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IMPACT OF NICOTINE REPLACEMENT THERAPY ON SMOKING BEHAVIOR

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■ **Abstract** This review summarizes evidence pertaining to the role of nicotine medications in smoking cessation and focuses particularly on evaluating evidence of the impact that nicotine replacement therapies (NRT) have had on altering population trends in smoking behavior. Accumulated evidence from controlled clinical trials has demonstrated that available forms of NRT (e.g., gum, transdermal patch, nasal spray, inhaler, and lozenge) increase quit rates compared with placebos by 50%–100%. However, despite the positive results from these studies, fewer than one in five smokers making a quit attempt do so with the benefit of NRT. Because not enough smokers are using NRT, the availability of NRT has not had a measurable impact on influencing population trends in smoking behavior. Among the factors contributing to the low utilization of nicotine medications are the inadequacies of the current dosage strengths and formulations of existing medications, smokers' perceptions of the high cost of the drugs, and concerns that many smokers have about safety and efficacy of nicotine medications.

INTRODUCTION

Considerable evidence supports the view that cigarette smoking is primarily maintained by an addiction to nicotine (51, 91). Nicotine creates dependence by activating the mesolimbic dopaminergic reward system, and physiologic withdrawal symptoms occur when nicotine is no longer administered (59, 67, 71). Nicotine is an agonist of neural nicotinic acetylcholine receptors (NAChRs), which are found presynaptically in the central nervous system and postsynaptically in the autonomic nervous system (73). These receptors modulate the release of neurotransmitters. As a person's exposure to nicotine increases, NAChRs also are increased, which results in nicotine tolerance (60). Thus, factors that decrease the bioavailability of nicotine are hypothesized to increase an individual's cravings and decrease the likelihood of cessation because more of the drug is needed to achieve a given level of dopamine (13). Extrapolating from this evidence has led to the development of smoking cessation treatment methods that emphasize nicotine replacement (31).

The present review provides a brief summary of evidence pertaining to the role of nicotine medications, alone or in combination with other therapies in smoking cessation, and a critical analysis of the impact that these medications have had on altering population trends in smoking behavior. The discussion considers the role of nicotine replacement therapy (NRT) in a comprehensive population-based program developed to reduce the harms caused by tobacco.

NICOTINE MEDICATION FOR SMOKING CESSATION

In the mid-1980s, the vast majority (>90%) of former smokers reported that they stopped smoking without using medications or receiving formal assistance or help from anyone (33). However, this statistic has changed dramatically in the past two decades with the introduction and wide-scale availability of nicotine medications (46). Two-milligram prescription-only nicotine gum was first introduced in the United States in February 1984 (17, 31). Prescription-only nicotine patches were introduced in 1992, followed by different nicotine dose and medication formulations including 4-mg nicotine gum (1992), a nasal spray (1996), inhaler (1997), and lozenge (2003) (17, 31). Table 1 provides a brief description of different nicotine medications sold in the United States.

Numerous clinical trials have assessed the efficacy of nicotine medications for smoking cessation (31, 85). A recent systematic review of studies evaluating commercially available forms of NRT (e.g., nicotine gum, the transdermal nicotine patch, nicotine nasal spray, nicotine inhaler and nicotine sublingual tablets/lozenges) concluded that these treatments increase quit rates approximately one and a half to twofold regardless of clinical setting and/or use of adjunct treatments (31, 85). Several studies have found that complete or nearly complete abstinence from smoking in the early weeks of an attempt to quit is a strong predictor of long-term cessation (39, 56, 99). Nicotine medications appear to help smokers in quitting by providing relief from nicotine withdrawal symptoms typically experienced during the first few days and weeks of abstinence from tobacco (31, 91).

In 1996, the U.S. Food and Drug Administration (FDA) made nicotine patches and gum available over the counter (OTC) in an effort to increase access to these medications (17). Shiffman and colleagues tracked sales of pharmacological aids for smoking cessation and found that nicotine gum and patch sales increased 250% in the year following approval of OTC status (81). Several new prescription nicotine (nasal spray, oral inhaler, lozenge) and nonnicotine (Zyban®) stop-smoking medications were introduced after 1996 (17). However, of the new medications introduced after 1996, only Zyban® appears to have had any impact on medication-assisted cessation attempts (17). Of the various nicotine medications sold, the nicotine patch and nicotine gum are the most frequently used stop-smoking medications (3, 17; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). National survey data reveal that approximately 40% of

TABLE 1 FDA-approved nicotine replacement therapies[a]

Nicotine medication	Year approved	Dose	Advantages	Disadvantages
Gum	1984 (2mg Rx) 1992 (4mg Rx) 1996 (OTC)	2 or 4 mg per piece	Oral administration; comes in different flavors	Low compliance; under dosing is common
Patch	1992 (Rx) 1996 (OTC)	16-hour patch: 15, 10, 5 mg; 24-hour patch: 21, 14, 7 mg	Once a day administration	Fixed dose; slow delivery not conducive to treating acute cravings
Nasal spray	1996 (Rx)	10 mg/ml, 0.5 mg per spray	Fast delivery of nicotine	Unpleasant side-effects discourage repeated use
Inhaler	1997 (Rx)	10 mg per cartridge	Hand-to-mouth action simulates smoking habit; comes in menthol flavor	Low compliance; under dosing is common
Lozenge	2003 (OTC)	1, 2, or 4 mg per piece	Oral administration; faster nicotine delivery than gum	Low compliance; under dosing is common

[a]OTC, over the counter; Rx, prescription.

smokers indicate that they have used some form of nicotine medication in the past (3).

A number of studies have reported on the characteristics of smokers who have used nicotine medications (21, 23, 68, 69, 90; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). In the period before OTC NRT, current and former smokers who reported having used prescription nicotine patches or gum were more likely to be female, Caucasian, have higher average household incomes, have private insurance, and to smoke more than a pack per day (21, 23, 68, 69, 90; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). The characteristics of smokers using NRT changed after nicotine patches and gum were made available OTC. In cross-sectional surveys of Massachusetts smokers in 1993 and 1999, the use of NRT in nonwhites decreased from 21% to 3% and increased from 5% to 20% in those aged 18 to 30 years, while use remained constant in other age, race, gender, and income categories (90). Longitudinal data from the Community Intervention Trial for Smoking Cessation cohort study (COMMIT) retrospectively re-created smokers' NRT use history between 1993 and 2001 (A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished

manuscript). This study revealed that annual NRT usage rates nearly doubled from the three years before (1993–1995) OTC availability compared with the three-year period after OTC availability (1997–2000). Comparing usage patterns during the pre- and post-OTC periods revealed that use of NRT decreased among Hispanics and increased among those with lower desire to quit at baseline, among lighter smokers, and among those with lower annual household incomes.

On the basis of these data, it appears that part of the increased sales of NRT since becoming available OTC may be due to increasing utilization in populations that previously had lower utilization of NRT, including younger smokers, those with lower levels of daily consumption and desire to quit, and possibly those with lower incomes. However, OTC availability of nicotine patches and gum may only partially explain why NRT usage increased in younger smokers and those with lower incomes. During this same period health insurance coverage has favored nicotine medications, including state-financed public insurance programs for the poor (e.g., Medicaid) (11, 40).

EFFECT OF NRT ON QUIT RATES

A recent meta-analysis of eight studies that examined either active OTC NRT versus placebo of OTC NRT or OTC NRT versus prescription-only concluded that OTC NRT produces similar quit rates compared with NRT obtained by prescription (50). As expected, when no adjunct behavioral support was provided, quit rates were slightly lower (31, 85). However, even in the absence of a behavioral support program, evidence showed that gum and patches increased quit rates more than that seen for placebo (31, 48, 85). Given these results, one might anticipate that OTC availability of NRT would positively impact rates of smoking cessation in the population.

Estimating the impact that NRT has had on smoking behavior in the population has been difficult because of self-selection in who uses NRT and because there are many external influences on smoking behavior that may confound measurement of population-wide trends in smoking behavior. Time series analyses of national cigarette consumption and NRT sales from 1976 to 1998 suggest that sales of NRT were associated with a modest decrease in cigarette consumption immediately following the introduction of the prescription nicotine patch in 1992 (45). However, no statistically significant effect was observed after 1996, when the patch and gum became available OTC. Thus, in spite of the apparent success of OTC NRT, during the period between 1990 and 1998, population-based data reveal that annual quit rates as well as age-specific quit ratios remained stable, especially for those between the ages of 25 and 64, the age group most likely to use NRT (16).

Repeated cross-sectional surveys from Massachusetts found that quit attempts and quit rates were no different in the period after 1996 compared with before 1996 (90). Cross-sectional surveys from California indicate a greater utilization

of NRT after 1996 but show little impact on quit rates (69). Only one prospective study has investigated the impact of OTC availability of NRT on quit rates (A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). In the COMMIT study, annual use rates of the nicotine skin patch increased from an average of 3.6% between 1993 and 1995 to 6.0% between 1997 and 2000. Among those who used the patch to stop smoking, the average quit rate was 15.3% between 1993 and 1995 and 15.5% between 1997 and 2000. The same pattern was observed for use of nicotine gum. Nicotine gum use increased from 1.8% to 2.4% before and after the OTC reclassification, whereas quit rates among gum users increased from 9.7% before OTC to 14.5% after OTC. Relapse rates among patch users were slightly higher in the OTC period compared with before, whereas no difference was seen for gum users. Thus, on balance it appears that OTC reclassification has increased access to NRT without changing quit rates among those using NRT (A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript).

WHO QUITS WITH NRT?

The current clinical practice guideline for treating nicotine dependence recommends that NRT should be used by all smokers who are trying to stop smoking (31). Researchers have investigated differential effects of NRT depending on patient characteristics and comorbid conditions (e.g., depression, other substance abuse problems). Some studies have found that those who smoke in excess of a pack of cigarettes or more per day derive greater benefit from higher dosage forms of NRT; however, amount smoked daily has not been found to be a consistent effect modifier in predicting treatment success using NRT (25, 31, 42, 85). A few studies have reported that women who use NRT have lower success rates than do men (8, 66, 95). In general, the results of studies investigating patient factors that interact with NRT to predict quit rates have been equivocal, which is why the current practice guidelines recommend NRT for all smokers who are making a quit attempt (31).

A new area of research involves identifying genetic characteristics of smokers who may derive a proportionately greater benefit from NRT. One study found that quit rates were significantly higher after 12 weeks among 755 subjects in a randomized nicotine skin patch trial among those who exhibited a certain genotype of a dopamine receptor gene (DRD2). The DRD2 gene is involved in the synthesis of noradrenalin from dopamine (54). Improved understanding of how genetic factors contribute to smoking cessation could potentially lead to improved treatment matching. However, more research is needed to clarify the utility and potential cost-effectiveness of pharmacogenetic treatment–matching approaches for smoking cessation.

WHY HASN'T NRT INFLUENCED QUIT RATES MORE?

A number of reasons could explain why increased use of NRT has not influenced quit rates more substantially in the population at large. Some authors have speculated that the availability of OTC NRT has merely encouraged quit attempts by less-motivated smokers who, to begin with, are less likely to quit (69, 90; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). Thus, although usage rates might increase, this benefit would be offset by higher rates of relapse among those who are less committed to making a quit attempt. There is some evidence to support this view (69; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). Several studies have reported that NRT use increased among less-dependent and less-motivated smokers in the post-OTC period (69, 90; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). Audit studies of NRT purchases reveal that, for both patch and gum, most purchase episodes last a month or less (38; J.R. Hughes, J.L. Pillitteri, P.W. Callas, R. Callahan, M. Kenny, unpublished manuscript). In the COMMIT study, the OTC switch led to a decline in the median number of days the patch was used, decreasing from 30 days to 21 days (A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). Other studies have found that it is common for smokers to report concurrent smoking while also using NRT (3, 21, 64, 68, 82). However, long-term concurrent use of NRT and smoking is rare, and most smokers who use NRT say they do so to quit smoking, not to reduce their smoking (3, 7; S. Shiffman, J.R. Hughes, unpublished manuscript).

Data do support the view that combining some type of in-person or telephone behavioral counseling support with NRT increases quit rates, especially for those using nicotine gum (31, 58, 84, 85). Counseling support appears to enhance the impact of NRT by helping smokers understand how the medications work and how to use them appropriately (31, 85). Counseling also reinforces the smoker's motivation for quitting and remaining tobacco-free. However, despite the benefits of combining behavioral counseling with NRT, most smokers quit without receiving behavioral counseling (100; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). In the COMMIT cohort, fewer than 10% of NRT-assisted quit attempts were accompanied by attendance in a stop-smoking program, and this percentage decreased after nicotine patches and gum were made available OTC (A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript).

Most Quit Attempts Are Made without NRT

Another reason why NRT has not had a greater impact on quit rates in the population-at-large is that most cessation attempts are still made without the benefit of nicotine medications (3, 50, 69, 90; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). A 2001 national telephone

survey of 1046 adult smokers revealed that although most had heard of nicotine medications (i.e., patches, 97%; gum, 94%; inhaler, 41%; nasal spray, 9%), only 17% of those who had made a quit attempt in the past year reported using a stop-smoking medication in their quit attempt (3). Thus, unlike a cigarette tax hike, worksite smoking ban, or mass media campaign that might be expected to reach nearly all smokers, NRT is reaching only a fraction of smokers (20). Among the factors contributing to the low utilization of NRT are smokers' perceptions of the high cost of the medications and concerns about safety and efficacy of NRT (3, 29).

Among smokers who have never used any stop-smoking medication, cost is the most frequently cited reasons for never use (3). An 8–12-week course of NRT can cost anywhere between $200–$350. Increasingly, health insurance companies are providing coverage for NRT (40). However, most insurance companies require smokers who get NRT to obtain a prescription and/or attend a stop-smoking class (11, 40). Many insurance companies also limit the number of courses of NRT a person can obtain in a given time period, which may deter smokers from making another quit attempt. OTC NRT products are also packaged in a way that make them noncost competitive with tobacco products (93). Most tobacco products are packaged so the user can get a one-day supply of nicotine (e.g., pack of cigarettes, tin of moist snuff). The smallest supply of nicotine gum or patches is a one-week supply, which requires the user to pay a minimum of $28–$35 just to obtain the product. Most of the OTC starter kits for NRT are packaged with a minimum of two or even four weeks of medication, requiring the consumer to spend even more just to get started with a quit program. Although it could be argued that the initial high cost of purchasing OTC NRT products helps separate out those smokers who are truly motivated to quit, growing evidence suggests that the initial high cost of obtaining the medication is a deterrent to smokers to use NRT to help them quit (3).

Evidence from several studies shows that when cost barriers are reduced, utilization of NRT increases (1, 24, 38, 77; N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript). Research supports the idea that many more smokers would be induced to try NRT if the cost were reduced or the medication was made available for free (1, 38, 86; N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript). For example, in 2003, in a random sample telephone survey of 815 adult smokers in upstate New York, 53% said they would think seriously about quitting if offered free nicotine patches/gum (38).

In a recent cessation program sponsored by the New York City Department of Health and Mental Hygiene, smokers of 10+ cigarettes per day who were willing to make a commitment to quit smoking were offered a free 6-week supply of nicotine patches (N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript). This unique program, marketed through a single press

release, resulted in over 400,000 calls to obtain the free nicotine patches. The offer of discounted nicotine patches in New Zealand resulted in over 80,000 calls to their government-sponsored quit line (1). A recent follow-up study of a random sample of the 35,000 participants in the New York City patch give-away program revealed that more than 87% of participants made an attempt to stop smoking and 33% were not smoking 6 months later, yielding an average cost per quit of about $300 (N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript). Population-based efforts such as those conducted in New Zealand and New York City appear to be effective in increasing the reach and utilization of NRT and thus have the potential to increase the overall quit rate in the population at large (1, 34, 86; N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript).

Although the perceived high cost of NRT is clearly a factor that can influence NRT use, cost alone is not the only explanation for the low utilization of nicotine medications by smokers. Recent studies of smokers and former smokers reveal that many smokers worry about using nicotine medications because of safety concerns (3, 29). Even though nicotine in the dosage strengths available in stop-smoking medications is fairly safe (7, 31), many smokers worry that concurrent smoking while using NRT will trigger a heart attack or may even cause cancer (3, 29). Many smokers also express skepticism about the efficacy of NRT to help them quit (3, 29). In a recent survey of 500 adult smokers, Etter & Perneger (29) found that only 16% agreed that nicotine medications help people quit smoking. Studies reveal that knowledge deficits are especially pronounced among smokers who have never used nicotine medications in the past, particularly those who are older, those who are less educated, and users of light and ultralight cigarettes (3).

In an effort to market NRT products, the pharmaceutical industry has invested heavily in consumer advertising. Much of this advertising appears to be targeted to smokers who are already primed to stop smoking on their own, which may help explain why NRT has had little impact on quit rates even though the percentage of medication-assisted quit attempts has gone up in the past decade (3; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). Recently, Bolton and colleagues (L.E. Bolton, J.B. Cohen & P.N. Bloom, unpublished manuscript) have speculated that advertising of stop-smoking medications may have a boomerang effect, unintentionally undermining smokers' risk perceptions about smoking and thus delaying smokers' efforts to quit. Because advertising of stop-smoking medications conveys a message that there is a remedy for addiction to tobacco, it is thought that a smoker's worry about the risks of smoking might be dampened by their belief that the medications can help them quit easily. Whether or not this boomerang effect is a real phenomena that can undermine motivation for cessation of smoking remains to be demonstrated, although a recent national survey of smokers found that 39% believed that it is

easier for smokers to stop smoking today because of the availability of stop-smoking medications (22).

USE OF NRT FOR SMOKING REDUCTION

Some smokers express an interest in using NRT to cut back on their smoking but not to quit altogether (26). This is a controversial subject because the health benefits of reduced smoking appear to be minimal (87). Reducing cigarette consumption may decrease dependence and increase the likelihood of future cessation. However, smokers who reduce their consumption may feel they have lowered their disease risk due to smoking and do not need to make any more effort toward cessation. Data from clinical trials where medication is used to assist in reduction reveal that smokers who are not interested in quitting can reduce their consumption by as much as 50% and maintain this consumption level for at least 6 months or more (9, 15, 28, 94). Higher quit rates were observed among reducers in each of these studies.

Outside the clinical setting, relatively few smokers in the general population can maintain large consumption reductions over extended periods of time (30, 47, 52), and those who reduce their consumption by at least 50% may have a greater likelihood of future cessation, although these studies examine smokers who self-select for smoking reduction. Investigators do not know what impact a smoking reduction message, as opposed to a cessation-only message, would have on the general population; this topic warrants additional research.

CAN NICOTINE MEDICATIONS BE IMPROVED?

Yet another explanation for why NRT has not had a more pronounced effect on influencing population trends in smoking behavior concerns the inadequacies of the current dosage strengths and formulations of nicotine medications (6, 80). The reinforcing effect of nicotine depends on the amount of nicotine and the way in which nicotine enters the blood stream (5, 6, 27, 41, 80, 91). Nicotine in cigarette smoke is absorbed in the lungs (91). It takes ~7–10 sec for nicotine to reach the brain and for the smoker to feel the effects (91). By contrast, nicotine in gum is absorbed through the mucus membrane in the mouth and takes longer to reach the brain (6, 80). Nicotine in the patch is absorbed even more slowly through the skin and takes more than an hour to reach peak levels (5, 80). Nicotine medications designed to deliver nicotine more rapidly into the blood stream would very likely be more effective in helping smokers alleviate withdrawal symptoms when they quit, thus increasing quit rates (5, 80). The prescription nicotine nasal spray was designed precisely to deliver nicotine more rapidly than other nicotine medications (31). Placebo-controlled studies evaluating the nasal spray do show slightly higher quit rates compared with other nicotine medications, especially

among more dependent smokers (31, 85). However, the downside of the nasal spray is that most smokers experience nasal and throat irritation that discourages repeated use of the product (31, 85, 92). Thus, compliance with the nasal spray is typically lower than with other types of nicotine medications (78).

A quick review of the patent literature reveals that many companies are working on developing faster nicotine-delivery medications (36, 65). A fast nicotine-delivery tablet has been developed and tested in Scotland, and a faster nicotine-delivery gum has been patented and tested in the United States (63, 70). Some public health officials have even advocated supporting wider marketing of medicinal nicotine and even oral smokeless tobacco products as a safer alternative for cigarette smoking (35, 57, 88). A number of other nicotine delivery products including nicotine aerosol inhalers, water, straws, wafers, and even lollipops have been patented and may soon find their way into the marketplace (36, 65). Tobacco manufacturers including Philip Morris, R.J. Reynolds, and Japan Tobacco hold patents for devices that could be used to deliver aerosolized nicotine into the lungs providing a potentially safer alternative to conventional cigarettes (36, 44, 78).

Another approach to improving nicotine medications is to offer them in different dosage strengths. Studies show that there is a dose-dependent relationship between NRT formulations and quit rates, although side effects become more common as the nicotine dose is increased (25, 42). There is wide individual variation in how smokers metabolize and respond to nicotine, which may help explain variation in treatment effects (54, 79). In particular, heavy smokers may not get enough nicotine from the current high-dose forms of nicotine medication now available. Some evidence supports the idea that more closely matching NRT dosage with an individual's daily biological dose of nicotine received while smoking can increase quit rates (25).

Rather than feeding one's dependence on nicotine in an effort to wean smokers from cigarettes, new therapies are now being developed and tested that treat nicotine dependence by blocking or replacing the effect of nicotine in the brain (37). Bupropion, marketed as Zyban®, is a non-nicotine medication that promotes smoking cessation by inhibiting dopamine reuptake in the brain, thereby dampening the reinforcing benefits of nicotine (31). Clinical trials support the use of bupropion for smoking cessation (31, 72). Prescription Zyban® was introduced in the United States in 1997 and has become, after nicotine patches and gum, the third most popular stop-smoking medication used by smokers (17). To date there is only one published study comparing the efficacy of bupropion with NRT. In the study by Jorenby et al. (55) quit rates were higher for bupropion alone and bupropion and patch combined at 6 and 12 months, compared with placebo and nicotine patch alone.

A number of other non-nicotine pharmacotherapies targeting nicotine receptors and the dopamine system are undergoing evaluation in human placebo-controlled trials (18, 43). One of the more interesting research efforts under way concerns the development of a vaccine for the treatment of nicotine addiction (89). The vaccine treatment is intended to block nicotine delivery to the brain, thereby removing the

main reinforcement for smoking. The vaccine works by stimulating the immune system to produce antibodies that find and attach to nicotine molecules. The resulting compounds are too large to pass through the blood-brain barrier so that most of the nicotine is unable to reach the brain. Animal studies have clearly demonstrated that the vaccine can work; however, it remains unclear if human smokers will respond to the vaccine by increasing cigarette consumption to compensate for the lack of nicotine (43). Should this treatment modality work it would have profound implications for addressing the problem of nicotine dependence.

NICOTINE MAY NOT BE THE ONLY SOLUTION

Other investigators have speculated that efforts focusing solely on nicotine replacement or blockage are doomed to fail because nicotine may only partially explain smoking behavior (74). The airway sensations associated with smoking as well as the rituals of lighting, holding, and puffing on a cigarette are important reinforcing features of the act of smoking. Previous studies indicate that smokers report missing the behavioral aspects (i.e., actions that are ritualistic/repetitive) as well as the sensory cues of smoking such as taste, aroma, respiratory tract sensations/airway stimulation, and irritant reactions in the mouth, throat, and tracheo-bronchial tree (2, 12, 27, 76, 96, 97). Baldiner et al. (2) has suggested that the tar level of the product, not nicotine, seems to regulate puffing behavior. Brauer et al. (4) reviewed nine clinical trials that looked at the sensory impact of denicotinized cigarettes and concluded that denicotinized cigarettes help reduce cravings and withdrawal for cigarettes, especially among highly dependent smokers. This could be explained by classical conditioning theory, where inhalation impact turns to a conditioned stimulus as a result of being associated with nicotine exposure, which can function as an unconditioned stimulus.

Regardless of the mechanism, NRT is not entirely efficacious over the long term likely because the sensory and psychomotor aspects of smoking are inadequately addressed in cessation treatments (74). Many current cessation methods focus first on stopping smoking (which abruptly disrupts sensory and motor/behavior associated with smoking), followed by a course of nicotine replacement therapy to compensate for withdrawal symptoms, and concluding with discontinuation of the therapy to wean the smoker of the pharmacological effects resulting from the nicotine in the medication. This process, in effect, does not consider the sensorimotor cues thought to be very important in the addiction process. Several previous studies have shown that the sensory airway effects of smoking are important in relieving craving for cigarettes, as well as facilitating smoking abstinence (4, 12, 14). A sound theoretical basis predicts that smoking cessation treatments that address both sensorimotor and pharmacological aspects of a smoker's addiction will be more efficacious than either approach alone (74). Findings of one small study that combined a denicotinized cigarette (i.e., Next) and nicotine patch therapy revealed that 50% of subjects using Next in combination with a nicotine skin

patch were off cigarettes after four weeks, confirmed by a breath carbon monoxide test (75).

SUMMARY

Tobacco control research literature reveals that the most potent demand reducing influences on tobacco use include interventions, such as higher cigarette taxes, smoke-free policies, comprehensive advertising bans, and paid counter-advertising campaigns, that reach the most consumers and directly impact their behavior (20, 92). This review shows that NRT has had little impact on influencing population trends in smoking behavior over the past decade. The main reason for the limited impact of NRT on smoking behavior has to do with low utilization of NRT by smokers (3).

Making NRT more accessible to smokers by providing it free and/or packaging the medication in single daily doses has the potential to vastly increase utilization (1, 34, 80, 88; N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript). Research is needed to understand better who would utilize such products, the products' effectiveness for cessation, optimal dosing and packaging, and the cost effectiveness of using different strategies to provide NRT for smokers. Counseling and behavioral therapies for smoking cessation can increase the effectiveness of NRT, yet are underutilized in clinical practice (9, 32; A. Hyland, H. Rezaishiraz, G. Giovino, J.E. Bauer, K.M. Cummings, unpublished manuscript). Research is needed to determine how to cost-effectively provide to smokers using NRT such behavioral support services perhaps via telephone quit lines and the Internet (1, 58, 84, 86; N. Miller, T.R. Frieden, S.Y. Liu, S.Y. Matte, F. Mostashari, D. Deitcher, K.M. Cummings, C. Chang, U. Bauer, M.T. Massett, unpublished manuscript). Finally, more research is needed to test the benefits and potential harms associated with producing new faster-delivery forms of nicotine medication (61, 80).

In the United States, nicotine medications are licensed only as aids for smoking cessation (16, 31). However, some other countries have permitted NRT to be used as a way to reduce smoking or temporarily treat nicotine withdrawal. Liberalizing government regulations so that cleaner forms of nicotine become more acceptable and accessible to smokers when compared with tobacco products has the potential to revolutionize the way the tobacco problem is perceived and addressed in the future (19, 88, 93).

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