

Seven-Day Continuous Abstinence Rate from Smoking at 1, 2, or 3 Years after the Use of Varenicline

Jin Se Kim, M.D., Ju Young Jang, M.D., Eun Hye Park, M.D., Joo Young Lee, M.D., Kang Mo Gu, M.D., Jae Woo Jung, M.D., Jae Chol Choi, M.D., Jong Wook Shin, M.D., In Won Park, M.D., Byoung Whui Choi, M.D. and Jae Yeol Kim, M.D.

Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

Background: Varenicline, a selective partial agonist/antagonist of the $\alpha 4\beta 2$ nicotinic receptor, has proven effectiveness for smoking cessation by several randomized, controlled trials. Because few studies have evaluated the long-term efficacy of varenicline, we tried to evaluate the smoking status of varenicline users up to 3 years after the initial prescription of the drug.

Methods: We interviewed varenicline users who were prescribed the drug from June 2007 to May 2010 by telephone, from June 2010 to May 2011.

Results: One-hundred and thirty-three of 250 varenicline users (53.2%) were available for the survey. Seven-day continuous abstinence from smoking was adhered to by 17 of 39 respondents (43.6%) at 1 year, and 11 of 36 (30.6%) and 19 of 58 (32.8%) at 2 and 3 years since the first use of varenicline, respectively. Compared to current smokers, successful quitters were older (55.0 years vs. 49.9 years, $p=0.01$), had better compliance to the 12-week course (27.7 vs. 9.3%, $p=0.01$), and had taken varenicline longer (10.1 vs. 5.9 weeks, $p=0.01$). Fifty-four of 71 current smokers (76.1%) were willing to stop smoking in the near future. The preferred ways to cease smoking were will-power (48.1%), varenicline (25.9%), nicotine replacement therapy (11.1%), and others (14.9%).

Conclusion: Smokers should be encouraged to stick to the proven way for recommended period of time for successful cessation of smoking.

Keywords: Compliance; Smoking; Varenicline

Introduction

Varenicline is a selective partial agonist/antagonist of the $\alpha 4\beta 2$ nicotine acetylcholine receptor and it is used to assist in smoking cessation¹. When varenicline binds to the $\alpha 4\beta 2$ nicotine receptor, it stimulates the release of small amounts of dopamine. Released dopamine reduces nicotine withdrawal symptoms. In addition, varenicline has an antagonistic effect. By blocking the nicotine from binding to its receptor, varenicline reduces the rewarding aspects of tobacco smoking². The efficacy of varenicline was well demonstrated in randomized controlled trials from several countries³⁻⁵. In a meta-analysis, continuous abstinence at 6 months or longer was higher with varenicline than with placebo⁶. Although the clinical evidence supporting the varenicline is strong, the situation might be dif-

Address for correspondence: Jae Yeol Kim, M.D.

Department of Internal Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 156-755, Korea

Phone: 82-2-6299-1396, **Fax:** 82-2-825-7571

E-mail: jykimmd@cau.ac.kr

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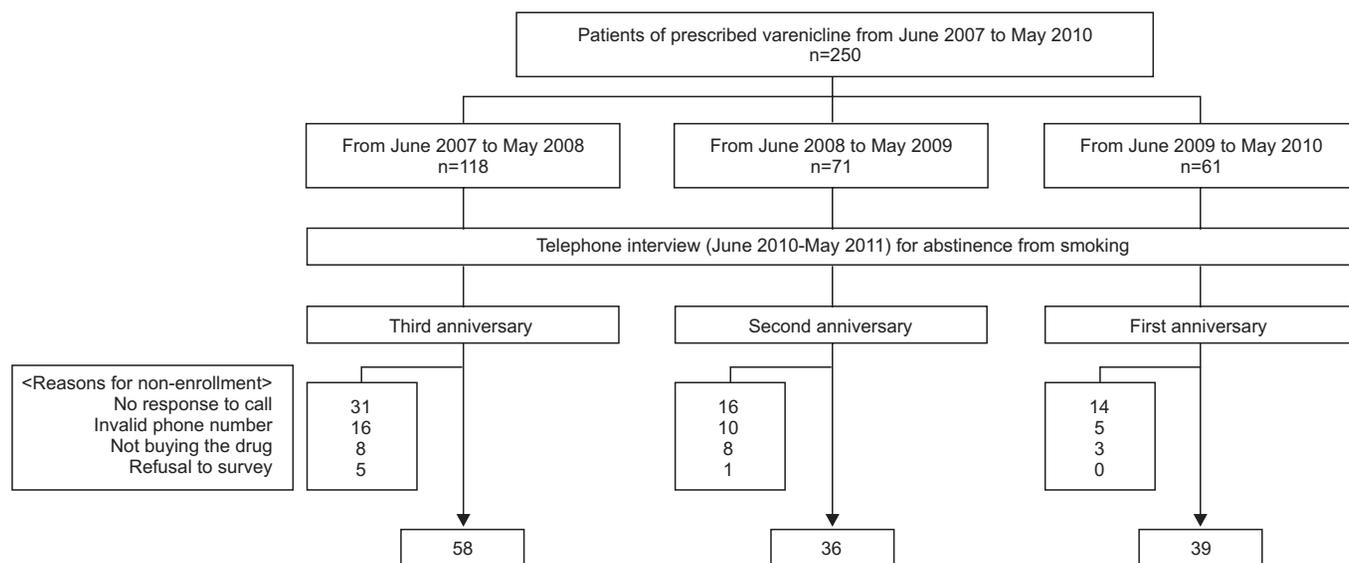


Figure 1. Flow chart of enrollment in the study. Telephone survey was tried from June 2010 to May 2011 around the first, second, or third anniversary dates of these patients' first varenicline prescription.

ferent in a real clinical setting. Usually, participants of clinical trials are well educated about the harmful effects of smoking. For this reason, they are more likely to be motivated and compliant with drug therapy compared to average, real smokers. In our previous study, compliance to the 12-week course of varenicline therapy was only 15% in real clinical practice setting⁷. The long-term efficacy of varenicline is another important, unexplored issue. Temporal quitters experience great difficulty in permanently abstaining from smoking and smoking can relapse even several years after cessation⁸. However, most studies of varenicline for smoking cessation have focused on the endpoint of abstinence at 1 year⁹. Varenicline has been available in South Korea since 2007. With accumulated experience, we attempted to evaluate the long-term abstinence status of varenicline users from smoking who were prescribed the drug at our clinic. We also evaluated the preferred ways of smoking cessation among current smokers who had experienced varenicline.

Materials and Methods

1. Subjects

Varenicline has been available at our clinic since June 2007. From June 2007 to May 2010, 250 patients have taken varenicline for the purpose of smoking cessation after counseling and education from pulmonologist at the pulmonary clinic of Chung-Ang University Hospital. A telephone survey was conducted from June 2010 through May 2011 around the first, second, or third anniversary dates of these patients' first pre-

scription of varenicline. Smoking cessation status at 3 years since the prescription of the varenicline was collected from the patients who were prescribed the drug from June 2007 to May 2008. In the same way, we evaluated smoking cessation status at 2 years and at 1 year since the use of the drug in patients who took the drug from June 2008 to May 2009 and from June 2009 to May 2010, respectively (Figure 1). This study was approved by Institutional Review Board of Chung-Ang University Hospital.

2. Questionnaire

The survey was conducted through telephone interview using a pre-designed questionnaire (Appendix 1). The contents of the survey included the 7-day continuous abstinence from smoking. If the interviewee did not smoke, the duration of abstinence was recorded. If they currently smoked, we evaluated addiction to nicotine by Fagerström's nicotine dependence test. We asked current smokers about their willingness to attempt smoking cessation in the near future. If they expressed their willingness, their preferred ways for ceasing smoking were recorded. In addition to the telephone interview, the total period of varenicline administration was confirmed by reviewing the medical records of the subjects.

3. Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical variables were indicated as frequency and percentage and continuous variables as median and range. To compare the group of smoke-free patients to

the group of current smokers, the chi-square test, Fisher exact test and Mann-Whitney's U-test were used. Multiple logistic regression analysis for sex, age, amount of previous smoking, duration of varenicline prescription and duration of previous smoking cessation period was performed to identify the predictors for smoking abstinence and the results were presented with the odds ratios (OR) and 95% confidence intervals (CI). The chi-square test for linear trends was used to analyze the trend of variables according to survey year. A p-value less than 0.05 was considered significant.

Results

1. Clinical characteristics of the study subjects

Among the 250 patients who were prescribed varenicline from June 2007 to May 2010, 133 (53.2%) were available for telephone interview. The reasons for unavailability were no response to the registered phone number (61), no valid phone number at the time of contact (31), no purchase of varenicline after prescription (19), and refusal to participate in the telephone interview (6) (Figure 1).

The average age of the 133 responders was 51.7 years. The respondents were predominantly male (125 vs. 8). The average amount of smoking was 33.7 pack-years. Average duration of administration of varenicline was 7.3 weeks, and 21 patients (15.8%) took varenicline for more than 12 weeks. Underlying diseases were chronic obstructive pulmonary disease (34, 25.6%), bronchial asthma (12, 9.0%), pneumonia (4, 3.0%), and non-pulmonary diseases (24, 18.0%) (Table 1).

2. Seven-day continuous abstinence from smoking

Seven-day continuous abstinence from smoking was adhered to by 17 among 39 respondents (43.6%) at 1 year, and 11 out of 36 (30.6%), and 19 among 58 (32.8%) at 2 and 3 years since the first use of varenicline, respectively (Figure 2). There was no significant difference in the 7-day continuous abstinence rate among the three periods surveyed ($p=0.429$). The average non-smoking period was 6.8 ± 4.42 , 16.3 ± 9.41 , and 26.9 ± 13.10 months in those who succeeded in smoking ces-

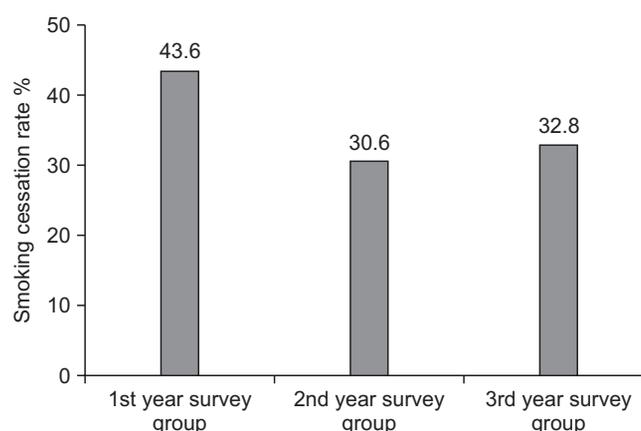


Figure 2. Seven-day continuous abstinence rates from smoking at 1, 2 and 3 years since the first dose of varenicline. Among 133 available respondents, the 7-day continuous abstinence rates were 43.6% (17/39) in the 1st year survey group, 30.6% (11/36) in the 2nd year survey group and 32.8% (19/58) in the 3rd year survey group, respectively.

Table 1. The characteristics of patients prescribed varenicline

| Baseline characteristic | Total patients (n=133) | 3rd year survey group (n=58) | 2nd year survey group (n=36) | 1st year survey group (n=39) |
|--|------------------------|------------------------------|------------------------------|------------------------------|
| Age, yr | 51.71±11.00 | 53.78±10.89 | 50.78±10.81 | 49.51±11.05 |
| No. of males | 125 (94.0) | 54 (93.1) | 34 (94.4) | 37 (97.9) |
| Amount of previous smoking, pack-years | 33.68±16.30 | 36.98±17.77 | 32.28±14.41 | 30.05±15.05 |
| Duration of varenicline prescription, wk | 7.34±9.48 | 8.23±11.63 | 5.82±8.19 | 7.41±6.63 |
| No. of participants that completed a 12-wk course of varenicline | 21 (15.8) | 12 (20.7) | 3 (8.3) | 6 (15.4) |
| Underlying diseases | | | | |
| Chronic obstructive pulmonary disease | 34 (25.6) | 20 (34.5) | 9 (25.0) | 5 (12.8) |
| Bronchial asthma | 12 (9.0) | 7 (12.1) | 2 (5.6) | 3 (7.7) |
| Pneumonia | 4 (3.0) | 2 (3.4) | 1 (2.8) | 1 (2.6) |
| Other pulmonary diseases | 35 (26.3) | 13 (22.4) | 9 (25.0) | 13 (33.3) |
| Non-pulmonary diseases | 24 (18.0) | 6 (10.3) | 10 (27.8) | 8 (20.5) |
| Healthy | 24 (18.0) | 10 (17.2) | 5 (13.9) | 9 (23.1) |

Values are presented as mean±standard deviation or number (%).

sation at 1, 2, or 3 years since their first prescription of varenicline, respectively.

3. Difference between those that were successful and those not successful in smoking cessation

Multiple logistic regression analysis showed statistical significance for successful cessation with age ($p=0.041$, OR, 1.056; 95% CI, 1.002–1.112), and completion of 12-week course of varenicline ($p=0.031$, OR, 3.019; 95% CI, 1.107–8.228). In addition, compared to those that failed smoking cessation, those that succeeded took the drug longer (5 weeks vs. 3.5 weeks, $p=0.011$) (Table 2). There were no differences in the amount of cigarettes smoked, duration of maximum abstinence from smoking, or underlying diseases between the groups ($p>0.05$).

4. Fagerström's nicotine dependence test and future plans to quit smoking among those that were unsuccessful

Over half of the 86 patients who failed to quit smoking showed a moderate level of nicotine addiction (Figure 3). The proportion of patients with severe nicotine dependence increased with each year after the first prescription of varenicline (0%, 24.0%, and 30.8%, respectively; p for trend=0.007).

Fifty-nine failed quitters (68.6%) are willing to stop smoking in the near future. Preferred ways were will-power (48.1%), varenicline (25.9%), nicotine replacement therapy (11.1%), and

others (14.9%).

Discussion

The prescription of varenicline was available at our clinic since June 2007. In the present study, we evaluated the seven-day continuous abstinence rate from smoking among varenicline users. Telephone interviews were done from May 2010 to June 2011. We attempted to contact them around the date of first, second, or third anniversary according to their first prescription of varenicline. Among the 250 who were prescribed varenicline, 133 (53.2%) were available for the telephone interview. Seven-day continuous abstinence rates were 43.6% (17/39), 30.6% (11/36), and 32.8% (19/58) around the first, second, and third anniversary dates, respectively.

In an open-label randomized trial of 757 smokers, the 52-week continuous abstinence rate (week, 9–52) was 26.1% among recipients of a 12-week standard regimen of varenicline¹⁰. In another study, carbon monoxide-confirmed continuous quit rates from week 4 to week 52 was 14.4% in varenicline users¹¹. Compared to these studies, our abstinence rate of 43.6% at the first anniversary date is high. However, there was a difference in the measured way of smoking cessation between our study and the previous ones. The above studies were well-designed and controlled clinical trials and most of the participants completed the targeted period of varenicline prescription. As such, they were able to measure the continuous abstinence rate for almost a year. In the present study which reflects real clinical practice, only 15% of patients completed a 12-week course of varenicline. For this reason, we measured the 7-day continuous abstinence rate around the first, second, or third anniversary dates since the first dose of varenicline. It may have increased the abstinence rate compared to the studies which evaluated continuous abstinence rate for longer period. In addition, we were able to contact slightly over 50% of varenicline users. Considering the reasons for unavailability (no response to the registered phone number, no valid phone number at the time of contact, no purchase of varenicline, and refusal to participate in the telephone interview), the chances are high that we selected those who were more willing to follow the recommendation of doctors for smoking cessation (Figure 1). In addition, we surveyed smoking status only by self-reported telephone interview. Objective confirmation of smoking cessation by carbon monoxide-breath test or urine cotinine test could have selected out false quitters. All of these factors may have contributed to the higher quitting rate at one year since the first experience of varenicline in our study.

Almost all studies of varenicline have evaluated long-term efficacy at 52 weeks or less^{3-5,7,10,11}. There were a few study about long term abstinence rate of varenicline^{12,13}. Hsueh et al.¹² demonstrated the 3-year continuous abstinence rate was

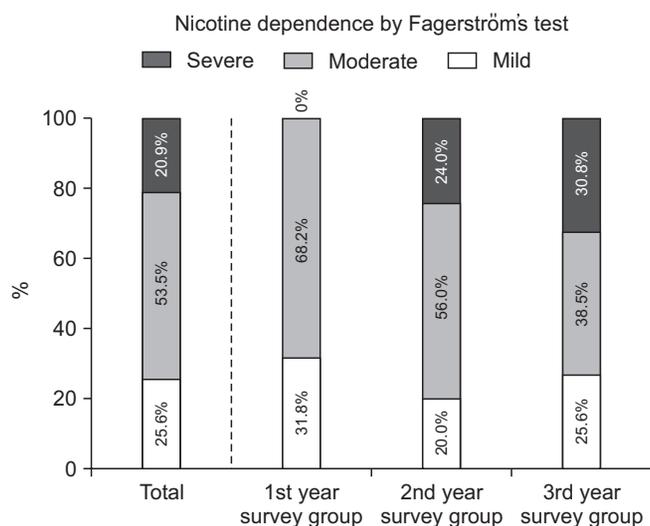


Figure 3. Fagerström's nicotine dependence test in patients who failed to stop smoking. The proportion of patients with severe nicotine dependence was 0%, 24.0%, and 30.8% at 1, 2, and 3 years after the first dose of varenicline, respectively, which shows successive increases with each year since the first dose of varenicline (p for trend=0.007). The severity of dependence by score of Fagerström's nicotine dependence test. Mild, 0–3; moderate, 4–6; severe, 7–10.

Table 2. Predictors for abstinence from smoking

| Variable | Success group (n=47) | Failure group (n=86) | p-value |
|--|----------------------|----------------------|---------|
| Age, yr | 53 (30–78) | 51 (24–73) | 0.031 |
| No. of males | 43 (91.5) | 82 (95.3) | 0.296 |
| Amount of previous smoking, pack-years | 30 (5–100) | 30 (8–80) | 0.298 |
| Duration of varenicline prescription, wk | 5 (2–54) | 3.5 (1–54) | 0.011 |
| No. of participants that completed a 12-week course of varenicline | 13 (27.7) | 8 (9.3) | 0.006 |
| Duration of previous smoking cessation period, mo | 2 (0–60) | 1 (0–48) | 0.363 |
| Underlying diseases | | | |
| Chronic obstructive pulmonary disease | 10 (29.4) | 24 (70.6) | 0.402 |
| Bronchial asthma | 6 (50.0) | 6 (50.0) | 0.265 |
| Pneumonia | 2 (50.0) | 2 (50.0) | 0.443 |
| Other pulmonary diseases | 10 (28.6) | 25 (71.4) | 0.329 |
| Non-pulmonary diseases | 7 (29.2) | 17 (70.8) | 0.485 |
| Healthy | 12 (50.0) | 12 (50.0) | 0.079 |

Values are presented as median (range) or number (%).

Regardless of years since the prescription of varenicline, those who stick to 7-day continuous abstinence from smoking were classified to “Success group,” which was decided during the telephone survey from June 2010 to May 2011.

18.9% in 8 weeks varenicline user. In 3-year follow-up data in Turkey, the smoking cessation rate was 32.5% in varenicline group¹³. In the present study, we determined the smoking status of varenicline users at 1, 2, and 3 years since the first prescription. The 7-day continuous abstinence rates maintained a high range not only in the first year but also in the second and third years (Figure 2). In addition, the average non-smoking period increased with each passing year (6.8±4.42, 16.3±9.41, and 26.9±13.10 months, respectively). Considering these findings, varenicline may be helpful in the long-term abstinence from smoking among some users.

Successful quitters experience difficulty in remaining abstinent from smoking permanently. Smoking can relapse after several years of successful abstinence. Long-term tracking revealed that 35% to 40% of patients relapse between one and 5 years after quitting^{14,15}. Nearly two-thirds of smokers who relapse report wanting to quit again within 30 days. Therefore, they should be encouraged to re-start a smoking cessation program as soon as possible¹⁶. It would be helpful to remind smokers that most smokers require multiple attempts at smoking cessation before permanently quitting. If a previous medication was helpful, the same therapy is typically recommended for the next trial. In our telephone survey, 70% of current smokers who experienced varenicline wanted to stop smoking cessation in the future. However, nearly half of them selected their own will-power for the cessation method and only one-fourth chose varenicline. Notably, the proportion of subjects with severe nicotine dependence increased successively each year after the first prescription of varenicline (Figure 3). Too much dependence on their own will and high

level of nicotine dependence would make their next attempt of smoking cessation pessimistic. It is well-known that only one-fourth of smokers who try to quit seek help, and even fewer use the most effective treatment¹⁷. Our study found that successful quitters were older, had better compliance to a 12-week course, and had taken varenicline longer compared to those who failed (Table 2). Smokers should be persuaded to use evidence-based methods for a designated period of time for their next attempts at smoking cessation.

This study has several limitations. Although we prospectively interviewed varenicline users by telephone, their experience with the drug was not strictly controlled in a clinical practice. The number of respondents was 133 out of 250 total patients, indicating that slightly less than half of varenicline users were unavailable for the survey. In addition, we relied on the responses of the subjects for smoking status without objective measurement of exhaled carbon monoxide or a urine cotinine test. Finally the success of non-smoking was assessed by a seven-day continuous abstinence rate which is too short to evaluate the long-term efficacy of anti-smoking aids. Nonetheless, this study provides valuable information about the long-term abstinence state from smoking among varenicline users as far as 3 years since the first prescription in real clinical practice.

In conclusion, the use of varenicline was associated with long-term smoking cessation as long as three years after its first prescription. Old age, good compliance to a 12-week course, and a longer duration of varenicline use were related to successful smoking cessation. Failed quitters should be encouraged to adopt proven ways for subsequent attempts to

quit smoking.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Appendix 1. Questionnaire for telephone interview
Case report form

| | | | | | |
|---|------------------------------|-------------------------------|---------------------------------|--------------------------|--------|
| Serial number | | Subject # | | | |
| Name | | Gender | | Age | |
| Mobile phone number | | | | | |
| Underlying diseases | | | | | |
| Date of telephone survey | | | | | |
| Date of starting varenicline prescription | | | | | |
| Total days of varenicline prescription | | | | | |
| 7-day continuous abstinence from smoking, | | Yes, No | | | |
| If you succeeded in stopping smoking, duration of abstinence from smoking | | | | | |
| Did you use non-smoking aids other than varenicline? | | Yes, No | | | |
| What kind of non smoking aids? | | | | | |
| Drug | Nicotine replacement therapy | Stop smoking aiding cigarette | Stop smoking aiding acupuncture | Others | |
| | | | | | |
| If you failed stopping smoking, | | | | | |
| Fagerström's nicotine dependence test | | | | | |
| 1. How soon after you wake up do you smoke your first cigarette? | | Within 5 minutes (3) | | | |
| | | 6–30 minutes (2) | | | |
| | | 31–60 minutes (1) | | | |
| | | After 60 minutes (0) | | | |
| 2. Do you find it difficult to refrain from smoking in places where it is forbidden? | | Yes (1) | | | |
| | | No (0) | | | |
| 3. Which cigarette would you hate most to give up? | | The first in the morning (1) | | | |
| | | Any other (0) | | | |
| 4. How many cigarettes per day do you smoke?? | | 10 or less (0) | | | |
| | | 11–20 (1) | | | |
| | | 21–30 (2) | | | |
| | | 31 or more (3) | | | |
| 5. Do you smoke more frequently during the first hours after awakening than during the rest of the day? | | Yes (1) | | | |
| | | No (0) | | | |
| 6. Do you smoke even if you are so ill that you are in bed most of the day? | | Yes (1) | | | |
| | | No (0) | | | |
| Nicotine dependent assessment | | | | | |
| Mild dependency(0-2) | | Moderate dependency (3–5) | | Severe dependency (6–10) | |
| | | | | | |
| Are you willing to stop smoke in the future | | | Yes, No | | |
| Prefer way to smoking cessation | | | | | |
| Drug | Nicotine replacement therapy | Stop smoking aiding cigarette | Stop smoking aiding acupuncture | Will power | Others |
| | | | | | |