Effect of Nicotine Polyestex Gum on Smoking Cessation and Quality of Life†

Suthat Rungruanghiranya MD, FCCP*, Chatchai Ekpanyaskul MD, MSc**,
Yongyos Hattapornsawan MD***, Yongyuth Tundulawessa PhD****

† *This study was supported by Thai Health Promotion Foundation, and Srinakharinwirot University*
* *Department of Medicine, Faculty of Medicine, Srinakharinwirot University, Bangkok*
** *Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Bangkok*
*** *Department of Medicine, Royal Irrigation Hospital, Nonthaburi*
**** *Department of Chemistry, Faculty of Science, Srinakharinwirot University, Bangkok*

Objective: *To determine the effectiveness and safety of the novel nicotine polyestex gum for smoking cessation, along with its impact on the quality of life (QOL).*
Material and Method: *A double-blind, placebo-controlled, randomized clinical trial was conducted on 43 smokers. All of them received either nicotine gum or placebo. Only those who could quit completely and continuously by the end of 3 months were considered total abstinence. QOL was also measured using WHO questionnaires.*
Results: *Treatment with nicotine polyestex gum resulted in significantly greater abstinence rate at 3 months compared with placebo (50% vs. 9%; p = 0.003). Adverse events were modest and not encountered more often than those seen in the placebo group. QOL at 3-months improved in both groups, but there was no statistically significant difference between the groups.*
Conclusion: *Nicotine polyestex gum is effective and safe for smoking cessation. It is also associated with significant improvement in the QOL.*

Keywords: *Nicotine gum, Nicotine dependence, Smoking cessation, Quality of life*

J Med Assoc Thai 2008; 91 (11): 1656-62
Full text. e-Journal: *http://www.medassocthai.org/journal*

Smoking is the leading preventable cause of diseases and death in the developing countries[1]. Accordingly, several clinical guidelines require physicians to provide counseling and effective treatment for all smokers [2-4]. However, relatively few smokers succeed in quitting each year. Since the urge to smoke is directly related to a need for nicotine, nicotine replacement therapy (NRT) has been developed to relieve the craving and withdrawal symptoms. Several forms of NRT are currently available; however, patches and gum have been the most widely used formulations over the past decade. While nicotine transdermal patches deliver nicotine slowly through the skin, nicotine polacrilex gum can release nicotine faster, therefore, allow smokers to combat acute episodes of craving. Unfortunately, nicotine polacrilex gum is expensive and inaccessible to people in the developing world. Recently, the novel nicotine polyestex gum has been approved for use by the Thai Food and Drug Administration (FDA) and was introduced at a much lower price. The present study is aimed to determine the efficacy and safety of nicotine polyestex gum as an aid in smoking cessation. Changes in quality of life at the end of the treatment were also measured.

Correspondence to: Rungruanghiranya S, Department of Medicine, Faculty of Medicine, Srinakharinwirot University, Ongkarak, Nakornnayok 26120, Thailand. Phone: 037-395-085 ext.11003, Mobile: 08-9441-3959, Fax: 037-395-085 ext. 11003, E mail: suthat109@yahoo.com

Material and Method

Subjects and randomization

This double-blind, placebo-controlled, randomized clinical trial was performed at two sites

(HRH Princess Mahachakri Sirindhorn Medical Center, Srinakharinwirot University, Nakornnayok; the Royal Irrigation Department Hospital, Nonthaburi) and approved by each center's institutional review board. Participants were recruited between July 2006 and November 2007. To be eligible for the present study, subjects had to be 18 years of age or older, had smoked an average of 10 cigarettes or more per day for the past year, and were interested in quitting smoking within the next 30 days. Only one smoker per household was allowed. Exclusion criteria included pregnancy, previous use of other smoking cessation aids in the past month, a history or current diagnosis of coronary artery disease, stomach ulcers, uncontrolled hypertension, diabetes mellitus, use of illicit drugs, and non-adherence to treatment. Written informed consent was obtained from all participants.

At the baseline-visit, all smokers had a detailed record of their usual cigarette consumption. Exhaled carbon monoxide (CO) concentration was also measured. The 6-item Fagerstrom Test (FTND) with a score ranging from 0 to 10 was obtained to determine the degree of nicotine dependence; a score of 6 or greater indicates high levels of dependence[5]. All subjects were randomly assigned to receive either active gum or placebo by block randomization technique. To match the taste of nicotine, placebo gum which contained no nicotine was made identical in appearance and was minted. Dose of gum provided was based on the levels of nicotine dependence. The highly-dependent smokers were assigned to the 4-mg dose (2 pieces of 2-mg gum), and the others to the 2-mg dose (1 piece of 2-mg gum). Subjects set a target quit date; however, all of them were encouraged to completely stop smoking on the first day of treatment. They returned at 2, 4, 6, and 12 weeks after their quitting date for follow-up. At each visit, the physician asked each subject whether he or she smoked, consumption gum daily, and experience adverse events related to gum use. If yes, they were advised to stop smoking or maintain abstinence, to help them eliminate craving, and arranged a follow-up visit. Participants who failed to maintain abstinence (assessed by self-report and results of exhaled CO verification) were discontinued from the present study. At the final visit, all participants were requested to fill in WHOQOL-BREF questionnaires before leaving the clinic.

Nicotine polyestex gum

Nicotine polyestex gum was supplied by Srinakharinwirot University, Thailand. Each piece of active gum contained 2 mg of nicotine. All subjects were given the same instructions about the gum. They were advised to use the gum whenever they felt an urge to smoke. The correct technique for using the gum was also instructed and repeatedly discussed at every visit. A leaflet with step-by-step instructions on how to quit smoking, and how to use correctly the gum was also provided.

Behavioral support

Each subject received a brief, personalized message to stop smoking from the physician and self-help material. Individual counseling was also provided approximately 10 to 15 minutes by a study assistant at each visit.

Outcome measures

Total abstinence rate is the primary efficacy measure of the present study. Only the participants who could quit completely and continuously by the end of 3 months from day zero were considered total abstinence. Their reports of abstinence were subjected to verification by an exhaled CO level of 10 ppm or less. Those who either restarted smoking, admitted using another nicotine replacement therapy or other smoking cessation aids during the present study period, had exhaled CO levels > 10ppm, or did not appear for a visit were counted as unsuccessful abstinence. Each adverse reaction related to the active gum and placebo experienced by all participants at least once was also recorded and compared.

Another outcome measure of the present study was to evaluate the change of QOL after smoking cessation using World Health Organization Quality of Life (WHOQOL)-BREF questionnaires[6]. WHOQOL-BREF has been shown to well correlate with the WHOQOL-100 with good discriminate validity, content validity and test-retest reliability[7,8]. The internal consistency was also tested in the pilot study with Cronbach's alpha of 0.88. All participants had to complete the validated Thai-version of the WHOQOL-BREF questionnaires upon the entry to the present study, and at the end of the treatment. WHOQOL-BREF is a 26-item abbreviated version of the WHOQOL-100[7]. WHOQOL-BREF is based on a four-domain structure: physical, psychological, social, and environmental. The scale of each item gives continuous scores ranging from 1 to 5. All questions were used to compute the QOL scores. Domain scores were calculated according to the WHO guidelines. The increment of WHOQOL-BREF scores at the end of the treatment were compared to that of baseline value.

Statistical analysis

Statistical analysis was performed using a software program. Normality of continuous data was checked by using the Kolmogorov-Smirnov test. For that in normal distribution, the parametric test was used to assess the statistical significance. On the other hand, nonparametric testing was used when data were not in normal distribution. Demographic and baseline characteristics of the groups were compared using either student t-test or Mann-Whitney U test for continuous variables and Chi-square or Fisher's Exact test for categorical variables depending on assumptions. Rates of total abstinence and adverse reactions seen in both groups were evaluated with the use of Chi-square test or Fisher's Exact tests. To detect the difference between the two groups in QOL, student t-test or Mann-Whitney U test were performed. Paired t-test or Wilcoxon Signed Ranks Test was used to compare the QOL scores among both the active and placebo group at the beginning and at the end of the present study. A p-value of less than 0.05 was considered significant.

Results

A total of 46 subjects underwent screening. Two of them were excluded because they previously used other smoking cessation aids in the past month, whereas another one was not included due to his recent diabetes mellitus. Of the remaining 43 participants, 20 (46.5%) were randomized to receive nicotine polyestex gum and 23 (53.5%) were randomized to placebo. The baseline characteristics of the subjects are shown in Table 1. Participants' average age was 44 years, with more than 20 years of smoking. Most subjects enrolled were male (97.7%), and had high levels of nicotine dependence (97.7%) with mean FTND of 6.42 $\pm$ 1.30 points. Most had previously tried and failed to give up smoking. When comparing between the active gum and placebo groups, there were no significant differences detected.

Total abstinence rates & adverse reactions

The number of subjects who successfully stopped smoking is shown in Table 2. At the end of the treatment phase (3 months after the quitting date), the total abstinence rate for the active gum group was significantly better than for the placebo group (50% vs. 9%, p = 0.003).

All adverse reactions reported one or more times by the subjects in any given treatment group are shown in Table 3. There was no serious adverse event reported during or immediately after the treatment. Jaw

Table 1. Baseline characteristics of the subjects

Characteristic	Study group		p-value
	Nicotine gum (n = 20)	Placebo (n = 23)	
Gender			
Male	20 (100%)	22 (95.7%)	0.535[a]
Female	0	1 (4.3%)	
Age (yr)	45.05 $\pm$ 11.83 (median = 46.50)	43.00 $\pm$ 11.86 (median = 45.00)	0.566[b]
Maximal number of cigarettes smoked per day	23.50 $\pm$ 5.64 (median = 20)	24.48 $\pm$ 7.29 (median = 20)	0.966[c]
Duration of smoking (yr)	26.20 $\pm$ 10.60 (median = 25.00)	23.09 $\pm$ 9.30 (median = 23.00)	0.504[b]
No.of cigarettes smoked per day	19.70 $\pm$ 5.25 (median = 20)	20.78 $\pm$ 5.80 (median = 20)	0.461[c]
Previous attempts to quit			0.554[a]
Never	1 (5.0%)	2 (8.7%)	
Yes	19 (95.0%)	21 (91.3%)	
No. of previous quit attempts	2.15 $\pm$ 3.53 (median = 1)	1.30 $\pm$ 1.06 (median = 1)	0.907[c]
Fagerstrom Test at entry	6.20 $\pm$ 1.40 (median = 6)	6.61 $\pm$ 1.20 (median = 7)	0.689[b]

[a] Fisher's Exact test; [b] t-test; [c] Mann-Whitney U test

ache, sore mouth, and dyspepsia were the most common reactions seen during the treatment. No dizziness was noted in any participants from both groups. Although sore mouth and dyspepsia occurred more commonly among those who received active gum, there were no statistically significant differences for these adverse effects when compared between the groups. Despite all adverse effects occurred, there was no participants dropped out of the present study. Interestingly, in the present study, jaw ache was reported more frequently in the placebo group (65.2% vs. 35%, p = 0.048).

Table 2. Total abstinence rates at the end of treatment (3 months)

Outcomes	Study groups		p-value
	Nicotine gum (n = 20)	Placebo (n = 23)	
Successful	10 (50.0%)	2 (9.0%)	0.003[a]
Failure	10 (50.0%)	21 (91.0%)	

[a] Chi-square test

Table 3. Adverse reactions reported at least once during the treatment

Adverse reactions	Study groups		p-value
	Nicotine gum (n = 20)	Placebo (n = 23)	
Sore mouth	6 (30.0%)	5 (21.7%)	0.536[a]
Dyspepsia	4 (20.0%)	2 (8.7%)	0.393[b]
Jawache	7 (35.0%)	15 (65.2%)	0.048[a]
Dizziness	0	0	-

[a] Chi square test; [b] Fisher's Exact test

Quality of life

Upon the entry of the present study, all participants had the mean all-domain WHOQOL-BREF scores of 81.37 $\pm$ 9.99 (range 62 to 101). The initial QOL scores in each domain among the two groups are shown in Table 4. There was no significant difference seen between active gum and placebo groups at the entry of the present study. After the treatment, the mean QOL scores went up to 90.30 $\pm$ 7.87. Those who received active gum had the mean changes in all-domain QOL scores of 10.3 $\pm$ 5.8, whereas the mean scores of the other group increased by 7.74 $\pm$ 3.63 after the present study (Table 4). In each group, the increment of QOL scores when compared those from before and after the present study are statistically significant ($p < 0.01$). Fig. 1 represents the changes of QOL scores of all participants in each domain. Those who received active gum tended to have a higher increment of QOL scores in every domain than those who were given placebo, but this difference did not reach statistical significance. When comparing the increment of QOL scores among those who successfully quit and those who failed, no statistically significant difference was found.

Discussion

The present study demonstrated the efficacy and safety of nicotine polyestex gum as an aid for

Table 4. WHOQOL-BREF scores in each domain of participants before and after the study

QOL Scores	Study group			
	Nicotine gum (n = 20)		Placebo (n = 23)	
	Before	After	Before	After
All domain	79.40 $\pm$ 10.42 (median = 79)	89.70 $\pm$ 7.89 (median = 90)	83.09 $\pm$ 9.49 (median = 84)	90.83 $\pm$ 8.00 (median = 94)
Physical	20.95 $\pm$ 3.83 (median = 20.5)	23.70 $\pm$ 2.66 (median = 24)	22.87 $\pm$ 3.53 (median = 23)	24.78 $\pm$ 2.83 (median = 26)
Psychological	19.10 $\pm$ 2.83 (median = 18)	21.60 $\pm$ 2.87 (median = 22)	19.13 $\pm$ 2.30 (median = 18)	21.22 $\pm$ 2.37 (median = 22)
Social	9.25 $\pm$ 1.59 (median = 9)	10.55 $\pm$ 1.23 (median = 10)	10.00 $\pm$ 1.48 (median = 10)	10.96 $\pm$ 1.36 (median = 11)
Environmental	24.55 $\pm$ 3.19 (median = 24)	27.20 $\pm$ 3.09 (median = 27)	24.78 $\pm$ 3.30 (median = 23)	27.13 $\pm$ 2.69 (median = 28)

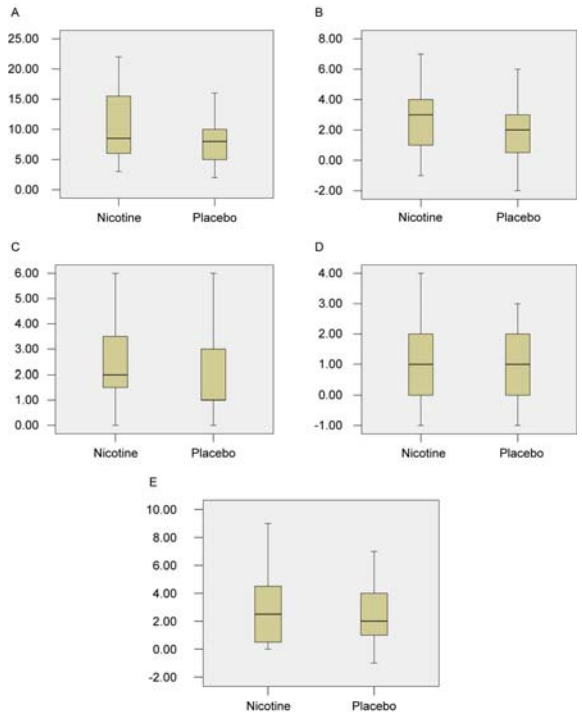

Fig. 1 Comparison of the QOL-score changes before and after the smoking cessation treatment among participants who received active gum and placebo
A = all domain; B = physical domain; C = psychological domain; D = social domain; E = environmental domain

smoking cessation. Total abstinence rate after 3 months of treatment using this novel gum was 50% compared with 9% in that of the placebo group. The present results are in accordance with previous studies that used nicotine polacrilex gum[9-11]. All of them have reported the superior success rates of nicotine gum compared with placebo. Abstinence rates were reported ranging between 35% and 50% at 3 months, similar to what was found in the present study. Recently, a meta-analysis by Wu P, and et al[12] which included 70 trials of NRT VS placebo also showed that NRT can effectively augment the 3-month abstinence rates with an odds ratio of 1.98 (95% CI 1.77-2.21). Consistent superiority of nicotine gum to placebo have underscored the critical role of pharmacotherapy in smoking cessation, particularly in those with a high-level of nicotine dependence, like most participants in the present study. The role of pharmacotherapy is so important that the US Public Health Service (USPHS) recommended that all physicians prescribe certain types of pharmacological aids to all smokers who are making an attempt to quit unless they are contraindicated[2]. However, this recommendation cannot be accomplished in the developing countries due to the high-cost of all smoking cessation aids and budgetary constraints of those countries. Nicotine polyestex gum could, therefore, be a solution. This novel gum is not only effective, but also much cheaper than nicotine polacrilex gum, the pre-existing formulations. Moreover, in terms of manufacturing process, the resin for nicotine polyestex gum is simply made from glycerol ester of edible fatty acids, which is readily available in the country[13]. This is in contrast to the pre-existing one that has a more complex structure, which can lead to more complicated manufacturing process, and thus is more expensive.

Regarding its safety, adverse effects related to the use of nicotine polyestex gum, particularly sore mouth and dyspepsia, tend to occur more frequent than those seen in placebo, although the difference does not reach statistical significance. This is in agreement with a previous study by Herrera N et al, which found the incidence of adverse reactions to be in the range of 23%-25%[9]. There were no serious adverse events noted in the present study, which is another clear evidence confirming its safety profiles. In the present study, the authors found jaw ache more commonly occurred among those who received placebo than those in the active gum group. The reasons behind this finding remains to be discovered, but could partly be explained by the individual chewing techniques, and additives in the placebo gum.

To the authors' knowledge, this is the first study to report the improvement in QOL associated with the treatment of tobacco dependence. Unlike other previous reports[14,15] which showed the effectiveness of the complicated smoking-cessation program that included extensive behavioral modification, the present study was designed to mainly focus on the effects of real-life practice, which usually consists of a brief counseling and providing pharmacological aids, onto the QOL. The QOL scores of participants of the active gum and placebo gum groups improved significantly after the treatment. Although the QOL score increment of those receiving active gum tends to be higher than that of the other group, no statistically significant difference was noted in the present study. These findings might imply that the use of either placebo or nicotine gum, along with brief counseling process, can improve QOL. However, inadequate power to detect the statistical difference due to limited sample size of the present study cannot be excluded. Secondly,

the time interval of three months to re-measure the QOL may be too short to detect the significant changes in QOL between both groups. In addition, the treatment effect may be alleviated by the influence of regression toward the mean. A larger study with different designs to avoid those artifacts will be needed to re-examine the degree of change in QOL scores between these two groups.

Based on these findings, brief counseling along with pharmacological treatment, either nicotine gum or placebo, can contribute to the improvement of QOL. However, when taken together with the superiority of total abstinence rate, safety, and improvement of QOL, nicotine gum undoubtedly plays a critical role in smoking cessation therapy, particularly when used in combination with the counseling process.

The strengths of the present study include use of a randomized double-blinded controlled trial, use of total abstinence rates as the successful treatment measures, and measurement of QOL. Moreover, the present study was designed to determine the effectiveness of nicotine gum, along with only brief individual counseling, similar to how most physicians in this country practice. The present study did not include the extensive behavioral modification techniques and other psychological measures, as usually seen in other previous reports [14,15]. These findings are therefore clear evidence to confirm the effectiveness of smoking cessation therapy in the real-life practice. Whether it is effective when used in combination with other pharmacological aids remains to be determined.

In conclusion, this novel nicotine polyestex gum is an effective and safe treatment for smoking cessation. Pharmacotherapy for smoking cessation is not only crucial to help smokers to quit, but also can improve QOL.

Acknowledgements

The authors wish to thank Professor Dr. Somsri Phaosavasdi, Thai physician alliance against tobacco network, and Thai Health Promotion Foundation for their strong support of this study, Associate Professor Dr. Siribha Changsirikulchai for her excellent help and suggestions, and Assistant Professor Dr. Manaphol Kulpraneet for his assistance.

References

1. World Health Organization. WHO Report on the global tobacco epidemic 2008: The MPOWER package. Geneva: WHO; 2008.
2. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA 2000; 283: 3244-54.
3. Schroeder SA. What to do with a patient who smokes. JAMA 2005; 294: 482-7.
4. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Health Education Authority. Thorax 2000; 55: 987-99.
5. 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.
6. World Health Organization. The World Health Organization quality of life (WHOQOL)-BREF. Geneva: WHO; 2004.
7. The World Health Organization. Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995; 41: 1403-9.
8. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000; 9: 121-4.
9. Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. Chest 1995; 108: 447-51.
10. Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. Br Med J (Clin Res Ed) 1982; 285: 537-40.
11. Russell MA, Wilson C, Feyerabend C, Cole PV. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal. Br Med J 1976; 2: 391-3.
12. Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. BMC Public Health 2006; 6: 300.
13. Tudulawesa Y, Chutrtong W, Disataporn T, Leossrisuksun S, Chantaarnon P, Intapichai S. The study of nicotine releasing factors for chewing gum polymer. Srinakharinwirot University Science Journal 2006; 22: 21-33.
14. Erickson SR, Thomas LA, Blitz SG, Pontius LR. Smoking cessation: a pilot study of the effects on health-related quality of life and perceived work

performance one week into the attempt. Ann Pharmacother 2004; 38: 1805-10.
15. Zillich AJ, Ryan M, Adams A, Yeager B, Farris K. Effectiveness of a pharmacist-based smoking-cessation program and its impact on quality of life. Pharmacotherapy 2002; 22: 759-65.

ประสิทธิภาพของหมากฝรั่งนิโคตินโพลีเอสเท็กซ์ในการช่วยเลิกบุหรี่ และผลต่อคุณภาพชีวิต

สุทัศน์ รุ่งเรืองหิรัญญา, ฉัตรชัย เอกปัญญาสกุล, ยงยส หัถพรสวรรค์, ยงยุทธ ตัณฑุลเวสส

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพ ความปลอดภัยในการช่วยเลิกบุหรี่ของหมากฝรั่งนิโคตินโพลีเอสเท็กซ์ พร้อมศึกษาถึงผลต่อคุณภาพชีวิต*

วัสดุและวิธีการ: *เป็นการศึกษาแบบสุ่มโดยใช้อาสาสมัครที่ติดบุหรี่และประสงค์จะเลิกบุหรี่จำนวนทั้งสิ้น 43 ราย อาสาสมัครทุกรายจะได้รับหมากฝรั่งนิโคตินหรือหมากฝรั่งรสมิ้นท์ที่ไม่มีนิโคติน อย่างใดอย่างหนึ่ง ผู้ที่สามารถเลิกบุหรี่ได้อย่างต่อเนื่องจนถึง 3 เดือนหลังการรักษา เท่านั้นจึงจะถือว่าเลิกได้สำเร็จ ทุกคนต้องตอบแบบสอบถามคุณภาพชีวิตขององค์การอนามัยโลกตอนเริ่มต้นและสิ้นสุดโครงการ*

ผลการศึกษา: *อัตราการเลิกบุหรี่สำเร็จที่ 3 เดือนในกลุ่มที่ได้รับหมากฝรั่งนิโคตินโพลีเอสเท็กซ์สูงกว่ากลุ่มที่ได้ยาหลอกอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 50 และร้อยละ 9, p = 0.003) ส่วนผลข้างเคียงที่พบนั้นไม่แตกต่างจากกลุ่มที่ได้รับยาหลอก ทั้งสองกลุ่มมีคุณภาพชีวิตที่ดีขึ้น โดยกลุ่มที่ได้รับหมากฝรั่งนิโคตินโพลีเอสเท็กซ์ มีแนวโน้มที่คุณภาพชีวิตเพิ่มขึ้นมากกว่ากลุ่มยาหลอกแต่ไม่มีนัยสำคัญทางสถิติ*

สรุป: *หมากฝรั่งนิโคตินโพลีเอสเท็กซ์มีประสิทธิภาพดีและปลอดภัยในการช่วยเลิกบุหรี่ อีกทั้งช่วยปรับปรุงคุณภาพชีวิตให้ดีขึ้นได้*