SAFETY E-CIGS: CLINICAL STUDIES

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SAFETY ECIGS: clinical studies

Table 1. Types of studies performed to determine safety and to estimate risk from EC use.

Type of studies	Research subject	Advantages	Disadvantages
Chemical studies	Evaluate the chemical composition of liquids and/or aerosol. Examine environmental exposure (passive 'vaping').	Easier and faster to perform. Less expensive. Could realistically be implemented for regulatory purposes.	Usually targeted on specific chemicals. Unknown effects of flavorings when inhaled. No validated protocols for vapor production. Provide no objective evidence about the end results (effects) of use (besides by applying theoretical models).
Toxicological studies	Evaluate the effects on cell cultures or experimental animals.	Provide some information about the effects from use.	Difficult to interpret the results in terms of human *in vivo* effects. More expensive than chemical studies. Need to test aerosol and not liquid. Standards for exposure protocols have not been clearly defined.
Clinical studies	Studies on human *in vivo* effects.	Provide definite and objective evidence about the effects of use.	Difficult and expensive to perform. Long-term follow up is needed due to the expected lag from initiation of use to possible development of any clinically evident disease. For now, limited to acute effects from use.

Source: Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: A systematic review. *Ther Adv Drug Saf*, 2014, 5: 67–86.

SAFETY ECIGS: clinical studies

BLOOD COUNT

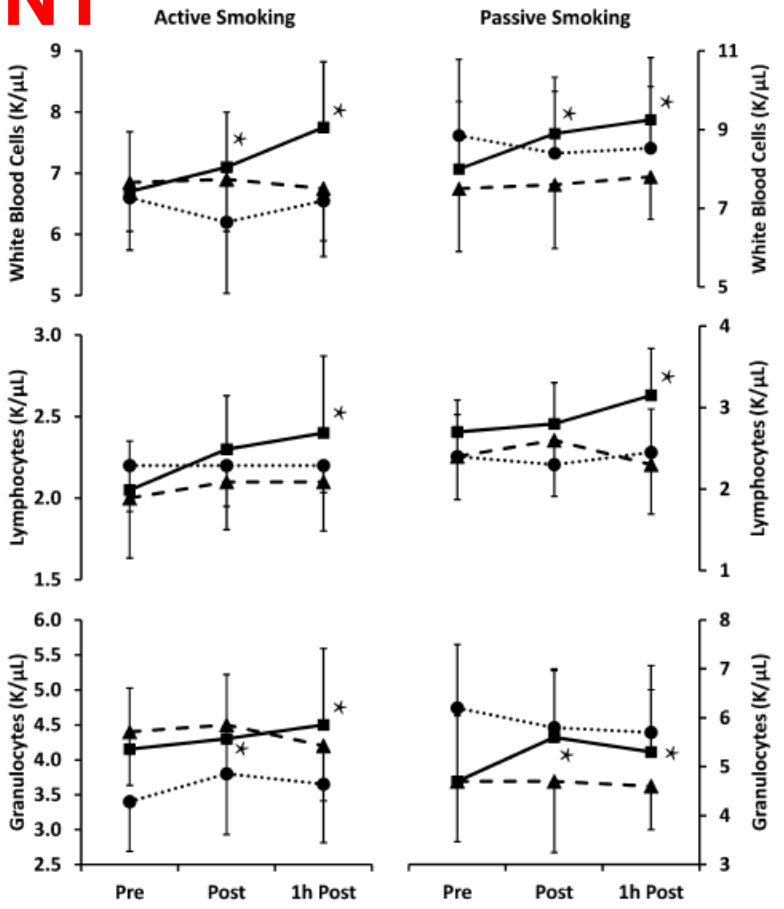


Fig. 1. White blood cell count, lymphocyte count, and granulocyte count prior to, immediately following, as well as 1 h following active (left graphs) and passive (right graphs) smoking in smokers and never smokers, respectively. Results are presented as median ± mean absolute deviation. Squares with solid lines represent tobacco cigarette smoking, triangles with dashed lines represent e-cigarette smoking, while circles with dotted lines indicate the control session. Asterisks indicate statistically significant change from baseline (i.e., pre) values.

Source: Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxico*l., 2012, 50: 3600-3603.

SAFETY ECIGS: clinical studies

LUNG FUNCTION

- NOT significantly affected by
  e-cigarette smoking (active or 1 h passive e-cigarette smoking)
  passive tobacco cigarette smoking
- significantly affected by
  active tobacco cigarette smoking

Source: Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxico*,. 2013, 25: 91-101.

SAFETY ECIGS: clinical studies

CORONARY CIRCULATION

Electronic cigarette use does not affect the oxygenation of the heart

no immediate effects

https://www.youtube.com/watch?v=__ztrGafEg4

Source: Immediate effects of electronic cigarette use on coronary circulation and blood carboxyhemoglobin levels: comparison with cigarette smoking. *European Heart Journal*, 2013, 34, Issue suppl 1, 01.

SAFETY ECIGS: clinical studies

MYOCARDIAL FUNCTION

Table 2 Haemodynamic and Doppler flow measurements in electronic cigarette users (ECIG, n = 40) and smokers (SM, n = 36), before and after device and cigarette use respectively

Parameter	Before use	After use	Change	P-value[a]	P-value[b]
Systolic BP (mmHg)					
ECIG	123.9 ± 8.6	124.6 ± 9.9	0.7 ± 4.6	0.374	< 0.001
SM	123.0 ± 9.8	129.6 ± 9.2	6.6 ± 5.2	< 0.001	
P-value[c]	0.653	0.025			
Diastolic BP (mmHg)					
ECIG	75.6 ± 6.1	78.5 ± 5.9	3.0 ± 3.6	< 0.001	0.079
SM	75.8 ± 5.6	80.2 ± 5.8	4.4 ± 3.3	< 0.001	
P-value[c]	0.834	0.209			
Heart rate (beats/m)					
ECIG	67.1 ± 10.3	67.5 ± 10.6	0.4 ± 4.8	0.649	< 0.001
SM	67.5 ± 7.9	73.5 ± 6.8	5.9 ± 4.7	< 0.001	
P-value[c]	0.841	0.005			

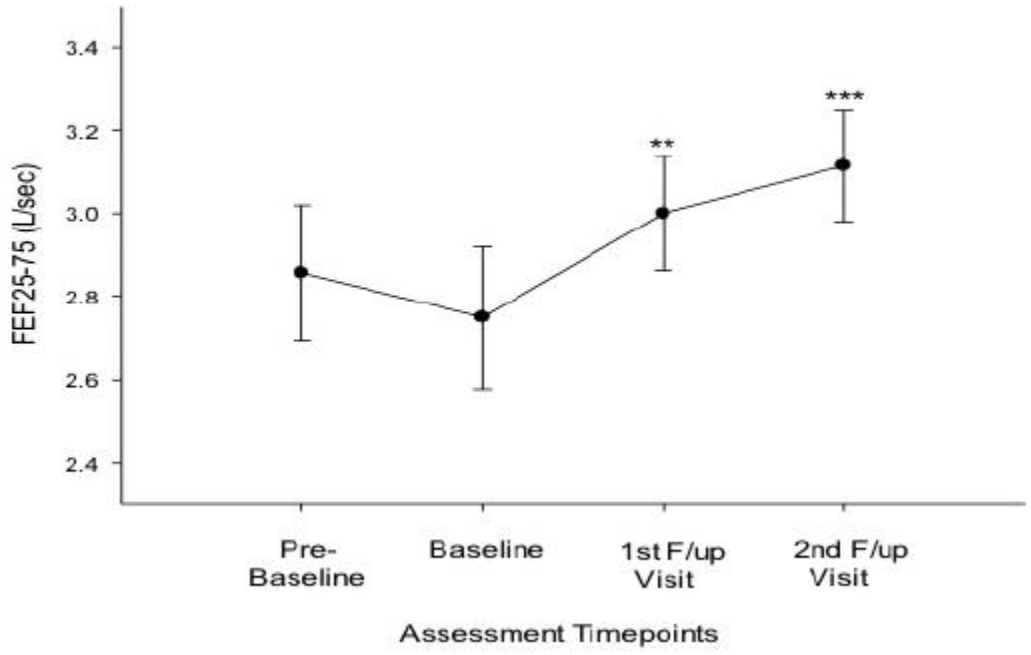
Source: Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: Comparison with the effects of regular cigarettes. *BMC Cardiovascular Disorders,* 2014, 14:78.

SAFETY ECIGS: clinical studies

HARM REVERSAL IN ASTHMATIC SMOKERS

Figure 1. (**A**) Forced expiratory volume (FEV1) at the four timepoints of assessment for all 18 patients; (**B**) Forced vital capacity (FVC) at the four timepoints of assessment for all 18 patients; (**C**) Forced expiratory flow (FEF) 25–75 at the four timepoints of assessment for all 18 patients.

(C)

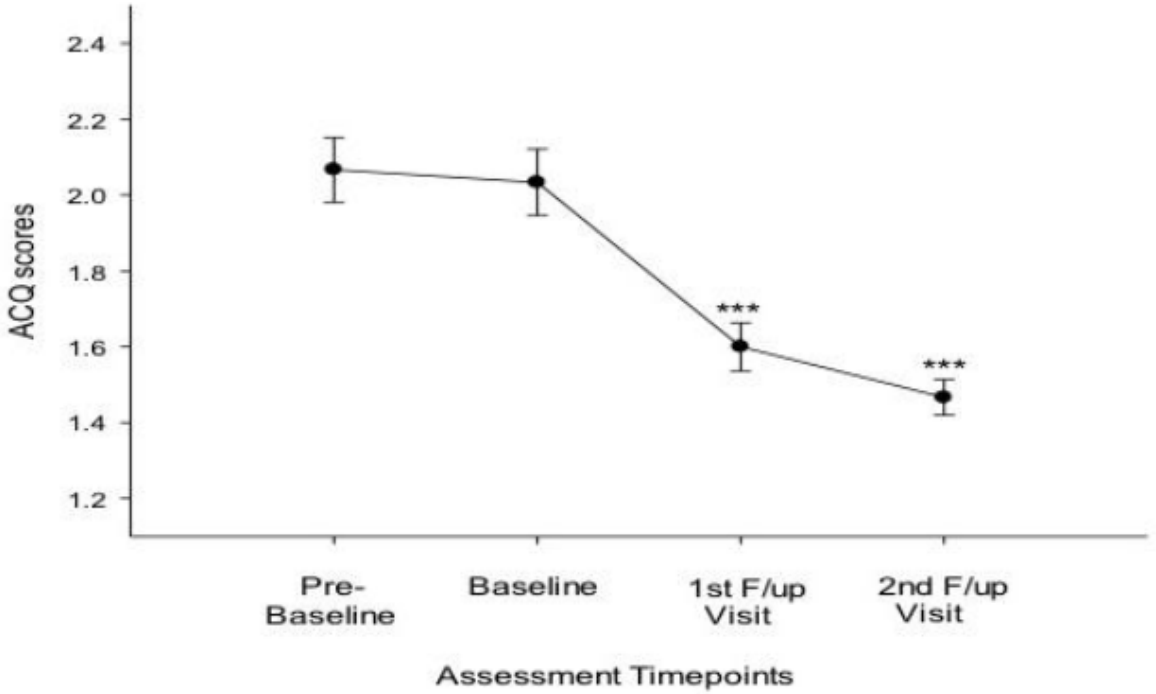


Source: Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: Evidence for harm reversal. *Int. J. Environ. Res. Public Health,* 2014, 11: 4965-497.

SAFETY ECIGS: clinical studies

HARM REVERSAL IN ASTHMATIC SMOKERS

Figure 2. Asthma control questionnaire (ACQ) score at the four timepoints of assessment for all 18 patients.



Notes: Compared to baseline significant *p* values of ***—≤0.001; All data expressed as mean and error bars are standard error of the mean; Abbreviations: F/up—follow-up.

Source: Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: Evidence for harm reversal. *Int. J. Environ. Res. Public Health,* 2014, 11: 4965-497.

SAFETY ECIGS: propylene glycol

"*However, the larger data set indicates that these compounds have low sensitization potential in animal studies, and therefore are unlikely to represent human allergens. The existing safety evaluations of the FDA, USEPA, NTP and ATSDR for these compounds are consistent and point to the conclusion that the propylene glycols present a very low risk to human health.*"

Source: A toxicological review of the propylene glycols. *Critical Reviews in Toxic*ology, 2013, 43: 363-390.

NICOTINE SAFETY

Arch Toxicol
DOI 10.1007/s00204-013-1127-0

GUEST EDITORIAL

How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century

Bernd Mayer

The discrepancy between the 60-mg dose and published cases of nicotine intoxication has been noted previously (Matsushima et al. 1995; Metzler et al. 2005), but nonetheless, this value is still accepted without scrutiny and taken as the basis for worldwide safety regulations of tobacco and other nicotine-containing products. Nicotine is a toxic compound that should be handled with care, but the frequent warnings of potential fatalities caused by ingestion of small amounts of tobacco products or diluted nicotine-containing solutions are unjustified and need to be revised in light of overwhelming data indicating that more than 0.5 g of oral nicotine is required to kill an adult.

Source: How much nicotine kills a human? Tracing back the generally accepted legal dose to dubious self-experiments in the nineteenth century. *Arch Toxicol*, 2014, 88: 5-7.

NICOTINE SAFETY

Effect of long-term (two years) inhalation of nicotine on rats: compared to controls NO increase

- in mortality
- in atherosclerosis
- in frequency of tumors

"*No indication for any harmful effect of nicotine when given in its pure form by inhalation*."

Source: Long-term effects of inhaled nicotine. *Life Science, 1996, 58:* 1339–1346.

NICOTINE SAFETY

Mills *et al. Tobacco Induced Diseases* 2010, **8**:8
http://www.tobaccoinduceddiseases.com/content/8/1/8

TOBACCO INDUCED DISEASES

RESEARCH Open Access

Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals

Edward J Mills[1*], Ping Wu[2], Ian Lockhart[3], Kumanan Wilson[4], Jon O Ebbert[5]

Source: Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tobacco Induced Diseases*, 2010, 8:8.

NICOTINE SAFETY

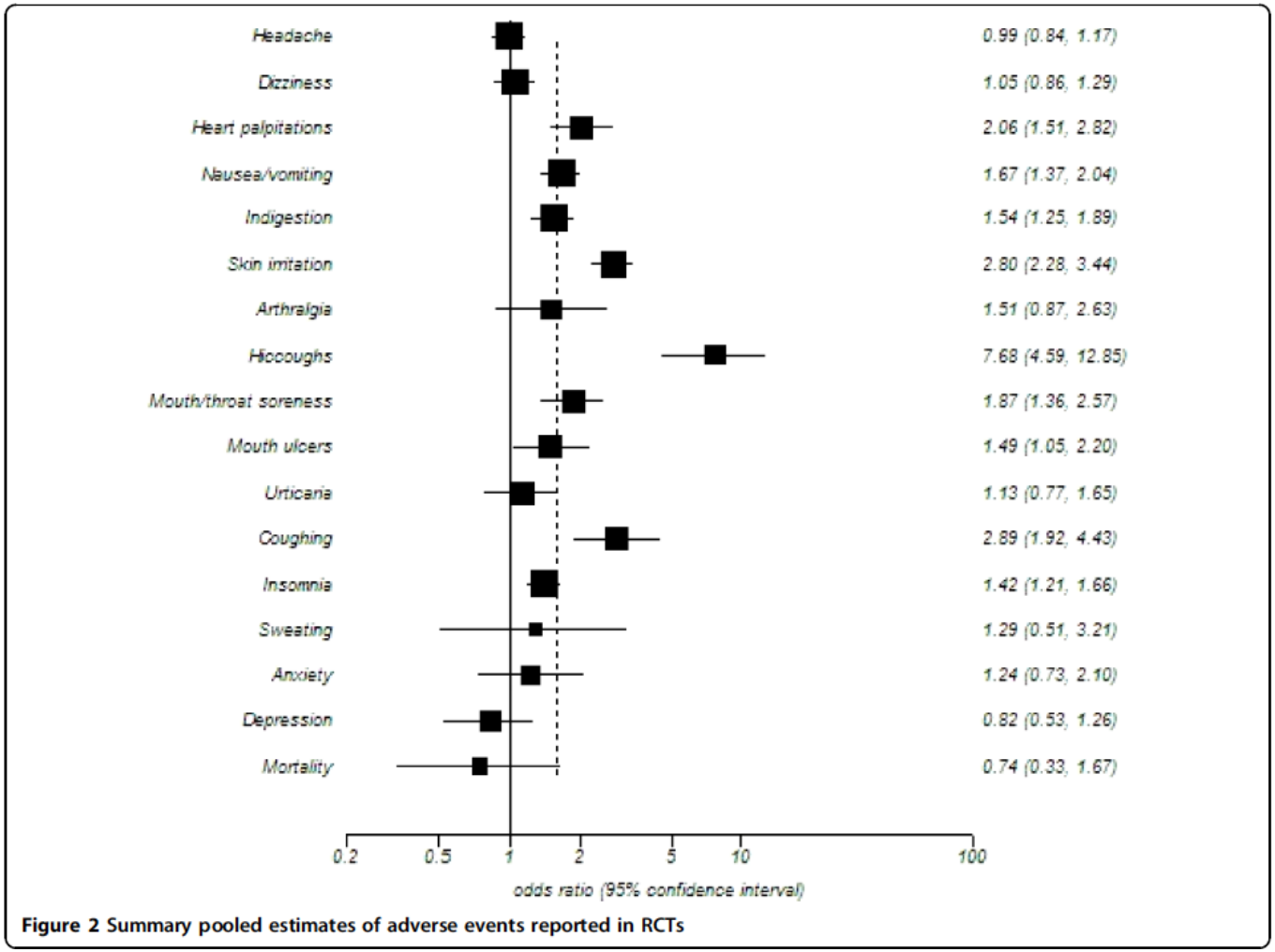


Figure 2 Summary pooled estimates of adverse events reported in RCTs

Source: Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tobacco Induced Diseases*, 2010, 8:8.

NICOTINE SAFETY

Nicotine & Tobacco Research, Volume 11, Number 9 (September 2009) *1076–1082*

Original Investigation

Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study

Robert P. Murray, John E. Connett, & Lisa M. Zapawa

Abstract

Introduction: Recent genetic evidence has implicated nicotine as a possible cause of cancer, suggesting the need to examine the potential contributions of nicotine itself to cancer versus the confounding effects of addiction and thus exposures to known carcinogens. The objective of this study was to examine the relationship between nicotine replacement therapy, smoking, and cancer outcomes.

Methods: The Lung Health Study enrolled 5,887 participants in a randomized trial to prevent chronic obstructive pulmonary disease. The present study used surveillance data on 3,320 intervention participants who enrolled in the Lung Health Study for 5 years and who were then followed by the Lung Cancer Substudy for 7.5 years. Nicotine replacement therapy use and smoking exposure were recorded during the 5-year Lung Health Study trial. Surveillance for lung cancer, gastrointestinal cancer (including oral cancers), and all cancers began following the Lung Health Study.

Results: Adjusted Cox proportional hazards regressions assessed the hazards of nicotine replacement therapy and smoking for each diagnosis group. In the adjusted models for lung cancer, nicotine replacement therapy alone was not a significant predictor ($p = .57$), while smoking during the Lung Health Study was a significant predictor ($p = .03$). When nicotine replacement therapy and smoking were entered in the same model, nicotine replacement therapy remained not significant ($p = .25$) and smoking was clearly significant ($p = .02$). Nicotine replacement therapy and smoking were not significant predictors of cancer in the models for gastrointestinal cancer or all cancers.

Discussion: Although the surveillance time was short, smoking predicted cancer in this analysis and nicotine replacement therapy did not.

Source: Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. *Nicotine & Tobacco Research*, 2009, 11: 1076–1082.

NICOTINE SAFETY

Table 2. Estimated relative risk (RR) and 95% confidence intervals (CIs) produced by random effects pair-wise meta-analysis for cardiovascular events in smoking cessation RCTs

Number of Studies	Comparison	All CV Events			MACE Events		
		Events	RR	I^2	Events	RR	I^2
All trials							
21 RCTs[10, 30-46, 49, 53, 68]	NRT vs placebo	202/6329 vs. 83/5318	1.81 (1.35-2.43)	0%	12/6329 vs. 7/5318	1.38 (0.58-3.26)	0%
27 RCTs[13-15, 47-49, 51-71]	Bupropion vs placebo	50/5947 vs. 42/4455	1.03 (0.71-1.50)	0%	15/5947 vs. 25/4455	0.57 (0.31-1.04)	0%
18 RCTs[22, 54, 55, 72-79, 81-87]	Varenicline vs placebo	63/5469 vs. 41/3603	1.24 (0.85-1.81)	0%	22/5469 vs. 13/3603	1.44 (0.73-2.83)	0%
2 RCTs[54, 55]	Bupropion vs varenicline	1/686 vs. 2/696	0.74 (0.05-10.5)		1/686 vs. 0/696	3.07 (0.12-75.09)	
3 RCTs[49, 53, 68]	Bupropion vs NRT	4/367 vs. 2/366	1.40 (0.25-7.82)	2%	0/367 vs. 1/366	0.34 (0.01-7.94)	
1 RCT[80]	Varenicline vs NRT	0/378 vs. 2/379	0.20 (0.01-4.16)		0/378 vs. 2/379	0.20 (0.01-4.16)	
High risk patients only		*k=13*			*k=9*		
3 RCTs[10, 46, 53]	NRT vs placebo	33/454 vs. 26/374	1.24 (0.77-2.02)		6/454 vs. 4/374	1.48 (0.42-5.19)	**NA**
8 RCTs[13-15, 47, 53, 59, 61, 64]	Bupropion vs placebo	27/1241 vs. 25/1234	1.04 (0.59-1.83)	0%	9/1241 vs. 15/1234	0.63 (0.28-1.41)	0%
3 RCTs[22, 74, 77]	Varenicline vs placebo	30/754 vs. 26/745	1.15 (0.69-1.92)		14/754 vs. 11/745	1.35 (0.61-3.01)	0%
	Bupropion vs varenicline		NA			NA	
1 RCT[53]	Bupropion vs NRT	3/50 vs. 0/50	7 (0.37-132.10)		0/50 vs. 0/50	NA	
	Varenicline vs NRT		NA			NA	

Source: Cardiovascular events associated with smoking cessation pharmacotherapies: A network meta-analysis. *CIRCULATIONAHA*.113.003961v1

NICOTINE SAFETY

Current Drug Facts Labeling	Proposed Drug Facts Labeling
Warnings:	
Do not use • if you continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products	None. The "Do not use" statement would be deleted.
Directions:	
• stop smoking completely when you begin using the [NRT product]	• begin using [the NRT product] on your quit day
• it is important to complete treatment. Stop using [the NRT product] at the end of [a specified number of] weeks. If you still feel the need to use [the NRT product], talk to your doctor	• it is important to complete treatment. If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider

Nicotine Replacement Therapy Labels May Change

Source: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm