

Science and Future Research Directions for Reduced Nicotine Content Cigarettes

Tobacco Control Update

National Cancer Advisory Board, February 6, 2008

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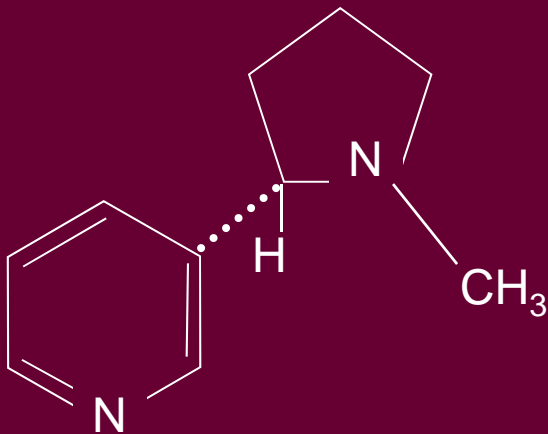


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Why study reduced nicotine content cigarettes?

- All tobacco products contain nicotine.
- Nicotine is the addictive agent in tobacco products.
- Nicotine is responsible for the progression from initiation to regular smoking and difficulty with cessation.



Establishing a nicotine threshold for addiction-- The implications for tobacco regulation

- Goal:
 - To prevent nicotine addiction in youth.
- Threshold for addiction:
 - Dose to establish and maintain addiction
~ 5 mg/day.
- Proposal:
 - A gradual reduction of nicotine content of cigarettes over 10-15 years.



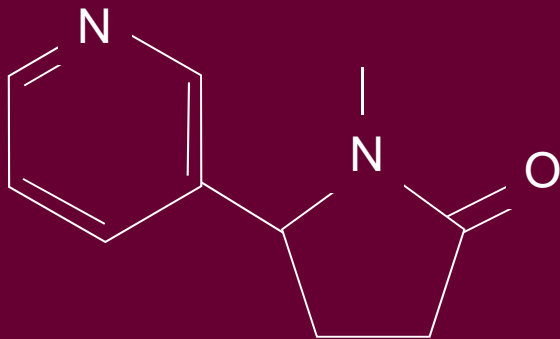
The NEW ENGLAND
JOURNAL of MEDICINE

Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. (1994). *N Engl J Med*, 331(2), 123-125.



Potential Risks of Nicotine Reduction Strategy

- Compensatory oversmoking
- Black market
- Starter product for non-smokers



Nicotine Yield Reduction Studies: Key Issues

- Reduced Nicotine Content (RNC) cigarettes vs. commercial low yield cigarettes
- Safety of progressive nicotine reduction
- Consumer acceptability of reduced nicotine content cigarettes
- Lowering level of nicotine addiction
- Promoting smoking cessation

Cancer Epidemiology
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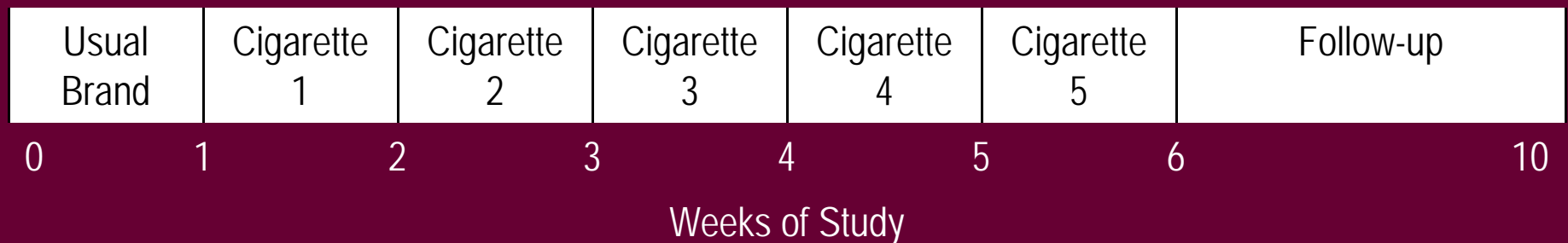
ACR

Benowitz, N. L., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D., & Jacob, P., 3rd. (2007). Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers Prev*, 16(11), 2479-2485.

CA78603

Nicotine Content Reduction Study: Pilot Study Design

- Reduced Nicotine Content and Low Yield Commercial Cigarettes
- Uncontrolled, sequential, within-subject design
- Smokers of at least 10 cigarettes/day, not intending to quit in next 6 months
- Usual brand and 5 test cigarette brands
- Nicotine yield reduced at weekly intervals
- Brief cessation counseling at the end of the tapering phase
- 4 week follow-up



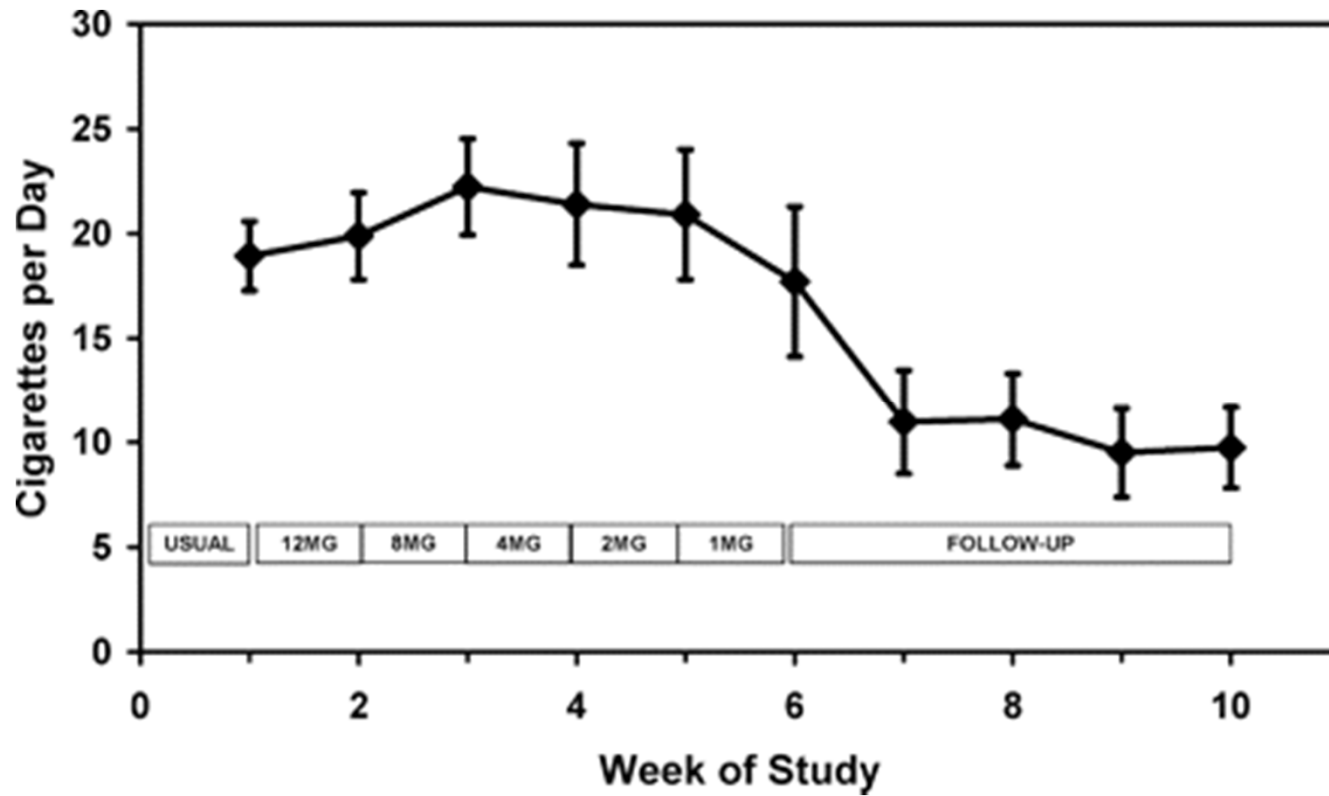
Characteristics of Research Cigarettes

	Machine-Determined Nicotine Yield (mg)	Machine-Determined Tar Yield (mg)
<u>RNC Study Research Cigarette</u>		
Nicotine Content		
12mg	0.9	10.9
8mg	0.6	10.9
4mg	0.3	7.8
2mg	0.2	9.2
1mg	0.1	10.2

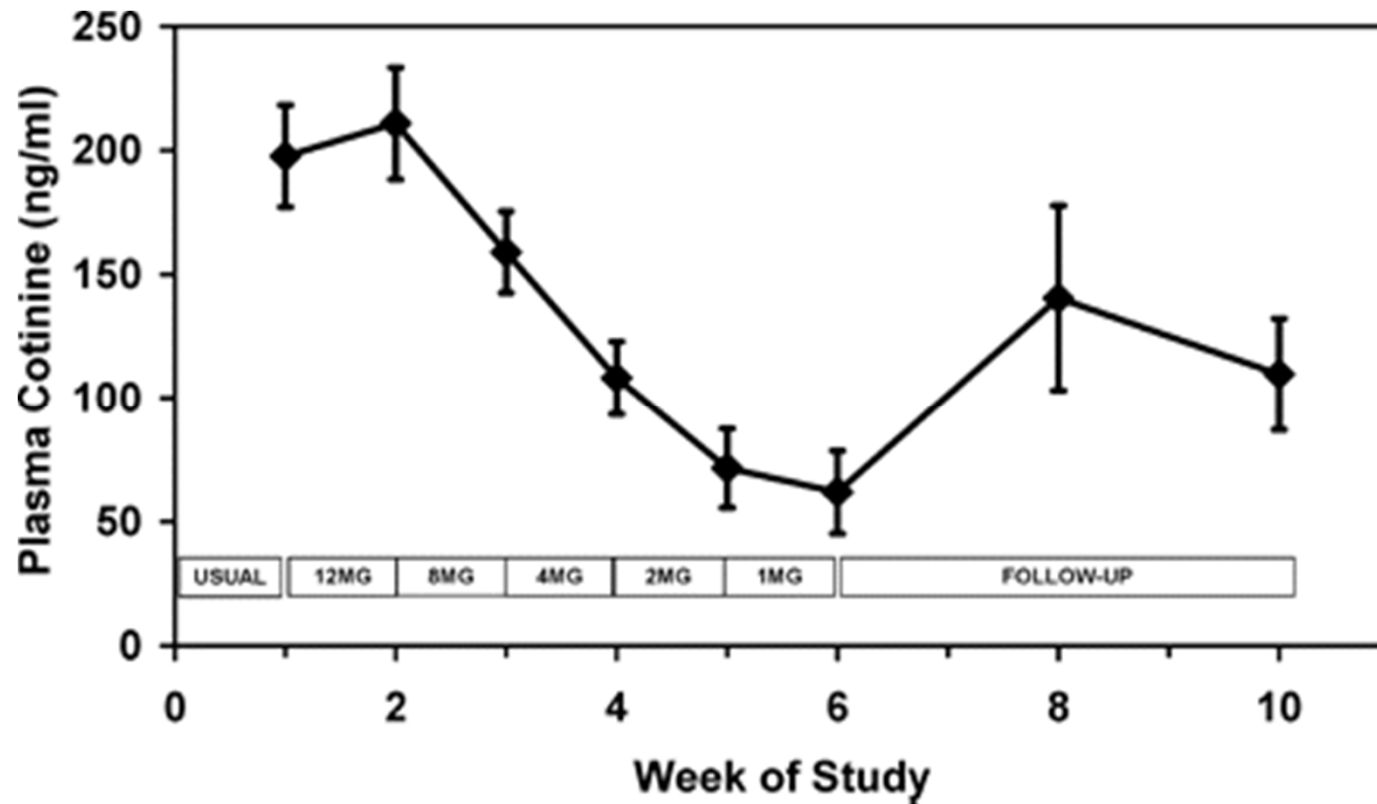
Characteristics of Research Cigarettes

	Machine-Determined Nicotine Yield (mg)	Machine-Determined Tar Yield (mg)
<u>Commercial Cigarettes</u>		
Pall Mall Light 100s	0.9	12
Merit Kings	0.6	8
True Kings	0.4	4
Now 100s	0.2	2
Carlton 100s	0.1	1

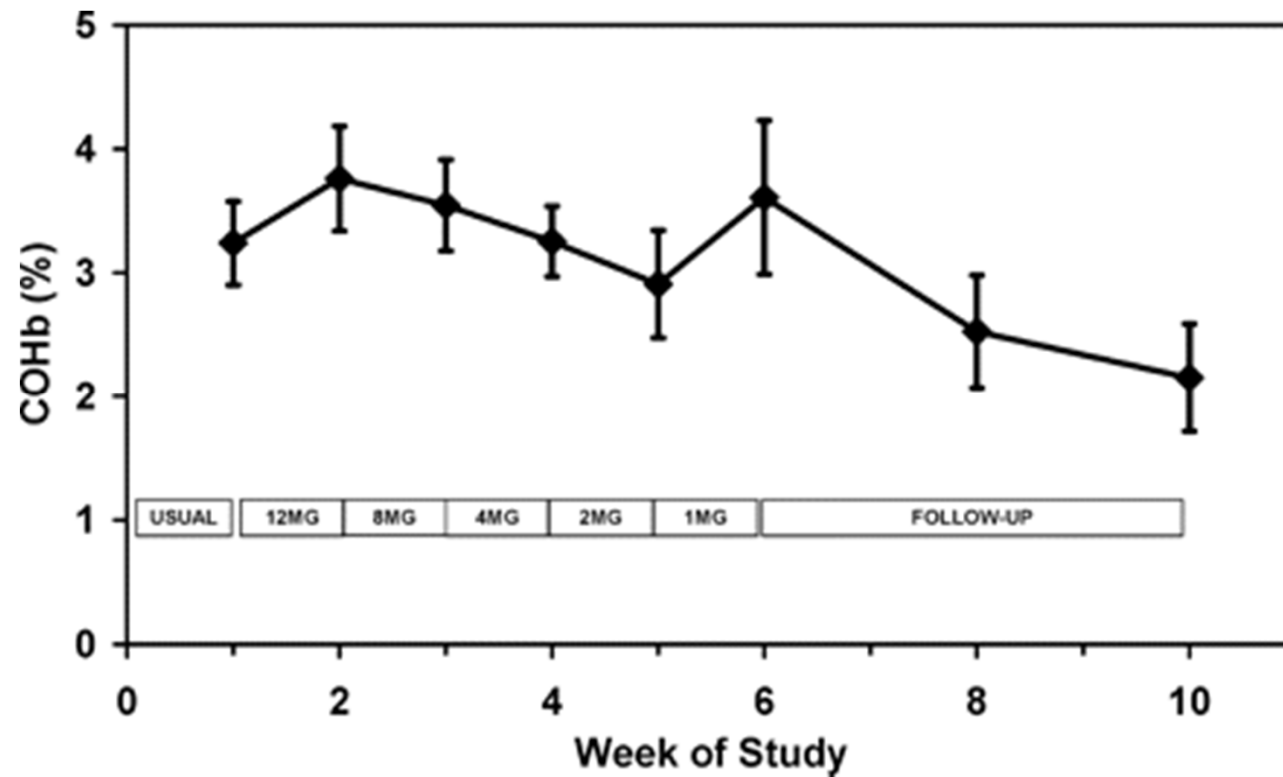
RNC Study Cigarettes Per Day



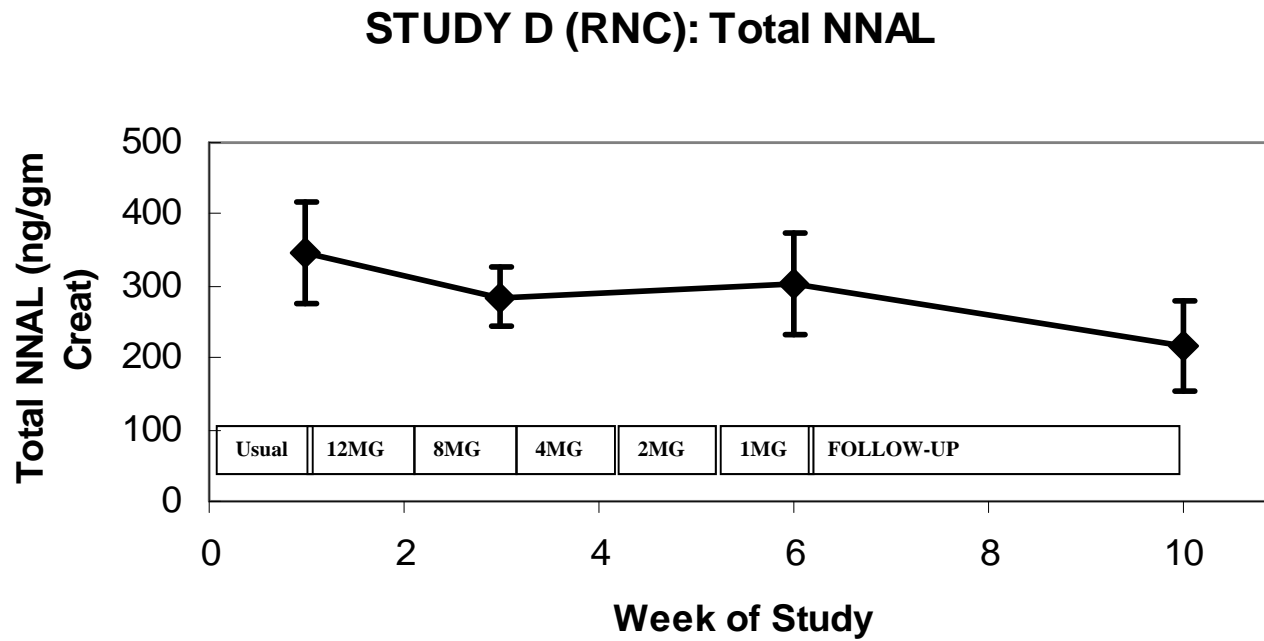
RNC Study Plasma Cotinine



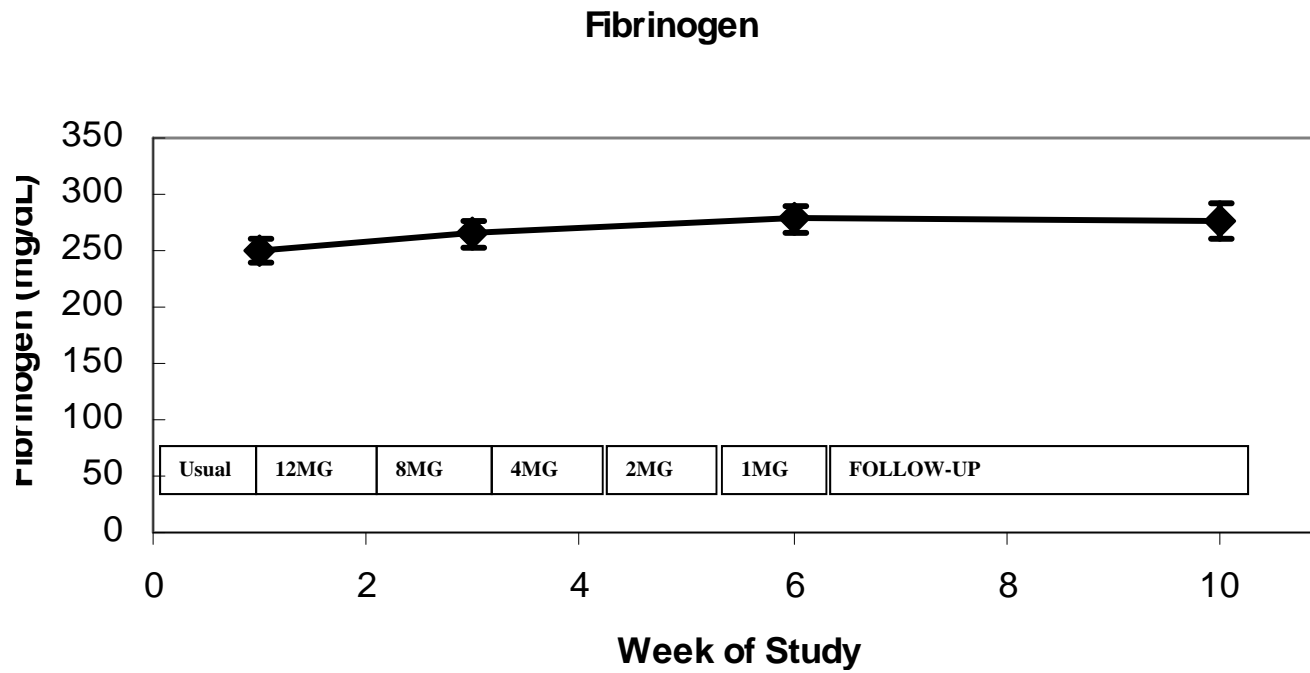
RNC Study Carboxyhemoglobin



RNC Study Urine Total NNAL



RNC Study Fibrinogen



Summary

- Gradual reduction of nicotine content in cigarettes results in a progressive (70%) reduction of nicotine exposure.
- There is little evidence of smoking compensation, and no evidence of increased exposure to toxicants, or evidence of adverse effects on cardiovascular biomarkers.
- RNCs are acceptable to smokers, although not as good as usual brand cigarettes.

Summary

- After the end of the study, cigarette consumption was substantially reduced and dependence scores were lower, consistent with achieving a lower level of dependence.
- Approximately 25% of subjects achieved abstinence at 4 weeks after end of taper.
- Reduction of nicotine, CO and possibly TSNA exposure was observed with commercial cigarettes, but only at the two lowest exposure levels (ultra-low yield cigarettes).

Conclusion

- Regulation of the nicotine content of cigarettes and the use of a nicotine reduction strategy to prevent or reduce the level of nicotine addiction appears to be safe and feasible, at least in the short term. Long-term studies are needed.

Cessation Studies using Reduced Nicotine Content Cigarettes : Key Issues

- Among a population of dependent smokers interested in quitting, what are the effects of denicotinized cigarettes on:
 - Reducing dependence?
 - Promotion of cessation?
 - Toxicant exposure and toxicity?
 - Consumer perception of the health risks?

Quest: Nicotine and Toxicant Modification

Step your way to Nicotine Free!

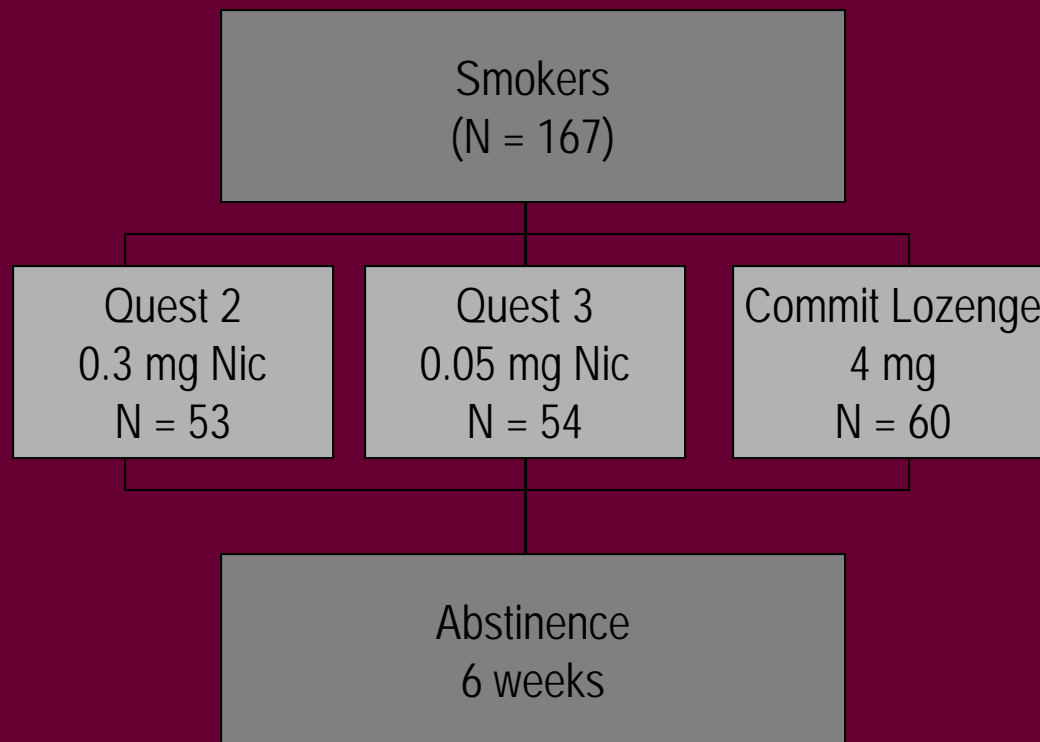


From: <http://www.questcigs.com/home.asp>,
accessed November 14, 2002

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Study Design: Quest vs. Nicotine Lozenge

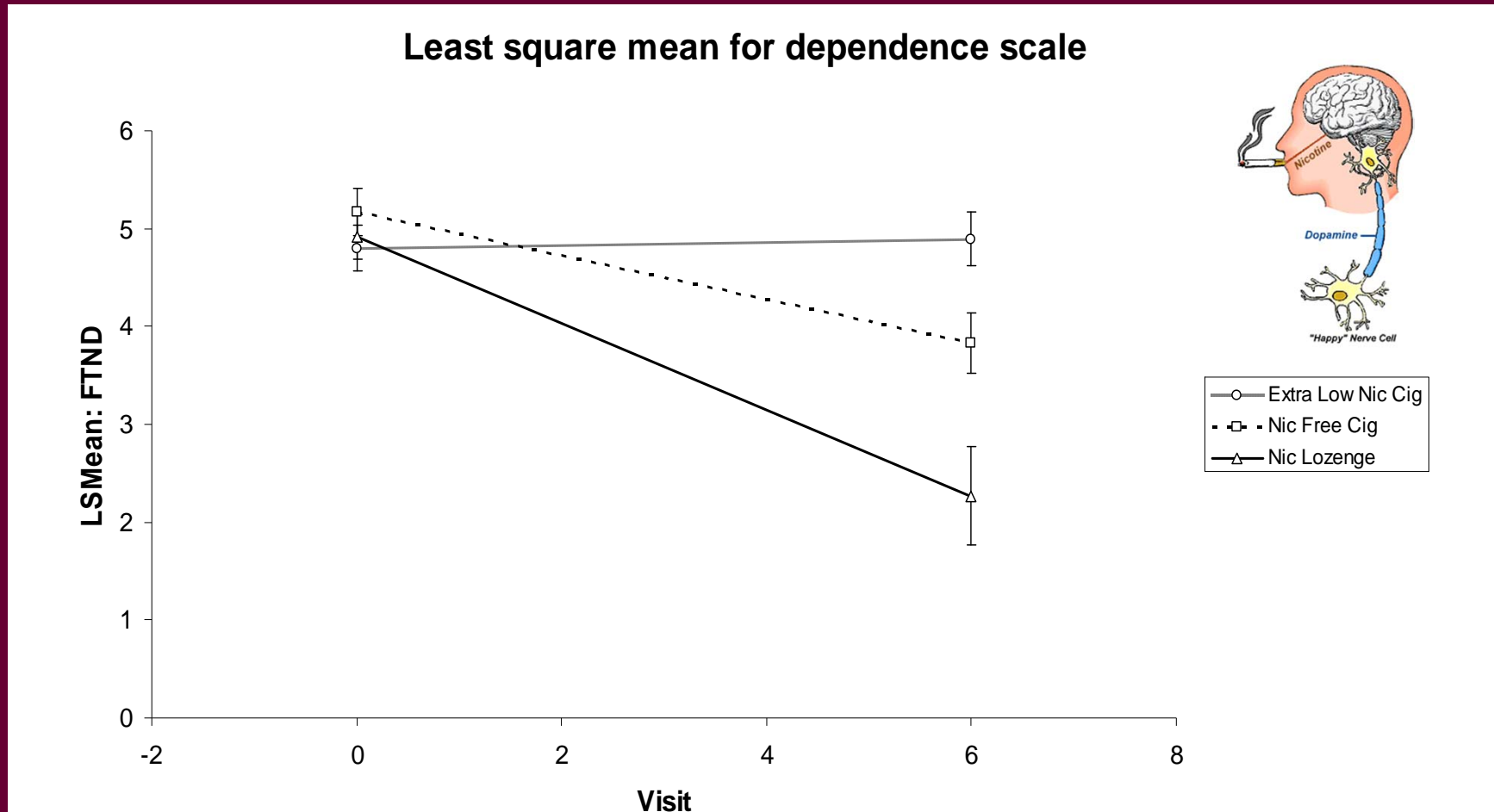


Advertisement

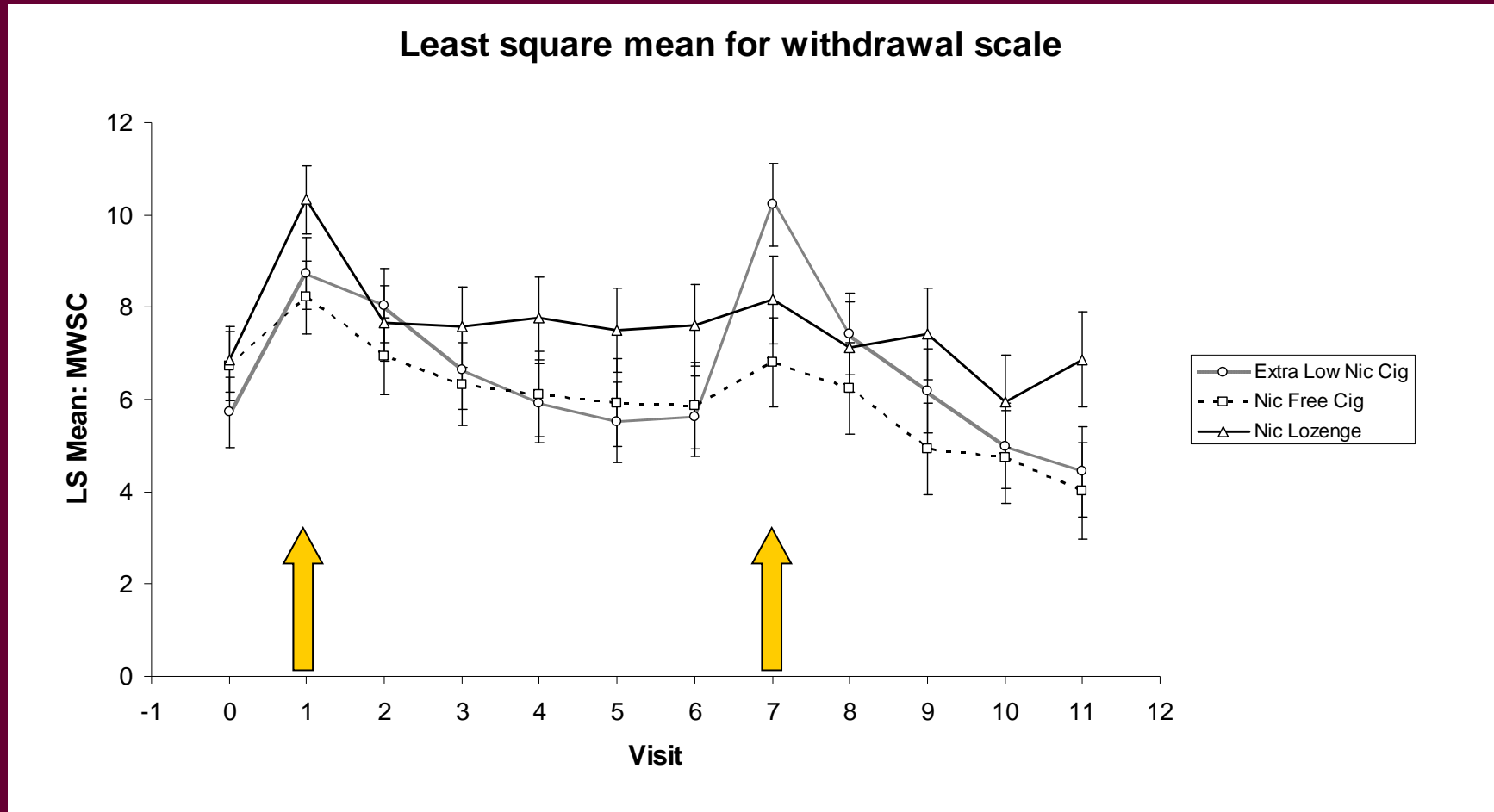
....University of Minnesota is looking for participants for a research study. This study examines a novel approach to quitting by using a new tobacco product as a steps towards becoming smoke free. The study will look at health effects of this new product.



Effects of Switching on Dependence Scores



Effects of Switching on Withdrawal Symptoms

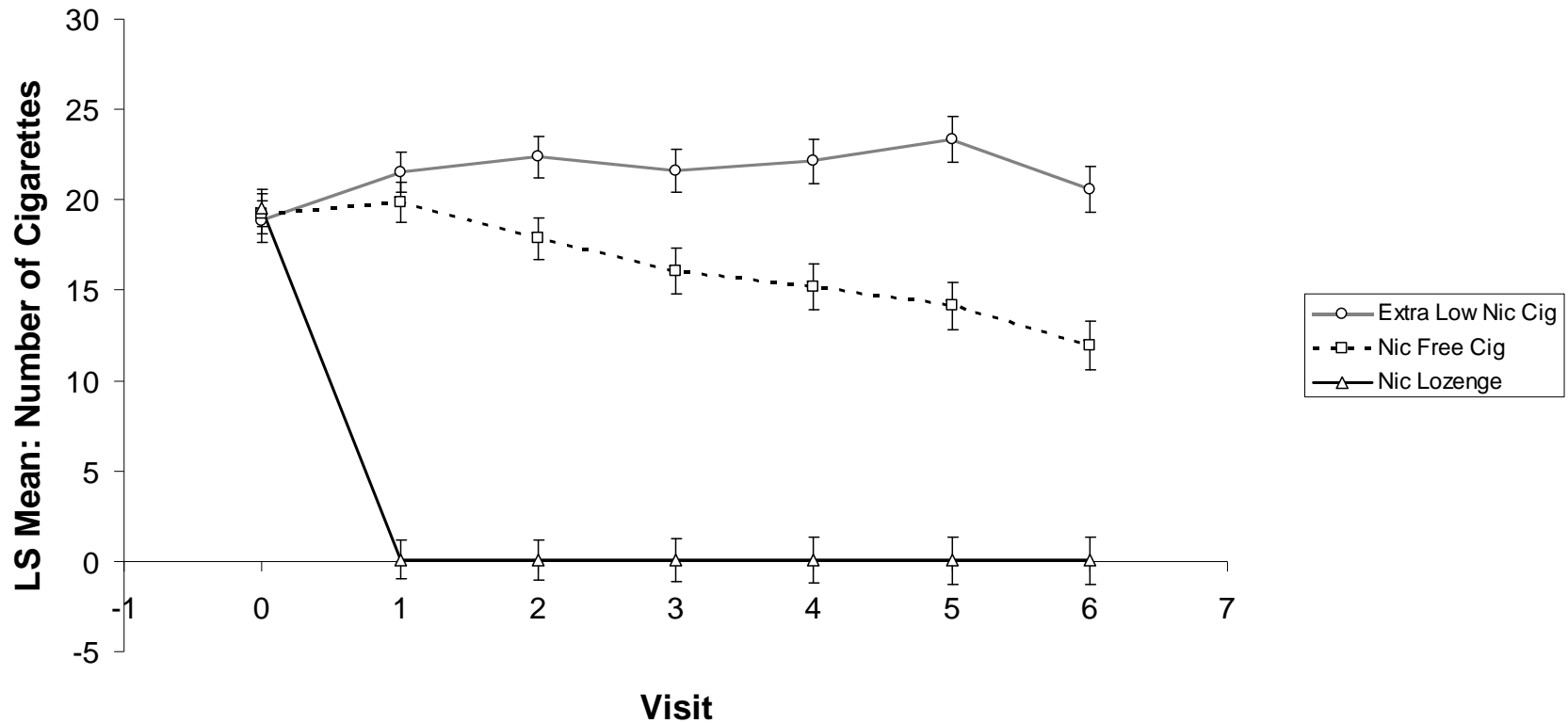


Abstinence rates: Intent-to-treat 4 week continuous abstinence (Weeks 9-12)

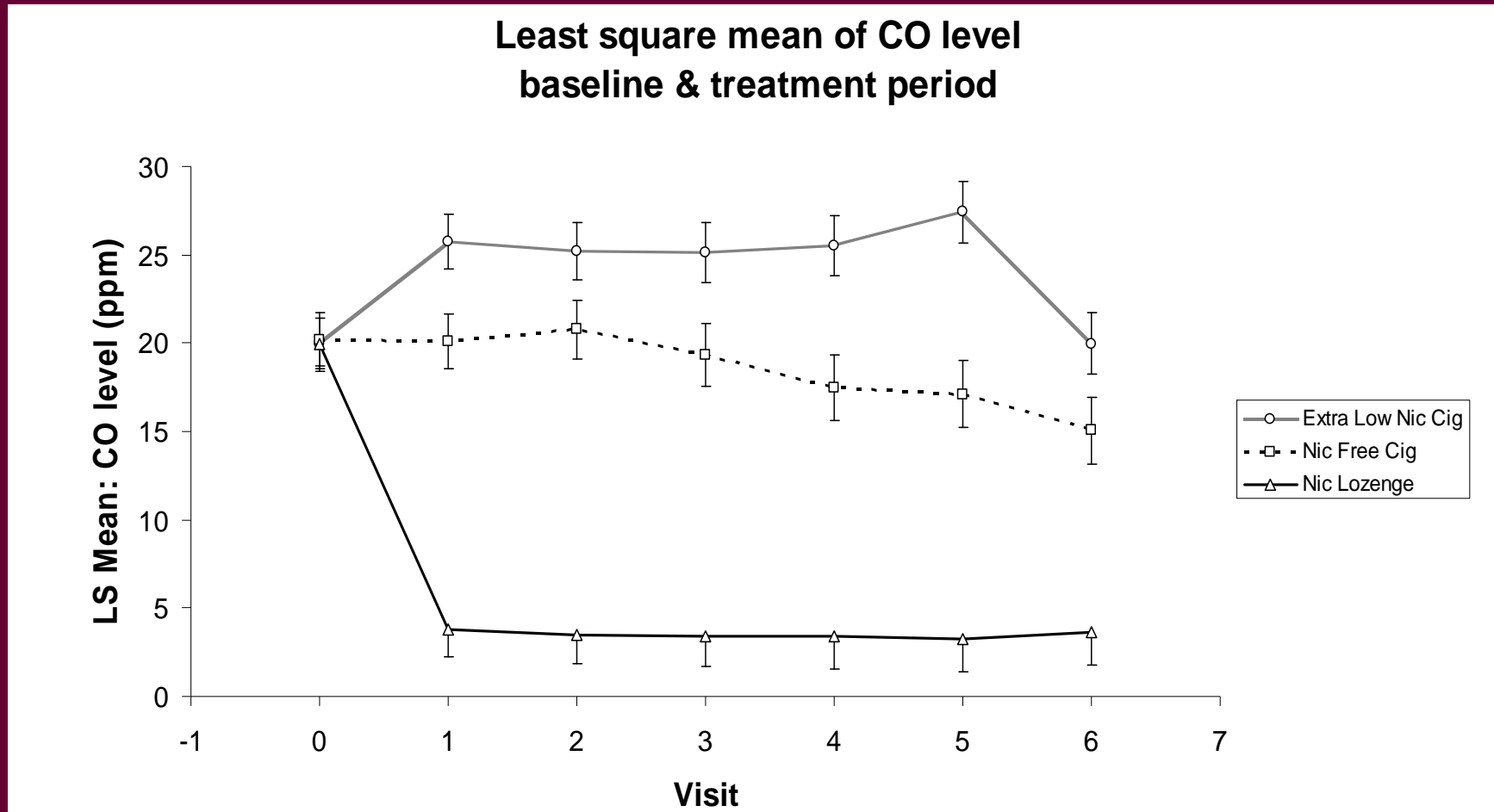
Quest 3 (0.05 mg nicotine) N=54	Quest 2 (0.3 mg nicotine) N=53	Nicotine lozenge 4 mg N=60
43.4%	21.2%	28.3%
p=0.04		

Cigarettes per Day

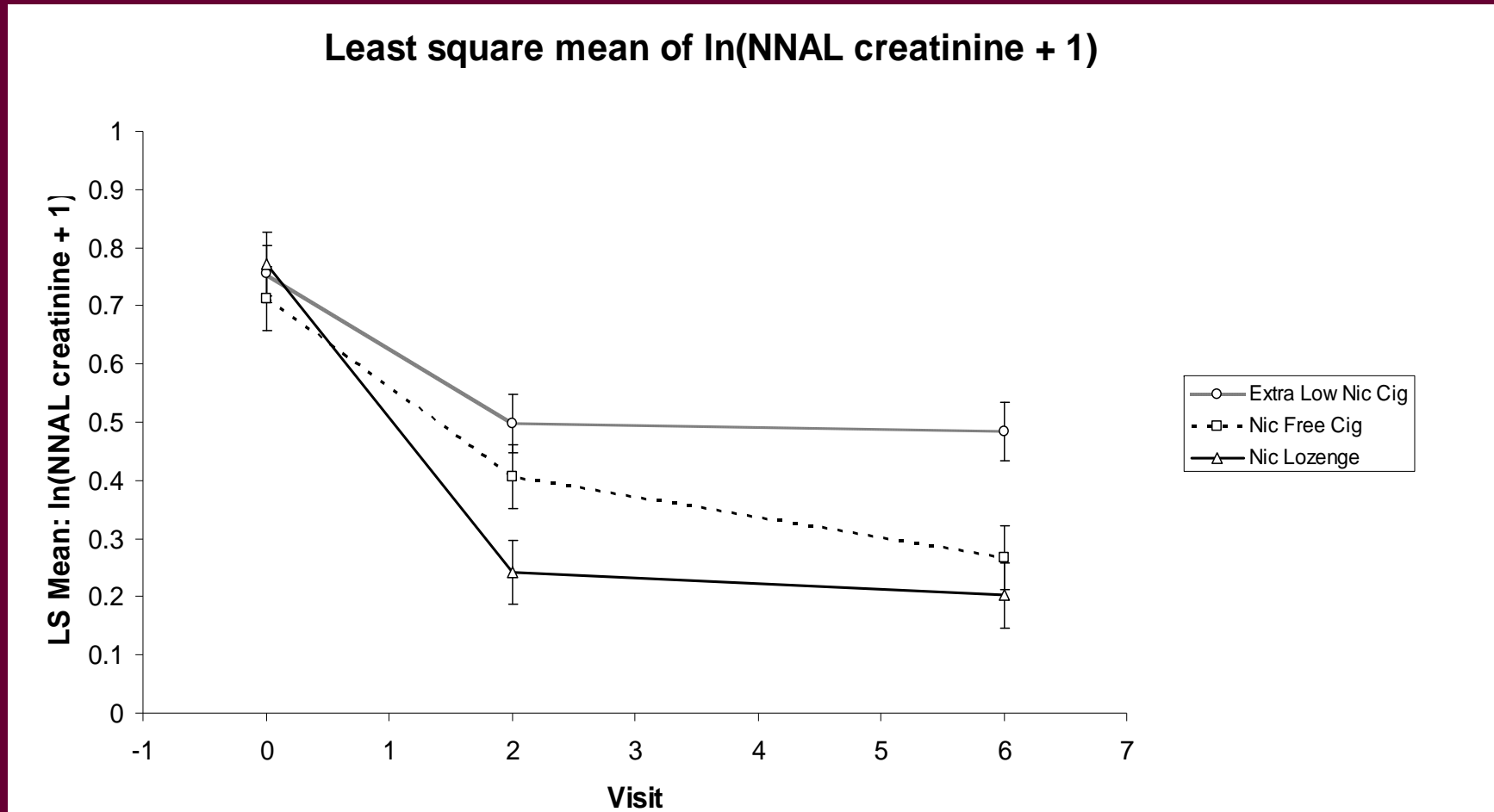
Least square mean of number of cigarettes used
(usual brand at baseline and Quest at treatment period)



Effects of Switching on CO

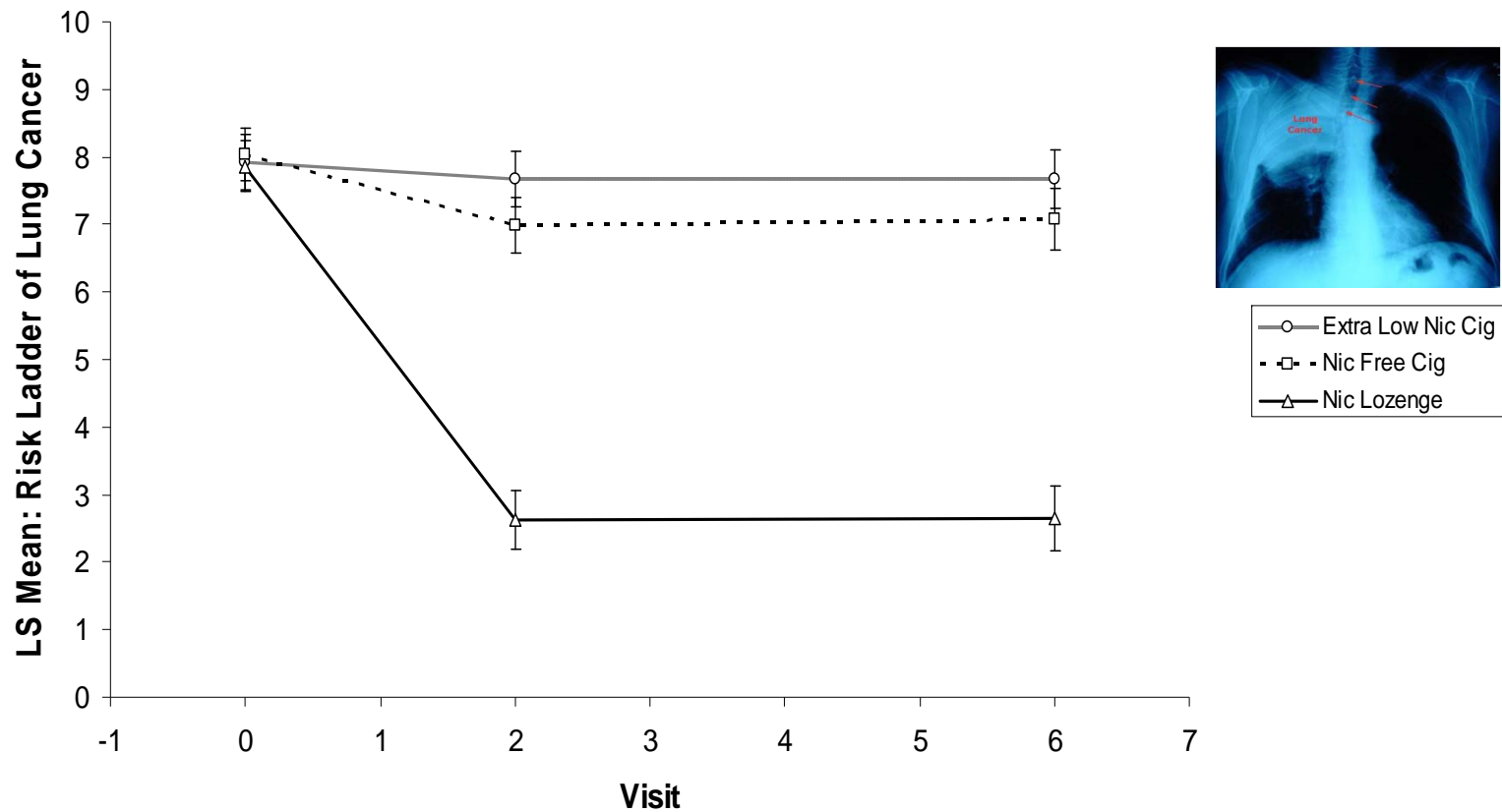


Effects of Switching on Total NNAL (NNK Metabolite)



Effects of Switching on Perceived Risk of Lung Cancer

Least square mean of risk ladder of lung cancer



Summary

- Among smokers interested in quitting, denicotinized cigarettes:
 - Reduced dependence
 - Facilitated abstinence
 - Reduced toxicant exposure
 - Did not change perceived risk for disease

Conclusion

- Denicotinized cigarettes hold significant promise in helping smokers quit.
- Sensory aspects of smoking play a role in tobacco addiction.
- Larger, longer-term trial and follow-up is needed.

Goals of Conference on Nicotine Regulation

- Present the current science on topics related to nicotine regulation.
- Discuss whether or not reducing nicotine levels may be feasible as a policy measure and under what conditions.
- Establish a research agenda to determine the feasibility and practicality of nicotine reduction as a policy measure.

Conference Conclusions and Recommendations

- Science base exists to support further investigation.
- Strong support to consider reducing nicotine levels as a potential method to reduce harm.
- However, the best approach to accomplish this goal is not yet known.

Research Questions

- What important constituents and design features contribute to addiction potential?
- Can a threshold dose for nicotine addiction be identified?
- As nicotine is reduced in cigarettes, can tobacco users use medications for cessation to reduce compensatory smoking and nicotine withdrawal?

Research Questions

- Are there any unintended consequences from nicotine reduction in tobacco?
- How do reduced nicotine cigarettes affect vulnerable populations (e.g., low SES, individuals with mental health disorders, and others)?

Potential for Tobacco Product Regulation

- Framework Convention on Tobacco Control
 - Article 9: Regulation of the contents of tobacco products
- Proposed legislation to provide FDA with authority to regulate tobacco products
 - Section 907(a)(4) authorizes issuance of a product standard by FDA “for the reduction of nicotine yields of the product”
 - The legislation forbids FDA from taking nicotine levels to zero, but allows FDA to issue a standard to lower nicotine yields to levels that cannot create or sustain addiction

What does the future hold?

- Science can inform public health and help guide how regulatory agencies control ingredients, toxicant emissions, and any aspect of tobacco product design and manufacture that affects nicotine delivery.
- Novel treatment mechanisms and methods to help smokers quit can be determined.