Nicotine Chewing Gum and the Medicalization of Smoking

DESPITE INSUFFICIENT evidence to their advertised claims of success, expensive commercially available aids and clinics for smoking cessation proliferate. Methods include hypnotherapy, hydrotherapy, acupuncture, biofeedback, rapid smoking, special diets, filters, self-help books and tape cassettes, aversive conditioning with electric shocks, vivid films on smoking-related diseases, and even a live-in stop-smoking program (1). In Schwartz's comprehensive review (2) of tried but unproved methods for smoking cessation over the last century, chemical remedies abound: silver acetate, quinine sulfate, meprobamate, hydroxyzine, diazepam, amphetamines, anticholinergic agents, local anesthetics, astringent mouthwashes, garlic, vegetable-based products, placebos, nicotine substitutes such as lobeline (for example, the over-the-counter preparations Nikoban [Thompson Medical Company, Inc., New York, New York] and Bantron [Jeffrey Martin, Inc., Union, New Jersey]), and nicotine itself in various forms.

Studies of a buffered-resin chewing gum containing nicotine (Nicorette; Merrell Dow Pharmaceuticals, Inc., Cincinnati, Ohio) led the Drug Abuse Advisory Committee of the Food and Drug Administration (FDA) in 1983 to recommend approval of the substance in the United States. The drug went on sale in March 1984.

Experimentation with nicotine gum began 15 years ago in Sweden. The gum is sold by prescription in Sweden, Germany, Austria, England, Ireland, and Canada and is available over the counter in Switzerland. More than 1.2 million persons are said by the manufacturers (in Sweden AB Leo, Helsingborg, Sweden; Merrill Dow Pharmaceuticals, Inc. elsewhere) to have used the product.

In its new drug application for Nicorette in March 1981, Merrell Dow submitted 14 studies to the FDA, 12 of which were rejected either for lack of efficacy or for critical flaws in design, conduct, or analysis. The two remaining studies showed some evidence of efficacy but were insufficient to meet the standards for FDA approval. The FDA required that two adequate and well-controlled prospective studies be provided; the primary efficacy variable to be decided in the studies was defined as a statistically significant difference in the proportion of persons who achieve cessation of smoking while taking the drug compared with those taking placebo at 1 month after the initiation of treatment.

Before approval of the gum, questions were raised about the adequacy of an assessment period of 1 month. One member of the Drug Abuse Advisory Committee pointed out that many modes of treatment intended for short-term use, such as anorexic agents for weight control, might show positive results at 1 month but no lasting effect when stopped (3). Nonetheless, on the basis of two newly submitted studies, the committee found that nicotine gum increased the likelihood of smoking cessation among participants in "acceptable counseling programs" (originally to have read "behavior-modification programs"). In approving the gum, the FDA has made the judgment that short-term exposure to nicotine through a prescription product is preferable to nicotine exposure through cigarette smoke. Such a ruling in regard to a toxic substance may be unprecedented in the history of the FDA.

Questions remain about the safety and efficacy of nicotine chewing gum in potential users. It is ironic that a substance alleged to have been used widely was approved in the United States on the basis of only one American study (4) and one foreign study (5) involving a total of 324 persons. Indeed, the original purpose of the lone American study (4, 6), a randomized controlled trial in 208 persons, was to investigate the influence of the gum on oral soft tissues. Measurement of success rates for smoking cessation at 6 weeks was a spin-off of this study of oral pathology.

Although the authors of the lengthier and more thorough study (5) believe that their results clearly confirm the usefulness of the gum (48% abstinence at 1 month and 31% at 1 year compared with 24% and 14%, respectively, in the placebo group), several aspects—notably a small target population and an extraordinary degree of compliance—limit their findings. One hundred sixteen persons attending a hospital-based smokers clinic in England were randomly assigned to receive either nicotine gum (2 mg of nicotine in each piece) or placebo gum (containing 1 mg of nicotine and lacking an alkaline buffer to promote absorption through the buccal mucosa); participants also attended six group meetings with an experienced therapist. More than 90% of the participants returned 1 year later for expired air carbon monoxide tests, a rate that suggests an unusually well-motivated group. No significant difference in relapse rates was seen between the groups, and the authors used a one-tailed test for the most significant criterion (no smoking at all from the 1st week of use of the gum to 1-year follow-up), which was barely significant. The authors themselves have noted the unusual result of a higher abstinence rate at 1 year than at 6 months among those persons using the active gum. Also, although persons randomly assigned to the active gum smoked significantly more cigarettes per day before entry into the study than persons assigned to placebo, the mean pretreatment plasma nicotine concentration was substantially lower in the active gum group.

In essence, this prospective, randomized, double-blind, placebo-controlled study in heavy smokers attending a hospital-based clinic may not have used a study population representative of all smokers. Most people who want to stop smoking do not go to a hospital. Seldom, in fact, do persons visit a physician primarily because they wish to stop smoking. Although in a more recent report (7) several authors from the research unit that conducted this hospital-clinic study have attempted to broaden the application of their findings to the physician's office-based practice, they do so at a cost. The authors claim that the offer and prescription of nicotine chewing gum enhance the efficacy of the general practitioner's advice to

stop smoking. Yet although they acknowledge that the gum has a placebo component, the authors admit that no placebo control was given. This flaw does not prevent them from superimposing conclusions from earlier studies in which a placebo control had been included. Clearly, the earlier findings were not replicated in the office setting. Moreover, in a recent study by a subcommittee of the Research Committee of the British Thoracic Society (8) involving 1550 patients randomly assigned to four treatment groups, verbal advice when reinforced with a pamphlet or with a pamphlet and 2-mg buffered nicotine or placebo chewing gum did not produce greater success than verbal advice given alone. The subcommittee has concluded that the effectiveness of the nicotine gum reported in other studies seems to be related to the careful preselection of study participants, a high degree of motivation, and the specialized experience and greater time spent by the therapists involved.

The lack of supportive studies is not the only question raised by the introduction of Nicorette. Although Raw and colleagues (9) have claimed that the gum is cost-effective in terms of the therapist's time (because only a few minutes are needed to prescribe it and to record progress) and that it is "a practical method for busy doctors," whether the gum is cost-effective for consumers is open to interpretation. In clinical trials, the gum has been provided free of charge. In practice, the gum is sold in boxes of 96 for approximately $20. Extrapolating from the hospital-clinic study, in which persons used a mean of 7 pieces per day, the cost of the gum is at least as expensive as cigarettes.

More importantly, the FDA has sidestepped closer scrutiny of the presumption that smoking is synonymous with addiction to nicotine. Although the Drug Abuse Advisory Committee noted the interaction of environmental influences, biological factors, and learning behavior that initiate and perpetuate smoking, it did not challenge the accepted central role of nicotine in the dependence-producing process. Although blood nicotine levels in smokers of so-called low-nicotine cigarettes are similar to those in smokers of high-nicotine brands (suggesting that smokers seek nicotine by inhaling more deeply) (10), the role of advertising and other social reinforcement may be at least as important as physical dependence in perpetuating smoking behavior. If smoking were primarily a nicotine addiction, cigarette manufacturers would be foolish to spend enormous sums of money on advertising ($1.5 billion/year, more than for any other product in society) to aim at an already "hooked" population. Nor would it make sense for them to keep introducing new brands, filters, package designs, and apparent health claims, such as "low tar" or "ultra low tar."

A related concern arises from current advertising in medical journals and the publicity in the mass media by the manufacturer of Nicorette that blames nicotine dependence for the failure to stop smoking. Such messages reinforce the notion that cigarette smoking is a medical problem that has a simple, prescribable, non-individualized solution.

Little information is available on the long-term safety of nicotine gum. That side effects (principally hiccups, nausea, and indigestion) are common, if not the rule, in even inveterate smokers who use the gum is cause for concern. The effects on adolescents and the elderly, who may ask their physicians to prescribe the gum as its publicity increases, are unknown. In pregnant women, a group with strong motivation to stop smoking, the gum is contraindicated because of potential harm to the fetus, and the gum is not recommended in nursing mothers.

When Nicorette was introduced in Canada a few years ago, advertisements (since withdrawn) in medical journals specifically recommended it for patients with cardiovascular disease. It was reasoned that because the level of nicotine absorbed per lozenge approximates that absorbed after smoking a cigarette, the nicotine absorption from the gum is less hazardous than the inhaled combination of carcinogenic hydrocarbons and toxic gases. However, no studies have shown the safety of Nicorette in patients with known or suspected coronary heart disease. The required professional labeling information urges the prescriber to weigh the benefits versus the risks in such patients. Specifically, patients with a history of myocardial infarction, angina pectoris, serious cardiac arrhythmias, Buerger's disease, or Prinzmetal variant angina should be carefully examined if the gum is to be prescribed.

The manufacturer does not suggest that nicotine gum will work in a person who is not highly motivated. All researchers emphasize that continued motivation, social support, and encouragement to tolerate the unpleasantness of the gum are essential to prevent a return to smoking. Who, then, among the estimated smoking population of 56 million will benefit most from nicotine gum? The likely candidates are those who smoke most heavily or who already have chronic obstructive pulmonary disease.

Thus, although nicotine gum may be worth prescribing in some patients, it is by no means a panacea. The most important single influence in smoking cessation remains the caring attitude of the physician (8, 11). It goes without saying that persons are further helped to stop smoking—or never to start—when given frequent positive social reinforcement (such as counteradvertising in the mass media and the institution of a smokefree workplace) and financial incentives (for example, lower health, life, and fire insurance premiums) for not lighting up. Such efforts warrant the increased support of all physicians—and pharmaceutical companies. (ALAN BLUM, M.D.; *Editor,* New York State Journal of Medicine; *Lake Success, New York*)

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Treatment of Ventricular Arrhythmias—Suppression, Survival, and the Problem of Bias

VARIOUS INNOVATIVE DRUG, surgical, and electrical treatments have been used recently for patients with ventricular tachyarrhythmias (1-8). Each approach has enthusiastic advocates who compare studies and attribute fewer recurrent arrhythmias or improved survival to a particular treatment. However, no adequate comparative studies between these therapies have been done. Furthermore, because of ethical and practical constraints, randomized placebo-controlled studies that may approximate an ideal comparison may never be done for some of these therapies (9). Because of reports of promising, albeit uncontrolled, data, many physicians are understandably reluctant to withhold a particular treatment from a patient considered to be at high risk of sudden death. How then are these various therapies to be judged?

An ideal comparative study should determine what happens when a treatment is applied to a given patient population, and what would happen had those patients not been given that treatment. The differences in outcome are then attributable to the treatment, and the benefits (or lack of them) can be quantitated. Such a hypothetical study is clearly impossible, but the rationale underlying such an approach has been used in a recent study analyzing mortality in patients in whom an automatic internal defibrillator had been implanted (7). Because this device does not prevent the initiation of a ventricular tachyarrhythmia but rather terminates an arrhythmia should it occur, a syncopal episode occurring outside the hospital that is corrected by the device may be assumed to represent an aborted sudden death. If this assumption is correct, life-table analysis shows a 52% reduction in the occurrence of sudden death at 1 year. Thus, the efficacy of a particular treatment can be estimated.

However, because the purpose of drug and surgical treatments generally is to prevent the recurrence of cardiac arrhythmias and sudden death, an alternative analysis must be done. Because of the sporadic occurrence of cardiac arrhythmias, a population that can be compared with the treatment group must be found. To be meaningful, the outcome in the comparison group should closely approximate the expected outcome in the treatment group had they not received the treatment in question. Examples of comparison groups that may be used include randomized control groups, nonrandomized control groups, and historical control groups. If any of these control groups is to serve as an adequate comparison, differences other than in the specific treatment given should be minimal. When these comparisons are attempted, adequate data should be presented to allow the reader to assess the comparability of the groups and therefore to assess the extent of possible biases.

Random assignment to treatment or placebo is the most efficient way of establishing a comparison group if the investigator can prescribe which treatment a patient is to receive. Randomization affords protection against physician or patient selection biases and facilitates the detection of causes of observed differences. No randomized control studies to date have compared treatments in patients presenting with ventricular tachycardia or fibrillation, but randomized control studies have been used to assess the ability of antiarrhythmic drugs to prevent ventricular tachyarrhythmias in patients with acute myocardial infarction or chronic stable ventricular arrhythmias (10-12). Random assignment of patients to a standard antiarrhythmic treatment rather than to placebo may be useful when placebo studies are not justifiable.

Nonrandomized studies are frequently the only practicable and ethically justifiable studies in patients with ventricular tachycardia or fibrillation. In such studies, a careful clinical and statistical analysis is necessary to minimize bias in interpreting the results (13). Many studies of new therapies for ventricular arrhythmias are of this type; they may compare various subsets of treated patients, for example, patients in whom arrhythmias are not suppressed (internal controls) and patients in whom arrhythmias are suppressed. The assumption of such an analysis is that if patients considered to be successfully treated live longer or have fewer recurrent arrhythmias than patients not successfully treated, then the treatment has conferred a benefit. Studies claiming to show benefit from a therapy using invasive electrophysiologic procedures or Holter monitoring follow this pattern (2-6).

The difficulty with such studies is that the ability to suppress arrhythmias may simply separate patients who are going to do well from those who are not, the prognosis for individual patients being determined by other in-