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Varenicline and Nicotine Patch Therapies in Young Adults Motivated to Quit Smoking: A Randomized, Placebo-controlled, Prospective Study

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Abstract: This study compares the nicotine patch to placebo in young adult light smokers, and the nicotine patch to varenicline in heavy smokers. Volunteer daily smokers were recruited into a randomized, placebo-controlled study via community media, colleges and the army (aged 18–26 years). Those subjects with light tobacco dependence were randomized to (i) placebo patch (n = 86) and (ii) nicotine patch 10 mg/16 hr for 8 weeks (n = 94), and those with stronger dependence to (iii) nicotine patch 15 mg/16 hr for 8 weeks (n = 51) and (iv) varenicline for 12 weeks (n = 60). The primary outcome variable was self-reported smoking abstinence at week 12. Secondary outcome variables were self-reported smoking abstinence at weeks 4 and 26, and self-reported abstinence verified by saliva cotinine level at week 12. The prevalence of self-reported smoking abstinence did not differ statistically significantly in light smokers during the follow-up (week 4: 19.8% for placebo patch and 26.6% for nicotine patch 10 mg/16 hr; week 12: 17.4% *versus* 23.4%; week 26: 15.1% *versus* 20.2%), but the groups of heavy smokers differed significantly for 12 weeks (week 4: 19.6% for nicotine patch 15 mg/16 hr and 73.3% for varenicline, $p < 0.001$; week 12: 15.7% *versus* 36.7%, $p = 0.018$). This statistically significant difference did not endure for the entire follow-up (week 26: 9.8% *versus* 18.3%, $p = 0.280$). However, saliva cotinine verified abstinence at week 12 did not support self-reported abstinence. Varenicline may be more effective than the nicotine patch as a smoking cessation pharmacotherapy among young adult heavy smokers in the short-term.

Tobacco use is known to be a major health risk. The tobacco habit is often adopted at a young age: throughout the European Union, about 29% of 15- to 24-year-olds smoke [1]. Nicotine replacement therapy (NRT), bupropion and varenicline have been shown to be effective in smoking cessation in adults [2], but there are no evidence-based guidelines for smoking cessation targeted especially to young smokers [3–7]. This is particularly true for young adults, a group that has been rarely analysed separately from either adolescent or adult smokers [7,8].

Some clinical trials have evaluated NRT in young smokers (aged 13–21 years; n = 40–257) [9–13] reporting the following findings: end-of-treatment abstinence rates: 0% for NRT nasal spray [13], 6.5% for nicotine gum [10] and 0–28% for nicotine patch [9–12], and after 26-week follow-up, 9% for nicotine gum and 21% for nicotine patches [10]. Two of these studies did indicate that NRT could be more effective than placebo in the short-term. Moolchan *et al.*[10] claimed that the nicotine patch was more effective than placebo at the end of the treatment (nicotine patch group 18% *versus* placebo 3%). The difference was no longer statistically significant at the 26-week follow-up. In addition, Scherphof *et al.* [11] reported that nicotine patches were significantly more effective than placebo at the end of the treatment only in the 'high-compliant' group.

The end-of-treatment abstinence rates in four randomized clinical studies investigating bupropion [14–17] (aged 12–21 years; n = 22–312) ranged from 8% to 55% with two studies [14,17] reporting a statistically significant difference compared to placebo. After 26 weeks, the abstinence rates had declined to 3–14% [16,17] without any statistically significant difference compared to placebo.

So far, no placebo-controlled studies focusing on the efficacy of varenicline have been conducted in young smokers. One study [18] has provided preliminary results on the tolerability and safety of the drug in this age group. Varenicline was associated with adverse events similar to those described in adults, but no discontinuations were reported because of adverse events. One small randomized trial (n = 29; age 15–20 years) compared varenicline to bupropion [19] without encountering any serious adverse events; the end-of-treatment abstinence rates after 8 weeks of treatment were 27% for varenicline and 14% for bupropion but after 12 weeks, none of the subjects in the varenicline group were still abstinent and only one in the bupropion group.

Young adults are more likely to smoke than any other age group in many Western countries, and they smoke more regularly than adolescents and thus they develop an increasing dependence

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on nicotine [20,21]. At the same time, very few smoking cessation interventions focusing on this age group have been conducted. Clearly, more smoking cessation trials are needed to create evidence-based guidelines for smokers at this critical age to help these young adults quit smoking as early as possible in order to prevent smoking-related damage to their health.

This study investigates the efficacy of varenicline and the nicotine patch as a smoking cessation aid in volunteer daily smokers in their twenties. It compares placebo to the nicotine patches 10 mg/16 hr in subjects with mild-to-moderate dependence on tobacco, and stronger nicotine patches (15 mg/16 hr) to varenicline in those smokers with stronger dependence levels. Based on the results of smoking cessation studies in adults, we suggested that both nicotine patches and varenicline therapy would be effective and furthermore that varenicline would be superior to the nicotine patch in heavy smokers.

Methods

This is a randomized, placebo-controlled clinical study with the intent-to-treat principle and simple randomization protocol. Subjects were recruited on a voluntary basis during spring 2012 until spring 2014 via community media, colleges and the army in northern parts of Finland (cities of Rovaniemi, Kemi and Tornio, municipality of Sodankylä). The study was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. Our study protocol has the registration ID NCT01531049 in the ClinicalTrials.gov.

The recruited subjects were 18- to 26-year-old men and women, who had smoked daily for at least the past month and smoked 100 or more cigarettes in their life; they were motivated to quit smoking and to be volunteers in this study that investigated different pharmacological treatments for smoking cessation as well as being willing to participate in the 52-week follow-up with the associated monitoring visits arranged in Lapland Central Hospital in Rovaniemi. Exclusion criteria were current drug or alcohol abuse, known allergy towards medications used in the study, lactation, pregnancy or intention to become pregnant during the study period.

The targeted sample size was estimated on the basis of findings from Cochrane systematic reviews [22,23]. It is known that the standard placebo smoking cessation treatment methods achieve a good outcome in about 10% of the smokers. We postulated that if the tested nicotine patch 10 mg/16 hr treatment could increase the success by up to 24% and varenicline by up to 28%, this would be clinically important. An increase of this size with a two-tailed p-value of 0.05 and power 0.80 would require a total sample size of 300 young adult daily smokers which became our target sample size. The placebo to the nicotine patch 10 mg/16 hr comparison would require 180 smokers with mild-to-moderate nicotine dependence, and the nicotine patch 15 mg/16 hr to varenicline comparison would need 120 smokers with strong nicotine dependence.

Table 1 describes the study protocol. All subjects provided written informed consent. The study nurse conducted all control contacts with the subjects during the study. Counselling visits included an individualized smoking cessation counselling (30 min.) using the technique of a Motivational Interview [24] provided by the study nurse.

Current nicotine dependence was assessed with the Heaviness of Smoking Index (HSI) [25,26]. The HSI consists of two questions: (i) How soon after you wake up do you have your first cigarette? A. within 5 min. (3 points), B. 6–30 min. (2 points), C. 31–60 min. (1 point) and D. after 60 min. (0 points). (ii) How many cigarettes do you typically smoke per day? A. 31 or more (3 points), B. 21–30 (2 points), C. 11–20 (1 point) and D. 10 or fewer (0 points). Mild dependence was 0–1 points, moderate dependence 2 points, strong dependence 3 points and very strong dependence 4–6 points. Light smokers had mild-to-moderate dependence (HSI 0–2 points), and heavy smokers had strong-to-very strong dependence (HSI 3–6 points). The subject was repeatedly asked at all contacts to assess his/her motivation to quit smoking on a scale from 1 to 10 points (1 = low motivation, 10 = high motivation).

Light smokers were randomly assigned into two groups: placebo patch for 8 weeks (group 1) or nicotine patch 10 mg/16 hr for 8 weeks (group 2). Heavy smokers were randomized to receive stronger nicotine patches, 15 mg/16 hr for 8 weeks (group 3) or 12 weeks of varenicline treatment (group 4).

If a subject reported mild-to-moderate dependence for cigarettes (HSI 0–2), but strong-to-very-strong dependence for Swedish moist snuff (snus), then the HSI grading to be used in the randomization was raised to the more severe dependence level (HSI 3–6) to avoid underestimating the dependence on nicotine. Snus dependence was assessed with the HSI questions modified for snus use, that is these two questions: (i) How soon after you wake up do you have your first snus? (ii) How much snus do you typically use every day? The grading was the same as in the HSI. One gram of snus was estimated to be one portion.

After assessment of the HSI grade by the study nurse at the baseline visit, simple randomization with a computer-generated random list (allocation ratio 1:1) was used to allocate study subjects into the different treatment groups. Randomization was conducted by a professional from Medical Informatics and Statistics Research Group in the University of Oulu who was not otherwise part of the study group.

All subjects using psychiatric medication on a daily basis were excluded from randomization because the Pharmaceutical Medication Centre in Finland does not recommend that varenicline should be given to subjects with unstable mental illness or to those estimated to have an increased risk of suicidal behaviour.

In clinical practice, the recommended nicotine patch dosing is adjusted according to the patient's nicotine dependence level, and varenicline is mainly prescribed for highly dependent smokers motivated to quit smoking. In this study, we used HSI to assess each subject's nicotine dependence, and the nicotine patch dosing was dependent on the HSI value (10 mg/16 hr or 15 mg/16 hr patch). We chose 8 weeks as the duration of nicotine patch treatment. In previous studies, the duration of nicotine patch treatment has varied widely, but there is no evidence that a treatment period longer than 8 weeks

Table 1.
Schedule of study contacts in prospective study of young adult smokers.

	Contacts					
Measurements	Baseline visit	First counselling visit (0 week)[1]	Phone call (4 weeks)	Counselling visit (12 weeks)	Phone call (26 weeks)	Counselling visit (52 weeks)
Questionnaire[2]	x		x	x	x	x
Saliva cotinine level				x		x

[1]Starting point of the treatment.
[2]Including information about current tobacco use status, Heaviness of Smoking Index, motivation to quit smoking, and after beginning of the treatment also use of the smoking cessation pharmacotherapy, adverse events or other concerns related to the intervention enquired in an open question.

would be more efficacious [22]. As a result, we decided to compare the placebo patch with the nicotine patch 10 mg/16 hr in light smokers (HSI 0–2 points) and to test varenicline against the nicotine patch 15 mg/16 hr in heavy smokers (HSI 3–6 points).

The placebo patch (Leukomed T®, BSN Medical, Luxembourg, Luxembourg) was not identical to the nicotine patch, but selected because it did resemble a medication-type patch. It was packed into packages each containing 56 patches without the trade name. The nicotine patch was removed from its original packaging and replaced into boxes also containing 56 patches. The trade name of the nicotine patch was printed on the patches. Each subject was recommended to change the patch daily.

The first week of varenicline use included dose titration: 0.5 mg once daily for 3 days and then 0.5 mg twice a day till the end of the first week. From the 2nd week until the end of the 12th week, the dosing was 1 mg twice a day. The dosing and the duration of varenicline treatment followed the manufacturer's recommendations. Varenicline (Champix®, Pfizer, Sandwich, Kent, United Kingdom) was supplied in the original package. Therefore, the subjects were aware of what they had been given.

Smoking abstinence at 4, 12 and 26 weeks was recorded if the subject reported that he/she had quit smoking and had not smoked for about 1 week. The primary outcome variable was self-reported smoking abstinence at the end of the treatment (week 12). Secondary outcome variables were self-reported smoking abstinence at 4 and 26 weeks and self-reported smoking abstinence as verified by saliva cotinine level ≤10 ng/ml at week 12. We compared the efficacy of placebo patch treatment to the nicotine patch 10 mg/16 hr in young adult light smokers, and on the other hand, the stronger nicotine patch, 15 mg/16 hr, to varenicline in heavy smokers.

All statistical analyses were conducted using IBM SPSS Statistics, version 21 software. The distribution of categorical variables between the study groups was compared with cross-tabulation. The difference between the observed proportions of abstinence (with 95% confidence interval) in the study groups was used as the effect size measure. The statistical significances of differences in tobacco abstinence rates (primary and secondary outcomes) and compliance were further evaluated with the chi-square test. Distributions of body height, smoking initiation age, duration of smoking and HSI points between the study groups were compared using mean values and standard deviations. Because of the right-skewed distribution, the study groups were compared in terms of age, body weight, motivation to quit smoking and number of daily cigarettes with medians and interquartile ranges. Those subjects who were lost to follow-up were considered as continuing to smoke. If a subject missed a control visit but attended subsequent controls, his/her smoking status at the missed control was assumed to be the same as that recorded at the time when he/she came to the next control session. All randomized subjects were analysed according to the intent-to-treat principle.

Results

A total of 291 daily smokers were analysed. Figure 1 describes the progression of subjects through the study.

Table 2 shows the characteristics of the subjects. The median age was 21. The study groups were similar in terms of age, weight, height, baseline motivation to quit smoking and proportion of female sex (table 2), as well as educational level (data not shown). In contrast, heavy smokers seemed to have a longer smoking history and had begun to smoke at a younger age than light smokers (table 2). In addition, heavy smokers consumed more cigarettes and had higher HSI than light smokers (table 2).

At week 4, a total of 96 (33.0%) subjects had quit smoking. There were no statistically significant differences in the abstinence rates between placebo and nicotine patch 10 mg/16 hr treatments, but varenicline was significantly more effective than the nicotine patch 15 mg/16hr treatment in heavy smokers at this time-point ($p < 0.001$; table 3). The smoking abstinence rates at week 4 were as follows: placebo patch group 19.8%, nicotine patch 10 mg/16 hr 26.6%, nicotine patch 15 mg/16 hr 19.6% and varenicline 73.3%.

At week 12, a total of 67 subjects (23.0%) had quit smoking. There were no statistically significant differences between the treatment groups of light smokers in self-reported smoking abstinence (17.4–23.4%), but the differences were significant between the groups of heavy smokers ($p = 0.018$; table 3): in the varenicline group, 36.7% had been successful in achieving smoking abstinence, whereas those treated with the nicotine patch 15 mg/16 hr displayed a significantly lower smoking abstinence rate, 15.7%.

Out of a total of 67 smoking abstinent subjects, 52 (77.6%) came to the counselling visit conducted on week 12. Saliva cotinine was measured from 50 of these subjects. Four subjects reported using nicotine gum at the time of the saliva cotinine measurement, and two spontaneously reported having been recently exposed to environmental tobacco smoke although exposure to environmental tobacco smoke was not specifically asked at the 12-week control session. Fourteen subjects participating in the 12-week control visit reported that they had quit smoking but were using snus, although often infrequently. The expired-air CO level was measured in 11 of these 14 snus users, all had CO levels ≤5 ppm, confirming their self-reported abstinence of smoking.

Therefore, 30 self-reported smoking abstinent subjects did not report any confounding factor which could have interfered with the saliva cotinine assay. Nonetheless, self-reported smoking abstinence poorly correlated with saliva cotinine measurement: only seven subjects had their self-reported smoking abstinence confirmed by saliva cotinine levels ≤10 ng/ml: two subjects in the placebo group, one in the nicotine patch 10 mg/16 hr group, one in the nicotine patch 15 mg/16 hr group and three in the varenicline group. A low positive (10–30 ng/ml) was measured in 20 of these subjects. Three subjects exhibited a clearly positive saliva cotinine test value (30–100 ng/ml n = 2; 100–200 ng/ml n = 1). The expired-air CO level was measured in eight low-positive subjects and one with a definite saliva cotinine 30–100 ng/ml, and all had their CO level ≤5 ppm supporting their self-reported smoking abstinence.

At week 26, 16.5% (n = 48) had quit smoking (table 3). The smoking abstinence rates were as follows: placebo patch 15.1%; nicotine patch 10 mg/16 hr 20.2%; nicotine patch 15 mg/16 hr 9.8%; varenicline 18.3%, and there were no statistically significant differences between the two groups of light or heavy smokers (table 3).

The varenicline group was the most compliant group: 76.7% used the drug for over 2 weeks and 20.0% completed the treatment. The corresponding values for placebo patch were 36.1% and 10.5%, for nicotine patch 10 mg/16 hr 51.1% and 21.3%, and for nicotine patch 15 mg/16 hr 37.3% and 9.8%. There was a statistically significant difference in the

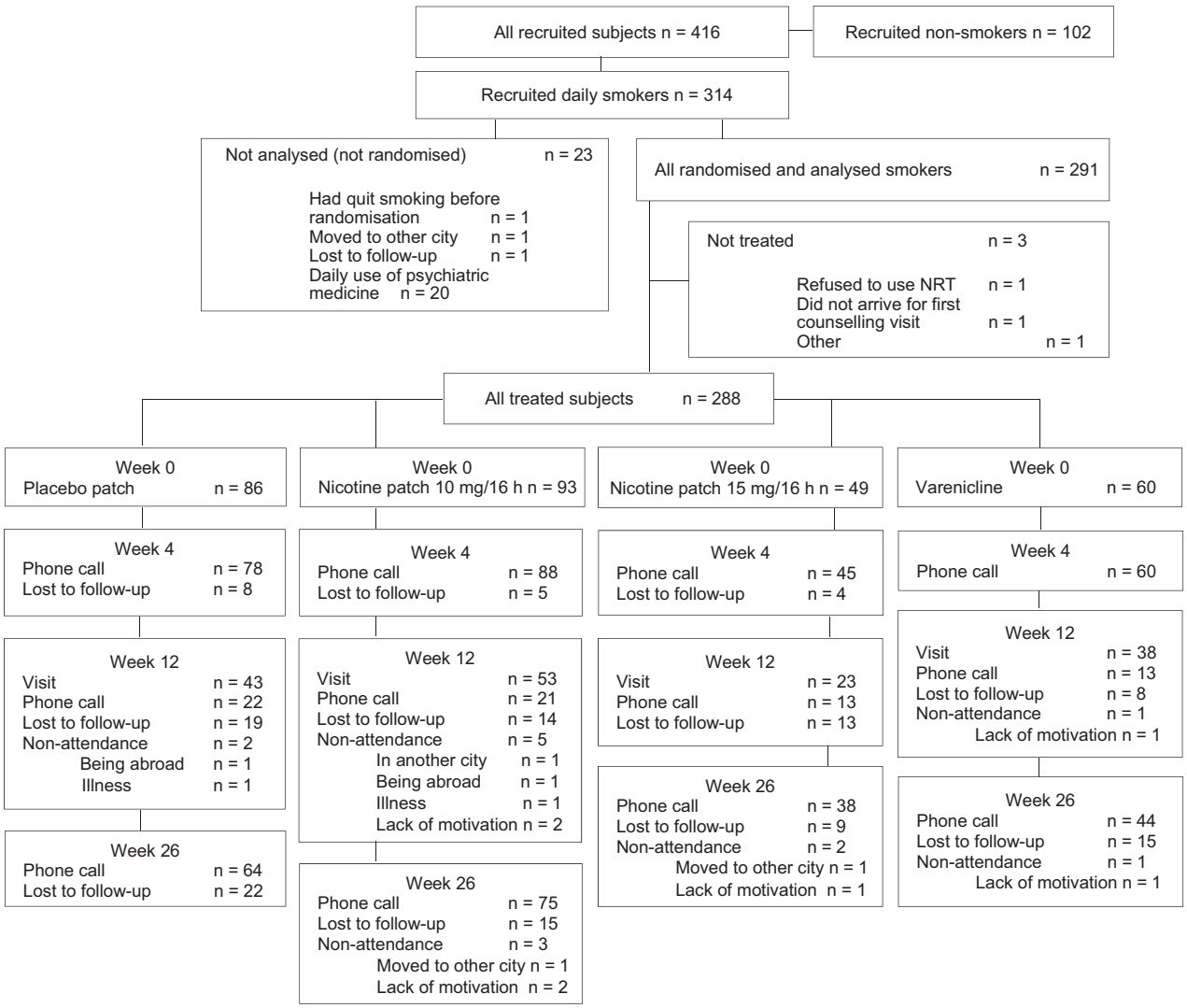

Fig. 1. The timeline of the study with numbers of participants at each stage.

Table 2.

Subject characteristics of young adult daily smokers.

	Placebo patch n = 86 Median (IQR)	Nicotine patch 10 mg/16 hr n = 94 Median (IQR)	Nicotine patch 15 mg/16 hr n = 51 Median (IQR)	Varenicline n = 60 Median (IQR)	Total n = 291 Median (IQR)
Age (years)	20 (18.0–23.3)	21 (19.0–23.0)	22 (19.0–24.0)	21 (19.0–23.8)	21 (19.0–23.0)
Weight (kg)	70.1 (61.0–82.7)	70.5 (62.0–78.2)	71.2 (61.5–82.9)	72.6 (62.2–79.7)	70.7 (61.7–80.5)
Motivation to quit at baseline(1–10)[1]	8 (7.0–8.0)	7 (6.0–8.0)	7 (6.0–8.0)	7 (6.0–8.0)	7 (6.0–8.0)
Number of daily cigarettes	10 (8.0–15.0)	10 (7.0–14.3)	18 (15.0–20.0)	18 (15.0–20.0)	14 (10.0–20.0)
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Height (cm)	170.6 (8.7)	170.1 (8.9)	171.7 (10.3)	169.9 (7.8)	170.5 (8.9)
Smoking initiation age (years)	14.8 (2.3)	15.3 (2.0)	14.4 (2.0)	14.1 (1.9)	14.7 (2.1)
Duration of smoking (years)	5.8 (3.1)	5.9 (3.0)	7.0 (2.7)	7.3 (2.8)	6.4 (3.0)
HSI points	1.3 (0.8)	1.3 (0.8)	3.3 (0.9)	3.5 (0.7)	2.1 (1.3)
	n (%)	n (%)	n (%)	n (%)	n (%)
Female gender	44 (51.2)	49 (52.1)	23 (45.1)	30 (50.0)	146 (50.2)

HSI, Heaviness of Smoking Index; IQR, interquartile range; S.D., standard deviation.
[1]Two missing values in the nicotine patch 15 mg/16 hr group.

Table 3.
Distributions of the outcome variables (self-reported smoking abstinence at 4, 12 and 26 weeks) by study groups.

	Placebo n = 86 n (%)	Nicotine patch 10 mg/16 hr n = 94 n (%)	*p*-Value[1]	Nicotine patch 15 mg/16 hr n = 51 n (%)	Varenicline n = 60 n (%)	*p*-Value[1]	Total n = 291 n (%)
Abstinence at week 4							
Yes	17 (19.8)	25 (26.6)	0.296	10 (19.6)	44 (73.3)	<0.001	96 (33.0)
No	69 (80.2)	69 (73.4)		41 (80.4)	16 (26.7)		195 (67.0)
Effect size % (95% CI)	6.8 (−5.6 to 18.8)			53.7 (35.9 to 66.6)			
Abstinence at week 12							
Yes	15 (17.4)	22 (23.4)	0.360	8 (15.7)	22 (36.7)	0.018	67 (23.0)
No	71 (82.6)	72 (76.6)		43 (84.3)	38 (63.3)		224 (77.0)
Effect size % (95% CI)	6.0 (−6.0 to 17.5)			21.0 (4.4 to 25.7)			
Abstinence at week 26							
Yes	13 (15.1)	19 (20.2)	0.437	5 (9.8)	11 (18.3)	0.280	48 (16.5)
No	73 (84.9)	75 (79.8)		46 (90.2)	49 (81.7)		243 (83.5)
Effect size % (95% CI)	5.1 (−6.3 to 16.1)			8.5 (−5.1 to 21.4)			

[1]Chi-square exact test *p*-Value.

extent of compliance between nicotine patch 15 mg/16 hr and varenicline (chi-square exact test $p < 0.001$), but not between placebo and nicotine 10 mg/16 hr patch groups (chi-square exact test $p = 0.136$).

Even though after 4 weeks, varenicline users reported experiencing some degree of adverse events more often (60.0%) than those in nicotine patch groups (27.7–31.4%) and placebo group (17.4%), most of the varenicline users experiencing an adverse event persisted with their treatment. However, treatment discontinuations caused by an adverse event were most often encountered in the varenicline group (13.3% for varenicline, 5.9–8.5% for nicotine patch and 3.5% for placebo). The specific reasons that resulted in discontinuation of the treatment were as follows: cutaneous irritation (n = 2) and unsteady feeling (n = 1) in placebo group, cutaneous irritation (n = 7) and pain at the site of the patch (n = 1) in nicotine patch 10 mg/16 hr group, cutaneous irritation (n = 3) in nicotine patch 15 mg/16 hr group, and nausea (n = 6), shift of moods (n = 1) and abnormal dreams (n = 1) in the varenicline group. The most common adverse events were as follows: for placebo patch cutaneous irritation and nervousness, for nicotine patch 10 mg/16 hr cutaneous irritation and nausea, for nicotine patch 15 mg/16 hr cutaneous irritation and pain at the site the patch, whereas for varenicline, the most common reasons were nausea and abnormal dreams. No serious adverse events were reported as judged by the investigators.

Five subjects (5.8%) in the placebo patch group expressed their suspicion of having placebo patches. Furthermore, one subject in the nicotine patch 15 mg/16 hr group reported this suspicion. Some subjects reported having heard rumours that varenicline was actually a placebo although none of them reported this suspicion by themselves.

Discussion

These preliminary results indicate that varenicline might be significantly more efficacious in young adult heavy smokers than nicotine patches in achieving tobacco abstinence in the short-term (at weeks 4 and 12). The difference in self-reported abstinence did not last for the entire duration of the trial (week 26). In contrast, the nicotine patch did not seem to be more efficacious than a placebo patch in young adult light smokers. Both varenicline and nicotine patches were generally well tolerated. In most cases, the adverse events were mild and rarely resulted in any need to discontinue treatment.

As expected, heavy smokers had higher cigarette consumption and HSI compared to light smokers. In addition, the age to start smoking and years of smoking seemed to differ between the study groups. The heavy smokers had smoked longer than their counterparts in the study groups with light smokers. The differences in smoking initiation age and duration of smoking are not surprising and probably reflect the fact that randomization was based on the HSI value: subjects randomized to varenicline and nicotine 15 mg/16 hr groups were more addicted to nicotine according to their HSI assessment. Smoking from adolescence to early adulthood is a progressive habit where smoking becomes both more regular and more addictive with time [20,21]. Therefore, those individuals that had begun to smoke at earlier ages were more likely to have developed a stronger dependence than those starting at an older age.

In this study, we assayed the saliva cotinine concentration to verify self-reported abstinence at the end of the treatment. Only seven subjects gave a negative saliva cotinine test result (≤10 ng/ml) to confirm their self-reported smoking abstinence. One reason for this discrepancy is that 54.0% (n = 157) came to the counselling visit, but 23.7% (n = 69) stated that they were unable to come to this session but instead participated over the phone. On the other hand, we did not ask subjects to report all confounding factors which might have interfered with this measurement such as recent exposure to environmental tobacco smoke. Furthermore, some smoking abstinent subjects continued to use snus, at least to some extent. After noting this problem, it was decided to measure the expired-air

CO level from all of those exhibiting a positive saliva cotinine test result. These results did indicate that the individuals claiming to have stopped smoking were reliable, as none of them a CO level over 5 ppm.

Our study indicates that varenicline is more effective than nicotine patches in young adult heavy smokers, at least in the short-term. We could not find any smoking cessation trials comparing varenicline to nicotine patch treatment in young smokers. A few earlier studies have found support for the belief that treatment with nicotine replacement therapy would be effective in young smokers trying to quit [3,4,6]. In our light smokers, nicotine patches were not any more effective than a placebo patch in either the short or long-term. Furthermore, our results are partly in line with adult smoking cessation studies where varenicline has been shown to be more effective than nicotine patches, but in contrast to the situation in young smokers, in adults, nicotine patch treatment does appear to be more effective than placebo [2].

During the follow-up period, some individuals reported having quit smoking but were still using snus, at least to some extent. Although complete success in conquering the nicotine dependence in these subjects is arguable, the aim of this study was to evaluate the effectiveness of smoking cessation pharmacotherapy in smokers motivated to quit smoking.

This is a real-life study with a relatively large sample size of volunteer young adult smokers, but has some limitations that need to be considered. Firstly, the study was not conducted in a blinded manner. Randomized and double-blinded trials in young adult smokers will be needed to confirm our preliminary results that varenicline seems to be an effective smoking cessation aid in this age group over the short-term. Secondly, the nicotine and placebo patches were not identical. In addition, we did not obtain similarly looking placebo tablets such as the varenicline tablets to be used in this study. One limitation is the lack of comprehensive verification of self-reported smoking abstinence with CO level assessment.

More studies will be needed to investigate the efficacy and safety of varenicline and nicotine patch treatment in young adult smokers with daily psychiatric medication or concomitant drug/alcohol abuse – subgroups that were not included on our analysis. The introduction of novel medicines for such subgroups needs a tailored approach to avoid adverse drug reactions [27].

Our study involved treatment with two different strengths of nicotine patches, 10 mg and 15 mg with daily use (16 hr) for 8 weeks. The dosing and the duration of varenicline therapy used in our study are those recommended by the patch manufacturer. Therefore, it should be noted that the varenicline group received a longer treatment than the nicotine patch groups. However, previous studies in adults have not found any consistent evidence that a longer duration or higher dosing of the patches would improve smoking abstinence rates [22]. Finally, compliance in our study was generally low. Even though compliance was moderate after 2 weeks of treatment, only about 10–20% fully completed the treatment as recommended. This problem has been commonly encountered in smoking cessation trials focusing on younger age groups [4].

In conclusion, varenicline seems to be superior to nicotine patch in helping young adult heavy smokers to quit smoking although both approaches seem to be well tolerated. Smoking cessation is a process where relapses are common. After successful short-term abstinence with or without pharmacological help, in order to avoid relapses, the new ex-smoker must be provided with motivation to avoid restarting to smoke.

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Disclosure Statement

The authors declare no conflict of interest.

References

1 Gibson G, Loddenkemper R, Sibille Y, Lundbäck B. European Lung White Book. European Respiratory Society, Sheffield, 2013.
2 Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;**5**:CD009329.
3 Stanton A, Grimshaw G. Tobacco cessation interventions for young people. Cochrane Database Syst Rev 2013;**8**:CD003289.
4 Bailey SR, Crew EE, Riske EC, Ammerman S, Robinson TN, Killen JD. Efficacy and tolerability of pharmacotherapies to aid smoking cessation in adolescents. Paediatr Drugs 2012;**14**:91–108.
5 Tobacco Dependence and Cessation. Working group set up by the Finnish Medical Society Duodecim and the Finnish Association for General Practice. http://www.kaypahoito.fi (last accessed on 15 September 2015).
6 Kim Y, Myung SK, Jeon YJ, Lee EH, Park CH, Seo HG *et al.* Effectiveness of pharmacologic therapy for smoking cessation in adolescent smokers: meta-analysis of randomized controlled trials. Am J Health Syst Pharm 2011;**68**:219–26.
7 Suls JM, Luger TM, Curry SJ, Mermelstein RJ, Sporer AK, An LC. Efficacy of smoking-cessation interventions for young adults: a meta-analysis. Am J Prev Med 2012;**42**:655–62.
8 Villanti AC, McKay HS, Abrams DB, Holtgrave DR, Bowie JV. Smoking-cessation interventions for U.S. young adults: a systematic review. Am J Prev Med 2010;**39**:564–74.
9 Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. Nicotine Tob Res 2003;**5**:515–26.
10 Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ *et al.* Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 2005;**115**:407–14.
11 Scherphof CS, van den Eijnden RJ, Engels RC, Vollebergh WA. Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. J Subst Abuse Treat 2014;**46**:120–7.

12 Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community-based pilot randomised controlled trial. Tob Control 2006;**15**:373–6.
13 Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB. A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics 2008;**122**:595–600.
14 Niederhofer H, Huber M. Bupropion may support psychosocial treatment of nicotine-dependent adolescents: preliminary results. Pharmacotherapy 2004;**24**:1524–8.
15 Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW *et al.* Bupropion SR and contingency management for adolescent smoking cessation. J Subst Abuse Treat 2011;**40**:77–86.
16 Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C *et al.* Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. J Consult Clin Psychol 2004;**72**:729–35.
17 Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Arch Pediatr Adolesc Med 2007;**161**:1068–74.
18 Faessel H, Ravva P, Williams K. Pharmacokinetics, safety, and tolerability of varenicline in healthy adolescent smokers: a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2009;**31**:177–89.
19 Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP. Varenicline versus bupropion XL for smoking cessation in older adolescents: a randomized, double-blind pilot trial. Nicotine Tob Res 2012;**14**:234–9.
20 Hammond D. Smoking behaviour among young adults: beyond youth prevention. Tob Control 2005;**14**:181–5.
21 Bachmann MS, Znoj H, Brodbeck J. Smoking behaviour, former quit attempts and intention to quit in urban adolescents and young adults: a five-year longitudinal study. Public Health 2012;**126**:1044–50.
22 Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K *et al.* Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2012;**11**:CD000146.
23 Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;**10**:CD008286.
24 Dunn C, Deroo L, Rivara FP. The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. Addiction 2001;**96**:1725–42.
25 Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict 1989;**84**:791–9.
26 Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991;**86**:1119–27.
27 Campbell SM, Godman B, Diogene E, Furst J, Gustafsson LL, MacBride-Stewart S *et al.* Quality indicators as a tool in improving the introduction of new medicines. Basic Clin Pharmacol Toxicol 2015;**116**:146–57.