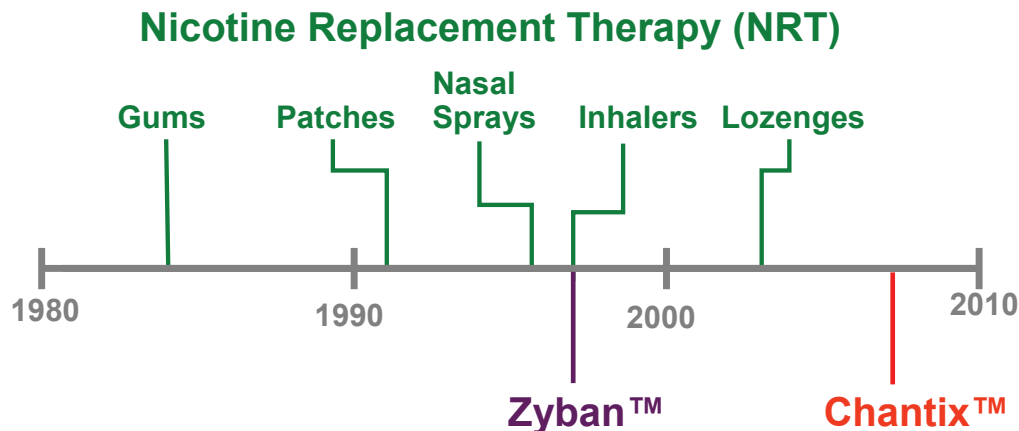




SMOKING CESSATION THERAPIES BRIEF REVIEW

APPROVED PRODUCTS. All products marketed in the U.S. to aid in quitting must be approved by the FDA. There are 44 million adult smokers in the U.S. and 1.3 billion worldwide. Smokers currently have few choices of FDA-approved products for quitting: varenicline (Chantix™), bupropion (Zyban™) and nicotine replacement therapy (NRT) in several forms—gums, patches, nasal sprays, inhalers and lozenges. Use of these products results in relapse rates that can be as high as 90 percent in the first year after a smoker ‘quits.’ The dates these products were first approved by FDA is shown below.



Although it is generally accepted that Chantix™ has higher quitting efficacy than NRT and Zyban™, in July 2009 the FDA required a ‘Boxed Warning,’ the most serious type of warning in prescription drug labeling, for Chantix™ and Zyban™. The FDA stated, “The warning will highlight the risk of serious mental health events including changes in behavior, depressed mood, hostility, and suicidal thoughts when taking these drugs.” See [FDA press release](#).

The majority of the 44 million adult American smokers do not attempt to quit each year making it imperative that new, effective and more appealing treatments (with minimal side effects) are made available. In a 2007 report titled, *Ending the Tobacco Problem: A Blueprint for the Nation*, The Institute of Medicine states:

There is an enormous opportunity to increase population prevalence of smoking cessation by reaching and motivating the 57 percent of smokers who currently make no quit attempt per year.

MEASURING QUITTING EFFICACY. The standard threshold and primary endpoint of smoking cessation clinical trials is ‘4-week continuous abstinence.’ This means the patient cannot smoke at all over 4 continuous weeks after the ‘quit date’ or else he or she is not considered abstinent (quit). This is easily confirmed through simple biomarker tests given to patients during visits in smoking cessation trials, including for example, sampling saliva or urine for cotinine (the major metabolite of nicotine) or expelled breath for elevated carbon monoxide (CO) levels, which entails patients to blow into a machine.

In clinical trials of FDA-approved smoking cessation products, 4-week continuous abstinence is determined while patients are taking the subject medication. For example, Pfizer’s prescription drug Chantix™ is promoted as having a 44 percent quit rate, however, this quit rate is calculated during the final 4 weeks of the 12-week treatment period—while patients are still taking the medication. The relapse rate of the 44% of patients who have ‘quit’ with Chantix™ in clinical trials is demonstrated below.

POTENTIAL SMOKING CESSATION THERAPEUTICS

Very Low Nicotine Cigarettes. Clinical trials demonstrate that very low nicotine (VLN) cigarettes, whether used exclusively or in conjunction with NRT, increase quit rates.¹⁻⁷ Other studies confirm that VLN cigarette reduce withdrawal symptoms from and cravings for conventional cigarettes.⁸⁻¹¹

A **controlled clinical trial** compared the quitting efficacy of a VLN cigarette (Quest 3™), a low nicotine cigarette (Quest 2™), and an FDA-approved nicotine lozenge (4-mg) in a total of 167 patients treated for 6 weeks. The trial was led by Dr. Dorothy K. Hatsukami, Director of the Transdisciplinary Tobacco Use Research Center at the University of Minnesota Cancer Center. Patients exclusively using the VLN cigarette achieved a 43% quit rate (confirmed 4-week continuous abstinence) compared to 28% for the group exclusively using the nicotine lozenge and 21% for the group exclusively using the low nicotine cigarette.¹⁻² Smoking abstinence at 6 weeks after the end of treatment was 47% for the VLN cigarette group, 32% for the nicotine lozenge group and 23% for the low nicotine cigarette group.

	6-Week Treatment Period		
	VLN Cigarette n=54	Nicotine Lozenge (4mg) n=53	Low Nicotine Cigarette n=60
4-Week Continuous Abstinence QUIT RATE (Weeks 9-12) p=0.04	43.4%	28.3%	21.2%
Abstinence at 6-week follow-up p=0.03	47.2%	31.7%	23.1%

During the 6-week treatment period, patients in the VLN cigarette group smoked less cigarettes per day than they previously had of their usual brand (baseline), and their daily cigarette usage continued to decline as they approached the quit date. In contrast, patients in the low nicotine cigarette group smoked more cigarettes per day than their baseline.

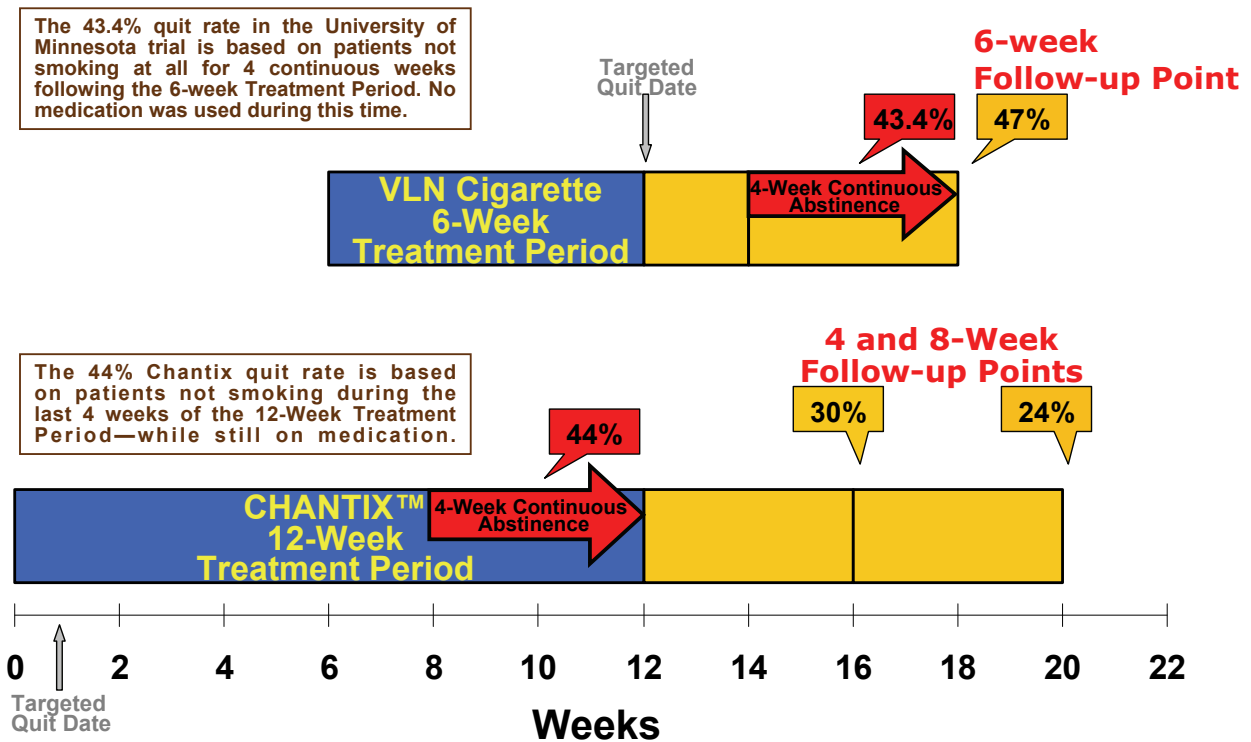
Although larger clinical trials are needed to validate efficacy, VLN cigarettes hold significant promise in assisting smokers to quit since they reduce nicotine dependency, facilitate abstinence,^{2,4} and compared to conventional or reduced nicotine cigarettes, reduce toxicant exposure.

Since potential quitters are already smokers, VLN cigarettes do not expose smokers to any new compounds and do not introduce any new side effects. Most smokers continue to smoke their usual brand during other cessation treatments. In a clinical trial, 76% of patients treated with Chantix™ smoked between the targeted quit date (day 8) and the

end of the 12-week treatment period.¹² The Chantix™ Medication Guide (July 2009) informs patients that they can keep smoking during the first week of taking the drug.¹³

The below chart illustrates how ‘4-week continuous abstinence’ follows the 6-week treatment period in the University of Minnesota trial, compared to the Chantix™ clinical trials, wherein ‘4-week continuous abstinence’ is during the last 4 weeks of 12-week treatment period—while patients are still taking the medication. The resulting quit rates are also shown along with short-term follow-up points.

Comparison of “4-week continuous abstinence”



After patients stopped taking Chantix™, the 44 percent quit rate quickly declines to 30 percent after 4 weeks of being off medication, then declines to 24 percent after 8 weeks, and continues to decline thereafter. See [Chantix™ label](#) at Figure 3.

22nd Century believes that an FDA-approved VLN cigarette has potential to significantly expand the existing cessation market by encouraging more smokers to attempt to quit by offering them a more acceptable product, which is not only more familiar but has no new side effects. 22nd Century is planning further clinical trials and has received guidance from the FDA for a phase II-B optimization trial and phase III trials for the company’s X-22 smoking cessation aid.

Nicotine Content. There is an important distinction between a VLN cigarette (sometimes referred to as ‘nicotine free’ or ‘denicotinized’) and a ‘low nicotine’ or ‘reduced nicotine’ cigarette. Although a VLN cigarette is often referred to as a low or reduced nicotine cigarette, it is the level of nicotine content that can greatly differentiate the two.

All reduced nicotine cigarettes used in the University of Minnesota trial¹⁻² and a 346-patient phase II trial⁴ contained 22nd Century's proprietary tobacco. This VLN tobacco contains only 5% of the nicotine of tobacco in popular low-yield or 'light' cigarette brands. The 20 fold difference in nicotine content equates to about 1 mg/gm (1000 ppm) versus 20 mg/gm (20,000 ppm).

22nd Century's proprietary VLN tobacco was the only tobacco in the VLN cigarette (Quest 3™) used in both these trials. The 'low nicotine' cigarette (Quest 2™), also used in both trials, had a blend of this VLN tobacco and typical tobacco resulting in a nicotine content (blended) of about 8 mg/gm (8000 ppm). In this example, the difference in nicotine content between a VLN cigarette and a low nicotine cigarette (assuming the same tobacco weight in each) is about 8 fold, thereby having important implications for compensatory smoking, dependence, and efficacy in smoking cessation.

Nicotine Vaccines. Nicotine vaccines are under development but in clinical trials have not yet achieved the efficacy within the treated population of other FDA-approved therapies. Nicotine itself is not recognized by the body as a foreign compound since the molecule is too small. In order to stimulate the production of antibodies, nicotine must be attached to a carrier to make the vaccine work. Different vaccine development programs use different carriers. Four companies, Cytos Biotechnology AG, Celtic Pharmaceuticals Holdings, Nabi Biopharmaceuticals, L.P. and Independent Pharmaceutica AB have vaccine candidates in clinical trials. Cytos exclusively licensed its nicotine vaccine candidate to Novartis in 2007. In October 2009, it was announced that it failed to show efficacy in a Phase II trial. Also in October 2009, Nabi received a \$10 million grant from **NIDA** to continue clinical trial development if its nicotine vaccine.

The treatment entails getting five to seven monthly injections. Expectations are that the treatment would have to be repeated every 12-18 months to assist in preventing relapse. Dr. Michael C. Fiore, Co-principal Investigator of the Transdisciplinary Tobacco Use Research Center at the University of Wisconsin, Madison, has estimated that any approval of a nicotine vaccine may be 5 to 10 years away.

Electronic or E-cigarettes. Although the FDA has not evaluated e-cigarettes for quitting and there has not been any published result of a controlled clinical trial, e-cigarettes are included here since there have been unconfirmed claims that these products facilitate cessation. E-cigarettes have been the subject of much controversy for this and various other reasons, including that these products are actually not cigarettes or tobacco products at all but are battery-operated devices filled with nicotine, flavor and other chemicals. They turn nicotine and other chemicals into a vapor that is inhaled.

E-cigarettes have very similar nicotine kinetics and bioavailability as nicotine inhalers,¹⁴ a prescription NRT product already approved by the FDA. The Agency believes e-cigarettes, "Meet the definition of a combination drug-device product under the Federal Food, Drug and Cosmetic Act," which is the reason the Agency has been detaining imports of e-cigarettes. Many countries have banned these products as has the state of Oregon and other states are in the process of banning them. See July 2009 **FDA press release**.

Whether or not e-cigarettes ever get evaluated by the FDA for quitting, there is no basis to believe that these products are more effective than any FDA-approved nicotine replacement product, especially the nicotine inhaler. 22nd Century believes the smoking experience is much more complex than smokers simply seeking nicotine. Tobacco smoke has other active compounds besides nicotine. If nicotine alone was the answer to quitting, approved nicotine replacement products would be much more effective.

References

1. Hatsukami DK et al, *Addiction*, in press
2. Hatsukami DK. 2008. Science and future research directions for reduced nicotine content cigarettes. *Tobacco control update, National Cancer Advisory Board, February 6*. Accessed September 16, 2009 from http://deainfo.nci.nih.gov/advisory/ncab/145_0208/presentations/Wednesday/900am_Hatsukami.ppt
3. Walker N , Bullen C, McRobbie H. 2009. Reduced–nicotine content cigarettes: Is there potential to aid smoking cessation? *Nicotine & Tobacco Research* 11(11):1274-9. Epub 2009 Sep 30. <http://www.ncbi.nlm.nih.gov/pubmed/19793786>
4. Becker KM, Rose JE, Albino AP. 2008. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. *Nicotine & Tobacco Research* 10(7):139-1148. <http://www.ncbi.nlm.nih.gov/pubmed/18629723>
5. Rezaishiraz H, Hyland A, Mahoney MC, O’Connor RJ, Cummings KM. 2007. Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings? *Nicotine & Tobacco Research* 9(11):1139-1146. <http://www.ncbi.nlm.nih.gov/pubmed/17978987>
6. Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. 2007. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology, Biomarkers & Prevention* 16(11):2479-85. <http://www.ncbi.nlm.nih.gov/pubmed/18006940>
7. Donny EC, Houtsmuller E, Stitzer ML. 2007. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction* 102:324-34. <http://www.ncbi.nlm.nih.gov/pubmed/17222288>
8. Pickworth WB, Fant RV, Nelson RA, Rohrer MS, Henningfield JE. 1999. Pharmacodynamic effects of new denicotinized cigarettes. *Nicotine & Tobacco Research* 1:357-64. <http://www.ncbi.nlm.nih.gov/pubmed/11072433>
9. Butschky MF, Bailey D, Henningfield JE, Pickworth WB. 1995. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacol Biochem Behav.* 50:91–96. <http://www.ncbi.nlm.nih.gov/pubmed/7700960>
10. Gross J, Lee J, Stitzer ML. 1997. Nicotine-containing versus denicotinized cigarettes: effects on craving and withdrawal. *Pharmacol Biochem Behav.* 57:159–165. <http://www.ncbi.nlm.nih.gov/pubmed/9164567>
11. Rose JE. 2006. Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology* 184:274-285. <http://www.ncbi.nlm.nih.gov/pubmed/16362402>
12. Gonzales D, Hatsukami D, Rennard SI, Baker CL, Zou KH, Lee TC. Predicting Delayed vs. Intermittent Quitting: A Pooled Analysis of Smokers Treated for 12 Weeks with Varenicline vs. Bupropion SR and Placebo. Poster POS5-81. Society for Research on Nicotine and Tobacco. Dublin meeting: 2009 Joint Conference of SRNT and SRNT-Europe, April 26-30, 2009.

13. Pfizer Labs; Division of Pfizer Inc. July 2009. LAB-0328-8.0. Medication Guide CHANTIX[®] (varenicline) Tablets. <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088569.pdf>

14. Bullen CR, McRobbie H, Thornley S, Chen X, Glover M, Laugesen M. Effect of an Electronic Nicotine Inhaler on Cravings, Withdrawal, Acceptability and Nicotine Delivery. Poster POS5-50. Society for Research on Nicotine and Tobacco. Dublin meeting: 2009 Joint Conference of SRNT and SRNT-Europe, April 26-30, 2009. http://www.healthnz.co.nz/ecig_effect-2.pdf