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A Comparison of the Effectiveness of Varenicline and Transdermal Nicotine Patch in Outpatients Following a Standardized Smoking Cessation Program in Southern Taiwan

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Abstract

'Varenicline use has been shown to produce greater long-term smoking cessation rates than bupropion but has no clear differences compared to the transdermal nicotine patch. We performed this study to compare the effectiveness of varenicline with the nicotine patch at 3 and 6

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months of follow-up of patients in an outpatient smoking cessation program provided by a hospital in Southern Taiwan. The sample consisted of 463 patients who attended the smoking cessation program at the outpatient family medicine clinic at Kaohsiung Veterans General Hospital between March 2006 and December 2008. All patients were aged $\geq$18 years and either smoked $\geq$10 cigarettes per day or scored $\geq$4 on the Fagerström Test for Nicotine Dependence. Patients were seen by a physician for up to 8 sessions in 90 days. Medication use was guided by patient preference (208 opted for varenicline and 255 for the nicotine patch). The primary outcomes of the study were self-reported 7-day point prevalence abstinence rates at 3 and 6 months from the first clinic visit. Varenicline users had a significantly higher abstinence rate than those using nicotine patch at 3-month (47.1% vs. 30.6%; odds ratio [OR] = 2.02, 95% confidence interval [CI] = [1.38, 2.96]) and 6-month follow-up (41.3% vs. 30.6%; OR = 1.60, 95% CI [1.09, 2.32]). Both groups had similar incidences of adverse events. Varenicline use in a sample of treatment-seeking-dependent smokers was associated with significantly higher abstinence rates than the nicotine patch.

Keywords
varenicline, transdermal nicotine patch, effectiveness, smoking cessation clinic

Introduction

Varenicline is an alpha$_4$-beta$_2$ nicotine acetylcholine receptor partial agonist that was licensed as a smoking cessation therapy by the U.S. Food and Drug Administration (US FDA, 2007) and European Agency for the Evaluation of Medicinal Products (EMEA) in 2006. It has been reported to increase cessation rates 2.5 to 3 times more than placebo at 6- to 12-month follow-up (Gonzales et al., 2006; Jorenby et al., 2006; Tsai et al., 2007). Varenicline is also associated with significantly higher long-term abstinence rates than bupropion. A meta-analysis of data from three randomized double-blind trials comparing varenicline and bupropion showed that cessation rates for those using varenicline were 1.52 times greater than in those using bupropion at 1 year (95% CI [1.22, 1.88]; Hughes, Stead, & Lancaster, 2007). A recent multiple treatment meta-analysis also revealed that varenicline use was associated with higher long-term abstinence rates than other smoking cessation medicines (Mills et al., 2012).

Few studies have compared varenicline with the nicotine patch. One randomized open-label trial using a multinational, mainly Caucasian sample of 746 smokers found that varenicline increased the odds of continued abstinence 1.7 times more than nicotine patches during the last 4 weeks of treatment. Abstinence also increased 1.4 times more in varenicline users than nicotine patch users at the 1-year follow-up, although this difference did not reach statistical significance (Aubin et al., 2008). A Japanese study of 32 participants showed no difference in continued abstinence between users of varenicline and the nicotine patch at 12 and 24 weeks (Tsukahara, Noda, & Saku, 2010), and a randomized parallel clinical study in Iran with 272 paticipants (91 received brief counseling, 92 used nicotine patches, and 89 used varenicline) also revealed that varenicline was slightly more effective than the nicotine patch, although this difference was not statistically significant (Heydari, Talischi, Tafti, & Masjedi, 2012).

Further studies are required to compare varenicline and the nicotine patch both in clinical trials and cohort studies in "real-world" settings.

The nicotine patch and varenicline have been approved by Taiwan's Department of Health in 1993 and 2007, respectively. To the best of our knowledge, no study comparing the effectiveness of the two has been undertaken here.

Method

Study Participants

We recruited 469 patients who had come to the Department of Family Medicine outpatient department at Kaohsiung Veteran General Hospital, Taiwan, to receive medical help for quitting smoking, between March 2006 and December 2008. To be included in this study, participants were required to be smokers of 18 years and older, who were either smoking $\geq$10 cigarettes per day (CPD) or who had received a score of $\geq$4 on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The cost of therapy for all patients was partially covered by Taiwan's National Insurance Program. Both the nicotine patch and varenicline were subsidized NT$250 (approximately US$8.3) per week. Under the reimbursement, participants needed to pay approximately NT$500 (approximately US$16.7) per week for the nicotine patch and NT$950 (approximately US$31.7) per week for varenicline. Participants could choose the medicine they wanted to use and were allowed to switch from one medicine to another at any subsequent visit if they found that the medicine was unsuitable or they were unable to tolerate their first choice. However, data for participants who did switch were not

included in the analyses. Exclusion criteria included pregnancy and patients who received treatment for acute cardiac conditions in the 3 months before the onset of the study. We excluded five clients who used both varenicline and the nicotine patch and one whose data were incomplete, leaving 463 participants; 208 used varenicline and 255 used the nicotine patch. Informed consent was collected from each participant. The protocol for this study was approved by the Ethics Review Committee of Kaohsiung Veterans General Hospital.

Intervention

According to the Department of Family Medicine protocol for smoking cessation, each patient receives 15–20 min of counseling from a physician, educational materials explaining smoking cessation techniques, and a prescription for either varenicline or the nicotine patch at the first visit. Participants were also instructed to try to stop smoking when starting to use the patch, if possible. Varenicline users were instructed to set their quit day 8 days after starting the medication. Both drugs are administered according to the manufacturer's directions, and a 1- to 2-week supply of medicine was prescribed at every clinic visit. Both nicotine patch and varenicline users could receive their medications for 8 weeks. During the therapy course, physicians were allowed to adjust the nicotine patch and varenicline dosage according to tolerability. However, most adverse events were mild to moderate and well tolerated in both groups. For participants who chose varenicline, physicians emphasized that if there were any uncontrolled depressed moods, suicidal thoughts, or attempts, they were to cease varenicline treatment and consult a physician immediately.

After the first visit, patients were encouraged, but not required, to consult the clinic physician every 1 to 2 weeks for a maximum of 8 visits in the following 90 days. Each physician counseling session lasted up to 10 min. The content of the counseling provided depended on their physical dependence, withdrawal symptoms, drug adverse events, and their perceived barriers to quitting. If the patient did not show for one of the follow-up visits, they would not receive prescriptions for the drugs they were taking. No assumption was made at that time on the success or failure of the therapy they were receiving. The client cases were followed-up by telephone at 3 and 6 months.

Data Collection and Outcome Measures

When registering for the first visit, each patient completed a questionnaire that collected demographic information and data related to smoking status,

Table 1. Reported Adverse Events

Kind of Adverse Events (%)	Varenicline ($N = 147$)	Nicotine Patch ($N = 152$)	p Value
Any adverse events or withdraw syndrome	62 (42.2)	76 (50.0)	.175[a]
1. Anxiety	4 (2.7)	2 (1.3)	.442[b]
2. Restlessness	0 (0.0)	4 (2.6)	.123[b]
3. Low concentration	0 (0.0)	5 (3.3)	.061[b]
4. Increased appetite	2 (0.7)	5 (3.3)	.448[b]
5. Insomnia	22 (15.0)	23 (15.1)	.968[a]
6. Dizziness or headache	14 (9.5)	10 (6.6)	.878[a]
7. Weariness	4 (2.7)	10 (6.6)	.114[a]
8. Nausea	24 (16.3)	4 (2.6)	<.001[a]
9. Vomiting	4 (2.7)	0 (0.0)	.057[b]
10. Itchy skin	0 (0.0)	34 (22.4)	<.001[b]
11. Skin rash	1 (0.7)	26 (17.1)	<.001[b]

[a] χ^2 test.
[b] Fisher's exact test.

nicotine-dependence level (measured on the FTND), and the choice of smoking cessation medication. During subsequent visits, physicians interviewed them on withdrawal symptoms, drug adverse events, and the perceived barriers to quitting. At each clinic visit, participants were shown a document that listed potential adverse events and withdrawal symptoms, and they were instructed to mark "yes" to any that they had experienced since the last visit. The results of these assessments are shown in Table 1.

The primary outcomes of the study were self-reported 7-day point prevalence abstinence rates at 3 and 6 months after the first visit. Any smoking behavior in the 7 days prior to the phone call was defined as a failure. Three call attempts were made at follow-up times. If the participants could not be contacted, they were considered to be smoking.

Statistical Analysis

We compared group differences in abstinence rates at 3- and 6-month follow-up. Factor analysis for continuous variables was performed using a t test, and for categorical variables, chi-square analysis or Fisher's Exact analysis. We also ran a logistic regression to control for baseline differences. All statistical operations were performed using SPSS 12.0.

Table 2. Baseline Characteristics

Characteristics	Varenicline ($N = 208$)	Nicotine Patch ($N = 255$)	p Value
Age (year)	43.68 ± 12.36	45.49 ± 15.11	.157[a]
Sex			
Male	181 (87.0%)	216 (84.7%)	.479[b]
Female	27 (13.0%)	39 (15.3%)	
Cigarettes per day			
<20	40 (19.2%)	54 (21.2%)	.605[b]
≥20	168 (80.8%)	201 (78.8%)	
Education level			
Elementary or less	24 (11.9%)	51 (21.4%)	<.001[b]
High school	59 (29.4%)	90 (37.8%)	
University or above	118 (58.7%)	97 (40.7%)	
Unknown	7 (3.4%)	17 (6.7%)	
Years of smoking cigarettes	23.52 ± 11.04	25.15 ± 13.84	.159[a]
CO level (at first visit)	17.87 ± 11.00	18.35 ± 12.04	.661[a]
FTND score	6.82 ± 2.15	6.05 ± 2.50	<.001[b]
0–3	14 (6.7%)	39 (15.3%)	
4–6	68 (32.7%)	104 (40.8%)	
7–10	126 (60.6%)	112 (43.9%)	

Note. CO, carbon monoxide; FTND score, Fagerström Test for Nicotine Dependence score.
[a] t test.
[b] χ^2 test.

Results

Table 2 shows a summary of baseline characteristics of the sample. There were no significant differences between the two groups regarding age, sex, CPD, years of smoking, number of visits to the clinic, or weeks that their medicines were prescribed. Although the number of women was similar in both groups, relatively few women participated in this study. Compared to patients who were prescribed the nicotine patch, those using varenicline had significantly higher FTND scores ($p < .001$) and educational levels ($p < .001$).

Varenicline users had a significantly higher abstinence rate than the nicotine patch group in the third month (47.1% vs. 30.6%; odds ratio [OR] = 2.02, 95% confidence interval [CI] = [1.38, 2.96]) and in the sixth month (41.3% vs. 30.6%; OR = 1.60, 95% CI [1.09, 2.32]).

To control for baseline differences in the levels of education and tobacco dependence, we analyzed the effects of education levels, FTND, and medicine use (varenicline or nicotine patch) on 3- and 6-month cessation

rates using logistic regression. We found that FTND and education level have no significant effect on smoking cessation rates, but medicine use (varenicline vs. nicotine patch) was a significant predictor of abstinence at 3 months (Adjusted Risk Ratio [ARR] = 2.17, 95% CI [1.45, 3.24], $p < .001$) and 6 months (ARR = 1.74, 95% CI [1.16, 2.61], $p = .007$).

An association between the period of medicine use and abstinence was also observed. In the varenicline group, quitters at the 3-month follow-up had a longer average use (weeks) than smokers (4.42 $\pm$ 2.31 vs. 3.12 $\pm$ 2.37; $p < .001$). This was also the case at the 6-month follow-up (4.29 $\pm$ 2.29 vs. 3.34 $\pm$ 2.45; $p = .004$). In the nicotine patch group, the patch use (weeks) for quitters was also longer than for smokers at the 3-month (4.28 $\pm$ 2.63 vs. 2.93 $\pm$ 2.27; $p < .001$) and 6-month follow-up (4.01 $\pm$ 2.55 vs. 3.05 $\pm$ 2.37; $p < .001$).

Reported Adverse Events

The reported adverse events are listed in Table 1. Only information from patients who made two or more visits was included. No serious adverse events (SAEs) were reported in either group (any admission or consultancy in an emergency department, fatal or nonfatal suicidal behavior or thought, or deaths during treatment course). Overall, there were no significant group differences in the percentages of those reporting adverse events and withdrawal symptoms. However, we found that the most frequently reported adverse event in the varenicline group was nausea, whereas itchy skin (22.4%) and skin rash (17.1%) were more common in the nicotine patch group.

Discussion

Our study, which focuses on the real-world clinical use of two smoking cessation medicines, found that users of varenicline had significantly higher abstinence rates than those using nicotine patches at 3 and 6 months, and that both groups had approximately the same incidence of mild to moderate adverse events.

Two clinical trials, totaling 778 participants, did not find varenicline to be significantly superior to the nicotine patch at 24 weeks when the two drugs were directly compared (risk ratio = 1.13, 95% CI [0.94, 1.35]; Cahill, Stead Lindsay, & Lancaster, 2011). The differences observed in our study may have been a result of differences in the characteristics of patients in each group. Those choosing to use varenicline were more highly educated but were on the other hand more highly dependent. However, when

we analyzed the educational levels and FTND of those included in the 3- and 6-month cessation rates, we found no significant differences in education levels between quitters and smokers at the 3-month ($p = .141$) and 6-month ($p = .165$) follow-up. We did however find lower cessation rates in those with higher FTND scores in the third-month (quitters vs. smokers $= 6.09 \pm 2.30$ vs. 6.59 ± 2.41, $p = .028$) and sixth-month (quitters vs. smokers $= 5.98 \pm 2.30$ vs. 6.63 ± 2.39, $p = .005$) follow-up, a finding consistent with another previous study (Ferguson et al., 2003). Although we found no other significant differences between varenicline and nicotine patch users, there may have been differences in factors that we did not measure (e.g., history of mental health illness or urges to smoke during therapy course).

Other than FTND and education levels, no significant differences were found between the two groups regarding age, sex, CPD, years of smoking cigarettes, initial CO levels, and numbers of visits to the clinic during the treatment period or the duration on the medications. Varenicline and nicotine patch users reported similar incidences of adverse events or nicotine withdrawal symptoms. As in previous studies, varenicline users reported nausea more frequently (Aubin et al., 2008; Cahill et al., 2011), and nicotine patch users reported more frequently regarding skin rash and itching (Fiore, Jorenby, Baker, & Kenford, 1992).

In previous clinical trials, varenicline showed a greater variation in 24-week abstinence rates, Gonzales et al. (2006) reported a 7-day point prevalence abstinence rate of 33.5%, whereas another study involving only Taiwanese participants indicated a relatively high 7-day point prevalence abstinence rate of 57.1% (Tsai et al., 2007). The relatively high abstinence rate in Taiwan's trial (Tsai et al., 2007) need to be investigated in order to explain the high level of abstinence but may also provide an indirect explanation of why the smoking cessation intervention in our study was shorter than previous clinical trials that lasted from 9 to 12 weeks (Aubin et al., 2008; Fiore et al., 1992; Gonzales et al., 2006; Jorenby et al., 2006) but with similar abstinence rate. A previous study reported an association between greater frequencies of clinic visits to long-term abstinence (Hsueh, Chen, Yang, & Huang, 2010). Therefore, encouraging adherence to therapeutic recommendations is important in real-world smoking cessation programmers.

Our study has several limitations. First, this is a cohort study where patients could self select the medicine they wanted to use, rather than a randomized controlled trial; thus, there are more opportunities for undetectable bias. Second, the participants were contacted by phone to collect information on their 7-day abstinence rates at 3 and 6 months. This was performed

without any biochemical validation, and although self-reporting with a phone call without validation is an acceptable outcome measure (Velicer & Prochaska, 2004), biochemical verifications of abstinence would provide more objective and credible results. Third, participants who could not be contacted at the 3rd- or 6th-month follow-up were considered smokers, as they had been considered in previous clinical trials (Fiore, Smith, Jorenby, & Baker, 1994; Gonzales et al., 2006; Tsai et al., 2007). This would cause some bias or miscalculation in smoking cessation rates. Moreover, service fees were only partially subsidized by the National Health Insurance (NT$250 per week); thus, participants in the varenicline group paid approximately NT$950 a week, and those in the nicotine patch group only paid NT$500, meaning that the price of varenicline was greater than that of the nicotine patch. We are uncertain as to how the cost of therapy influences outcome or adherence, but perhaps participants taking varenicline had a greater motivation to quit and were therefore willing to pay more money. Participants with higher education levels could also have had higher incomes and could afford varenicline more easily. Another limitation is that the study only collected information on short-term outcomes. Longer term studies would add more insight into whether real cessation has occurred. Finally, the adverse events and withdrawal symptoms in both groups were obtained only from patients who came for their clinical visits and, therefore, could have been underestimated.

Conclusion

In a real-world smoking cessation clinic, the abstinence rate was higher in the group of patients receiving varenicline than in the group of patients receiving nicotine patches at 3- and 6-month follow-up. Great adherence to treatment leads to higher abstinence rates in both groups. Adverse events and withdrawal symptoms were similar with no SAEs reported during treatment or at follow-up.

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Declaration of Conflicting Interests

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