Tobacco Use, Treatment Strategies, and Pharmacological Adjuncts: An Overview

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INTRODUCTION

The colorful history of tobacco use has been reviewed by several authors (e.g., Bell and Grabowski 1983; Jaffe and Kanzler 1981; Surgeon General's Report, (USDHEW) 1964, 1979; Ray 1972; Jarvik 1970 and has been described in numerous historical treatises and papers.

The suggested hazards of tobacco use were enumerated shortly after its introduction to Europe in the 16th century. At the same time its presumed virtue as a general purpose medicament was extolled (Ray 1972). Since then the proponents and opponents of tobacco use have vigorously debated their positions. Ample evidence of potential harm has accumulated indicating disease conditions correlated with tobacco use. These data have been presented in many scientific articles and in the summaries provided by the Surgeon General's Reports between 1964 and 1984.

The wealth of findings on adverse health effects of tobacco use have generated vigorous efforts in two domains. The first is development of techniques to prevent young nonusers from initiating tobacco use. The second is to establish optimal techniques for eliminating tobacco use in those who smoke or otherwise consume tobacco products. A concise statement of the character of the dilemma is often attributed to Mark Twain: "I can quit smoking if I wish; I've done it a thousand times." Recent restatements of this problem by scientists are evident in the change of focus from cessation alone (i.e., quitting) to maintenance of cessation (e.g., USDHHS 1980; Hall 1980, 1984).

Efforts to eliminate tobacco use began a short time after its introduction. Diverse remedies have been described, some ludicrous, others macabre. In recent years, five categories of reasonable cessation efforts have had prominence, including: (1) public information campaigns, (2) "self-help" programs, (3) group support programs, (4) individualized behavioral intervention programs, and (5) pharmacological interventions. Although identified as distinct and separate, many efforts, of course, have combined elements of the various approaches. Indeed, most recently
it has become evident that optimal programs may include combinations of behavioral intervention, group support, and use of pharmacological adjuncts (e.g., Hall and Killen, this volume).

INFORMATION AND LEGISLATIVE MASS INTERVENTIONS

The five cessation intervention categories differ in a variety of ways. One dimension is degree of external intervention which usually covaries with the size of the population intervened upon. For example, there have been several forms of governmental efforts to reduce tobacco use. One is announcements to the press. Although these efforts have been ongoing for many years, they became clearly focused following publication of the first Surgeon General's Report (USDHEW 1964). Other widely distributed public health messages are the advertising campaigns developed by the National Cancer Institute, National Heart, Lung, and Blood Institute, Office on Smoking and Health, and the National Institute on Drug Abuse.

Still another media-based effort is that developed by the National Cancer Institute and the National Heart, Lung, and Blood Institute. The program had a local television news personality go through his or her personal smoking cessation program in full view of the public. Throughout the several weeks of the program viewers were encouraged to follow the instructions and guidance by the status model provided. These broad-based public efforts reach large numbers of people, with varying degrees of effect. An advertising campaign reaches many people but can, by virtue of the technique, convey only simple messages. The "Status Model" strategy reaches a lesser number, provides many specific and clear instructions on smoking cessation techniques, but has no genuine followup interaction provisions.

Other broad efforts with less personal "direction" have taken the form of substantial tax increases on tobacco products and labelling of tobacco products as well as advertising (in the United States, cigarettes only) with warnings. Indeed, the rotational warning label system used in other countries will soon be introduced in the United States.

Taxation, an indirect mechanism, can have a dramatic effect on many people if properly implemented. To the extent that price affects purchase, consumption is likely to be dramatically altered if the increase is large. Data from a Canadian report (Ontario Council of Health 1982) indicated a clear relationship between cigarette price and consumption. With some exceptions, it is evident that cigarette consumption is highest in countries where price is lowest. In those countries where extremely high taxes have been levied (e.g., Norway), the consumption of manufactured cigarettes declines, but there is increased likelihood that smokers will "roll their own." However, they do not override the effect of the tax; i.e., consumption remains lower than before the tax. The Canadian report suggests that the optimal taxation is one which doubles the price. It results in decreased consumption but does not induce a dramatic shift from manufactured to hand-rolled cigarettes. It appears that
price increases are most likely to decrease purchases by young people (Lewit 1983). This may generate a considerable benefit in prevention.

Large-scale programs sacrifice precision, are variably successful, and resultant indicators of change are indirect. However, it is probable that these advertising and social intervention approaches have had an effect, since major shifts in populations smoking and numbers of smokers have occurred. Since at least some of these efforts are based on advertising strategies with documented effectiveness, parallel consequences in affecting smoking behavior can justifiably be assumed.

Nevertheless, it has been suggested that mass communication strategies do have limits. For example, they appear to require an underlying foundation of receptive personal views, social influence, and environmental circumstances favorable to enhancement of the message (USDHHS 1982, 1984). In the case of tobacco use, this change in perspective is only gradually occurring. In addition, it is unclear whether the message and favorable conditions extend to all forms of tobacco use or are limited to cigarette use. If current public understanding of hazards is limited to cigarette smoking, one unfortunate effect of current mass communication efforts might be a shift by some individuals from one preparation form to another (e.g., cigarettes to chewing tobacco).

Overall it appears likely that just as an integrated effort is optimal at the individual level, it is necessary to combine diverse elements in the health and behavior messages aimed at broad audiences. Legislative, health agency, and broadcast media efforts in concert will be most effective, interacting with the messages provided at the individualized program level.

SELF-HELP PROGRAMS IN SMOKING CESSATION

There has been recent emphasis on self-help and other "cost-effective" approaches. The concept of self-help has gained popularity for a number of reasons. Popularity derives in part from popular notions of "self-control," "free will," and "bootstrap" progress. Such efforts are also considered to be economical of time and money by some. Evidence of less immediate cost in a given program can probably be provided. However, "self-help" programs may rely heavily on diverse long-term efforts which are both expensive and time-consuming. Thus, the actual effectiveness of the program may reflect decades of costly advertising, legislation, and influence on the individual and his or her social group. These efforts include the time and money spent in preparing elaborate self-help materials, as well as media and other public health efforts supportive of nonsmoking. Also, the success rates for unassisted self-help "bibliotherapy" (Glasgow and Rosen 1978) are generally not substantial, although some favorable results have been noted (USDHHS 1982).
Self-help materials probably require a user well versed in the strategy and goal of the self-help approach. The level of sophistication required of the user may deter some individuals and preclude success of others. Thus, it is likely that such materials are best used in concert with instruction from a knowledgeable professional. It is perhaps ironic that substantial efforts have been made to develop intensive clinically guided therapies for users of various other drugs associated with less persistent drug-seeking than cigarettes. The cigarette smoker is more often relegated to the self-help efforts.

A comment is warranted about the individuals who quit "cold turkey," without assistance. In this culture, the volume and scope of the antismoking campaigns and materials are such that most, if not all, smokers have been influenced in some degree, and thus have received some aid in quitting. It should also be noted that only a small percentage (10%-27%) of those who engage in "spontaneous cessation" continue as nonsmokers for 1-5 years. In addition, as many as 90% of smokers verbalize an interest in quitting. Therefore, the need for effective intensive interventions remains.

GROUP AND SOCIAL SUPPORT PROGRAMS

A number of public agencies (e.g., American Cancer Society; National Heart, Lung, and Blood Institute), private nonprofit groups (e.g., American Lung Association), and for-profit groups (e.g., Smokenders) have implemented smoking cessation programs. The common element in the programs resides in use of a standardized intervention package with groups which meet regularly. Social pressure and social reinforcement are common treatment mechanisms. The leaders of all such programs typically strive to develop behavioral analysis skills in the participants. The smokers (now exsmokers) learn to examine the behavior itself and the conditions under which it occurs, and they plan a cessation date. Some form of followup intervention is characteristic. These programs have varying degrees of success, which may be influenced by many factors, including leader expertise and subject characteristics. Unfortunately, few data are available on the long-term results of such programs. That is, all tend to be effective in producing cessation, but the rate at which cessation is maintained is not clear. Furthermore, it is likely that particular intervention strategies will be more effective with some people than with others. Indeed, the problem in terms of success is likely to parallel that observed for the common treatment approaches for many behavioral disorders. That is, there is a need to match each client with an appropriate therapy.

INDIVIDUALIZED PROGRAMS

Individualized smoking programs are uncommon. The number of cigarette smokers who actually seek a clinician for an individualized behavioral intervention program is probably minimal, although no data are available. However, this does not take into
account physician-implemented, pharmacological interventions which, with the introduction of nicotine gum will likely be extremely common but lacking in meaningful behavioral intervention components. For example, 700,000 prescriptions for the gum were written in its first 2-1/2 months on the market (Consumer Reports 1984). The appropriateness of applied behavioral techniques coinciding with administration of this pharmacological adjunct is unknown, despite the manufacturer's efforts to educate physicians in its optimal use. However, the effort may well be enhanced by recent coverage in professional information sources (e.g., JAMA 1984).

A substantial literature of case reports, as well as more systematic experimental analyses of smoking behavior and cessation attempts has been reviewed. The primary problem with individualized programs will be, of course, that they are costly. On the other hand, if individualized programs, or standardized programs with latitude for individual modification, can be demonstrated to be effective for many clients, the long-term benefits in reduced medical costs may be substantial. It appears that integrated programs of the sort described by Hall and Killen (this volume) or Pomerleau and Pomerleau (1977) will prove most useful in the quest for successful intervention. Again, the broader view suggests that all will be more effective against a backdrop of concerted public health advertising, legislation, and other social interventions.

PHARMACOLOGICAL INTERVENTIONS

Over the years, a wide range of agents has been proposed as possible pharmacological adjuncts for treatment of cigarette smoking. In an interesting review, Kozlowski (1984) has noted that completely ineffective pharmacological techniques have been promulgated as "cures" for tobacco use. Various studies have also examined mechanisms by which pharmacological agents demonstrably effective for other purposes might alter cigarette smoking.

Pharmacological interventions for tobacco use derive from several assumptions in part related to putative "reasons" for smoking. While many properties of nicotine align it with prototypic "stimulant-like" drugs, cigarette smokers often refer to calming effects.

Multiple possible origins exist for these reported disparate effects. There may, of course, be dose-dependent variations in the dominant effect of nicotine (Domino 1973). The behavioral effects of nicotine may be dependent on the baseline level of activity of the individual. This has been amply demonstrated with other behaviorally active agents. Thus, a rate-dependent decline, or "subduing effect," may occur under conditions of high activity, while rate-increasing, or "activating" effects may emerge when baseline activity is low. The possibility of interaction between certain classes of behavior and observed effect may be important. Interaction of doses, behaviors, and environmental conditions may be perceived as enhancing or decreasing activity. For example,
increasing focus of attention and decreased distractibility may, despite their derivation from a stimulant action, be effectively calming to the smoker.

An entirely different and seldom considered mechanism by which "sedative" actions might be achieved are those associated with regulation of carbon monoxide levels or potential interactions between this gas and nicotine. Thus, while nicotine is likely the dominant pharmacological reinforcer in tobacco use, maintenance of comparatively high carbon monoxide levels cannot be ignored in terms of potential behaviorally relevant physiological effects. Finally, another source for the apparent disparity in the reported effects of smoking may also reside in the pharmacological profile of nicotine itself. While nicotine is often noted for its similarity to drugs such as dextroamphetamine, it differs along several dimensions (Domino 1973), although the effects on standard measures of rates of behavior are similar. The critical issue in all such discussions appears to be dose. It must be recalled that the doses obtained via smoking are relatively low, and it is in the low dosage range that primarily stimulant-like effects have been reported.

Depending on the effects of nicotine thought to be dominant in maintaining tobacco use, sedatives, anxiolytics, or stimulants might be administered to decrease cigarette smoking. Indeed, the range of options parallels that for other forms of pharmacological intervention in cases of drug dependence. Another alternative approach is blocking of nicotine's effects. The most obvious and direct strategy, however, is to administer nicotine itself in an alternative form. Several authors have provided overviews of the rationale for various pharmacological strategies for smoking cessation (e.g., Kozlowski 1984; Schuster et al. 1977; Jarvik 1973). In the main, these reside in substitution for the presumed primary effect.

The optimal and practically unattainable drug would, of course, reduce cigarette use independent of the subject or client's "desire" to stop smoking. Sedatives and anxiolytics have generally been noted to be ineffective in reducing smoking in either acute or longer term demonstrations (e.g., Whitehead and Davies 1964; Schuster et al. 1977; Kozlowski 1984). Thus the notion of parallels with "anxiety-reducing" agents is minimized despite the common subjective report of this property of tobacco self-administration. Conversely, the view of tobacco use as having generalized energizing characteristics for which other "stimulant-like" drugs might substitute is countered by the results of Whitehead and Davis (1964) and Schuster et al. (1977). Indeed, Schuster et al. (1977) reported acute increases in cigarette smoking as a function of dextroamphetamine administration.

Other drugs administered to decrease tobacco use have included lobeline, naloxone, propranolol, alkalizing agents, and mecamylamine. Schuster et al. (1977) demonstrated that lobeline has no practical effect at the doses recommended. It is nevertheless sold over the counter under several brand names. Naltrexone, a relatively short-acting narcotic antagonist, has been reported to
reduce puffs/cigarette, and number of cigarettes over its duration of action (Karras and Kane 1980), although the elaborate neurochemically based rationale for its effectiveness is not compelling, since general reductions in food and water intake have also been observed. Nevertheless, given the current availability of longer acting variants, e.g., naltrexone, further research might be of interest. In addition, some investigators appear to be defining more precisely the specific neuroregulatory and reinforcement mechanisms of smoking (Pomerleau and Pomerleau 1984). Propranolol, an effective antihypertensive which has also been noted to relieve some physiological correlates of anxiety, has been reported to be ineffective in a large double-blind study (Farebrother et al. 1980).

The rationale for the use of sodium bicarbonate or other alkalizing agents to change urine pH and thereby sustain nicotine blood levels has complex underpinnings. As Schachter et al. (1977) noted, increasing urine alkalinity "can have at best trivial effects on plasma level nicotine." Nevertheless, the approach gained some acceptance because of presumed interactions between stress, nicotine metabolism and urine pH, and the belief that the alkalizing effect would, under certain conditions, not be trivial. There are at present few proponents of using the alkalizing strategy in smoking cessation programs. However, much has been published in the scientific and popular press on the topic.

One other proposed pharmacological intervention, mecamylamine, is logically reasonable but may be lacking practical merit. It has been argued, as is mentioned by Henningfield and Nemeth-Coslett (this volume) and Henningfield et al. (1982) that mecamylamine, as a nicotine blocking agent, might be a useful adjunct in smoking cessation. There is clear evidence of mecamylamine's effectiveness in blocking nicotine's action at doses which have no untoward effects. Theoretically, its value is apparent, and a cogent case for its utility was made more than a decade ago by Jarvik (1973). However, Jaffe (1973) noted, with respect to use of narcotic antagonists in treatment of opiate abuse, that antagonist treatment is "largely a promise unfulfilled." The problem parallels that arising in the use of disulfiram in the treatment of ethanol abuse, or naltrexone for opiates, i.e., patients select other options.

In the main, pharmacological adjuncts without at least modest inherent reinforcing properties have not been widely accepted by patients (e.g., Grabowski et al. 1979; Grabowski 1984). In this regard, mecamylamine would likely be no exception, particularly when more reinforcing options such as nicotine exist. Nevertheless, the potential utility of the drug in patients who are "highly motivated" or for whom nicotine is contraindicated is considerable. Effectively blocking nicotine's direct effects may therefore have promise if combined with behavioral intervention strategies. Indeed, the potential clinical utility of mecamylamine has been demonstrated in a study by Tennant et al. (1983) and was considered a "viable withdrawal treatment for some case of recalcitrant nicotine dependence." The most obvious pharmacological adjunct is nicotine itself, and it is the major focus of the present volume. Introduction of a nicotine-laced chewing gum approved by
the U.S. Food and Drug Administration in the spring of 1984 has generated considerable interest in both the scientific and lay communities. It has been extensively discussed in the scientific and quasi-scientific literature and lay press (e.g., Consumer Reports 1984). The origins of the widespread interest are likely three-fold. First, the U.S. distributor has, of course, made sweeping publicity efforts. Second, the scientific community is encouraged not only by the therapeutic implications of the product, but also by its usefulness in human research requiring nicotine administration. Third, it is probable that much of the cigarette-using population of the U.S. has been awaiting a "magic bullet" which would eliminate the behavior and alleviate all discomfort coinciding with cessation, however ill-advised this view may be.

The rationale for administration of nicotine gum to maintain cigarette abstinence is clear. It entails substitution of one nicotine preparation form for another. It parallels in some respects administration of methylphenidate or antidepressants for treatment of cocaine abuse (Kleber and Gawin 1984; Khantzian 1983), the use of methadone for heroin abuse, or perhaps controlled administration of various sedatives or anxiolytics in the treatment of alcohol abuse.

Since nicotine is dominantly "stimulant-like" at the lower doses typically self-administered by tobacco users, the cocaine-methylphenidate analogy is perhaps most apt (e.g., Henningfield and Nemeth-Coslett, this volume). Therefore, positive reinforcing effectiveness, rather than "withdrawal symptoms," may be the primary factors maintaining self-administration (Hatsukami et al., this volume). Substitution of a distinctly similar alternative agent, or the same agent in a different form is reasonable. It precludes the loss of reinforcing effects of self-administration while terminating the behavioral components which exist at high strength in long-time smokers.

Krivokapich et al. (this volume) have evaluated cardiovascular effects of nicotine gum. They have further substantiated its apparent absence of pronounced cardiovascular effects within the recommended dosage range. Given the fact that for individuals in good health, the effects of nicotine at standard doses are relatively safe, clear advantages exist in self-administration of nicotine via the buccal route, rather than combined with the diverse chemical and particulate constituents in cigarette smoke. Indeed, while not specifically approved for treatment of chewing tobacco use, nicotine-laced gum conceptually approximates the behaviorally ideal adjunct in this case also.

The issue of effectiveness of nicotine gum in smoking cessation is, of course, as complex as the behavior itself. As discussed by Henning and Jones (this volume), differing behavioral patterns exist among smokers, most of which lead to inhalation of significant amounts of nicotine; these can be modulated by administration of gum. Henningfield and Nemeth-Coslett (this volume), among others, make an excellent case for the role of nicotine in the maintenance
of cigarette smoking and report data concerning the characteristics of nicotine self-administration via the buccal route (gum preparation form).

Further supporting the case for nicotine self-administration as an important factor in maintaining cigarette smoking for some individuals is the report by Hatsukami et al. (this volume) which provides data suggesting the importance of positive reinforcement as a major factor sustaining smoking behavior. Their data add to the case that behavioral correlates of smoking and cessation, rather than physiological symptomatology per se, must be the primary focus of cessation maintenance efforts. The data also further support the potential usefulness of nicotine-laced chewing gum in attaining this goal. Hughes and Hatsukami (this volume) further delineate the physiological and behavioral parameters of nicotine administered via the buccal route.

The crucial issue concerning nicotine gum as a pharmacological adjunct is whether it does, in fact, increase cessation maintenance, an issue explicitly addressed in this volume by Schneider and Jarvik, Russell and Jarvis, Fagerstrom and Melin, and Hall and Killen. It is evident that smoking is a behavior modulated and determined by complex interacting behavioral, social, sensory, and pharmacological factors.

Schneider and Jarvik (this volume) address the clinically pertinent individual characteristics. Their data point to the relationship between degree of behavioral dependence on cigarette smoking and the effectiveness of the gum. Russell and Jarvis (this volume), in addition to providing a thorough review, address the relevance of individual social factors and the role of the clinician in cessation efforts. They note on one hand the direct effect of the gum, but likewise note that whatever placebo effects may exist can be used to advantage.

Fagerstrom is among the most experienced investigators of the gum's effects in clinical settings. Fagerstrom's notable efforts with both development of innovative measures of dependence and analysis of the usefulness of the gum in clinical settings have been of value to numerous investigators. These studies and strategies are reviewed in this volume.

It appears that behavioral programs combined with nicotine gum and emphasis on relapse prevention produce the best outcome (e.g., Hall et al. 1985; Hall and Killen, this volume). These group-based procedures, which rely on social reinforcement, including a variety of specific positive reinforcement and punishment techniques, and which include followup support, will likely prove the most beneficial strategy for most smokers.

AN INTEGRATED VIEW OF PHARMACOLOGICAL ADJUNCTS AND TREATMENT

Concerns which have existed about pharmacological adjuncts for other drug-use problems also prevail with respect to nicotine gum and
would likely arise for any other new agent. Many of these concerns were addressed during the course of the U.S. Food and Drug Administration's review of data in support of efficacy of nicotine gum.

The fundamental question, of course, is whether or not the gum will effectively enhance smoking cessation. If nicotine is the primary pharmacological agent maintaining tobacco use, then administration of nicotine in alternative forms providing similar nicotine blood levels should be effective in terms of the pharmacological component. Nicotine gum does this, but there are differences in onset characteristics which make it less likely to be effective as a reinforcer (although Henningfield and Nemeth-Coslett, this volume, indicate that chewing characteristics can alter onset).

If it is effective as a reinforcer, the question arises whether it is likely to be misused or used excessively for its positive reinforcing effects. An objective analysis suggests that this is possible, although the most likely form of "misuse" will probably be continuation of use beyond the tentatively recommended period of 3 to 6 months. Indeed, several investigators have already suggested that use of the gum at higher doses for longer periods will probably generate more favorable long-term abstinence percentages. Interestingly, this parallels data available for other substitution treatments (Dole and Nyswander 1983).

The issue is whether "misuse" or prolonged use of the gum is likely to be a significant problem in Switzerland, where the gum is available without prescription, no significant problems have been reported. In any case, another point arises when prolonged use is considered. Chronic use of the gum results in nicotine levels paralleling those which an individual would attain through smoking. These are achieved without the bolus and rapid onset produced by smoking which could arguably be a problem to individuals with cardiovascular problems. Thus, the hazards of carbon monoxide, hydrocarbons, particulate matter, and numerous chemicals are eliminated when the individual chew the gum rather than smokes cigarettes. Obviously, the gum does not have the hydrocarbon and chemical hazards associated with chewing tobacco. Overall, the health advantages in terms of reduced risk using the gum are numerous.

Questions about conditions of use and usefulness do exist. Results of many studies with the gum have been equivocal. Others have produced more favorable results. However, as with other pharmacological adjuncts for drug abuse or tobacco use which have been mentioned, the gum is not a "magic bullet" or panacea. It is likely that many people will at first use the gum without success. The critical determinants of successful use appear to be related to whether the gum, in fact, used as a pharmacological adjunct in conjunction with an appropriate array of behavioral intervention techniques and environmental influences. This volume and the literature in general adequately amplify the need for such a combined strategy in this and other areas of health and behavior.
REFERENCES


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