

## Factors influencing sustainable efficacy of smoking cessation treatment with varenicline beyond nine months

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### ABSTRACT

Pharmacological therapies play an important role in the success of interventions for smoking cessation; however, long-term follow-up studies with analysis of influencing factors are scarce. We examined the sustainable effects of smoking cessation therapy with varenicline, beyond nine months as well as the factors influencing effectiveness. Our sample consisted of 193 patients (126 men [68.2%], 67 women [31.8%], aged 26 to 85 years) who underwent varenicline therapy at the Nagoya University Hospital between January 2009 and October 2013. We examined their clinical records and also conducted a mail survey and evaluated success rates of smoking cessation therapy beyond nine months. Overall, 95.8% (185/193) of the patients had at least one complication. The response rate of questionnaires at the end of smoking cessation was 61.6% (119/193). The smoking cessation rate continued to decline for one year and leveled off afterwards. Smoking cessation rates tended to correlate with an increasing number of outpatient visits. Logistic regression analysis showed that two factors, young age and high Beck Depression Inventory-II (BDI-II) scores, were inversely correlated with success rates of smoking cessation. From the results of this study, aggressive intervention would be needed for younger patients or patients with higher BDI-II scores.

**Key Words:** smoking cessation therapy, smoking cessation rate, varenicline, BDI-II score

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### INTRODUCTION

Smoking negatively affects health and is the main cause of preventable morbidity and mortality worldwide.<sup>1)</sup> Given these negative sequelae as well as their preventable nature, smoking cessation therapy is critical in the prevention and treatment of disease. Smoking cessation significantly improves life expectancy and reduces healthcare costs associated with smoking-related conditions.<sup>2)</sup> Although the smoking rate has gradually decreased over the last ten years, as of 2014, 19.3% of the adult Japanese population still smoke. Smoking cessation attempts by smokers on their

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own often fail, mainly because smoking habits are strongly associated with nicotine dependency. Thus, the Japanese Circulation Society Study Group recommends a special smoking cessation program for individuals who have difficulty in accomplishing smoking cessation by themselves.<sup>3)</sup> In Japan, smoking cessation therapy has been covered by public health insurance since 2006, and varenicline became reimbursable in May 2008. Varenicline has a high smoking cessation success rate of 65.4% and its use is rapidly increasing in Japan.<sup>4)</sup> Varenicline binds to the  $\alpha 4\beta 2$  acetylcholine receptors, but it only partially activates the reward pathway. Its functions are similar to that of a light dimmer switch. There is no real “hit” as there is with nicotine. In addition, by binding to  $\alpha 4\beta 2$  acetylcholine receptors, varenicline blocks nicotine from binding and working, which helps to reduce the satisfaction patients receive from smoking. This mechanism is cited as the reason for the high smoking cessation rate of varenicline.<sup>5)</sup> However, cases exist in which individuals start to smoke again.<sup>6)</sup> Accordingly, the U.S. Department of Health and Human Services (HHS) recommends the evaluation of smoking cessation treatment to judge not only the rate of success immediately after smoking cessation treatment, but also the long-term rate of smoking cessation after one year.<sup>7)</sup> Currently, such follow-up is not routinely done in Japan. This study evaluated the effects of smoking cessation treatment with varenicline beyond nine months, six months after the last visit, and examined the factors influencing effectiveness.

## METHODS

### *Study population and procedure*

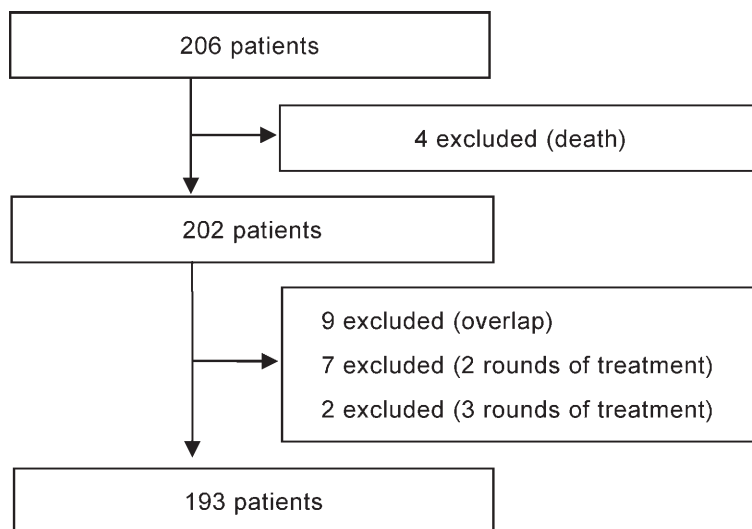
Two hundred and six patients who presented at the outpatient Smoking Cessation Clinic in Nagoya University Hospital between January 2009 and October 2013 participated in the study. Treatment was administered according to the standard procedure book for smoking cessation (6th Edition).<sup>8)</sup> Before starting treatment, we examined whether patients met all of the criteria for nicotine addiction set by the Japanese medical insurance system for nicotine-dependent outpatients: desire to receive treatment immediately, diagnosis of nicotine dependency, and scores  $>5$  (range, 0–10) on the Tobacco Dependence Screener (TDS) and  $>200$  on the Brinkman Index (BI). The TDS is a newly developed questionnaire to screen for nicotine dependence.<sup>9)</sup> The BI measures the number of cigarettes smoked per day multiplied by the number of years of smoking.<sup>10)</sup> All participants provided written informed consent. The study was approved by the Human Ethics Review Committee of Nagoya University (IRB approval number 4805).

### *Smoking cessation program*

Patients received 0.5 mg/day of varenicline for 3 days, followed by 1 mg/day (0.5 mg twice daily) for four days. On day eight, the varenicline dose was increased to 2 mg/day (1 mg twice daily). Treatment was continued for 12 weeks. We telephoned patients who missed an appointment to encourage the continuation of smoking cessation therapy. Smoking cessation was measured by self-assessment of four-week non-smoking continuation and confirmed by an exhaled carbon monoxide (CO) measurement of  $\leq 7$  ppm at the time of the clinic visit during the treatment period.<sup>8)</sup>

### *Study procedures*

From July 2014, a survey was conducted via post wherein patients were sent an envelope containing a request form, questionnaire, and return envelope. The same package was mailed a second time to patients who did not reply. To obtain information on the smoking status of patients who did not respond, we also used their medical records if available. Patients who did



**Fig. 1** Flow chart of the selection of study participants

not respond without available medical records were categorized as “patient who relapsed.” Figure 1 shows a flow chart of patient enrollment. Nine patients took more than one round of smoking cessation programs (seven patients took two rounds; two patients took three rounds). For those patients, we examined smoking status only for the period after the last program.

#### *BDI-II*

The Beck Depression Inventory-II (BDI-II) is one of the most commonly used instruments for detecting depression.<sup>11)</sup> It contains 21 items that assess depressive symptoms on a Likert scale of 0–3. The clinical interpretation of the scores is accomplished with the help of criterion-referenced procedures utilizing the following interpretive ranges: 0–13, minimal depression; 14–19, mild depression; 20–28, moderate depression; and 29–63, severe depression.

#### *Psychological disorders*

The presence of psychological disorders and eligibility for smoking cessation treatment were confirmed by a psychiatrist.

#### *Statistical analysis*

Statistical analyses were performed with JMP® 11 (SAS Institute Inc., Cary, NC, USA) for Windows 7. Data were expressed as percentages, means, and standard deviations, and odds ratios and 95% confidence intervals were provided. We adjusted for confounders using logistic regression. Results were considered statistically significance at  $P < 0.05$ .

## RESULTS

Table 1 shows a summary of baseline characteristics of the study population. Out of 193 patients, 126 (68.2%) were males and 67 (31.8%) were females, aged 26 to 85 years. Underlying diseases are presented in Table 2. Underlying cardiovascular disease was most common and

other underlying diseases accounted for 9.8% to 35.2% of the sample. Approximately 80% of the participants had more than one underlying diseases and 13% of the participants exhibited psychological disorders. The types of psychological disorders are given in Table 3; depression was most common. A total of 119 (61.6%) patients responded to the smoking cessation questionnaire. Table 4 shows the sustained abstinence rate over a 5-year period. The success rate immediately after the smoking cessation program (after three months) was 46.6%. Rates continued to decline over the next year, reaching 37.6%, and then plateaued. Smoking cessation rates tended to correlate with an increasing number of outpatient visits (Table 5). Univariate analysis showed that age, BI, and BDI-II scores had a positive effect on success ( $P < 0.05$ ) (Table 6). However, according to the logistic regression analysis, only age and BDI-II score had a significant effect on success ( $P < 0.05$ ) (Table 7).

**Table 1** Baseline characteristics (n=193)

Sex	male/female	126/67
Age	mean (range)	56.5 (26–85)
TDS <sup>a)</sup>	mean (range)	8.16 (5–10)
CO (ppm)	mean (range)	17.3 (0–59)
BI <sup>b)</sup>	mean (range)	871 (200–3000)
BDI-II <sup>c)</sup>	mean (range)	13.83 (0–57)
Underlying diseases	presence/absence	184/9
Psychological disorders	presence/absence	25/168

<sup>a)</sup> TDS = Tobacco Dependence Screener

<sup>b)</sup> BI = Brinkman Index

<sup>c)</sup> BDI-II = Beck Depression Inventory-II

**Table 2** Types of underlying diseases<sup>a)</sup>

Diseases	Male (%)	Female (%)	Total (%)
Cardiovascular diseases	53 (42.1%)	19 (23.9%)	72 (37.3%)
Metabolic diseases	46 (36.5%)	22 (32.8%)	68 (35.2%)
Respiratory diseases	33 (26.1%)	22 (32.8%)	55 (28.5%)
Digestive system diseases	22 (17.5%)	8 (11.9%)	30 (15.5%)
Malignant tumor	16 (12.7%)	9 (13.4%)	25 (13.0%)
Psychological diseases	14 (11.1%)	11 (16.4%)	25 (13.0%)
Neurological diseases	14 (11.1%)	10 (14.9%)	24 (12.4%)
Hepatic diseases	16 (12.7%)	4 (5.9%)	20 (10.3%)
Kidney diseases	16 (12.7%)	2 (3.0%)	19 (9.8%)

<sup>a)</sup> The breakdown of cases includes overlapping patients.

**Table 3** Types of psychological disorders<sup>a)</sup>

Disorder	Male	Female	Total
Depression	6	7	13
Schizophrenia	4	1	5
Alcoholism	2	1	3
Manic depression	2	0	2
Anxiety disorder	0	2	2
Panic attacks	1	1	1
Organic mental disorder	0	1	1

<sup>a)</sup> The breakdown of cases includes overlapping patients

**Table 4** Time-dependent continuous abstinence rate

	Smoking cessation rate	95% CI
End of outpatient care <sup>a)</sup>	90/193 (46.6%)	39.6–53.7%
9 months later	84/193 (43.5%)	36.4–50.8%
1 year later	71/189 (37.6%)	30.6–44.9%
2 years later	51/144 (35.4%)	27.6–43.8%
3 years later	34/109 (31.2%)	22.7–40.8%
4 years later	23/69 (33.3%)	22.4–45.7%
5 years later	9/25 (36.0%)	18.0–57.5%

<sup>a)</sup> The end of outpatient care is between 2 weeks and 3 months.

**Table 5** Number of times in outpatient care and the continuous abstinence rate after 6 months

Outpatient care	Abstinence/Total (%)	95% CI
1 time	1/10 (10.0%)	8.59–28.59%
2 times	4/16 (25.0%)	3.78–46.21%
3 times	5/16 (31.2%)	8.53–53.95%
4 times	7/26 (26.9%)	9.87–43.97%
5 times	67/125 (53.6%)	44.85–62.3%

**Table 6** Univariate analysis after 6 months of outpatient care

Background factor	Non-smoker	Smoker	<i>P</i> value
Sex (male/female)	61/23	65/44	0.068
Age	59.9 (36–77)	53.9 (26–81)	0.002
TDS: average	8.19	8.14	0.837
CO: average	16.5 (2–59)	17.7 (1–53)	0.653
BI: average	970 (200–3000)	816 (200–2580)	0.040
BDI-II: max score	11.2 (0–47)	15.9 (0–57)	0.018
Side effects (presence/absence)	44/40	61/48	0.663
Reducing drug (presence/absence)	32/52	35/74	0.446
Mental disease (presence/absence)	7/77	19/90	0.066

**Table 7** Multivariate analysis after 6 months of outpatient care

Background factor	Odds ratio (95% CI)	<i>P</i> value
Sex	1.51 (0.79–2.91)	0.217
Age ≤55	0.43 (0.20–0.90)	0.026
BI>900	0.76 (0.37–1.51)	0.416
Mental disease presence/absence	1.32 (0.50–3.76)	0.578
BDI-II ≤19	1.99 (1.00–4.05)	0.049

## DISCUSSION

This study shows the long-term effect of varenicline treatment on smoking cessation. We found that the rate of smoking cessation continued to decrease up to one year after treatment and thereafter remained unchanged. The factors that related to smoking cessation were: 1) young age and high BDI-II scores, which were inversely correlated with success rates of smoking cessation; and 2) number of outpatient visits, which was positively correlated with the rate of smoking cessation.

Smoking cessation rates at the end of varenicline therapy are around 45% in Europe and America<sup>12–14)</sup> and 50–60% in Asia.<sup>15)</sup> In Japan, the smoking cessation rate after pharmacotherapy was reported to be about 30–60%.<sup>4, 16–18)</sup> The smoking cessation rate at the end of the smoking cessation program in our hospital was 46.6%, which is similar to other data in Japan. In this study, we assessed the continuation of smoking cessation after the end of an outpatient visit. The average abstinence rate nine months after the first visit was 43.5%, which was slightly above normal compared with the result of a survey of actual smoking cessation rates.<sup>18)</sup> Thereafter, the rate of smoking cessation continued to decline until one year after treatment and thereafter remained unchanged. Our assessment of the long-term abstinence rate is important, because there have been few studies of this nature in university hospitals where patients present with diverse comorbidities.<sup>19, 20)</sup> The results of our study suggest that follow up for at least one year is critical for successful smoking cessation.

With regard to the influencing factors on smoking cessation rates, increased number of outpatient visits correlated with a higher success rate.<sup>18)</sup> We telephoned patients who missed an

appointment to encourage the continuation of smoking cessation therapy. This finding suggests that it may be important to actively intervene by offering sympathetic counseling and telephoning patients who missed an appointment to encourage the continuation of smoking cessation therapy.

The relationship between psychological status and smoking cessation rate was unclear in our study. In our study, high BDI-II scores were related to lower success rates of smoking cessation, but psychological disorders were not. Previous research found that rates of smoking are high and success of smoking cessation is low among patients with psychological disorders.<sup>21-24)</sup> However, several studies report an association between smoking cessation and reduced depression, anxiety, and stress, and improved positive mood and quality of life.<sup>25-27)</sup> Varenicline also increased cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety.<sup>28)</sup> In addition, other research suggests that among patients with high BDI-II scores and low success rates in smoking cessation, mental instability may be the cause of loss of motivation.<sup>11)</sup> Considering those results, we find no contraindication to introducing smoking cessation therapy to patients with psychological disorders, although high BDI-II scores may indicate relatively poor success rates.

Another factor we found to be negatively associated with success rates was age <55 years. This result is in agreement with a number of other studies reporting that older age is linked to a positive cessation outcome.<sup>20, 29, 30)</sup>

Despite the important implications of the present study, it has certain limitations. First, it was conducted at a single university hospital, so its findings have limited generalizability. Additional research in diverse settings is required. Second, some limitations stem from the nature of questionnaire-based research. Since patients lost to follow-up were not excluded from the study sample and were included in the smoking cessation failure group, the calculated smoking cessation rate may have been lower than the actual smoking cessation rate. Since it is difficult to assess long-term smoking cessation using objective indicators, such as breath carbon monoxide, smoking cessation rates were obtained using self-report measures. Thus, it is likely that actual smoking cessation rates may have been lower than the reported rates. Third, in this retrospective study, we interviewed patients about their smoking cessation status during a period between 9 months and 5 years after the completion of smoking cessation treatment. Results showed that seven patients who achieved smoking cessation with varenicline smoked again and began smoking cessation treatment again. This suggests that similar patients exist elsewhere. Finally, the recovery rate of questionnaire data was low from patients for whom a long time had passed since the completion of treatment, and our sample size was small.

## CONCLUSION

According to our study results, close follow-up of patients, especially young patients with higher BDI-II scores; visiting the outpatient clinic the prescribed number of times; and follow-up for at least one year will improve the therapeutic response to varenicline. Future studies using larger samples are required to evaluate long-term efficacy.

## CONFLICT OF INTEREST

Toyoaki Murohara and Yoshinori Hasegawa received payment for lectures, including serving on speakers' bureaus, from Pfizer Japan Inc. (Tokyo, Japan).

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