two cross-sectional U.S. Current Population Surveys—Tobacco Use Supplements (2003 and 2010–2011). Smokers and recent quitters 18 or older (N=34,869 in 2003, N=27,751 in 2010–2011) were asked if they had used varenicline, bupropion or nicotine replacement therapies (NRT) in their most recent quit attempt. The annual cessation rate, the percent of smokers who were quit for ≥ 3 months, was compared between surveys.

Results—Varenicline use increased from 0% in 2003 to 10.9% in 2010–2011, while use of bupropion decreased from 9.1% to 3.5%, and NRT from 24.5% to 22.4%. Use of any pharmacotherapy increased 2.4 percentage points. Varenicline users stayed on cessation aids longer and were less likely to relapse than users of other pharmacotherapies in the first three months of a quit attempt, after which the difference was no longer significant. The change in annual cessation rate was negligible, from 4.5% in 2003 to 4.7% in 2010–2011 (P=0.36).

Conclusion—Addition of varenicline to the list of approved cessation aids has mainly led to displacement of other therapies. As a result, there was no meaningful change in population

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COMPETING INTERESTS

None

CONTRIBUTORSHIP

Study concept and design: S-HZ, ACG, SEC
Acquisition of data: S-HZ, SW
Analysis and interpretation of the data: All authors
Drafting of the manuscripts: S-HZ, SEC, ACG
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cessation rate despite a remarkable increase in varenicline use. The population impact of a new therapy is a function of more than efficacy or reach of the therapy.

Keywords

Cessation; Nicotine; Health Services

INTRODUCTION

Varenicline generated considerable excitement when it was first shown to be efficacious in the treatment of nicotine dependence.[1–3] Part of the excitement was due to the fact that varenicline seemed to work better than existing therapies. The first group of clinical trials found that varenicline outperformed bupropion, an established first line prescription medication for nicotine dependence treatment.[1,4,5] Later trials confirmed its superior effect over nicotine replacement therapy (NRT), which is available over the counter.[6,7] Despite some early concern about its potential risk for increasing neuropsychiatric symptoms,[8–11] varenicline enjoys a strong market share as a relatively new and effective pharmacotherapy for smoking cessation.[12,13] It continues to attract attention from researchers and practitioners alike.[14–19]

Several studies have investigated how much the introduction of varenicline has led to an increase in overall use of pharmacotherapy. These studies differ in sample size and in methodology. Some have found significant increases while others have not[20,21,17,22]. No study to date has addressed the question of whether varenicline has impacted the population cessation rate.

The present study focuses on the effects of varenicline on smoking cessation at the population level. It compared the population use of pharmacotherapies and the smoking cessation rate before and after the introduction of varenicline in the U.S., using two large data sets from an ongoing national survey.

Several factors may work to increase varenicline's impact on smoking cessation. First, not long after varenicline came to the market, an updated U.S. Clinical Practice Guideline for treating nicotine dependence was issued.[23] The new guideline strongly recommends varenicline and notes its superior effect over NRT and bupropion. Second, varenicline came to the market at the time when there was a greater emphasis among the treatment community on increasing consumer demand for pharmacotherapy.[24–26] And finally, the requirement of a prescription could increase varenicline's impact since it requires physician involvement, which is known to increase cessation.[23,27]

To assess the population impact of varenicline, we examined cross-sectional data from two U.S. Current Population Surveys—Tobacco Use Supplement (CPS-TUS). The first survey was conducted 3 years before varenicline came onto the market and the second about 4 years after its introduction. We chose these particular surveys because they included questions about utilization of various cessation aids. The surveys sampled a large number of smokers that were representative of the smoking population in the U.S., making the data set appropriate for analysis of the population impact of varenicline. There were two hypotheses

being tested: 1) The addition of varenicline to the list of approved cessation aids would increase the utilization rate of pharmacotherapy; 2) The increased use of pharmacotherapy would increase the smoking cessation rate at the population level.

METHODS

Data Source

The Tobacco Use Supplement (TUS) is a periodic survey attached to the CPS and administered by the U.S. Census Bureau. The CPS uses a multi-stage stratified sampling procedure to interview a nationally representative sample of households of the non-institutionalized civilian U.S. population aged 15 and older. Detailed information on the design of the CPS has been published elsewhere.[28,29] Since 1992, the TUS surveys have been conducted roughly every three years in conjunction with the regular CPS. The sample size is about 240,000 individuals in each survey period. This study examined two CPS-TUS surveys, the 2003 and the 2010–2011: the former was administered 3 years before varenicline went on the market, and the latter 4 years after. The 2003 CPS-TUS had 183,810 respondents who were 18 years or older, including 34,869 smokers (smoked 12 months prior to the survey). The 2010–2011 CPS-TUS had 171,365 respondents age 18 or older including 27,751 smokers. The response rate for TUS, calculated as the number of people who completed the survey divided by the number who were eligible for it, was 63.6% for the 2003 survey and 61.2% for the 2010–2011 survey.

Participants

Subjects included in this study were self-respondents aged 18 or older who answered “everyday” or “some days” to the survey question: “Around this time 12 months ago, were you smoking cigarettes every day, some days, or not at all?”

Measures

Current smokers were defined as having smoked at least 100 cigarettes in their lifetime, and who were smoking everyday or some days at the time of the interview. Recent former smokers were those who smoked 12 months prior but were not smoking at the time of survey. A quit attempt was defined as having tried to quit and made it for at least 24 hours. The “annual cessation rate” was the percentage of those who had been quit for at least 3 months at the time of the interview among those who were smoking 12 months before the interview.[30,31]

The survey asked those who had made a quit attempt in the last 12 months, “thinking back to the last time you tried to quit smoking in the past 12 months—did you use any of the following products: a nicotine patch; nicotine gum or nicotine lozenge; nicotine nasal spray or nicotine inhaler; a prescription pill called Chantix or Varenicline; a prescription pill called Zyban, Bupropion, or Wellbutrin; another prescription pill?” Respondents indicated yes or no to each. Those who refused to answer were excluded from the analysis (about 1% of respondents). The use of NRT included those who had used the 1) patch, 2) gum, 3) spray/inhaler, or 4) lozenge. All respondents who indicated that they had used pharmacotherapy

were asked about the length of usage. If they used more than more therapy, the survey did not ask for specific length for each therapy separately.

Analysis

When comparing data between the two surveys, we defined someone as having used a particular therapy whether or not they used multiple therapies. Thus, the proportion of smokers using varenicline included all those who had used varenicline regardless of whether they had also used NRT or bupropion or other pharmacotherapies. In the survival analysis of the 2010–2011 survey, the focus was on comparing use of the new product against that of the established products. Thus, the analysis coded the new product use (varenicline) first, then coded established product use (NRT/bupropion). Therefore, if someone had used varenicline and NRT, they were coded as having used the former and not the latter.

Descriptive analysis was conducted using SAS statistical software, version 9.4 to obtain point estimates of demographic variables, use of medications, quit attempts, annual quit rates, and quitting for 3 months.[32] All point estimates were weighted using the published weights for the surveys, which accounted for the demographic makeup of the population being sampled and adjusted for nonresponse bias.[33,34] Responses of “don’t know” or refused were considered missing and were excluded from the analysis where the variable was involved. The variances of the point estimates were estimated by SUDAAN, version 11 as recommended by CPS to establish 95% confidence intervals (CI) for the point estimates.[35] Survival analyses were conducted to calculate the length of the last quit attempt using SUDAAN’s “kapmeier” procedure. Separate analyses were done for all smokers (daily and non-daily) and for daily smokers alone, since daily smokers are known to have lower quit rates than non-daily smokers. The analysis of the population dataset was approved by the UCSD Human Research Protection Program.

RESULTS

Table 1 shows the rate of pharmacotherapy use by demographics; patterns of use were similar in the two surveys. In both 2003 and 2010, women were more likely to use pharmacotherapy than men. Smokers from ethnic minority backgrounds, except American Indians, were less likely to use pharmacotherapy than Whites. Young smokers, especially those aged 18–24, were less likely than older smokers to use pharmacotherapy. Pharmacotherapy use generally increased with education level. Overall, there is an increase in usage between 2003 and 2010, although the differences by subgroups are not consistently significant.

Table 2 compares the rates of pharmacotherapy use in 2003 to rates in 2010. The top half of Table 2 includes all smokers and the bottom half includes daily smokers only. Among all smokers, usage rates increased from 28.7% to 31.1% ($P < 0.01$). Examination by type of pharmacotherapy showed an obvious increase in the use of varenicline from 0% to 10.9%. Meanwhile, the use of bupropion dropped dramatically, from 9.1% to 3.5%. The use of any NRT also dropped significantly from 24.5 to 22.4, due to decreased use of the nicotine patch and nicotine spray/inhaler. There was no significant change in the use of gum/lozenge.

Table 2 also shows that only the use of a single pharmacotherapy changed from 2003 to 2010 (20.0% to 23.0% for all smokers). The availability of varenicline did not lead to an increase in the use of multiple pharmacotherapies.

The bottom half of Table 2, which shows the overall use of pharmacotherapy among the subset of daily smokers, had data patterns similar to those described for all smokers. The usage rates for daily smokers were higher, but changed proportionately from 2003 to 2010, from 32.9% to 35.7%. There was a dramatic increase in the use of varenicline, from 0% to 12.8%, and there was a significant drop in the use of bupropion, patch, and inhaler/spray.

Use of varenicline, which requires a prescription, was associated with doctor's advice in the 2010–2011 survey among all smokers. The percent of having received doctor's advice to quit smoking was much higher among those who used varenicline (74.0%, 95% CI 71.3–76.6) than those who used NRT/bupropion (59.7%, 95% CI 57.6–61.9) and both groups were in turn more likely to have received doctor's advice than those who did not use any pharmacotherapy (44.5%, 95% CI 43.3–45.7).

Figure 1 shows the relapse curves for those who used the new product, varenicline, and those who used the established pharmacotherapies (NRT/bupropion), based on the 2010–2011 survey. In this analysis, those who used other pharmacotherapy in addition to varenicline were grouped with those who only used varenicline. Again, two analyses were done. The analysis shown in Figure 1a included all smokers (those who reported smoking daily or occasionally 12 months before the survey). Figure 1b included only those who reported smoking daily 12 months before the survey.

These two panels of curves show a very similar pattern. Smokers who used varenicline in their quit attempts were more likely to stay quit over time than those who used NRT/bupropion ($F=6.3$, $P<0.05$ for the upper panel and $F=7.3$, $P<0.01$ for the lower panel). The difference between the two curves, however, was much larger in the first 84 days, or 12 weeks, which is the recommended length of use for varenicline. It became much smaller and not statistically significant after that, mainly due to the drop in the varenicline curve after that point. The abstinence rates at 180 days were 13.2% [95% CI 10.9–15.8] and 11.9% [95% CI 10.1–13.8] for varenicline and NRT/bupropion, respectively, for Figure 1a. The rates are 13.1% [95% CI 10.6–15.8] and 11.8% [95% CI 9.9–14.0], respectively, for Figure 1b.

Smokers who used varenicline used their quitting aid for an average of 54.7 days [95% CI 49.8–59.6], which is significantly longer than the length of use for smokers who used NRT/bupropion. The latter used their quitting aid for an average of 37.1 days [95% CI 33.6–40.7].

Table 3 shows the total quit attempt rate and annual cessation rate (defined as having quit for at least three months at the time of the survey) for the 2003 and 2010–2011 survey years. These data include smokers whether or not they had used pharmacotherapy. There are no significant differences in quit attempt rates or in annual cessation rates across these surveys. The top panel shows that 40.5% of all smokers in 2003 made a quit attempt compared to 41.4% in 2010 ($P=0.09$). The annual cessation rate was 4.2% and 4.0%, for 2003 and 2010, respectively ($P= 0.39$). The bottom half shows the same pattern, except with lower values for

all because they were based on daily smokers, a group that is known to have a lower quit rate than non-daily smokers. The quit attempt was 37.0% in 2003 and 37.5% in 2010 (P=0.18). The annual cessation rate was 4.2% and 4.0, for 2003 and 2010, respectively (P= 0.39).

DISCUSSION

The addition of varenicline to the list of smoking cessation aids significantly increased the proportion of smokers using pharmacotherapy when they attempted to quit smoking. However, this increase was not associated with any noticeable change in either the total quit attempt rate or the annual cessation rate at the population level.

One explanation for the lack of a population effect of varenicline is that the increase in overall pharmacotherapy utilization, while statistically significant, was small in magnitude (28.7% to 31.1%). This 2.4 percentage point increase seems surprisingly small because the use of pharmacotherapy has been emphasized in the treatment community and insurance coverage for pharmacotherapy significantly increased during the time period under investigation.[36,37] Varenicline came to market during the study period as a new medication which, as with any new medication approved by FDA, raised fresh hope for smokers. The fact that varenicline outperformed existing therapies was a further selling point. However, adding varenicline as a new cessation aid had only a small effect on the overall use of pharmacotherapy.

The problem seems to be the following: the new medication, varenicline, mainly attracted smokers who would normally use other therapies, instead of recruiting a new group of smokers who would otherwise not use any therapy (Table 2). As such, even though the use of varenicline did increase dramatically (from 0% to 11% for all smokers and from 0% to 13% for daily smokers), the use of other therapies decreased significantly. The net result was a 2.4 percentage point increase in total therapy use among all smokers who made a quit attempt.

If smokers tend to replace older pharmacotherapy with newer pharmacotherapy, then it will be difficult to increase the overall pharmacotherapy use rate, even if new therapies continue to be introduced. This is largely what has happened in the U.S. over the last two decades. When the nicotine patch first came to market in 1992, there was little competition from other cessation aids. The increase in overall pharmacotherapy use was substantial, especially after patches became available over-the-counter.[31] Since then, the rate of pharmacotherapy use has increased much more slowly even though new forms of NRT and a non-nicotine product, bupropion, have come onto the market successively.[31,38,39] The addition of varenicline seems to repeat the same scenario; it has increased the overall use of pharmacotherapy, but only to a small degree.

The results from this study provide a partial answer to the question raised by previous studies about why the growing list of new therapies has not led to an increase in the population smoking cessation rate.[31,40] It seems that most smokers simply do not use any therapy when they try to quit smoking. A new therapy (or a new promotion of an old therapy) will cause more smokers to use the product being promoted, but most of these

smokers would have used other therapies. Only a small minority of these smokers are new users of pharmacotherapy, as was the case with the introduction of varenicline.

It is noteworthy, though not so surprising, that the use of varenicline was highly correlated with physician advice to quit smoking. Physicians' involvement might have enhanced the effect of varenicline, at least in the earlier part of the quit attempt: The relapse rate for varenicline users was lower than that for users of other pharmacotherapies (i.e., NRT/bupropion), especially in the first 3 months of the quit attempt. The difference in relapse may reflect the fact that varenicline users tended to stay on their cessation aid for a longer duration (presumably mainly using varenicline, as the survey did not distinguish which cessation aids when questioning the length). In any case, the greater success rate associated with varenicline at the earlier stage of quitting, compared to other therapies (NRT and bupropion), can be encouraging to both the users of varenicline and those who provide the medication. It may contribute to a greater enthusiasm for varenicline and thus lead more smokers to use it. The initial advantage, however, disappeared after 3 months, which coincides with the recommended length of use for varenicline. In other words, the difference between therapies became insignificant once smokers stopped using them. These results, of course, were based on smokers who self-selected to use either varenicline or other therapies. Although all of them were treatment seekers, these results do not represent the relative effectiveness of the therapies, as in the case of a clinical trial. Nevertheless, the greater relapse probability for varenicline users after 3 months is worth further investigation as these are results from the real-world setting.

The study is limited by the fact that only two cross-sectional CPS-TUS surveys, with a long interval between them, had information on pharmacotherapy use. This prevents the examination of year to year changes. The analysis, for example, cannot detect any possible significant increase in pharmacotherapy use immediately following the FDA-approval of varenicline. Several studies found that there was a significant increase in the use of pharmacotherapy immediately after the introduction of varenicline, although others reported no significant change in overall pharmacotherapy use.[20,21,17,22] The present study, with two large national samples, shows that the overall effect of varenicline on pharmacotherapy use was mainly to displace older therapies.

The main findings from the current study provide a framework to consider whether a new product could have a population impact. For example, there has been recent excitement and controversy about the possibility of electronic cigarettes (e-cigarettes) helping smokers quit conventional cigarettes. There are questions about whether or not e-cigarettes are an efficacious nicotine replacement therapy.[41–43] However, as we have seen with varenicline, demonstrating efficacy of a new product does not necessarily mean it will have an impact at the population level. To impact the population smoking cessation rate, e-cigarettes or any other new product must first appeal to smokers who would not have used existing therapies so as to significantly increase the total proportion of smokers using quitting aids.

In fact, even a significant increase in total use of quitting aids is only a necessary condition but not a sufficient condition for improving population cessation rate. The critical measure for assessing potential population impact of any new intervention is whether its introduction

increases the quit attempt rate of the population.[31] For example, a change in medication policy in National Health Service in England did lead to a significant increase in medication usage. However, the effort did not lead to an increase in quit attempt, and therefore resulted in no significant change in the population cessation rate.[31,44] Table 3 of this study illustrates the point. The introduction of varenicline to the treatment market has had a negligible impact on the quit attempt rate of the population. Accordingly, the change in the annual cessation rate from 2003 to 2010 is also negligible.

The smoking cessation field faces a serious challenge. It is important to develop new therapies to help individual smokers quit the addictive and destructive habit of smoking. However, the ultimate goal of developing any therapy should be to increase the quit rate of smokers at the population level. Results from this study show that the population impact of a new therapy is much more elusive than the efficacy of the therapy. The addition of an efficacious therapy needs to lead to a greater usage of therapies overall. Even more importantly, it needs to lead to a significant increase in the quit attempt rate among smokers before it can have a real impact on successful quitting at the population level.

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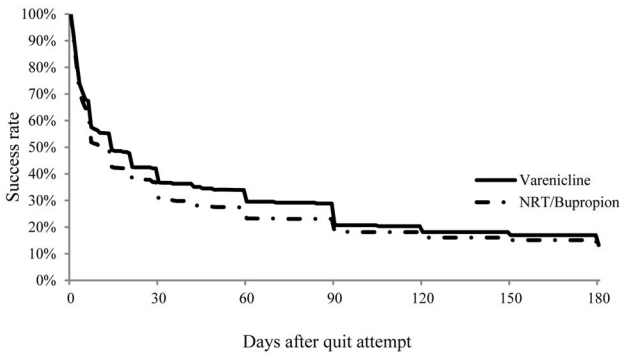
WHAT THIS PAPER ADDS

Clinical trials have shown that varenicline is more efficacious than other pharmacotherapies in treating nicotine dependence. However, few have examined the population impact of the introduction of varenicline into the cessation market.

This population-based study adds three main findings:

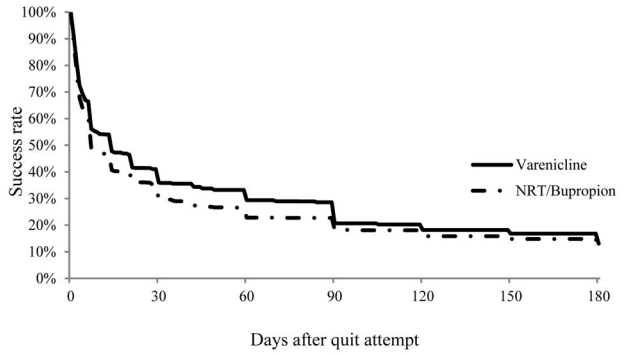
- The introduction of varenicline is associated with only a 2.4 percentage point increase in total pharmacotherapy use among those making a quit attempt. The main effect of varenicline coming to the market has been to displace the use of other existing pharmacotherapies (bupropion and nicotine replacement therapy).
- Increase in the use of varenicline has not been associated with an increase in quit attempts or in the annual cessation rate at the population level.
- Varenicline users have a higher abstinence rate than other pharmacotherapy users up to 3 months post quit attempt, after which the difference in survival probability is no longer significant.

Figure 1a



Data source: Current Population Survey Tobacco Use Supplement 2010-2011

Figure 1b



Data source: Current Population Survey Tobacco Use Supplement 2010-2011

Figure 1.

Figure 1a. Relapse Curve for All Smokers (Daily or Occasional) 12 Months Before the Survey

Figure 1b. Relapse Curve for Those Who Smoked Daily 12 Months Before the Survey

Table 1

Rate of Any Pharmacotherapy Use Among Smokers Who Tried to Quit in the Past 12 Months, by Demographics, 2003 and 2010–2011, United States

	2003 N=15,095 % (95% CI)	**2010–2011 N=12,928 % (95% CI)**
Over All	28.7(27.9–29.6)	31.1(30.1–32.2)
Gender		
Male	27.3 (26.0–28.7)	28.3 (26.9–29.8)
Female	30.2 (29.2–31.3)	34.3 (33.0–35.6)
Race		
White	32.5 (31.4–33.5)	34.8 (33.6–36.0)
Hispanic	15.7 (13.7–18.0)	16.7 (14.1–19.7)
Black	17.8 (15.7–20.0)	22.4 (19.8–25.2)
Asian	16.5 (11.7–22.6)	22.6 (17.0–29.4)
American Indian	26.8 (19.6–35.6)	30.5 (22.8–39.6)
Others	28.4 (23.4–33.9)	34.0 (27.6–41.1)
Age		
18–24	14.2 (12.4–16.1)	14.0 (11.9–16.3)
25–44	27.3 (26.1–28.6)	29.9 (28.3–31.5)
45–64	40.1 (38.4–41.8)	38.8 (37.2–40.4)
65+	29.8 (26.4–33.4)	38.0 (34.9–41.1)
Education		
< High School	23.5 (21.5–25.6)	26.6 (24.5–28.8)
High School Diploma	27.5 (26.1–28.9)	29.9 (28.2–31.5)
Some college	31.1 (29.4–32.8)	33.3 (31.5–35.2)
Bachelor or higher	33.2 (30.8–35.7)	34.9 (32.0–37.8)

Data source: Current Population Survey-Tobacco Use Supplement 2003 and 2010–2011

Table 2

Use of Pharmacotherapy, among Those Who Tried to Quit Smoking, 2003 and 2010–2011, United States

	2003 % (95% CI) N=15,095	**2010–2011 % (95% CI) N=12,928**
Overall for All Smokers	28.7 (27.9–29.6)	31.1 (30.1–32.2)
*Type of Pharmacotherapy		
Varenicline (Chantix)	0	10.9 (10.3–11.6)
Bupropion (Zyban)	9.1 (8.5–9.7)	3.5 (3.1–3.8)
Any NRT	24.5 (23.8–25.3)	22.4 (21.5–23.4)
Patch	17.6 (16.9–18.3)	15.5 (14.8–16.3)
Spray/Inhaler	2.1 (1.8–2.4)	1.2 (1.0–1.4)
Gum/Lozenge	10.2 (9.7–10.8)	10.6 (10.0–11.3)
Number of Pharmacotherapies		
1	20.0 (19.3–20.8)	23.0 (22.0–23.9)
2	6.0 (5.6–6.4)	6.0 (5.5–6.5)
3	1.7 (1.5–2.0)	1.6 (1.3–1.9)
4+	1.0 (0.8–1.2)	0.6 (0.4–0.7)
Overall for Daily Smokers	32.9 (31.9–34.0)	35.7 (34.5–37.0)
*Type of Pharmacotherapy		
Varenicline (Chantix)	0	12.8 (12.0–13.7)
Bupropion (Zyban)	10.8 (10.0–11.5)	4.0 (3.6–4.5)
Any NRT	27.8 (26.9–28.8)	25.5 (24.4–26.7)
Patch	20.3 (19.4–21.2)	18.2 (17.3–19.2)
Spray/Inhaler	2.4 (2.1–2.8)	1.4 (1.1–1.7)
Gum/Lozenge	11.2 (10.5–11.9)	11.7 (10.9–12.5)
Number of Pharmacotherapies		
1	23.0 (22.0–23.9)	26.2 (25.1–27.4)
2	6.9 (6.4–7.5)	6.9 (6.4–7.6)
3	1.9 (1.6–2.2)	1.8 (1.5–2.2)
4+	1.2 (1.0–1.5)	0.7 (0.5–0.9)

*Note: If more than one therapy was used, each therapy was counted

Data source: Current Population Survey Tobacco Use Supplement 2003 and 2010–2011

Table 3

The Quit Attempt Rate and the Annual Cessation Rate, 2003 and 2010–2011, United States

	2003	**2010–2011**
All Smokers	**N= 34,869 % (95% CI)**	**N=27,751 % (95% CI)**
Quit Attempt (≥24 hours)	40.5 (39.8–41.2)	41.4 (40.6–42.2)
Annual Cessation Rate (≥ 3 months)	4.5 (4.2–4.8)	4.7 (4.4–5.0)
Daily Smokers	N= 28,379 % (95% CI)	N=22,355 % (95% CI)
Quit Attempt (≥24 hours)	37.0 (36.2–37.7)	37.5 (36.7–38.3)
Annual Cessation Rate (≥ 3 months)	4.2 (3.9–4.5)	4.0 (3.7–4.3)

Data source: Current Population Survey Tobacco Use Supplement 2003 and 2010–2011