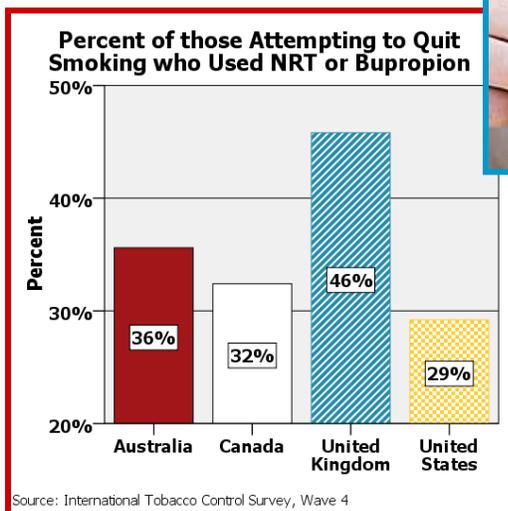


Barriers to Use of FDA-Approved Smoking Cessation Medications: Implications for Policy Action



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EXECUTIVE SUMMARY

45 million Americans continue to smoke cigarettes, and the massive toll of this epidemic of smoking-caused disease will be reduced more quickly if effective tobacco dependence treatment is provided to the millions of smokers who want to quit but are addicted. Less than half of current smokers try to quit each year, but fewer than one in 3 of them use an FDA-approved smoking cessation medicine each year, and less than 3% of doctor visits by a smoker result in a prescription for an effective smoking cessation medication. This review sought to identify barriers to consumer demand for FDA-approved smoking cessation medications and to suggest policy solutions.

The main conclusions are:

1. The evidence is very clear that use of Nicotine Replacement Therapy (NRT) is a safe and effective method of helping smokers quit. The health risk from nicotine is much lower than that from smoking, and should not be a deterrent to expanded NRT use. There is now strong evidence that longer term (>14 weeks) use of combined NRT products (e.g. patch plus gum) yields better smoking cessation outcomes.
2. The evidence supports the safety and effectiveness of NRT when used with minimal or no support and suggests that the results from clinical trials are a reasonable guide to the performance of these medications in more typical "real world" (including over-the-counter [OTC]) contexts.
3. NRT is safe and effective in cardiovascular patients and product labeling should be adjusted to be consistent with this. The evidence on safety and efficacy of NRT in adolescents and pregnant women, while somewhat reassuring, is not sufficiently clear to suggest the need for major changes from the current situation in which these groups are recommended to seek the advice of their medical doctor prior to embarking on NRT use.
4. Studies of public perception of NRT suggest widespread misconceptions and myths about the harms and benefits of NRT, characterized by an exaggerated concern about the safety of NRT, misperceptions of the role of nicotine in causing the physical harm from smoking, skepticism about the effectiveness of NRT, and over-optimism among smokers about their likelihood of success in quitting without use of any aid.
5. There is a lack of detailed research on providers' beliefs and attitudes to the use of FDA-approved smoking cessation medications in the United States. However, the consistent pattern of under-prescribing (compared with the U.S. Clinical Practice Guideline recommendation) and reports of doubts regarding efficacy, safety and lack of time to counsel patients, suggest that a lack of training on the use of medications and a lack of awareness of existing treatment guidelines is widespread among health professionals and consequently represents a barrier to more widespread use of effective tobacco treatment medications.
6. The vast majority of quit attempts do not involve an FDA-approved smoking cessation medication, and even when medication is used it is under-used (too little for too short a time). Smokers' misperceptions about the health risks of medication appear to be related to their underuse, and these problems are magnified in African American and Latino smokers.
7. The evidence from both clinical trials and studies of more naturalistic use of NRT suggests that while transient concurrent use of NRT and cigarettes often occurs, use for non-cessation reasons, abuse and dependence are rare. A far greater problem is under-use of NRT (using too little for only a very short duration), as this is associated with failure to quit smoking.
8. The relative price of cigarettes, the cost of the NRT, the presence of legislation providing smoke-free environments, media advertising and campaigns, OTC availability, insurance coverage and free medication via telephone quitlines are all factors that influence smoker demand for tobacco treatment medications.

9. Tobacco treatment medications that are easy to use and have a good side-effect profile are used much more frequently by smokers. Speed and dose of nicotine delivery may be important for use past the initial stages and for efficacy, but many smokers will either not initiate or will cease use of a product early in treatment if it is not easy to use, with mild side effects. For oral products, taste is a factor and for all products relative perceived harmfulness – (as indicated in the product labeling), is a common barrier to effective use.
10. Bupropion and varenicline are both safe and effective prescription-only, non-nicotine aids for smoking cessation. Perceptions of their risks are also exaggerated relative to risks from smoking. Their prescription-only status is appropriate and so the main barriers to use are lack of insurance coverage, lack of samples, physician reluctance to prescribe, and availability only in relatively expensive packs (e.g. \$130).

The main policy recommendations to increase consumer demand are:

1. Fund statewide and national Comprehensive Tobacco Control Programs as recommended by the Centers for Disease Control's *Best Practices for Comprehensive Tobacco Control Programs* (2007). A component of this should be a media campaign designed to correct misconceptions about treatment medications and portray the benefits of accessing treatment. This media campaign should be designed to reach minority populations.
2. Increase the excise tax on all tobacco products. Use part of the increased tax receipts to fund #1 above.
3. Implement legislation, regulations and policies that comprehensively ban smoking in all indoor public places and workplaces (i.e. including bars, restaurants and casinos). OTC smoking cessation products should be available for sale in all those places where cigarettes are sold (including bars, restaurants and casinos).
4. Require federal, state and private health insurance plans to provide comprehensive coverage for tobacco dependence treatment, including effective counseling and both prescription-only and OTC smoking cessation medicines.
5. Ensure that tobacco use assessment and treatment interventions are adequately covered in the training curricula for all health care professionals, and that the evidence-based Guideline on the Treatment of Tobacco Use and Dependence (and its revision) is widely disseminated and adopted as a critical part of continuing professional education by all health professionals.
6. Develop and fund a National Smoking Cessation Action Plan with adequate infrastructure to provide the full range of treatments (healthcare provider, medication, quitline, online, and community-based clinics) in a freely-available and seamless, coordinated system of care management.
7. Implement a set of principles for FDA regulation of smoking cessation medicines that aim to maximize the positive public health impact of these products and minimize the harmful effects of tobacco.

INTRODUCTION

Tobacco use, primarily in the form of cigarette smoking, remains the single largest cause of premature death in the United States, causing the premature death of over 400,000 people, and causing over eight million to suffer a serious smoking-caused illness, each year. Half of all continuing smokers will be killed by a smoking-caused illness, losing an average of 10 healthy life-years. This addiction costs the nation more than \$96 billion per year in direct medical expenses and more than \$97 billion in lost productivity. 45 million Americans continue to smoke tobacco, and if the massive toll of this epidemic of smoking-caused disease is to be significantly reduced it will require providing effective tobacco dependence treatment to the millions of smokers who want to quit but are addicted to tobacco¹.

Article 14 of the World Health Organization's Framework Convention on Tobacco Control (FCTC) focuses on demand issues concerning tobacco use and cessation, stating that each party shall, "facilitate accessibility and affordability for treatment of tobacco dependence including pharmaceutical products.²". In the United States, there are currently 7 main types of medications approved by the Food and Drug Administration (FDA) as aids for smoking cessation. These consist of five types of nicotine replacement therapy (nicotine gum, patch and lozenge, which are available over the counter [OTC], and prescription-only nicotine inhaler and nasal spray) and two prescription-only non-nicotine medicines: bupropion and varenicline. These medicines have been marketed both directly to consumers via television and other advertisements, and directly to health professionals via journal publications, smoking cessation trainings, and paid advertising.

Currently one in five adults living in the United States are cigarette smokers^{3,4}, and of these 70% or more state that they would like to stop smoking. However, only around 43% of U.S. smokers try to quit each year⁴, and 2-8% of these triers succeed⁵, meaning that 1-2% of smokers quit each year. One reason for both the low attempt rate and low success rate is the low use of effective treatments. Even in states that have been relatively progressive in supporting cessation services, as little as 10-20% of smokers use pharmacotherapy each year to assist a quit attempt^{6,7}. Nationally around a third of serious quit attempts are supported by a pharmacological aid⁸. On the provider side, despite the existence of treatment guidelines stating that all smokers should be offered a smoking cessation medication⁹, only 2.4% of doctor visits by smokers result in a prescription for a cessation medication¹⁰. This underutilization of tobacco treatment medications is one reason why the US government targets for reducing tobacco use by 2010 will remain unmet. In order to try to do a better job of helping smokers quit, the Society for Research on Nicotine and Tobacco (SRNT)^{*}, supported by the Robert Wood Johnson Foundation, sought to conduct a review of barriers to consumer demand for treatment medications and to suggest policy solutions. This topic was also discussed at a full-day symposium prior to the SRNT annual meeting in 2007. This report summarizes the results of that review process. It will focus firstly on nicotine replacement therapies before addressing the non-nicotine prescription-only medications separately. The review addresses a series of specific questions relating to demand for tobacco treatment medications, before proposing policy solutions. The review involved a literature search using the PUBMED online data-base using the combination of search terms most relevant to each question, a search of the most relevant additional articles cited in those papers, and also made use of various sources of unpublished information, including data presented at a symposium on this topic held immediately prior to the 2007 SRNT annual conference¹¹. The presentations at that symposium are available at: <http://roswelldocs.com/srnt.htm>.

* With support from The Association for the Treatment of Tobacco Use and Dependence (ATTUD) and The Campaign for Tobacco Free Kids (CTFK)

QUESTION 1: What is the scientific evidence regarding the efficacy, safety, and dependence potential of tobacco treatment medications?

Efficacy

The evidence for the efficacy of currently approved pharmacological treatments is extensive, and is based on more than a hundred randomized controlled trials in over 40,000 patients. Numerous authoritative reviews on the efficacy of tobacco treatment medications have been published, with the most recent being the updated Clinical Practice Guideline on Treating Tobacco Use and Dependence: 2008, sponsored by the U.S. Public Health Service¹². Among the most relevant conclusions from that report are the following (p6-8):

- Tobacco dependence is a chronic disease that often requires repeated intervention.
- Every tobacco user willing to make a quit attempt should be offered effective counseling and medications.
- All seven first-line medications reliably increase long-term quit rates over and above placebo.
- Certain combinations of first-line medications have been shown to be effective smoking cessation treatments. Effective combination pharmacotherapies are long term nicotine patch (14+ weeks)+ other NRT (gum or spray), the nicotine patch + the nicotine inhaler, or the nicotine patch + bupropion SR. (p118-120).

The 2008 Clinical Practice Guideline update (hereafter referred to as the '2008 Guideline') recognized that for some patients, it may be appropriate to continue medication treatment for periods longer than usually recommended, and commented that the data supports long term patch and gum use as efficacious. Part of the evidence for this conclusion came from the Lung Health Study of almost 4000 smokers with evidence of early COPD, which reported that about a third of long term quitters were still using nicotine gum at 12 months and some for as long as 5 years with no serious side effects.^{13,14,15,16} The 2008 Guideline stated that because these medications do not contain non-nicotine toxic substances (e.g., tar and carbon-monoxide) or produce dramatic surges in blood nicotine levels, they are less addictive than cigarettes, and long term use is clearly preferable to a return to smoking with respect to health consequences.¹² The report highlighted that the medication treatment producing the largest effects on abstinence rates, involved long-term nicotine patch therapy plus ad libitum NRT (e.g. nicotine gum or nasal spray).

Furthermore, numerous studies examining the combined use of the nicotine patch with an acute, short acting form of NRT have shown no significant increase in adverse events associated with the use of NRT.^{17,18,19} Side effects tend to be minor and, since users are experienced in managing nicotine levels, they quickly learn to use two forms of NRT effectively.

Safety

The health risk profile of medicinal nicotine was the subject of extensive review in the recent Royal College of Physician's report, "Harm Reduction In Nicotine Addiction", published in October, 2007.²⁰ The main conclusions of that review were as follows:

- Extensive experience with nicotine replacement therapy in clinical trial and observational study settings demonstrates that medicinal nicotine is a very safe drug.
- Adverse effects are primarily local and specific to the mode of delivery used.
- NRT does not appear to provoke acute cardiovascular events, even in people with pre-existing cardiovascular disease.
- There is no direct evidence that NRT is carcinogenic or influences the risk of other common smoking-related diseases in humans.
- Evidence on the safety of NRT during pregnancy is limited, but suggests that NRT does not increase the risk of major developmental abnormalities or reduce birth weight. However, NRT may increase the risk of minor musculoskeletal anomalies. Further evidence on these effects is needed.
- Evidence on the safety of long-term use of NRT is lacking, but there are no grounds to suspect appreciable long-term adverse effects on health
- In any circumstance, the use of NRT is many orders of magnitude safer than smoking.

Dependence Potential

The RCP report²⁰ acknowledged that the dependence potential of medicinal nicotine products relates to their speed of nicotine delivery. The nicotine nasal spray achieves the fastest absorption and so a slightly higher proportion of spray users become dependent on the spray (as defined by long-term use against advice,²¹). Nicotine gum, inhaler and lozenges have similar nicotine delivery profiles and provide some reinforcement, though much less than from a cigarette. Each of these products has some dependence potential and some users have difficulty stopping. In clinical trials 9-22% of gum users continue for a year after smoking cessation, and for the spray as many as 32-43% of one year cigarette abstainers keep using the nicotine spray.²² Long term use is much less common in settings where patients are self-purchasing their products.²¹ As nicotine patches release nicotine much more slowly, there is little reinforcement and dependence is not a problem.²¹ In a trial of nicotine patch, gum, inhaler and nasal spray in which participants paid around \$14 for each box (less than half retail price for a 2-weeks supply), 2-10% of those who started using the products were still using 15 weeks later, (i.e. beyond the recommended 12 weeks), which represented 8-37% of those who were abstinent from tobacco at 15 weeks.²¹ Each of these products delivers smaller doses at slower rates than smoked tobacco, and so they are correspondingly less addictive than cigarettes.

Conclusion 1: The evidence is very clear that use of Nicotine Replacement Therapy is a safe, effective method of helping smokers to quit. The health risks from nicotine are so much lower than those of smoking, that this should not be a deterrent to NRT use. There is now strong evidence that longer term (>12 weeks) use of combined NRT products (e.g. patch plus gum) yields better smoking cessation outcomes.

QUESTION 2: Is nicotine replacement therapy safe and effective outside the context of clinical trials?

Most reviews of the safety and efficacy of tobacco dependence treatment medications focus on randomized placebo-controlled trials as they provide the best opportunity to assess the effects of the active ingredient in the medication, while controlling for as many other variables as possible. Such trials frequently use a list of inclusion and exclusion criteria and involve a higher level of professional assessment, support and counseling than is typical in clinical practice or the over-the-counter (OTC) context. This sometimes leads to questions about whether these medicines are safe and effective outside of clinical trials. A meta-analysis of the effects of NRT in the OTC context has concluded that NRT is effective for smoking cessation in that context.²³ The long-term quit rates are not high, but because the cost of a treatment episode is low and the benefits to health for each quitter so great, NRT has been identified as one of the most cost-effective life-preserving interventions available to medical science.²⁴ Recent studies of the effects of offering free nicotine patches, often via a telephone quit-line, have also suggested that the patch is effective in promoting smoking cessation when provided with minimal additional support outside of a formal clinical trial.^{25,26}

A recent multinational prospective cohort study²⁷ examined smokers making a spontaneous quit attempt without formal behavioral support or bupropion. This study found that 30-36% of those making a spontaneous quit attempt (without support or bupropion) used NRT, and that those using NRT had 2.2 times the odds of reporting no tobacco use (over previous 90 days) at least 6 months after their quit attempt, as compared with those not using NRT, while controlling for their baseline level of dependence (as measured by Fagerström Test for Nicotine Dependence score). This study also examined the effect of using another non-NRT aid (e.g. hypnotherapy, acupuncture etc) and found that those smokers were no more likely to succeed in quitting smoking than those not using such an aid. The effect size of NRT in this study was broadly what would be expected from clinical trials, and, as it was not found in those using other aids, it does not appear to be a function of motivation to use some form of support. None of these studies raised any serious concerns about the safety of NRT in the OTC context.

Conclusion 2: The evidence supports the safety and effectiveness of NRT when used with minimal support and suggests that the results from clinical trials are a reasonable guide to the performance of these medications in more typical “real world” (including OTC) contexts.

QUESTION 3: Are there particular concerns regarding the safety and efficacy of tobacco treatment medications in special populations?

The 2008 Guideline¹² also addressed the use of medicines with certain other patient populations.

Adolescents:

With regards to adolescents, the panel concluded that, *“Although nicotine replacement has been shown to be safe in adolescents, there is little evidence that these medications and bupropion SR are effective in promoting long-term smoking abstinence among adolescent smokers. (p161)”*

Perhaps the best evidence for efficacy of NRT in adolescents came from a study by Moolchan, et al.²⁸ in which 120 adolescents were randomized to counseling plus either nicotine patch (and placebo gum), nicotine gum (and placebo patch) or double placebo. This study found CO-confirmed prolonged abstinence rates of 18% for the active-patch group, 6.5% for the active-gum group, and 2.5% for the placebo group; the difference between the active-patch and placebo arms was statistically significant. At the end of treatment (12 weeks) and 6 months after the target quit date logistic regression analyses showed a trend toward significance for the effect of the patch, compared with placebo (OR: 4.93; 95% CI: 0.95–25.6; $P = .058$), and no significant effect of gum (OR: 1.81; 95% CI: 0.31–10.4; $P = .51$). Given that these results for the patch are similar to those for adults, with no sign of safety problems, and that the study lacked statistical power (i.e. was too small) to detect a significant difference at 6 month follow-up, this study suggests that the nicotine patch (but not the gum) helps adolescent smokers to quit.

Pregnancy:

With regards to use of medications during pregnancy, the 2008 Guideline found three randomized trials of nicotine replacement therapy in pregnancy, but because of the mixed results from these studies the panel did not make a recommendation regarding medication use during pregnancy. One large placebo-controlled patch trial in Sweden²⁹ found no significant improvement in cessation, but found a significantly heavier birth weight (by 186g) among babies born to women allocated the nicotine patches as compared to women who used placebo patches. A recent study³⁰ randomized 128 pregnant women to counseling plus their choice of NRT or counseling alone. This study found significantly higher quit rates for those women using NRT at both 7 weeks post randomization (24% vs. 8%) and at 38 weeks (18% vs. 7%, $p=0.04$). Recruitment was suspended early by an Independent Data and Safety Monitoring Board (IDSMB) when an interim analysis found a higher rate of negative birth outcomes in the CBT+NRT arm than in the CBT-only arm. The IDSMB indicated that the study was terminated due to previously agreed stopping rules, but they did not believe that the adverse events were related to NRT use. In the final analysis, the difference between the arms in rate of negative birth outcomes was not statistically significant ($p=0.26$), when adjusted for previous history of preterm birth.

Smokers with a pre-existing cardiovascular disorder:

The 2008 Guideline¹² update specifically addressed the issue of NRT in cardiovascular patients. It reported that:

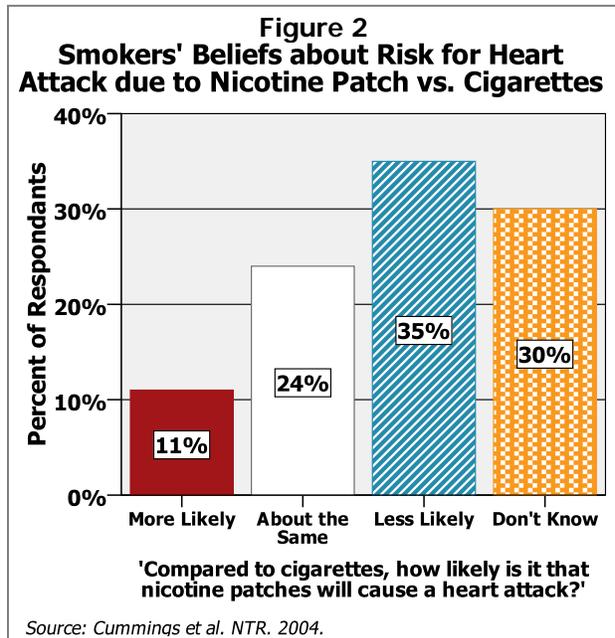
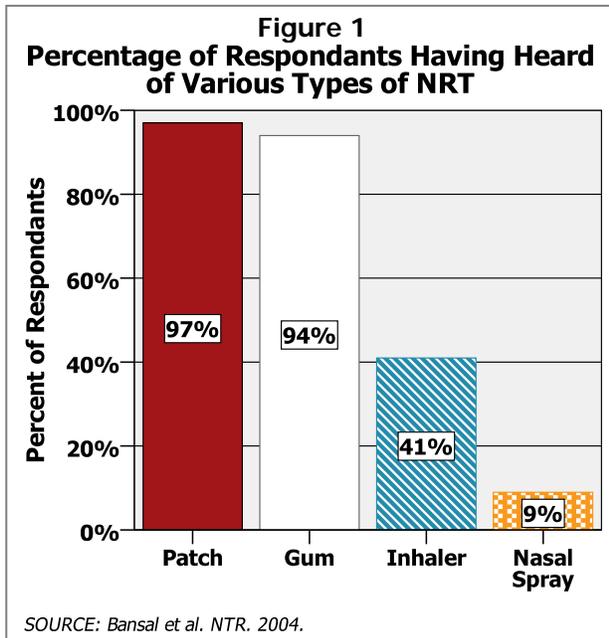
Separate analyses have now documented the lack of an association between the nicotine patch and acute cardiovascular events, even in patients who continued to smoke while wearing the nicotine patch...it may be important to inform patients who are reluctant to use NRTs that there is no evidence of increased cardiovascular risk with these medications. (p127)

It notes however that, “the package inserts recommend caution with acute cardiovascular diseases. (p127)”

Conclusion 3: NRT is safe and effective in cardiovascular patients. The evidence on safety and efficacy of NRT in adolescents and pregnant women, while somewhat reassuring, is not sufficiently clear to suggest the need for major changes from the current situation in which these groups are recommended to seek the advice of their medical doctor prior to embarking on NRT use.

QUESTION 4: What do smokers believe about the safety and efficacy of tobacco treatment medications?

Bansal, et al.³¹ conducted a nationally representative random digit dialed telephone survey of over a thousand adult cigarette smokers in the US. Nearly all (97%) of the respondents had heard of the nicotine patch, but only 9% had heard of the nicotine nasal spray (Figure 1). Many of the respondents had heard of safety concerns about specific NRT products but only a third correctly reported that nicotine patches were less likely to cause a heart attack than smoking cigarettes (Figure 2). Similarly, only a third correctly answered that nicotine is not a cause of cancer (Figure 3). Doubts about efficacy of NRT were also common. For example, of those who had never used NRT (68%), only 54% agreed with the statement that NRT “improves a smoker’s chances of quitting successfully.” This study concluded that



most smokers are misinformed about the health risks of nicotine and the safety and efficacy of NRT. However, when non-users were asked why they hadn't used various forms of NRT, the most common reason given (48-60% depending on the product) was “no need”. Given that two-thirds of the sample did not expect to quit smoking in the next year, it is not clear whether this “no need” response reflects overconfidence in ability to quit, lack of belief that NRT is effective, or simply lack of intent to quit. However, other studies have documented a consistent over-optimism among smokers about their ability to quit.^{32,33} For example, although less than 10% of adult smokers remain cigarette-free for a year after a serious quit attempt,⁹ 51-78% of adult smokers believe they will succeed in quitting at their next attempt.³³

Similar results suggesting many smokers are unaware of some nicotine replacement therapies and have doubts about their effectiveness have been found outside the US. For example, Hammond, et al.³⁴ in Canada found that although the nicotine patch is the most frequently recalled cessation aid, a third of smokers did not recall the patch as a cessation aid, and over a third of all smokers did not believe that NRT would increase their likelihood of quitting. Etter and Perneger³⁵ found that only 16% of Swiss smokers believe that NRT helps smokers to quit while 26% have concerns about the side effects of NRT. Comments that NRT is too expensive and is addictive were also frequently made in that survey. Roddy, et

al.³⁶ found that many economically deprived smokers in England regarded NRT as expensive and ineffective.

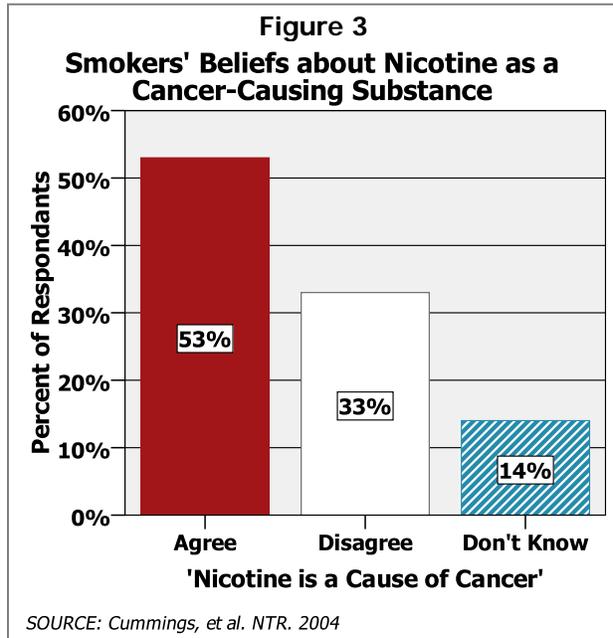
While studies have reported greater use of NRT among more educated smokers,³⁷ even students at one of the top US universities reported major misperceptions regarding the relative risks of nicotine replacement products and cigarettes. In a survey of students at John Hopkins University, 20% of respondents incorrectly perceived the nicotine patch to be as harmful as or more harmful than a regular cigarette; corresponding values were 24% for nicotine gum and 53% for the nicotine inhaler.³⁸ Numerous other studies^{39,40} have reported misconceptions about NRT in the general public. Those smokers holding negative beliefs about the safety and/or efficacy of tobacco treatment products are less likely to use them and if they do, they use them for a shorter duration. For example, Shiffman's⁴¹ analysis of the National Family Opinion research sample (weighted to match the 2000 National Health Interview Survey sample) found that of 3,203 smokers or recent ex-smokers, 66% agreed somewhat with the statement that "stop-smoking products with nicotine are just as harmful as cigarettes". Those holding beliefs that NRT may be harmful were significantly less likely to have used NRT, and if they had tried nicotine gum, they used significantly less of it (fewer pieces for a shorter duration). This data suggests that concerns about the safety of NRT is a barrier to smokers using NRT.

The sources of these misperceptions of NRT are numerous and include a widespread misunderstanding of the role of nicotine in causing smoking-caused diseases. Smokers being assessed for treatment frequently point to the wording on the labeling of these products as indicators that they may be dangerous. For example, the labeling on NRT products recommends caution in patients with cardiovascular problems and strongly advises against the concurrent use with other nicotine delivery products (including cigarettes). This leads many smokers to believe that it is highly dangerous to continue using the NRT if they smoke a cigarette. In reality, combining NRTs or wearing the patch for at least two weeks prior to quitting smoking are not only safe, but have been shown to enhance the chances of success in quitting smoking.

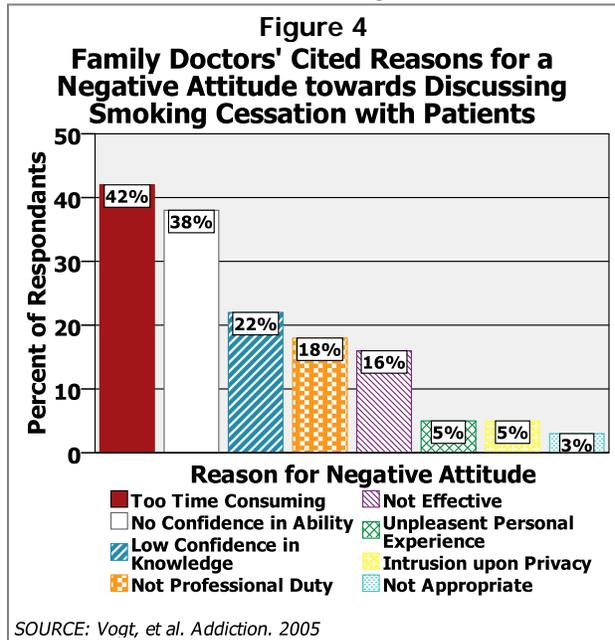
Conclusion 4: Numerous studies of public perception of NRT suggest widespread misconceptions exist about the harms and benefits of nicotine replacement therapy. This is characterized by an exaggerated concern about the safety of NRT, skepticism about the effectiveness of NRT, and over-optimism among smokers about their likelihood of success in quitting without the use of any aid. In part, this misperception may be due to exaggerated cautions on package labeling.

QUESTION 5: What do health professionals believe about the safety and efficacy of tobacco treatment medications?

While over 80% of physicians in the US believe that combination, NRTs and bupropion are effective treatments for smokers, as few as 50% believe that the nicotine nasal spray is effective for smoking cessation.⁴² Although the US Public Health Service Guidelines⁹ and the update¹² recommend that all patients should be asked about their tobacco use, and all smokers offered an approved medication to help them quit, it is clear that this is not happening. In an analysis of the 2001-2 national Ambulatory Care Survey, Steinberg, et al.¹⁰ found that tobacco counseling occurred in 22.5% of visits by tobacco



users, and cessation medications were prescribed on only 2.4% of occasions (with the odds being 15 times higher if the patient requested it). These rates are similar to previous analyses of this survey in 1991. In a study involving direct observation of physician encounters with patients, Ellerbeck, et al.⁴³ found that of 244 smokers identified, physicians provided assistance with smoking cessation for 38% (range among practices = 0%-100%). Bupropion and nicotine-replacement therapy were discussed with smokers in 31% and 17% of encounters, respectively. Numerous other studies have documented poor adherence of physicians to the basic recommendations in the 1996 and 2000 Tobacco Treatment Guideline⁹ regarding the “5 As” (Ask, Advise, Assess, Assist, Arrange), with particularly low rates of “advising” on use of medications and “arranging” follow-ups.^{44,45,46} This partly relates to lack of familiarity with the Guideline,⁴⁷ but time constraints and the perception that smokers are unreceptive to counseling were the two most common barriers cited by both physicians and office managers in one study.⁴⁸ Thorndike, et al.⁴⁹ reported that there has been a small increase in physicians’ rates of patients’ smoking status identification and a small decrease in rates of counseling smokers over the decade 1993-2003. This lack of progress may reflect barriers in the US health care environment, including limited physician time to provide counseling and inadequate reimbursement to clinicians for providing this intervention.



Studies of other health professionals find a similar pattern. For example, Hu, et al.⁵⁰ reported on the results of a survey that assessed the knowledge, attitudes and activities of 783 dentists, with respect to the 2000 Clinical Practice Guideline.⁹ Most dentists were unfamiliar with the guideline and usually did not follow its recommended steps. These authors concluded that lack of training is a major barrier to adherence. Other studies of dentists and other professional interventions with smokers have yielded similar results.^{51,52} Studies of doctors’ attitudes and practices in other countries yield remarkably similar results. For example, one UK study found that around 20% of family doctors had doubts about the efficacy of NRT and so did not plan to prescribe it.⁵³ Further, this study found that, as in the US, around two thirds of prescriptions for smoking cessation medications were initially suggested by the patient, rather than the doctor. A review of factors influencing providers’ smoking cessation interventions found that although the majority of family doctors do not have negative beliefs and attitudes towards discussing smoking with their patients, a sizeable minority do. As shown in Figure 4, the most common negative beliefs were that such discussions were too time-consuming (42%) and were ineffective (38%). Just over a fifth (22%) of physicians reported lacking confidence in their ability to discuss smoking with their patients, 18% felt such discussions were unpleasant, 16% lacked confidence in their knowledge, and relatively few considered discussing smoking outside of their professional duty (5%), or that this intruded upon patients’ privacy (5%), or that such discussion were inappropriate.⁵⁴ These negative beliefs about smoking cessation counseling likely impact on the chances these doctors’ patients will be advised to use an effective cessation medication.

A small qualitative/quantitative US study of 30 health professionals in 11 states⁵⁵ found that around a quarter of US health professionals believe that nicotine causes cancer and another 10% are unsure. Another basic attitude that was common among the health professionals interviewed was a kind of moral disapproval for needing help to quit smoking. This was expressed by an MD interviewed for the study as follows: “smokers who are committed to quitting shouldn’t need NRT.”

Kozlowski and 18 other experts on tobacco treatment⁵⁶ published a paper on “advice on using over-the-counter nicotine replacement therapy- patch, gum, or lozenge- to quit smoking” that aimed to counter misperceptions on the part of both providers and the public. This paper included a consensus statement that provided simple guidelines for consumers on the most effective ways to use OTC NRT, many parts of which contradict the labeling on the product box (See Appendix A for copy).

Studies of real-life use of both prescribed and OTC NRT suggest that smokers frequently receive little or no advice from doctors or pharmacists on how to best use these products, and so are reliant on the instructions on and inside the box. For example, Shiffman, et al.⁵⁷ analyzed interviews from 993 subjects who had filled prescriptions for patch (n=669) or gum (n=324) about physician behavior when prescribing patch and gum when these were available only by prescription. Eighteen percent did not actually meet with the doctor, 33% received no instructions on the use of the product and 50% were not told about potential side effects. Participants who received no intervention from their physicians were significantly more likely to be abstinent than those participants who received smoking cessation advice and support, likely because physicians offered help to those who most needed it (i.e., were more dependant).

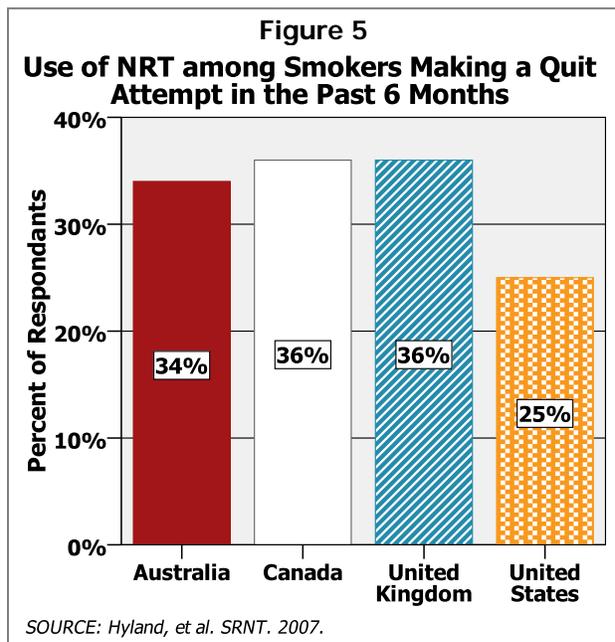
Conclusion 5: Overall, there is a lack of detailed research on providers’ beliefs and attitudes to NRT in the United States. However, the consistent pattern of under-prescribing (compared with Guideline recommendations) and reports of doubts regarding efficacy, safety and lack of time to counsel patients, suggest that a lack of training on the use of NRT and awareness of existing treatment guidelines is widespread among health professionals and consequently represents a barrier to more widespread use of effective tobacco treatment medications.

QUESTION 6: What is the typical pattern of use of tobacco treatment medications?

Hyland, et al.^{58,59} reported on a large representative telephone survey of over 2,000 adult smokers in each of four countries (Australia, Canada, UK, and USA). This study found that 40-45% of smokers in each of these countries had previously tried an approved smoking cessation medicine, although use in the past 6 months was lowest in the US compared to the other countries (25% versus 35% elsewhere) (Figure 5). In all countries, over 50% of previous users had tried the patch and over 25% had tried nicotine gum. In the US, 42% obtain their medication via prescription, 50% OTC and 8% “from a friend”. 61% paid in full, 19% obtained a discount and 20% obtained their medication for free. Sixty percent of US smokers agreed that these medicines make quitting easier (lower than the other three countries), less than 20% disagreed with the statement that “these medications are too expensive”, and 80% disagreed with a statement that “these medications are too hard to get”. However, less than 50% disagreed with a statement that “these medicines might be harmful to health.”

A cohort follow-up component of this study a year later (2003) found that those who believed that the medicines make quitting easier and who believed that they could not quit smoking without medication were more likely to have used NRT.

Shiffman, et al.⁶⁰ described utilization of NRT as indicated by the Current Population Survey (Tobacco Use Supplement) that was administered to just under 30,000 past-year smokers, 43.5% of whom had made a quit attempt in the past year. Thirty-two percent of those making a quit attempt in the past year



had used a medication, with 26% using OTC NRT and 12% also using prescription-only medication. They also pointed to existing evidence of real-world under-dosing with NRT. Thus, although the gum labeling recommends that consumers should use at least 9 pieces per day, in reality average use is 4.1 pieces per day.⁴¹ Similarly, although the label recommends NRT use for 10-12 weeks, most use for less than 5 weeks (85% for gum and 76% for patch).⁶¹ This lower than recommended use is problematic because there is evidence to show that among those trying NRT, under-use leads to poorer smoking cessation outcomes.⁶⁰

Shiffman⁴¹ found that a higher proportion of white smokers use smoking cessation medications, with African Americans and Latinos both having much lower utilization rates (20% using any med. versus 35% for whites). He also found that Black and Hispanic respondents had significantly more negative views of the harmfulness of NRT than did Whites. Other studies have also found lower NRT use by minority smokers.^{62,63} In the Fu, et al. study,⁶³ all participants had equal healthcare benefits for NRT and so affordability is not the only issue. It has been found that physicians are less likely to provide smoking cessation advice for Hispanic smokers,^{64,65} and also that Latino smokers may hold some of the typical anti-NRT beliefs more strongly, such as (a) belief that smoking is a weakness rather than an illness, (b) NRT is mistrusted, and (c) bupropion is widely rejected.⁶⁶

Conclusion 6: The evidence shows that the vast majority of quit attempts do not involve a proven medication, and even when NRT is used it is under-used (too little for too short a time). Smokers' misperceptions about the health risks of NRT appears to be related to underuse of NRT and these problems are magnified in African American and Latino smokers.

QUESTION 7: How frequently do NRT users become addicted to the medication, outside of clinical trials involving intensive behavioral support?

Randomized trials of NRT products have found that a proportion of the ad-lib NRT product users appear to develop some dependence on the product and that this occurs more frequently with the faster-acting nasal spray. One randomized trial involved relatively brief counseling and participants partially paying for the NRT compared the gum, patch, inhaler and nasal spray and defined dependent use as continued use at 15-week follow-up despite advice to cease use of the product at 12 weeks. Continued use of NRT at week 15 was related to rate of delivery of nicotine from the products - 2% for patch, 7% for gum and inhaler, and 10% for spray.²¹

Shiffman, et al.⁶¹ examined the frequency of long term nicotine gum use in a cohort of 2655 current smokers who purchased nicotine gum over-the-counter and enrolled in a clinical efficacy trial that did not involve face-to-face treatment. They found that at the 24-week assessment, 6% of participants reported current use of nicotine gum (i.e. persistent use) and at that point concurrent use with cigarettes was uncommon (2% of original sample). They concluded that OTC marketing of nicotine gum does not appear to have increased use contrary to labeling, nor resulted in patterns of use that should warrant clinical or public health concerns. Hughes, et al.⁶⁷ conducted a similar study by recruiting long-term gum users via newspaper advertisements. They concluded that (a) very few people use nicotine gum for non-cessation reasons, (b) concurrent use of gum and cigarettes is common but involves a small number of cigarettes and pieces of gum per day, and (c) the incidence of dependence on OTC nicotine gum is very small. Hughes, et al.⁶⁸ conducted a prospective telephone and internet survey of users of the nicotine inhaler. They found that although many used inhaler and cigarettes concurrently at some time (43-55%), few used inhaler for non-cessation reasons (4-9%) and few persisted in off label use (8-16%). No participant met ICD-10 criteria for harmful use/abuse and 8 subjects (1.4%) appeared to meet DSM-IV or ICD-10 criteria for dependence on the inhaler. A more recent four-nation study by Hammond, et al found that use of NRT for reasons other than cessation (e.g. reduced smoking) was fairly common, occurring in around a third of users.⁶⁹

Conclusion 7: The evidence from both clinical trials and studies of more naturalistic use of NRT suggests that while transient concurrent use of NRT and cigarettes is common and use for non-cessation reasons occurs, abuse and dependence are uncommon. Extended use

(beyond 12 weeks) is also uncommon, is associated with increased chances of smoking cessation and has not been documented as being harmful in any way. A far greater problem is under-use of NRT (using too little for only a very short duration), as this is associated failure to quit smoking.

QUESTION 8: What environmental factors influence the demand for tobacco treatment medications?

There is good evidence that the demand for NRT is influenced by the price of NRT as well as the price of cigarettes. Taurus, et al.⁷⁰ analyzed pooled cross-sectional time-series scanner-based data for 50 major metropolitan markets in the United States covering the period between the second quarter 1996 and the third quarter 1999, and concluded that decreases in the price of NRT and increases in the price of cigarettes lead to substantial increases in per-capita sales of NRT products.

Taurus, et al.⁷¹ conducted a similar analysis with an increased focus on advertising in the statistical modeling. They concluded that measures to increase peoples' awareness of NRT products through advertising, measures to decrease the price of NRT, and measures to increase the price of cigarettes are an effective means to increase the use of NRT.

Metzger, et al.⁷² analyzed pharmacy sales data to assess the impact of smoke-free workplace legislation, and an increase in cigarette taxes on demand for OTC NRT in New York City. They observed increases in NRT product sales during the weeks of the cigarette tax increases and the smoke-free workplace law. Pharmacies in low-income areas generally had larger and more persistent increases in response to tax increases than those in higher-income areas.

NRT was sold only by prescription until 1996. At that time, some products became available OTC and the rationale for this was based on the good safety and efficacy data on the products combined with a desire to increase access. Shiffman, et al.⁷³ analyzed sales and marketing data to compare the use of nicotine medications before and after non-prescription sales, and to estimate the impact of non-prescription sales on quit rates. They found a 150% increase in NRT sales after products became available OTC and concluded that the broader availability and promotion of nicotine gum and patch substantially increases the number of smokers availing themselves of the medications. This increased use was estimated to contribute substantially to the number of former smokers in the United States. Not every study has found that a switch to OTC is associated with increased NRT use. Thorndike, et al.⁷⁴ examined NRT use before and after the switch to OTC status in Massachusetts using the 1993-1999 Massachusetts Tobacco Use Survey data. They observed no increase in Massachusetts smokers' rates of using nicotine replacement therapy, making a quit attempt, or stopping smoking after nicotine replacement therapy became available for OTC sale and commented that there appear to be other barriers to the use of nicotine replacement therapy besides visiting a physician, especially among minority smokers. Among the possible factors influencing the results of this study were (a) unusually high NRT use in Massachusetts prior to the OTC switch, possibly associated with their existing Comprehensive Tobacco Control Program, (b) possible elevation of pre-OTC data by the 1992 surge in patch use following its launch in 1992, (c) launch of bupropion in 1997 and (d) fewer health insurance plans covering NRT after its switch to OTC status.

Shiffman et al.⁷⁵ reported on smoking cessation outcomes for the nicotine gum and patch, comparing those treated in an OTC setting with those prescribed by their physician. They concluded that smoking cessation rates achieved with nicotine gum and patch under OTC conditions were as good as those under real-world prescribing conditions.

Shiffman and Sweeney⁷⁶ reviewed the data on the Rx to OTC shift for NRT and concluded that OTC availability of NRT increased access to and utilization of NRT and that OTC NRT has been used safely and effectively, without substantial misuse or abuse, and with continued physician engagement and wide access to proven behavioral treatment.

Reed, et al.⁷⁷ used data from the 1996 California Tobacco Survey to compare the rates of nicotine replacement therapy (NRT) use and smoking abstinence in California for each month during a period immediately preceding and immediately following the OTC availability of nicotine gum and patches. They

found a significant increase in the fraction of smokers using the patch and gum immediately following their availability OTC. There was also a significantly higher proportion of smokers reporting abstinence with gum use and a significant increase in reported abstinence with patch use during the period of time immediately following the availability of these products without a prescription. The results of this study suggest that removing the prescription status of NRT products resulted in an immediate increase in quit attempts and smoking abstinence with the use of nicotine gum or patches.

Hughes et al.²³ conducted a meta-analysis of studies of OTC NRT and concluded that OTC NRT is pharmacologically efficacious and produces modest quit rates similar to that seen in real world prescription practice. The updated 2008 Clinical Practice Guideline¹³ also concluded that OTC nicotine patch is effective and its use should be encouraged.

The updated 2008 Clinical Practice Guideline¹² also concluded that providing smoking cessation treatments (both medication and counseling) as a paid or covered benefit by health insurance plans has been shown to increase the proportion of smokers who use cessation treatment, attempt to quit, and successfully quit. Many insurance plans have a formal or informal policy of not covering OTC medicines. There is no valid basis for such a policy, which is presumably designed to cut costs (reluctance to set a precedent for covering OTC medications) rather than improve health. Insurance plans should therefore cover NRT products regardless of their Rx/OTC status. West, et al.⁷⁸ used sales and survey data to examine the impact of full coverage (i.e. at no cost or co-pay only) of NRT and bupropion within the UK health service combined with NRT becoming available on a General Sale basis (like US OTC). They found that the proportion of smokers using medicines to support quit attempts more than doubled from 8-9% in 1999 to 17% in 2002. There was no increase in the proportion of smokers making quit attempts so the effect was solely on the proportion of quit attempts aided by medication (which increased from 28% to 61%). The nicotine lozenge was introduced during the study period and seemed to add to the total medication use rates rather than cannibalize the share of other medications.

Availability of NRT on an OTC basis presumably increases use of these medications partly by making them easier to access – no longer requiring a trip to the doctor to obtain a prescription. Insurance coverage presumably increases use by lowering the financial barrier. One method of reducing both the physical barrier (e.g. not involving a doctor or pharmacy visit) and the financial barrier is to provide NRT for free via a telephone “quitline”. New York state department of health have carried out a number of evaluations of this procedure. These evaluations have found that providing NRT for free via a telephone “quitline” stimulates high demand for NRT, together with good subsequent utilization and quit rates. For example, Miller, et al.²⁵ reported on the outcomes of over 34,000 eligible smokers who were provided with 6 weeks of nicotine patches after screening via a telephone quitline. Six months later, they assessed smoking status of 1305 randomly sampled NRT recipients and a non-randomly selected comparison group of eligible smokers who, because of mailing errors, did not receive the treatment. Of individuals contacted at 6 months, more NRT recipients than comparison group members successfully quit smoking (33% vs 6%), and this difference remained significant after adjustment for demographic factors and amount smoked. Those who received a counseling call were more likely to stop smoking than those who did not (246 [38%] vs. 189 [27%], $p=0.001$). With the conservative assumption that every 6-month follow-up survey non-respondent continued to smoke, the stop rate among NRT recipients was 20%. Most (64%) recipients were non-white, foreign-born, or resided in a low-income neighborhood. It was concluded that easy access to a free cessation medication distribution program via a telephone quitline was very effective for diverse populations could help many more smokers to stop smoking.

A study by Bauer, et al.⁷⁹ presents results from two population-based promotions for free cessation products used to induce smokers to call the New York State Smokers' Quitline. The first promotion was a press announcement urging smokers to call the quitline to get a voucher for a free 2-week supply of nicotine patches or gum. The second promotion involved comparing response to two newspaper advertisements for the quitline, one of which offered a free stop smoking guide and one that offered the guide plus a free stop smoking aid called Better Quit (BQ). The NRT voucher promotion increased median call volume 25-fold compared to pre-promotion levels, whereas the BQ newspaper advertisement increased median call volume 2-fold compared to a newspaper advertisement for the quitline. Seventy percent of follow-up survey respondents said that they had redeemed the NRT voucher and used the

medication to try to quit smoking. Twenty-two percent reported they were no longer smoking, compared with the 12 percent among a comparison group of quitline callers who had not received the free NRT voucher (odds ratio = 1.77; 95% confidence interval: 1.17-2.68). There was no difference in quit rates between those that were sent the BQ cigarette substitute and those that did not get the BQ. This study shows that offering a free 2-week voucher for NRT is a cost-effective method to increase calls to a stop smoking quitline and may also increase the odds of quitting for those who get the free NRT. A number of other studies (e.g., An, et al.,⁸⁰ Schwartz, et al.⁸¹) have found similar results demonstrating that making (even only a two-week supply) NRT available for free via a telephone counseling service generates a substantial increase in call volume and in the number of people accessing the medication and successfully quitting smoking.

The evidence showing increased demand for NRT when it is covered by insurance or provided free via quitlines suggests that cost is an important barrier to use. Unlike cigarettes, which are generally sold in packs approximating a daily dose, NRT is most frequently sold in packs designed to last for two weeks, requiring a large initial expenditure (typically \$40-\$60). Although some smaller sized packs and cheaper generic brands are now available, bringing the initial price down to around \$20-\$40 per pack, this is still many times more expensive than cigarettes, and smokers on a low income will struggle to cover the initial and recurring outlay.

Conclusion 8: The relative price of cigarettes, the cost of the NRT, the presence of legislation providing smoke-free environments, media advertising and campaigns, OTC availability, insurance coverage and free NRT via telephone quitlines are all factors that influence smoker demand for tobacco treatment medications.

QUESTION 9: Which characteristics of the treatment medications influence their use by smokers?

Existing data on use of tobacco cessation medications suggests that in addition to the medicine being available OTC, ease of use, and good side effect profile are important determinants of the number of people who will use the product. For example, whether one examines sales data in the US⁸² or stated preferences when products are offered to smokers in a neutral manner,⁸³ the nicotine patch is the preferred product even though it does not have better efficacy in clinical trials than other products. Conversely, the nicotine nasal spray that has at least as good outcomes in clinical trials is used by only a small fraction of the number using the patch, even in countries like the UK where it is also available OTC. Also, in studies where smokers are randomly allocated to one of the products, compliance is significantly better with the patch than the nasal spray.⁸⁴

Since its initial launch over 20 years ago, users of the nicotine gum have complained about its taste and this undoubtedly affected both compliance and the overall demand as word-of-mouth feedback spread that this is a product with an unpleasant taste. This was not initially perceived as a problem and if anything was seen as perhaps a good thing to prevent young people from using the product. Over time, it was realized that abuse of the product was extremely rare, whereas poor compliance was a clear barrier to its utility in helping smokers quit. More recently, more palatable flavors and formulations have been introduced and this should improve consumer demand.

While taste and initial sensory aspects have a large influence on initial reaction to and use of a product, longer term use and efficacy for smoking cessation are more closely determined by the dose and speed of nicotine delivery, with higher dose and faster delivery products having particular advantages for highly dependent smokers.¹² The difficulty for pharmaceutical companies is to develop a faster-delivery, high dose product with an acceptable side-effect profile, that will also not be frowned upon by regulators (and perhaps required to have prescription-only status) as it will also be more dependence-forming than the nicotine patch.

As recently pointed out by Kozlowski, et al.⁵⁶ part of the problem here is the tendency to compare the effects of the smoking cessation medicine with no or placebo treatment, when the more appropriate comparator is continued smoking of cigarettes, involving frequent delivery of 4000 toxins to the lungs along with rapid high-dose nicotine. As Kozlowski, et al.⁵⁶ have pointed out, tobacco products that

provide the most addictive nicotine delivery are readily available without detailed instructions in use and without detailed warnings. In contrast, much safer NRT products come with detailed warnings, cautions and instructions that may seem threatening to some, especially compared to the brief warnings on tobacco product labels. The regulation of NRTs ensures that they meet safety, efficacy and quality standards, yet the warning language and restrictions on use that accompanies them may give a false sense of risk to smokers and impede their ability to make sound comparative risk judgments about using these products to quit smoking. The current labeling and use restrictions placed on NRT may contribute to the widespread public misunderstanding of the harmfulness of these products.

The labeling and use restrictions also have an impact beyond the immediate impression given to the individual customer. It also affects health systems such as health insurance companies or quitlines who may be hesitant to provide or cover combination or long term NRT while the labeling warns against such use, and quitlines may be less inclined to provide the nicotine nasal spray or inhaler because of their prescription-only status.

Conclusion 9: Tobacco treatment medications that are easy to use and have a good side-effect profile are used much more frequently by smokers. Speed and dose of nicotine delivery may be important for use past the initial stages and for efficacy, but many smokers will either not initiate or will cease use of a product early in treatment if it is not easy to use, with mild side effects. For oral products, taste is a factor and for all products relative perceived harmfulness (in comparison to smoking) – as indicated in the product labeling, is a factor influencing use or non-use by smokers.

QUESTION 10: What are the barriers to use of prescription-only non-nicotine smoking cessation medications?

Bupropion and varenicline are the two currently approved forms of prescription-only, non-nicotine medications to aid smoking cessation.¹² Unlike NRT, which delivers a drug (nicotine) all smokers have already been exposed to, these medications (which come in pill form), involve the tobacco user in taking an entirely new drug. Serious adverse events with these medications are rare (e.g. seizure risk of <1/1000), but issues requiring a medical training (drug-drug interactions, co-administration with other drugs affecting seizure threshold etc) are relevant to their use and so they will most likely and appropriately remain as prescription-only medicines. While this may limit access to some extent, creative ways of providing these medications have been developed (e.g. mailing to patients using a comprehensive screening for potential contraindications and using a standing order protocol). Clinicians report that patients prefer the once-per-day form of Bupropion XL to the twice-daily (SR) form used in its marketing for smoking cessation (Zyban). While these medicines have suffered from inflated perception of risk relative to the risks from smoking, sometimes stemming from media coverage of unproven adverse events, their prescription status offers the opportunity for the doctor to correct any misinformation. The main barrier to their use stems from lack of insurance coverage and lack of availability of samples. This means that a sizeable section of the smoking population has difficulty affording these medicines and doctors have no way of offering samples to patients under financial hardship. Samples allow the patient to try the medicine and see if they can tolerate its side effects prior to spending a considerable amount of money for the first box (e.g. around \$130 for varenicline).

Conclusion 10: Bupropion and varenicline are both safe and effective prescription-only, non-nicotine aids for smoking cessation. Perceptions of their risks are also exaggerated relative to risks from smoking. Their prescription-only status is appropriate and so the main barriers to use are lack of insurance coverage, lack of samples, and availability only in relatively expensive packs (e.g. \$130 per box).

SUMMARY OF CONCLUSIONS

1. The evidence is very clear that use of Nicotine Replacement Therapy is a safe, effective method of helping smokers to quit. Although a small proportion of users may transfer their nicotine dependence from cigarettes to NRT, the health risks from nicotine are so much lower than those of smoking, that this should not be a deterrent to NRT use. There is now strong evidence that longer term (>14 weeks) use of combined NRT products (e.g. patch plus gum) yields better smoking cessation outcomes.
2. The evidence supports the safety and effectiveness of NRT when used with minimal support and suggests that the results from clinical trials are a reasonable guide to the performance of these medications in more typical “real world” (including OTC) contexts.
3. NRT is safe and effective in cardiovascular patients. The evidence on safety and efficacy of NRT in adolescents and pregnant women, while somewhat reassuring, is not sufficiently clear to suggest the need for major changes from the current situation in which these groups are recommended to seek the advice of their medical doctor prior to embarking on NRT use.
4. Studies of public perception of NRT suggest widespread misconceptions and myths about the harms and benefits of nicotine replacement therapy, characterized by an exaggerated concern about the safety of NRT, skepticism about the effectiveness of NRT, and over-optimism among smokers about their likelihood of success in quitting without use of any aid.
5. There is a lack of detailed research on providers’ beliefs and attitudes to NRT in the United States. However, the consistent pattern of under-prescribing (compared with Guideline recommendations) and reports of doubts regarding efficacy, safety and lack of time to counsel patients, suggest that a lack of training on the use of NRT and awareness of existing treatment guidelines is widespread among health professionals and consequently represents a barrier to more widespread use of effective tobacco treatment medications.
6. The vast majority of quit attempts do not involve a proven medication, and even when NRT is used it is under-used (too little for too short a time). Smokers’ misperceptions about the health risks of NRT appear to be related to underuse of NRT and these problems are magnified in African American and Latino smokers.
7. The evidence from both clinical trials and studies of more naturalistic use of NRT suggests that while transient concurrent use of NRT and cigarettes is common and use for non-cessation reasons occurs, abuse and dependence are uncommon. Extended use (beyond 12 weeks) is also uncommon, is associated with increased chances of smoking cessation and has not been documented as being harmful in any way. A far greater problem is under-use of NRT (using too little for only a very short duration), as this is associated failure to quit smoking.
8. The relative price of cigarettes, the cost of the NRT, the presence of legislation providing smoke-free environments, media advertising and campaigns, OTC availability, insurance coverage and free NRT via telephone quitlines are all factors that influence smoker demand for tobacco treatment medications.
9. Tobacco treatment medications that are easy to use and have a good side-effect profile are used much more frequently by smokers. Speed and dose of nicotine delivery may be important for use past the initial stages and for efficacy, but many smokers will either not initiate or will cease use of a product early in treatment if it is not easy to use, with mild side effects. For oral products, taste is a factor and for all products relative perceived harmfulness – (as indicated in the product labeling), is a common barrier to effective use.
10. Bupropion and varenicline are both safe and effective prescription-only, non-nicotine aids for smoking cessation. Perceptions of their risks are also exaggerated relative to risks from smoking. Their prescription-only status is appropriate and so the main barriers to use are lack of insurance coverage, lack of samples, and availability only in relatively expensive packs (e.g. \$130).

POLICY IMPLICATIONS

The conclusions of this review of barriers to increased use of tobacco treatment medications not only serve to underline the severity of the problem, but also point towards a number of potential policy solutions. Some of these solutions involve policy recommendations that have been made previously by other organizations. Where this is the case, this report will briefly draw a link between the barrier and the recommendation and will cite other authorities making a similar recommendation. However, we believe this review provides additional support for those recommendations and also points to additional policy solutions that may not have been recommended consistently before.

Policy must always exist in a context and so it is worth considering the recent context relevant to this issue in the United States. Cigarette smoking prevalence has continued to decline, albeit with some periods of plateau, over the past 25 years. However, although per capita cigarette consumption has fallen from its peak of almost 3000 (per adult per year) in the mid 1970s to less than 1300 in 2006, total cigarette consumption in the United States was actually similar (around 383 billion) in 2006 to what it was in 1955 (around 376 billion).^{85,86} Every year this vast volume of cigarette smoking causes hundreds of thousands of premature deaths and millions of cases of avoidable illness.

Another important part of the context is the pending legislation to grant the Food and Drug Administration authority to regulate tobacco products.⁸⁷ If this legislation were to be approved, it would mean that the same government administrative unit would be responsible for regulating tobacco products and tobacco dependence treatment pharmaceuticals. This may present a new opportunity to consider the regulation of all nicotine delivery products from a public health perspective.

An important recent driver of interest in quitting smoking has been the passing of legislation at state and municipality levels banning smoking in public places. This legislation has the effect of markedly restricting the number places a smoker may smoke, and makes smoking a much more inconvenient pastime, in addition to highlighting the social unacceptability of exposure to tobacco smoke pollution (ETS/SHD).⁸⁸ However, the tobacco industry continues to try to adapt to this environment. Over recent years, the industry has been particularly active in developing novel products that aim to be perceived as being less harmful to health. One of the recent developments has been that the major cigarette manufacturers have entered the smokeless tobacco market. Many public health experts are concerned that a major reason for this development is to try to provide customers with a tobacco product to use in smoke-free environments, with a resumption of smoking once the person is in an environment that permits smoking.^{89,90} There is particular concern that tobacco companies can relatively quickly move to producing and marketing new products with little regulatory oversight, whereas pharmaceutical companies are required to submit very large amounts of data in order to make even minor changes to product packaging, labeling, indications or flavor. The current uneven regulatory playing field facilitates the tobacco industry's efforts to keep people using tobacco and acts against the public health.

POLICY RECOMMENDATIONS

1. Fund Statewide and national Comprehensive Tobacco Control Programs as recommended by the Centers for Disease Control (2007).

Numerous organizations and expert review groups have concluded that adequate funding for comprehensive tobacco control is a highly efficient use of health funding.^{1,91,92} These programs address tobacco use at all levels, including mass media campaigns to educate adults and children about the dangers of tobacco, and encourage cessation. These programs consistently stimulate increased attempts to quit smoking and increased use of treatment services, including effective pharmacotherapy.

2. Increase the excise tax on tobacco products.

Increases in the real price of tobacco consistently results in increased quitting activity,⁹³ and results in a more favorable relative price of tobacco treatment pharmaceuticals. This is one of the most potent tools available to policy makers for reducing tobacco consumption and encouraging smokers to try to quit.⁹¹ However, it must be accompanied by attempts to prevent tax-avoidance (via online purchasing, cross-border smuggling etc).⁸⁷

3. Implement legislation that comprehensively bans smoking in all indoor public places and workplaces (i.e. including bars, restaurants and casinos).

In addition to reducing public exposure to tobacco smoke pollution, smoke-free air legislation typically results in a marked reduction in cigarette consumption and an increase in quit attempts,⁷¹ including quit attempts using FDA-approved medicines.

4. Require federal, state and private health insurance plans to provide comprehensive coverage for tobacco dependence treatment, including effective counseling and both prescription-only and OTC smoking cessation medicines.

Cost is a major barrier to use of effective tobacco treatment medicines. These highly cost-effective medicines should be covered in much the same way as other standard treatment and preventative medicines are covered (e.g. drugs for the treatment of hypertension, diabetes and asthma). The rationale and essential components of such coverage have been outlined in detail in document published by the Campaign for Tobacco Free Kids^{94,95} and the link between such coverage and other health systems policy changes have also been described in detail.^{96,97,98}

5. Ensure that tobacco use assessment and treatment interventions are adequately covered in the training curricula for all health care professionals, and that the evidence-based Guideline on the Treatment of Tobacco Use and Dependence (and its revisions) is widely disseminated and adopted as a critical part of continuing professional education by all health professionals.

Effective treatment guidelines exist^{9,12} and effective models of training health professionals in both the knowledge and skills required for tobacco treatment have been developed in the USA and abroad.^{99,100,101,102,103,104,105} Some specific specialty groups have produced explicit consensus statements on the need for adequate education and experience of tobacco treatment (e.g., Bernstein, et al.¹⁰⁶) and others have highlighted the need for better basic training.¹⁰⁷ There needs to be a more widespread acknowledgement that tobacco treatment should be adequately covered (and tested) in medical, nursing and other health professionals training (and professional exams), and this should be required for course accreditation.

6. Develop and fund a National Smoking Cessation Action Plan with adequate infrastructure to provide the full range of treatments (healthcare provider, medication, quitline, online, and community-based clinics) in a freely-available and seamless, coordinated system of care management.

Whereas some countries (e.g., the UK)^{108,109} have implemented national smoking cessation services, the United States has not, resulting in a situation in which existing services are fragmented,

inconsistent and vary considerably from state to state. The Subcommittee on Cessation of the Interagency Committee on Smoking and Health (ICSH) produced recommendations designed to substantially increase rates of tobacco cessation in the United States. The subcommittee's report, *A National Action Plan for Tobacco Cessation*, outlines 10 recommendations and includes both evidence-based, population-wide strategies designed to promote cessation (e.g., a national quitline network) and a Smokers' Health Fund to finance the programs (through a \$2 per pack excise tax increase).¹¹⁰ Implementation of this action plan would result in more quit attempts and greater use of NRT as a part of those quit attempts.

Recommendations 1-6 above are designed to broadly increase demand for smoking cessation, and access to treatment, with a high likelihood that this would simultaneously lead to increased use of effective medications. Most of these recommendations have been made before by various government and advisory groups. The following recommendation focuses more specifically on the ways that the products themselves are publicized and sold, and the nature of the accompanying consumer advice. These recommendations are a response to the evidence of widespread misconceptions and myths about the harms and benefits of nicotine replacement therapy, characterized by an exaggerated concern about the safety of NRT. Part of those exaggerated concerns stem from the labeling on the products and restrictions on their availability and use.

7. Develop and implement a set of principles for FDA regulation of smoking cessation medicines that aim to maximize the positive public health impact of these products and minimize the harmful effects of tobacco.

The mission statement of the FDA states that:

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

However, with regards to nicotine replacement products, we are currently in a situation in which the best science-based treatment recommendations contradict some of the information required by FDA and provided on the labeling of the products. For example, both the 2000 and 2008 versions of the Clinical Practice Guideline on the Treatment of Tobacco use and Dependence recommended combining the patch with another NRT product (e.g. the gum) as a safe and effective treatment, whereas the labeling on both products warns against the combining of NRTs.^{9,12} This problem has become so acute that experienced tobacco treatment scientists and clinicians have had to produce and publish their own consensus statements for consumers on the use of these products, partly because of concerns that the labeling of the products does not provide the best advice and causes underuse due to an impression portrayed in the labeling that the medication itself is relatively dangerous.⁵⁶ In addition, there are concerns that the labeling, indications, instructions for use, restrictions on pack size, and restrictions on place of sale all act as barriers to access and use of NRT. "Off-label" prescribing is common practice by MDs. However, a large proportion of tobacco treatment medications are sold OTC or with minimal contact with a prescriber. In those situations, the patient is more dependent on labeling, and so it is most important that labeling follow best practice.

Some specific recommendations for changes in the way NRT products are supplied to consumers are as follows:

- (a) Withdraw the conditions that restrict distribution and sale of OTC NRT to drugstores and other supermarkets selling OTC drugs, and allow the sale of NRT in every place that tobacco is currently sold.
- (b) Allow the sale of the nicotine inhaler and nicotine nasal spray as OTC products, available without a prescription, (as they are in many other countries).

- (c) Encourage, rather than prohibit, sale of affordable “trial size” or “one-day packs” of NRT, that can be priced to compete with cigarettes. Consumers typically have to purchase a 1-2 week supply at once, which can be prohibitively expensive.
- (d) Include on the labeling, statements comparing health the risks from NRT use with the risks from continued tobacco smoking.
- (e) Amend the statements on the labeling recommending against use along with other NRT products.
- (f) Amend the guidance on duration of use to allow longer-term use as necessary to successfully quit smoking
- (g) Allow specific use indications as follows (as is the case in many other countries):
 - to treat nicotine withdrawal symptoms and craving during a period of temporary tobacco abstinence
 - to assist the smoker in reducing their tobacco consumption prior to quitting

These recommendations are consistent with these resulting from a recent “National Consumer Demand Roundtable” which recommended “lowering the bar” for consumers to try or experiment with effective treatments by making them more accessible, for a wider range of potential.⁹⁷

As the evidence for public misunderstanding of the risks of smoking cessation medicines increases (e.g., Shiffman⁴¹), there is an increasing need for implementation of new principles designed to guide the FDA’s regulation of smoking cessation medications.¹¹¹ Recommendations for such guiding principles that would help ensure such regulations benefit public health are outlined in Appendix B.

CONCLUSION

This review has sought to identify barriers to consumer demand for effective FDA-approved tobacco treatment medications, and to suggest potential policy solutions. It identified widespread misconceptions about the harms and benefits of nicotine replacement therapy, characterized by an exaggerated concern about the safety of NRT and skepticism about the effectiveness of NRT. Many of the recommended solutions are consistent with those that have previously been recommended to reduce tobacco consumption generally. In addition, broadening indications and access conditions, and altering labeling for tobacco treatment products may enable these products to help more tobacco users to become tobacco-free. There is an urgent need for this policy action, because every additional year that hundreds of billions of cigarettes are smoked in this country results in hundreds of thousands of premature deaths and millions of cases of avoidable illness.

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APPENDIX A:

STATEMENT FOR CONSUMERS ON THE MOST EFFECTIVE WAY TO USE OTC NRT

Excerpted with permission* from: Kozlowski LT, Giovino GA, Edwards B, et al. Advice on using over-the-counter nicotine replacement therapy-patch, gum, or lozenge-to quit smoking. *Addict Behav.* 2007 Oct; 32(10):2140-50.

Table 1: Outline of statement to consumers

1. NRT is one good tool to help you quit smoking. But NRT can't do all the work for you—you have to help—and it is not the only tool to help you stop smoking.
2. Don't worry about the safety of using NRT to stop smoking: NRT is a safe alternative to cigarettes for smokers.
3. Do be cautious about using NRT while pregnant.
4. NRT is less addictive than cigarettes and it is not creating a new addiction.
5. Stop using NRT only when you feel very sure you can stay off cigarettes.
6. If the amounts of NRT you are taking do not help you stop smoking, talk with your health care provider about using (1) more NRT, (2) more than one type of NRT at the same time, (3) other smoking cessation medicines at the same time, or (4) telephone or in person advice on quitting tips.
7. If NRT helps you stop smoking, but you go back to smoking when you stop using NRT, you should seriously think about using NRT again the next time you try to stop smoking.
8. Make sure you are using the gum or lozenge in the best way:
 - Park the gum between your teeth for 2–3 min between chews—fast chewing doesn't allow the nicotine to be absorbed from the lining of the mouth and can cause nausea.
 - Don't drink anything (including coffee, orange juice, beer, wine, or sodas) for at least 15 min before and nothing while using nicotine gum or lozenge, so your mouth can absorb the nicotine.
 - Make sure you get the right amount of nicotine — people who smoke more than 10 cigarettes per day should use a 4 mg piece of gum or lozenge.
9. Make sure you are using the patch in the best way:
 - If you can't stop having a few cigarettes while using the patch, it is best to keep the patch on. Don't let a few slips with cigarettes stop you from using the patch to quit smoking.
 - You may need to add nicotine gum or lozenges to help get over the hump or you may need to use more than one patch at a time. Talk to your healthcare provider about this.
10. If the price of NRT is a concern, try to find “store brand” (generic) NRT products which are often cheaper than the brand name products.
11. Do whatever it takes to get the job done—it is not a weakness to use medicine to stop smoking.

“NRT” is Nicotine Replacement Therapy for helping tobacco users quit. NRT products include the nicotine patch, gum and lozenge, and these products are sold “over-the-counter” (OTC) without a healthcare provider's prescription. The nicotine in these products replaces, to some degree, the nicotine from cigarettes in a safe form to help smokers stop smoking. Reading NRT package labels and inserts gives important information about what it is and how it works. The makers of NRT are under strict rules on what can and cannot be written on the NRT label about how to use NRT.

If you are thinking about using NRT, you probably have some questions and an expert may not be on hand to answer them. To help smokers get all the answers they need, a group of smoking research experts and clinical experts wrote this statement containing some of the most helpful and important facts you need to know about using NRT. This statement has not been approved by the FDA (Food and Drug Administration) or by any other regulatory agency; but it does represent the judgment of research and clinical experts. If you are able to consult with your health care provider on these issues, we advise that you do so, knowing that there are some NRT products and other tobacco cessation products available only by prescription.

* The statement is written for smokers who use or who are thinking of using over-the-counter (OTC) Nicotine Replacement Therapy (NRT) but is also relevant for individuals using other forms of tobacco (e.g., pipes, cigars, smokeless tobacco) (Table 1). Note that in several countries, all NRT is OTC. We hope that policy makers and health care professionals will read and make use of the information in the statement, because it addresses widespread misunderstanding of NRT. We encourage health communication specialists to use this statement to help develop communications on NRT use. We support the dissemination of this statement for non-commercial purposes on multiple websites or photocopying this statement for distribution, provided credit is given to the source and a link is provided to the journal home page at <http://www.sciencedirect.com/science/journal/0306460>.

1. *NRT is one good tool to help you quit smoking. But NRT can't do all the work for you—you have to help—and it is not the only tool to help you stop smoking.*

You could be disappointed if you think using NRT or anything else will make quitting smoking easy. But using NRT could make quitting easier by reducing your cravings or the bad feelings you have when you stop smoking. Like other tools, NRT can help you—if you are also willing to put some work into it. Not everyone will find NRT helpful. Keep in mind that there are other tools available for stopping smoking. You can try other NRTs by prescription such as the oral inhaler and the nasal spray or non-nicotine medications in tablet form such as bupropion or Varenicline (Chantix). You also can talk to your health care provider, call your state telephone quit-line, or call 1-800-QUITNOW for tips on quitting.

2. *Don't worry about the safety of using NRT to stop smoking: NRT is a safe alternative to cigarettes for smokers.*

Studies show that NRT is a safe alternative to cigarettes for smokers, and DOES NOT cause cancer or heart attacks, even for smokers who already have had heart attacks or heart disease. Also, nicotine is not the really dangerous chemical in cigarettes. Cigarette smoke contains many harmful chemicals, and it is these, not nicotine, that are responsible for the heart attacks, cancer, and lung disease. The risks of cigarette smoking are much greater than the risks of NRT. Cigarette smoking causes suffering (such as breathlessness, difficult breathing or pain from cancer or heart disease) and, in the end, can cause early death in half of long-term smokers.

NRT has been found to be very safe for nearly every user, yet some smokers and even some health care workers have mistaken health concerns about NRT. Some people think that the nicotine patch is dangerous for heart patients, but this is not true.

Nicotine and thus NRT does not cause cancer, but some recent studies suggest that it might be better for those who are undergoing treatment for cancer to stop smoking without using NRT. Those diagnosed with cancer should talk with their doctor about whether they should prefer using an FDA approved non-nicotine stop smoking medication (e.g., bupropion [Zyban] or varenicline [Chantix] over NRT.

If you have just had some serious new heart or heart-related problem (for example, heart attack or stroke) within the past 4 weeks, NRT is likely safe to use at that time, but, under these circumstances, you should talk with your health care provider about taking this or any medication. Cigarettes should clearly be avoided just after a heart problem, and NRT, especially the short-acting gum or lozenge, has been used to help individuals with recent heart problems who are having trouble staying off cigarettes. Know that cigarette smoking is very dangerous compared to NRT and you should be avoiding smoking. For those who have not just had a new heart problem and have longer-term heart problems, NRT has been found to be safe to use.

NRT packages come with many warnings and directions that can lead a person to believe that NRT is far more risky than it actually is. It is a mistake to think that any NRT product is as dangerous as cigarettes. NRT does not kill, it saves lives!

3. *Do be cautious about using NRT while pregnant.*

Some studies suggest that pregnant women should try to stop smoking WITHOUT the use of NRT, if they can. It is very important for the health of the unborn baby to stop smoking cigarettes. If you can quit smoking without NRT, that is great. If you believe that you need NRT to stop smoking during pregnancy, talk to your health care provider; it may still be useful to get you off cigarettes. After the birth of the child, it is still very important for a mother not to smoke, and for NO ONE to smoke around the child.

4. *NRT is less addictive than cigarettes and it is not creating a new addiction.*

Some smokers worry about becoming addicted to NRT or becoming 'hooked on' the gum, lozenge, or patch. While it is true that the nicotine in NRT products is addictive, smokers are already addicted to nicotine—they get a lot more of it from each cigarette they smoke than from any NRT product.

Smokers usually do not get as much nicotine from NRTs as from cigarettes, nor do they find NRT as enjoyable to use as cigarettes. This is because breathing in smoke through the lungs gives the brain a rush of nicotine while NRT gives nicotine more slowly through the skin or lining

of the mouth. In fact, most smokers don't use enough NRT to get all the help they could to stop smoking. While some smokers could find it hard to stop using NRTs because of the nicotine in these products, there are two important things to remember: first, even using a NRT for a very long time is much less harmful to health than smoking for the same amount of time; second, stopping an NRT is not likely to be as hard as stopping smoking.

5. *So, how long should you use NRT?*

NRT product labels say that the product should be used for 8 or 12 weeks, depending on the product. For some smokers, this is enough time to stop smoking for good. Some smokers do not need to use NRT that long to stop smoking. Other smokers may need to use NRT for several months or even years to stay off cigarettes. If NRT is helping you not smoke, we suggest you do not even think about cutting down on it unless (a) you believe you have a side-effect from NRT or (b) you have 14 days in a row with no cravings or withdrawal or near slips back to smoking. Using NRT longer than 8 to 12 weeks is not dangerous. Going back to cigarettes is very dangerous and could kill you! In fact, it is a common problem with NRT, that people don't even use it for the whole recommended 8–12 week period. We suggest you stop using NRT only when you feel very sure you can stay off cigarettes. If it ever comes down to a choice of using NRT or returning to smoking, stay on the NRT. A good rule of thumb is that if you are able to easily resist smoking without any cravings in situations that would have made you smoke in the past, you are ready to stop the NRT.

6. *If the amounts of NRT you are taking do not help you stop smoking, talk with your health care provider about using (1) more NRT, (2) more than one type of NRT at the same time, (3) other smoking cessation medicines at the same time, or (4) telephone or in person advice on quitting tips.*

Even though the NRT packages say you should not use more than one NRT, most experts agree that, for some smokers, using more than one type of NRT product at the same time can be helpful in stopping smoking and is safe. The patch, for example, gets nicotine to your brain very slowly but does so for many hours. Nicotine gum and lozenge get nicotine to your brain faster than the patch (but not as fast as cigarettes) but they deliver nicotine for short periods of time. Nicotine gum or lozenge can be useful to increase nicotine levels at those times when it is very hard to keep from smoking while using the patch alone. Instead of smoking a cigarette when you are wearing the patch, try a piece of the nicotine gum or the lozenge to get over the urge first. These urges to smoke do not last very long. In using more than one NRT product at the same time, pay attention to how you are feeling—your own reactions can be a guide to whether you are getting too little nicotine or overdoing it. Prescription smoking cessation medicines can be used with NRT; but you need to talk with a health care provider about a prescription and whether using that medicine with NRT is a good idea for you.

7. *If NRT helps you stop smoking, but you go back to smoking when you stop using NRT, you should seriously think about using NRT again the next time you try to stop smoking.*

Many medicines need to be used over and over again to deal with health problems that do not go away completely. For problems like asthma, diabetes, and high blood pressure, medicine often needs to be taken for a long time—not just a few weeks. Just as an asthma medication that helped an asthma attack before is likely to help again, NRT is likely help a smoker stop again if it was helpful before.

Some smokers keep going back to cigarettes after quitting for a time. If that happens to you, you should try to stop smoking again as soon as you can and use ways or tools that helped you quit before. If NRT helped you stay off cigarettes, even for a few days, definitely think about using it again. New NRTs that work better and are more appealing may be available since the last time you quit. If NRT use was not that helpful to you, look for other ways to quit smoking but make sure you were using enough NRT and used it in the best way the first time before you give up on it.

8. *Make sure you are using the gum or lozenge in the best way:*

- Park the gum between your teeth for 2–3 min between chews — fast chewing does not allow the nicotine to be absorbed from the lining of the mouth and can cause nausea.

- Do not drink anything (including coffee, orange juice, beer, wine, or sodas) for at least 15 min before and nothing while using nicotine gum or lozenge, so your mouth can absorb the nicotine.
- Make sure you get the right amount of nicotine — people who smoke more than 10 cigarettes per day should use a 4 mg piece of gum or lozenge.

9. *Make sure you are using the patch in the best way:*

- If you can't stop having a few cigarettes while using the patch, it is best to keep the patch on. Do not let a few slips with cigarettes stop you from using the patch to quit smoking.
- You may need to add nicotine gum or lozenges to help get over the hump or you may need to use more than one patch at a time. Talk to your healthcare provider about this.

10. *The cost of NRT.*

If the price of NRT is a concern, try to find “store brand” (generic) NRT products which are often cheaper than the brand name products. There is no reason to think that brand name NRT works better than store brands. And keep in mind how much cigarettes cost. Putting your cigarette money toward NRT can in the long run save you a lifetime of cigarette money. And if you can find the money for cigarettes, you probably can find the money for NRT. Think about buying NRT over the Internet. It is legal to do so and can be cheaper. Some health benefit plans, including some Medicaid providers, pay for NRT, and some state Health Departments and telephone quitlines provide NRT at no cost if you engage in the telephone counseling.

11. *Do whatever it takes to get the job done—it is not a weakness to use medicine to stop smoking.*

Some people think that if you really want to quit smoking, you should be able to just do it without any help. While it is true that not everyone “needs” medicine to stop smoking, it is also true that not everyone needs medicine to treat asthma, diabetes, or high blood pressure. NRT is only one tool that can help in the hard job of stopping smoking. Those who quit smoking with or without NRT are both making the same smart move for their health—they are becoming ex-smokers.

Levels of addiction vary, and what life throws at you varies from person to person. Maybe one person had an easier time quitting because they were not living or working with other smokers. Maybe one person had a harder time because they had other problems (stress) to deal with. You are not competing with other smokers, you are competing against your cigarettes. If you find NRT helpful and you need to use it for a long time to stay off cigarettes, do not be disappointed or worried—be proud of yourself because you have stopped smoking.

The most important thing about quitting is to stop using cigarettes—it does not mean you are a “better person” with a “stronger will” if you try to quit smoking without using medicine or other help.

APPENDIX B: PRINCIPLES FOR REGULATING MEDICINES DESIGNED TO TREAT TOBACCO DEPENDENCE

BACKGROUND

Cigarette smoke contains over 4,000 chemicals and smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general. Cigarette smoking causes 420,000 premature deaths each year in the US. Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general¹. The risks for serious diseases and premature death caused by continued smoking are not small. For example, 50% of those who continue smoking will develop chronic morbidity from Chronic Obstructive Lung Disease². Similarly, 50% of those smokers who do not succeed in quitting will die prematurely from a disease caused by their smoking, losing an average of 10 healthy years of life³. The magnitude of the reduction in risks resulting from stopping smoking is also large. For example, smokers who quit smoking by age 50 have one half the risk of dying in the next 15 years, compared to continuing smokers⁴.

Because cigarette smoking is highly addictive, the vast majority of unaided quit attempts (around 95%) are unsuccessful⁵. Even among those smokers randomized to the placebo arm in pharmacotherapy trials the 6-12 month quit rate is typically only 10%, despite the fact that state-of-the-art medical screening and counseling is usually provided to all participants in such trials⁶. This means that when a smoker attempts to quit smoking without treatment, the most likely outcome (in at least 9 out of 10 cases) is that they will relapse to continued smoking within the next year.

Tobacco use and its consequences are not only significant medical problems for affected individuals, but also represent serious public health problems for the US population. A public health approach that encourages smokers to undertake efforts to quit smoking and that enhances the success of such efforts is needed. FDA's actions with respect to smoking cessation medications should be driven by a public health focus that promotes movement towards quitting and utilization of effective cessation methods.

All medicines are required by regulators to have evidence that they are safe and effective. This does not mean that they are required to be 100% risk-free or 100% effective. Rather the comparison is made with the likely clinical outcome if the drug is not used. Thus chemotherapies for cancer are known to have serious side effects, and are much less than 100% effective. Nevertheless, they are approved and used partly on the basis that the long term prognosis is very poor for those illnesses when left untreated. This same regulatory philosophy has not been applied to treatment for tobacco dependence. Current and previous regulatory frameworks for regulating NRT products appear to have been designed to minimize risks and restrict access without adequately considering that the likely consequence is continued dependent use of cigarettes, and the premature death of half of all long-term users, along with serious health effects for many others.

The following principles are therefore intended to guide FDA regulation of smoking cessation medicines in a manner that is more likely to maximize the positive public health impact of these medicines and minimize the harmful effects of cigarette smoking in the United States.

PRINCIPLES

1. Dependence on cigarettes is a chronic relapsing disorder that typically causes disabling diseases and premature death if not successfully treated. **The serious health effects of failing to quit smoking, and the high probability of that outcome in untreated smokers, should be given due weight when considering approval, labeling and/or indications of medicines for tobacco dependence treatment.**
2. Only a small proportion of those who could benefit actually use medicines for smoking cessation and, when medications are used, it is typically for shorter periods and in smaller quantities than recommended. This underuse appears to be due in part to overconcern about the safety and side-effects of the medicine relative to smoking. The labeling of medicines for smoking cessation likely

contributes to the perception that these medications are hazardous. Another cause is the high initial unit price for these medicines, which partly relates to the minimum pack size. **Labeling on medicines for smoking cessation should be designed to provide accurate information on the safety/risks of the medicine relative to continued smoking. In addition, any regulatory barriers to decreasing unit pack size should be removed.**

3. Current labeling on nicotine replacement products gives smokers the impression that the medicine is as dangerous as smoking, and that certain practices (e.g. combining nicotine replacement products, using an NRT product while smoking, using the medicine for longer than the recommended period, or using a high dose if a smoker of less than 25 cigarettes per day), may be particularly dangerous. Current evidence and clinical practice guidelines suggest that these uses of the medicines are not only safe, but may help smokers to quit⁷. **Changes to labeling and indications that allow more flexible use of NRT as the source for nicotine in the place of tobacco should be implemented.**
4. Many of the medicines approved for smoking cessation have been available for many years and now have far greater evidence on their safety than when originally approved. **The extensive post-approval experience and evidence base should be given due consideration when responding to requests for changes in labeling and indications.**
5. Many of the medicines approved in the United States for smoking cessation have been used in other countries with more liberal indications and labeling. **The evidence from other countries, including the post-marketing surveillance data from those other countries, should be given due consideration when responding to requests for changes in labeling and indications.**
6. Helping the public get the accurate, science-based information they need to use medicines and foods to improve their health, is an important role for FDA. **A public education campaign should be provided that is designed to provide more balanced information on the risks and benefits of approved medicines for smoking cessation in comparison with continued smoking.**

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