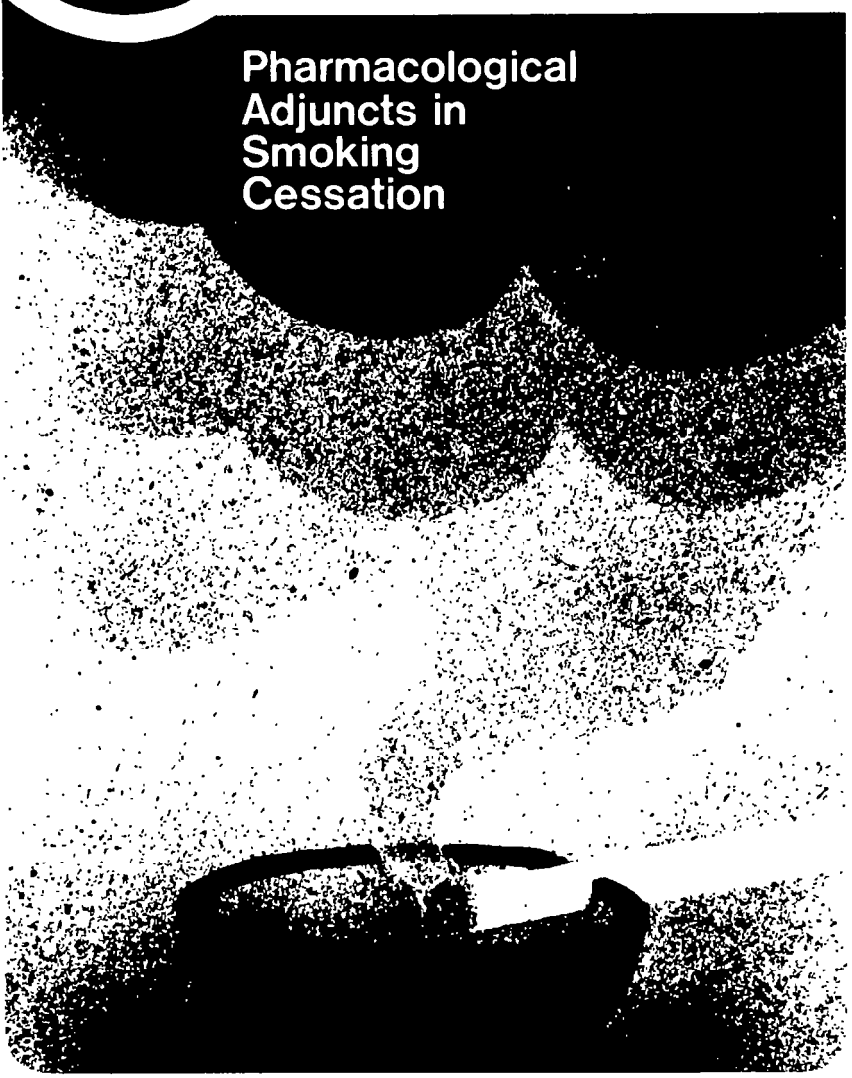
National Institute on Drug Abuse

Research 53

MONOGRAPH SERIES

Pharmacological Adjuncts in Smoking Cessation



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

Pharmacological Adjuncts in Smoking Cessation

Editors:

John Grabowski, Ph.D.
Division of Clinical Research
National Institute on Drug Abuse

Sharon M. Hall, Ph.D
Langley-Porter Institute
University of California, San Francisco

NIDA Research Monograph 53
1985

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
600 Fishers Lane
Rockville, Maryland 20857

For sale by the Superintendent of Documents, US Government Printing Office
Washington, D.C. 20402

NIDA Research Monographs are prepared by the research divisions of the National Institute on Drug Abuse and published by its Office of Science. The primary objective of the series Is to provide critical reviews of research problem areas and techniques. the content of state-of-the-art conferences, and Integrative research reviews. Its dual publication emphasis is rapid and targeted dissemination to the scientific and professional community.

Editorial Advisors

NIDA Research Monograph Series

Parklawn Building, 5600 Ashen Lane. Rockville, Maryland 20657

Pharmacological Adjuncts in Smoking Cessation

DHHS publication number (ADM)85-1333
Printed 1985

NIDA Research Monographs are indexed in the Index Medicus. They are selectively included in the coverage of American Statistics Index, Biosciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts, and Psychopharmacology Abstracts.

Foreword

The relationship between tobacco use and detrimental effects on health is clear. It is less clear how we can best assist those who are dependent on tobacco in their efforts to control or abstain from its use.

Tobacco dependence, with its pharmacological and behavioral complexity, has been the object of numerous and diverse forms of intervention. No single technique has been generally effective. This is not surprisng. Rather, substantial clinical and laboratory research efforts have pointed to multiple determinants in the maintenance of the behavior. This in turn dictates that the most effective interventions will, likewise, have multiple components. In general, administration of drugs to treat drugs dependence is neither novel nor universally effective; this generalization certainly holds true for tobacco. Over the years, many drugs have been tried as treatments for tobacco dependence; most have been proven to be ineffective when tested under well designed research conditions. Yet, given the millions of smokers who have difficulty stopping their use of tobacco, the potental value of a pharmacological agent as an adjunct to the treatment of tobacco dependence is evident.

Recently, several agents have been introduced or recommended on the basis of controlled trials. This volume reviews and samples the most recent literature and scientific work on nicotine and tobacco dependence. The findings point to the utility of integrating behavioral and pharmacological treatment strategies in tobacco dependence and have implications for the development of therapeutic interventions for other dependence disorders.

Jerome Jaffe, M.D.
Acting Director
National Institute on Drug Abuse

Contents

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

John Grabowski, Ph.D., and Sharon M. Hall, Ph.D.

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 Generals' 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 intervention or 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. There- fore, 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 dextro-amphetamine 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 dlsulfram 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., Grabowskl 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 Herning 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 chews 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 is, 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

Bell, C.S., and Grabowski, J. Overview of smoking research Issues. In: Grabowski, J. and Bell, C. (eds.). Measurement in the Analysis and Treatment of Smoking Behavior. National Institute on Drug Abuse (NIDA) Research Monograph 48. Washington, DC: Supt. of Docs., US Govt. Print. Off., 1983. pp 1-5.

Benowitz, N.L. The use of biologic fluid samples in assessing tobacco smoke consumption. In: Grabowski. J., and Bell, C.S. (eds.) Measurement in the Analysis and Treatment of Smoking Behavior. NIDA Research Monograph 48. Washington DC: Supt. of Docs., US Govt. Print. Off., 1983. pp 6-26.

Domino, E.F. Neuropsychopharmacology of nicotine and smoking. In: Dunn, W.L. (ed.) Smoking Behavior: Motives and Incentives. Washington, DC: V.H. Winston and Sons, 1973. pp 5-29.

Farebrother. M.J.B.; Pearce, S.J.; Turner, P.; and Appleton, D.R. Propranolol and giving up smoking. British Journal of Diseases of the Chest, 74: 95-96, 1980.

Glasgow, R.E., and Rosen, G.M. Behavioral bibliotherapy: A review of self-help behavior therapy manuals. Psychological Bulletin 85:(1):1-23. 1978.

Glasgow, R.E., and Rosen, G.M. Self-help behavior therapy manuals: Recent developments and clinical usage. Clinical Behavior Therapy Review 1:1-20, 1979.

Goldberg, S.R., and Spealman, R.D. Nicotine as punisher: Effects of chlordiazepoxide and mecamylamine on responding suppressed by intravenous nicotine injection or by electric shocks. In: Harris, L.S. (ed.) Problems of Drug Dependence, 1982. Proceedings of the Committee on Problems of Drug Dependence, Inc. NIDA Research Monograph 43. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1983. p 372.

Grabowski, J .; O'Brien, C.P .; Greenstein, R.; Ternes, J.; Long, M.; and Steinberg-Donato, S. Effects of contingent payment on compliance with a naltrexone regimen. American Jounral of Drug and Alcohol Abuse 6: 355-365, 1983.

Grabowski, J. Profiles of ideal drugs for therapeutic social use. Paper presented at the 92nd Annual Meeting of the American Psychological Association, August 1984.

Hall, S.M. Self-management and therapeutic maintenance: Theory research. In Karoly, P., and Steffan, J. (eds.). Improving the Long-Term Effects of Psychotherapy. New York: Gardner, 1980. pp 263-300.

Hall, S.M .; Tunstall, C.D.; Rugg, D.L.; Jones, R.G.; and Benowitz, N.L. Nicotine gum and behavioral treatment in smoking cessation. Journal of Consulting and Clinical Psychology 52:372-382, 1984.

Henningfield, J.E. Measurement issues in cigarette smoking research: Basic behavioral and physiological effects and patterns of nicotine self-administration. In: Grabowski, J., and Bell, C.S. (eds.) Measurement in Analysis and Treatment of Smoking Behavior. NIDA Research Monograph 48. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1983.

Henningfield. J.E.; Katsumasa, M.; Johnson, R.E.; and Jasinski, D. Rapid physiological effects of nicotine in humans and selective blockade of behavioral effects by mecamylamine. In Harris, L.S. (ed.) Problems of Drug Dependence, 1982. NIDA Research Monograph 43. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1983. pp 259-265.

Jaffe. J.H. Pharmacological and Societal Factors in the Management of Drug Dependence. In: Braude, M.C.; Harris, L.S.; May, E.L.; Smith, J.P.; and Villarreal, J.E. (eds.) Narcotic Antagonists. New York: Raven Press, 1973. pp 3-7.

Jaffe, J.H., and Kanzler, M. Nicotine: Tobacco use, abuse and dependence. In: Lowinson, J.H., and Ruiz, P. (eds.) Substance Abuse: Clinical Problems and Perspectives. Baltimore, MD: Williams and Wilkins, 1981. pp 256-273.

Jarvik, M.E. The role of nicotine in the smoking habit. In: Hunt, W.A. (ed.) Learning Mechanisms in Smoking. New York: Aldine, 1970. pp 155-190.

Jarvik, M.E. Further observations on nicotine as the reinforcing agent in smoking. In: Dunn, W.L. (ed.) Smoking Behavior: Motives and Incentives. Washington, DC: V.H. Winston and Sons 1973. pp 33-49.

Journal of the American Medical Association 252: (Special issue on tobacco use.) November 23, 1984.

Karras, A., and Kare, J.M. Naloxone reduces cigarette smoking. Life Sciences 27: 1541-1545, 1980.

Kozlowski, L.T. Pharmacological approaches to smoking modification. In: Matarazzo. J.D.; Weiss, S.M.; Herd, A.J.; et al. Behavioral Health: A Handbook of Health Enhancement and Disease Prevention. New York: Wiley, 1984.

Lewit, E.M. Economics of cigarette smoking. Paper presented at the 14th Annual Meeting of Environmental Mutagen Society, San Antonio, March 1983.

Lucchesi, B.R.; Schuster, C.R.; and Emley, G.S. The role of cigarette smoking frequency in man with observation on certain cardiovascular effects associated with the tobacco alkaloid. Clinical Pharamcology and Therapeutics, 8: 789-796, 1967.

Ontario Council of Health. Smoking and Health in Ontario: A Need for Balance. A Report for the Ontario Council of Health, Toronto; 1982.

Pomerleau, O.F., and Pomerleau, C.S. Breaking the Smoking Habit: A Behavioral Program for Giving Up Cigarettes. Champaign, IL: Research Press. 1977.

Pomerleau, O.F., and Pomerleau, C.S. Neuroregulators and the reinforcement of smoking: Towards a behavioral explanation. Neuroscience and Behavioral Reviews 8: 503-513. 1984.

Ray, O.S. Drugs, Society and Human Behavior. St. Louis: C.V. Mosby co., 1972.

Rosenberg, J; Benowitz, N.L.; Jacob, P.; and Wilson, K.M. Disposition kinetics and effects of intravenous nicotine. Clinical Pharmacology and Therapeutics 28: 517-522. 1980.

Schachter. S: Kozlowski, L.T.: and Silverstein. B. Effects of urinary p^H on cigarette smoking. Journal of Experimental Psychology: General 106: 13-19, 1977.

Schuster, C.R., and Johanson, C.E. An analysis of drugseeking behavior in animals. Neuroscience and Behavioral Reviews 5: 315-323, 1981.

Schuster, C.R.; Lucchesi, B.R.; and Emley, G.S. The effects of d-amphetamine, meprobamate and lobeline on the cigarette smoking behavior of normal human subjects. In: Krasnegor, N. (ed.) Cigarette Smoking a Dependence Process. NIDA Research Monograph 23. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979. pp 91-99.

Tennant, F.S.; Tarver, A.L.; and Rawson, R.A. Clinical evaluation of mecamylamine for diethdrawal from nicotine dependence. In: Harris, L.S. (ed.) Problems of Drug Dependence, 1983. NIDA Research Monograph 49. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off.. 1984. pp 239-246.

U.S. Department of Health. Education, and Welfare. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Center for Disease Control. PHS Pub. No. 1103. 1964.

U.S. Department of Health, Education, and Welfare. Smoking and Health: A Report of the Surgeon General. DHEW Pub. No. (PHS)79-50066, Washington, D.C.: Supt. of Dots., US Govt. Print. Off.. 1979.

U.S. Department of Health and Human Services. The Health Consequences of Smoking for Women: A Report of the Surgeon General. Rockville, MD: US Office on Smoking and Health, 1980.

U.S. Department of Health and Human Services. The Health Consequences of Smoking. The Changing Cigarette: A Report of the Surgeon General. DHHS Pub. No. (PHS)81-50156. Office of the Assistant Secretary for Health. Rockville, MD. Office on Smoking and Health, 1981.

U.S. Department of Health and Human Services. The Health Consequences of Smoking. Cancer: A Report of the Surgeon General. DHHS Pub. No. (PHS)82-50179. Office of the Assistant Secretary for Health. Rockville, MD: US Office on Smoking and Health, 1982.

U.S. Department of Health and Human Services. The Health Consequences of Smoking. Cardiovascular Disease: A Report of the Surgeon General. DHHS Pub. No. (PHS)84-50204, US Department of Health and Human Services, Office of the Assistant Secretary for Health. Rockville, MD: Office on Smoking and Health, 1983.

U.S. Department of Health and Human Services. The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General. DHHS Pub. No. (PHS)84-50205, US Department of Health and Human Services, Office of the Assistant Secretary for Health, Rockville, MD: Office on Smoking and Health, 1984.

AUTHORS

John Grabowski, Ph.D.*
Department of Psychiatry
School of Medicine
Louisiana State University, Shreveport
Shreveport, Louisiana 71130

Sharon Hall, Ph.D.
Center for Social and Behavioral Sciences
University of California, San Francisco
1350 Seventh Street
San Francisco, California 94143

*Current Address:

Treatment Research Branch
Division of Clinical Research
National Institute on Drug Abuse
5600 Fishers Lane
Rockville, Maryland 20857

Rational Basis for Chemotherapy of Tobacco Dependence

R. Nemeth-Coslett, Ph.D., and Jack E. Henningfield, Ph.D.

The forms of tobacco use are many, and it is likely that their number is matched by equally varied controlling variables. All the usual forms of tobacco use, however, share at least one commonality: nicotine is extracted from the tobacco and ingested in a manner that permits its distribution to the central nervous system. The tobacco cigarette is the prevalent means of nicotine self-administration in Western society, and cigarette smoking is the primary form of tobacco use addressed by legislative, research, and treatment efforts.

In 1983, the United States Public Health Service categorized cigarette smoking as a form of drug dependence in which nicotine was held to be the critical substance (USPHS 1983). Consistent with the drug dependence model of cigarette smoking, in 1984 a pharmacotherapeutic aid (nicotine gum) for the treatment of tobacco dependence was approved by the Food and Drug Administration. This paper will briefly review nicotine dependence and its implications for the use of chemotherapy in the treatment of tobacco dependence with respect to cigarette smoking.

TOBACCO DEPENDENCE: A DECEPTIVELY COMPLEX PHENOMENON

At first brush. tobacco dependence would seem readily amenable to study. In the form of cigarette smoking. the behavior is public, practiced by many, and appears to involve a simple act with a simple product. However, cigarette smoking has resisted many attempts at quantitative study, and studies have yielded data which often appears contradictory at the most elemental levels. For instance, the role of dose in the control of cigarette smoking has remained unclear despite decades of study. Since dose-response relations are arguably the most critical quantitative relations to be assessed in pharmacologic studies, the absence of consensual agreement as to the nature of dose-response relations has undoubtedly hindered the understanding and treatment of cigarette smoking.

There are specific reasons for some of the ambiguity concerning the role of dose in cigarette smoking. Table 1 provides a partial list of factors which obscure quantitation of dose-response functions.

These factors and others have been more thoroughly discussed elseswhere (cf. Benowitz, 1983; Henningfield, 1983, 1984; Kozlowski, Rickert, Robinson and Grunberg, 1980). In brief, compared to most other forms of drug self-administration, cigarette smoking involves a wider variety of confounding factors. In alcohol studies, for instance, ounces of ethanol ingested can be specified with great reliability, and resulting blood ethanol levels are related in some orderly fashion to these values. Similarly, in studies of sedatives, stimulants and opioids, the number of milligrams of actual drug which is swallowed or injected may be readily specified. In the case of cigarette smoking there is often disagreement as to which parameter to specify and the means of specification. One consequence of these difficulties was to delay the positive classification of cigarette smoking as a form of drug dependence. The next two sections will provide the evidence for this classification.

TABLE 1. Obstacles to the quantitation of dose-response functions in studies of cigarette smoking.

- o Many reports do not include any quantitative measure of dose.
- o Multiple dose parameters (e.g.. nicotine, tar and CO are frequently confounded.
- o Substances of possible functional significance (e.g., tar. CO, CO2) are especially difficult to specify since they are not even present in an unlit cigarette.
- o Federal Trade Commission dose level estimates are not necessarily related to either cigarette content or yield by the smoker.
- o The behavior of cigarette smoking varies across smokers and even across puffs within a single cigarette.
- o A variety of factors may affect absorption of smoke constituents (e.g., smoke pH, inhalation depth).

COMMONALITIES AMONG CIGARETTE SMOKING AND DRUG ABUSE

For centuries, a variety of parallels have been drawn between tobacco use and the use of opiates, alcohol and other substances. It seemed obvious to many observers of social behavior and physiologic effect that these substances were different from other substances of ingestion. such as food. Indeed, the American Indians knew that as other vegetables were "food for the stomach," "tobacco provided food for the spirit." Beyond these general observations, a variety of points common to cigarette smoking and classically studied forms of drug dependence (e.g., narcotic addiction and alcoholism) have been identified. The various commonalities have been described in greater detail elsewhere (Henningfield, Griffiths and Jasinski; 1981; Jaffe and Kanzler, 1979) and are summarized in Table 2.

TABLE 2. Common factors in tobacco use and drug dependence.

- o Spread is socially mediated and is persistent.
- o Patterns of relapse are similar following treatment.
- o Use persists in face of damage (individual & social).
- o Personality types overlap.
- o Centrally (CNS) acting substance (drug) is delivered.
- o The drug is a reinforcer for animals.
- o Deprivation increases drug seeking behavior.
- o Tolerance develops with repeated use.
- o "Therapeutic effects" may be produced.
- o Patterns of self-administration and dose-response functions are orderly.

These commonalities among various forms of drug dependence and tobacco use provide a rational basis for the theory that tobacco use may occur as a form of drug dependence. In brief, tobacco use, particularly in the form of cigarette smoking, is an orderly behavior that is lawfully controlled by the same behavioral and pharmacologic variables as are more commonly studied forms of drug dependence. The commonalities also suggest that treatment strategies which have proven effective in drug dependence may be applied to the treatment of cigarette smokers.

NICOTINE AS A DEPENDENCE-PRODUCING DRUG

While any substance may, under some conditions, be compulsively used, substances characterized by a certain constellation of features are likely to be compulsively used and abused under a much broader range of conditions, including those which lead to damage. In brief, the compound must be psychoactive (produce centrally mediated effects on mood and feeling states), must have euphoriant qualities similar to those of reference drugs (e.g., morphine, amphetamine. ethanol). and must serve as a biologic reinforcer (be voluntarily self-administered). Other qualities such as the ability to produce tolerance and physiologic dependence are interesting and may be of functional significance but are neither necessary nor sufficient determinants of drug dependence.

Two lines of study involving human subjects were undertaken by the Addiction Reseach Center of the National Institute on Drug Abuse. The first involved pharmacodynamic analyses which assessed the psychoactivity of nicotine and its possible qualities as a euphoriant. A variety of parameters were assessed when nicotine was given in the form of tobacco smoke and intravenous injections. The second line of study assessed the reinforcing properties of intravenous nicotine in cigarette smokers. The intravenous studies were critical in determining whether nicotine, in the absence of the usual confluence of stimuli involving the cigarettes themselves

(e.g., social and cultural), was characterized by the constellation of pharmacologic properties typical of those of known drugs of abuse.

Psychoactivity and Euphoriant Properties of Nicotine

The initial study showed that nicotine was psychoactive and produced orderly effects on measures of psychoactivity (Henningfield et al. 1985). Following either smoke inhalation or i.v. administration, nicotine was discriminated from placebo, and dose strength estimates were directly related to nicotine dose. These self-reported effects peaked within about 1 minute and dissipated within 3 to 5 minutes. Certain physiologic responses were also dose-related and showed similar temporal patterns of onset and offset: heart rate, pupil diameter, electroencephalographic response (Lukas and Henningfield 1983). A subsequent study showed that the ganglionic blocker, mecamylamine. attenuated physiologic and self-reported effects of nicotine (Henningfield et al. 1983). Variability of response on self-report measures was lower when nicotine was given intravenously than when it was given in the form of tobacco smoke, suggesting that the stimuli provided by cigarette smoking confound discrimination of the effects of nicotine.

Euphoria is objectively defined by the observation that administration of the drug, under controlled experimental conditions, produces dose-related increases in scores on the Liking scale of the Single-Dose Questionnaire, and scores on the Morphine Benzedrine Group (MBG or Euphoria) scale of the Addiction Research Center Inventory (ARCI) (Jasinski et al. 1984). In this study, nicotine, like drugs known to be abused, produced significant dose-related increases in scores on both the Liking and MBG scales (Henningfleid and Jasinski 1982; Jasinski et al. 1984). Additionally, intravenous injections of nicotine were most commonly identified as a prototypic euphoriant drug (cocaine) by subjects with extensive drug abuse histories.

These studies confirmed that nicotine produced critical functional effects of tobacco smoke and that nicotine is a psychoactive drug with properties of a euphoriant. These findings are consistent with those obtained in animal drug discrimination studies in which it has been shown that nicotine is readily discriminated and that its discriminative properties are more stimulant-like than depressant-like (cf.. review by Henningfield and Goldberg 1984).

Reinforcing Properties of Intravenous Nicotine

The ultimate test of whether nicotine is a dependence-producing drug is, in the abstract, a very simple test: namely, to determine if nicotine injections serve as positive reinforcers and thereby strengthen behavior leading to their administration. Practically, however, there are many difficulties in the safe and ethical conduct of such a study, and the initial study was only completed about 2 years ago (Henningfield et al. 1983). The critical finding of this study was that intravenously available nicotine was self-administered by each of the subjects tested. Furthermore,

patterns of self-administration were similar to those of humans smoking cigarettes or of animals self-injecting cocaine in analogous experimental preparations (Griffiths et al. 1980).

When saline was substituted for nicotine, patterns of injection were irregular and total number of Injections generally was lower. In a subject who stated that he disliked taking injections of any kind, the pattern of acquistion was similar to that of animals which are given access to intravenous nicotine for the first time (see Goldberg et al. 1982): Number of injections gradually increased across sessions; then, when saline was substituted for nicotine, the number of injections rapidly declined across sessions. Subsequent studies showed that nicotine was preferred to saline when both substances were concurrently available (Henningfield and Goldberg 1983a); that mecamylamine pretreatment attenuated the nicotine preference (Henningfield 1983); and that the lever was pressed as many as 1600 times per nicotine injection (study in progress).

The human self-administration study findings are consistent with animal studies in which nicotine has been shown to serve as a positive reinforcer in a variety of species including primates and nonprimates, and under a variety of experimental conditions (cf. review by Henningfield and Goldberg 1983b). It is noteworthy that establishment of nicotine as a reinforcer in animals eluded many investigators until effective confluences of parameters were discovered. Such Initial difficulty was not unique to nicotine but also characterized initial efforts to determine whether or not ethanol would serve as a reinforcer in animals (Melsch 1977).

CIGARETTE SMOKING AS A FORM OF DRUG DEPENDENCE: SUMMARY AND IMPLICATIONS FOR NICOTINE-BASED CHEMOTHERAPY

Nicotine is a prototypic drug of abuse, and many cigarette smokers are likely to be dependent. Strong, albeit circumstantial, evidence was provided by observations of the many critical commonalities between cigarette smoking and more commonly studied forms of drug dependence. Direct evidence was that the drug itself (nicotine, in isolation from tobacco smoke). was characterized by a profile of pharmacologic effects typical of that of known drugs of abuse such as opiates, stimulants, and alcohol. These data indicate that the role of nicotine in cigarette smoking is similar to the role of other constituent drugs of abused substances. That is, despite the apparently lower biologic reinforcing efficacy of nicotine than some of the more commonly studied drugs of abuse (Henningfield and Goldberg 1983b), the functional role of nicotine in tobacco smoke is similar to the role of cocaine in coca leaf use, to the role of morphine in opium poppy use, to the role of tetrahydrocannabinol (THC) in marijuana use, and to the role of ethanol in alcoholic beverage consumption.

The perspective that cigarette smoking often occurs as a form of drug dependence has specific implications for chemotherapeutic treatment strategies. A variety of nonspecific chemotherapeutic approaches to the treatment of cigarette smokers has been

reported. Most provide little documented efficacy; they have been reviewed elsewhere (Grabowski and Hall, this volume; Gritz and Jarvik 1977; Jarvik 1977).

One specific chemotherapeutic approach for drug dependence is to substitute a safer and more manageable form of the drug for the substance of abuse. The ultimate goal of such an approach is subsequently to withdraw the patient from the substituted drug. The currently available substitution pharmaceutical is the nicotine resin complex or nicotine chewing gum (American Hospital Formulary Service 1984). Use of nicotine gum in treatment of cigarette smoking is the subject of other chapters in this monograph and will not be discussed in detail here. Rather, a few observations will be made, following directly from the above-presented data, which show that cigarette smoking is a form of drug dependence. In addition, some preliminary data which bear on these observations will be presented.

Effective chemotherapy of other kinds of drug dependence is complex and involves systematic application of a variety of pharmacologic and behavioral strategies (cf. Grabowski et al. 1983). A major pharmacologic factor concerns the dose level of the chemotherapeutic drug. Table 3 summarizes a few of these dose-related issues.

TABLE 3. Dose-related issues in chemotherapy of drug dependence

- Dose must be sufficient to provide relief of withdrawal or deprivation effects.
- The rate of drug entry to the CNS is critical and may determine whether the particular route of administration used provides an acceptable substitute.
- Patient compliance in taking the therapeutic agent may vary as a function of dose.
- The degree to which nontherapeutic drug taking is suppressed may vary as a function of dose.

The importance of control over dose suggested the need for further study of such relations regarding the nicotine-delivering chewing gum. Two issues were of interest. The first was the possible functional effects of the rate at which individual pieces of gum were chewed. Since the nicotine in the gum is bound to an ion-exchange resin, chewing is required for its release; thus, rate of chewing should be one determinant of the rate at which nicotine is extracted from the gum. Results from a preliminary study of the effects of chewing rate are described below. The second issue concerned the fact that only one dose level of the gum is commercially available. In preliminary studies we found that rates of voluntary smoking were not affected by scheduled administration of either placebo or 2 mg gum, but were suppressed when subjects were given 4 mg gum (Jasinski et al. 1984; Nemeth-Coslett and Henningfield 1985). Furthermore, in a subpopulation of

heavy-smoking male polydrug abusers, little subjective or physiologic response was observed following administration of either 2 mg cr 4 mg gum. This observation suggested that, as is the case with other therapeutic drugs. there is a wide range of individual variability in response to a given dose, and that doses which are not tolerated by some patients may be safe and even necessary for others. Results from a preliminary study are also presented below in which such subjects were given either two or four pieces of 4 mg gum to chew.

PRELIMINARY STUDY: EFFECTS OF CHEWING RATE RESPONSE TO NICOTINE GUM

Four male subjects (average age = 34 years, range = 20-50) participated while residing on a pharmacology research ward. Their average weight was 75 kg (range = 67-100kg). and they smoked an average of 30 cigarettes per day (range 20 to 40 cigarettes, each delivering 1.1 mg nicotine). Mean scores on the Fagerstrom Tolerance Questionaire (Fagerstrom 1978) were 10.0 (range = 9-11). During predesignated days, each subject was cigarette deprived for 8 hours, after which time a l-hour test session was begun. Physiologic and self-report measures were collected during the initial 10 minutes of the test session. Subjects were then provided with one 4 mg piece of nicotine gum (Nicorette) which they were instructed to chew at a fixed rate for the next 10 minutes. Rates were set at one chew every 1, 2, 4, or 8 seconds, and compliance was assured by a nurse who observed that the subject was chewing in response to a timed "beep" which had been pretaped on a recorder. Each subject was exposed to the four different chew rates using a 4 x 4 Latin Square design. Most physiologic and self-reported responses were measured at 5-minute intervals. Visual line analog scores of positive ("pleasurable") and negative ("unpleasurable") were collected at 15-second intervals for the first 240 seconds after gum chewing and then at 5-minute intervals for the remainder of the test session. Additionally, measures of expired air carbon monoxide level were collected immediately before and after each session.

Preliminary analysis of the data suggests that chewing rate altered magnitude and duration of self-reported effects of the gum. Figure 1 shows the total visual line analog score (sum of negative and positive responses) at each observation for subject CO. Variability across subjects was considerable, however, and precluded meaningful lumping together of the data. No chewing rate produced significant increases on scales of the Addiction Research Center Inventory or the Single-Dose Questionnaire (Jasinski et al. 1984).

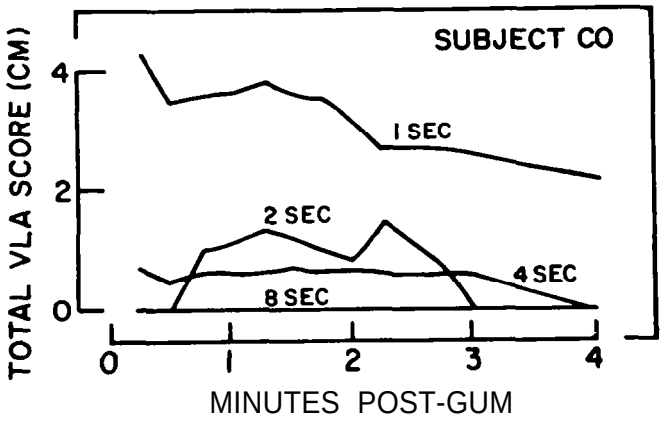


FIGURE 1. Values of self-reported scores on a lo-centimeter visual line analog scale, summed from both positive and negative effects, as a function of chewing rate and time after the gum was chewed (x-axis).

This study suggests that chewing rate does make a difference in the response to gum-delivered nicotine. It also raises several additional issues, some of which are being addressed in an ongoing study in which the amount of nicotine extracted from the gum, and nicotine plasma levels, will be assessed. An immediate implication is that the same kinds of difficulties in quantification of dose-response relations which occur when subjects are given cigarettes to smoke under uncontrolled conditions may arise when subjects are given gum to chew with no specification of the rate at which It is to be chewed.

PRELIMINARY STUDY: HIGH DOSES OF NICOTINE GUM

This study assessed the safety and effects of nicotine in subjects who were known to be relatively insensitive to 2 mg gum. The average age of the subjects was 33 years (range = 23-53). and they had smoked an average of 13 years (range = g-17). Their mean score on the Fagerstrom Tolerance Questionaire was 9.7 (range = 8-11). Subjects chewed either two or four pieces of 4 mg gum (total nicotine dose either 8 mg or 16 mg). Each piece of gum was chewed at a rate of 1 chew every 2 seconds for 10 minutes. Two subjects were tested at each of the dose levels twice a day for 2 days while two other subjects received one dose a day for 2 days. Immediately following gum chewing, subjects were asked to report verbally any side effects, their liking for the gum, and to rate the strength of the gum. Additionally, a staff nurse was required to record any observable signs or symptoms displayed by the subject.

The most common signs reported by the staff nurse were belching and hiccups. which showed a slight increase following exposure to 16 mg when compared to 8 mg. Other signs included restlessness, watery eyes, and irritability. However, for the six observations collected at each of the two doses, no observable effect was noted on four of the occasions following B mg chewing, and no effect was noted on two occasions following 16 mg chewing.

Subjects reported nausea and throat irritation more than any other symptoms. One subject reported no effect at either the 8 mg or 16 mg dose. Other complaints included nervousness, dizziness, headache, and heartburn. There was little increase at the 16 mg dose when compared to the 8 mg dose. Two subjects reported a dose-related increase in magnitude of effects between 8 mg and 16 mg, and three of the four subjects said that they would not voluntarily chew four pieces again but would chew two pieces. Two of these three subjects reported effects similar to those produced when marijuana was smoked ("high") at both doses and reported liking the feeling. The fourth subject reported no effects at either dose and identified the drug as placebo ("blank").

This study showed that high doses of nicotine-delivering chewing gum can be safely given. It is not clear what specific subject characteristics determine the tolerable dose level. For example, both body weight and level of nicotine intake would be factors of suspected importance. It is also remains to be determined whether high doses are of greater therapeutic efficacy for this population of cigarette smokers. The high doses produced some effects characteristic of those produced by drugs of abuse ("high"), but did not elevate scores on objective scales used to quantitate abuse liability.

DISCUSSION

A variety of theoretical, social, and treatment implications result from the identification of cigarette smoking as a form of drug dependence which is functionally similar to other forms of drug dependence. One implication related to nicotine-based chemotherapy is the role of dose, whether altered by chewing rate or by amount of nicotine-containing gum that is chewed. The results of the preliminary studies which were described raised more questions than they answered. However, some tentative conclusions may be drawn. First, rate of chewing may have functional consequences with regard to the effects produced by the gum. Second, subjects can tolerate higher chew rates and gum dosage levels than are typically employed in current treatment approaches (e.g.. Hughes and Miller 1984).

The observation that manipulations which affect the effective dose of a chemotherapeutic agent may have functional consequences is not surprising. Dose is a critical factor in other kinds of chemotherapy, and studies with nicotine in human and animal subjects show that nicotine's effects are dose related. Additionally, clinical observations (e.g.. one patient's description of how he used the nicotine gum: "I chew quick till I get the taste, then I

taper off") suggest that some patients have discovered on their own that chewing rate makes a difference in the effects of the gum. What is surprising is the lack of attention paid to dose in many studies of the behavioral pharmacology of the gum and of its treatment efficacy.

The finding that cigarette smoking may occur as a form of drug dependence offers exciting possibilities, burdens, and hope: Possibilities of applying chemotherapeutic treatment strategies to the treatment of cigarette smoking; the burdens of closely examining existing cigarette treatment programs and applying fundamental principles from drug dependence and alcoholism programs; and hope that these efforts will improve on the past rather dismal treatment programs. As shown by Hall and Killen elsewhere in this monograph. treatment approaches which apply both behavioral and pharmacologic treatment strategies are more effective that those which address only the pharmacologic or the behavioral aspects of tobacco dependence.

ACKNOWLEDGMENT

Dr. R. Nemeth-Coslett is supported at NIDA/ARC by the Merrell Dow Pharmaceutical Company through the Foundation for Advanced Education in the Sciences. The provision of the nicotine and placebo gum by Merrell Dow Pharmaceutical Company for the studies reported here is gratefully acknowledged.

REFERENCES

American Hospital Formulary Service. Drug Information 84 (Supplement B). Bethesda, Maryland: American Society of Hospital Pharmaceuticals, 1984. pp. 39B-44B.

Benowitz, N.L. Biochemical measures of tobacco smoke consumption. In: Grabowski, J., and Bell, C.. eds. Measurement in the Analysis and Treatment of Smoking Behavior. National Institute on Drug Abuse Research monograph 48. DHHS Pub. No. (ADM) 83-1285. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1983. pp. 6-26.

Goldberg, S.R.; Spealman, R.D.; and Goldberg, D.M. Persistent high-rate behavior maintained by intravenous self-administration of nicotine. Science, 214:573-575, 1981.

Grabowski, J.; Stitzer, M.L.; and Henningfield. J.E., eds. Behavioral Intervention Techniques in Drug Abuse Treatment. National Institute on Drug Abuse Research Monograph 46. DHHS Pub. No. (ADM) 84-1282. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1984.

Griffiths, R.R.; Bigelow, G.E.; and Henningfield, J.E. Similarities in animal and human drug taking behavior. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Greenwich, CT: JAI Press, 1980. pp. 1-90.

Gritz, E.R. Smoking behavior and tobacco abuse. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Greenwich, CT: JAI Press, 1980. pp. 91-158.

Gritz, E.R., and Jarvik, M.E. Pharmacological aids for the cessation of smoking. In: Steinfield, J.; Griffiths, w.; Ball, K.; and Taylor, R.M., eds. Proceedings of the Third World Conference -- Smoking and Health, Vol. II. Washington, D.C.: Supt. of Docs. U.S. Govt. Print. Off., 1983. pp. 575-591.

Henningfield, J.E. Measurement issues in cigarette smoking research: Basic behavioral and physiologic effects and patterns of nicotine self-administration. In: Grabowski, J., and Bell, C.. eds. Measurement In the Analysis and Treatment of Smoking Behavior. National Institute on Drug Abuse Research Monograph 48. DHHS. Pub. No. (ADM) 83-1285. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1983. pp. 27-38.

Henningfield, J. E. Behavioral pharmacology of cigarette smoking. In: Thompson, T., and Dews, P.B. eds. Advances in Behavioral Pharmacology, vol. IV, in press.

Henningfield, J.E., and Goldberg, S.R. Control of behavior by intravenous nicotine injections in human subjects. Pharmacol Biochem Behav 19:989-992, 1983 (a).

Henningfield, J.E., and Goldberg, S.R. Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav 19:1021-1026, 1983 (b).

Henningfield, J.E., and Goldberg, S.R. Behavioral Pharmacology: The Current Status. Seiden, L.S., and Balster, R.L., eds. New York: Alan R. Liss, 1984.

Henningfield, J.E.; Griffiths, R.R.; and Jasinski, D.R. Human dependence on tobacco and opioids: Common factors. In: Thompson, T.. and Johanson. C.E., eds. Behavioral Pharmacology of Human Drug Dependence. National Institute on Drug Abuse Research Monograph No. 37. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981. pp. 210-234.

Henningfield. J.E.; Myasato, K.; and Jasinski, D.R. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp Ther, in press.

Henningfield, J.E.; Miyasato, K.; and Jasinski, D.R. Cigarette smokers self-administer intravenous nicotine. Pharmacol Biochem Behav 19:887-890, 1983.

Henningfield, J.E.; Miyasato, K.; Johnson, R.E.; and Jasinski, D.R. Rapid physiologic effects of nicotine in humans and selective blockade of behavioral effects by mecamylamine. National Institute on Drug Abuse Research Monoaraph 43. Problems of Drug Dependence 1981. Washington,-D.C.: Supt. of Docs., U.S. Govt. Print. Off.. 1982. pp. 259-265.

Hughes, J. R., and Miller, S. A. Nicotine gum to help stop smoking. JAMA, in press.

Jaffe, J.H., and Kanzler, M. Smoking as an addictive disorder. In: Cigarette Smoking as a Dependence Process. National Institute on Drug Abuse Research Monograph 23. DHEW Pub. No. (ADM) 79-800. Washington, D.C.: Supt. of Docs. U.S. Govt. Print. Off., 1979, pp. 4-23.

Jarvik, M.E. Can drug treatment help smokers? In: Steinfeld, J.; Griffiths, W.; Ball, K.; and Taylor R.M., eds. Proceedings of the Third-World Conference -- Smoking and Health, Vol. II. Washington, D.C.: Supt. of Docs. U.S. Govt. Print. Off., 1977. pp. 509-513.

485-874 o - 85 - 2

Jasinski, D.R.; Johnson. R.E.: and Henningfield, J.E. Abuse liability assessment in human subjects: Trends in Pharmacol Sci 5:196-200, 1984.

Kozlowski, L.T.; Rickert, W.S.; Robinson, J.C.; and Grunberg, N.E. Have tar and nicotine yields of cigarettes changed? Science 209:1550-1551, 1980.

Lukas, S., and Henningfield, J.E. EEG correlates of physiological and behavioral effects of intravenous nicotine in humans. Paper presented at the 2nd World Conference on Clinical Pharmacology and Therapeutics, Washington, D.C., 1983.

Meisch, R.A. Ethanol self-administration: Infrahuman studies. In: Thompson, T., and Dews, P. B. eds. Advances in Behavioral Pharmacology. New York: Academic Press, 1977. pp. 35-84.

Nemeth-Coslett, R., and Henningfield, J.E. Dose-related effects of nicotine delivering chewing gum on rate of cigarette smoking. Manuscript in preparation, 1985.

U.S. Department of Health and Human Services, Public Health Service. Why People Smoke Cigarettes. Washington, D.C.: Supt. of Docs. U.S. Govt. Print. Off., 1983.

AUTHORS

R. Nemeth-Coslett
Jack E. Henningfield
National Institute on Drug Abuse
Addiction Research Center
4940 Eastern Avenue
c/o Baltimore City Hospitals
Baltimore, Maryland 21224

The Titration Hypothesis Revisited: Nicotine Gum Reduces Smoking Intensity

Ronald I. Herning, Ph.D., Reese T. Jones, M.D., and Patricio Fischman, M.D.

INTRODUCTION

Smokers alter puffing and inhalation patterns in response to changes in the characteristics of the cigarettes they smoke. Increasing ventilation or decreasing draw resistance increases smoking intensity (Dunn 1978; Sutton et al. 1978; Henningfield and Griffiths 1980). Shortening cigarette length increases puffing rate and the total number of cigarettes smoked (Goldfarb and Jarvik 1972; Gritz et al. 1976; Ashton et al. 1978; Russell et al. 1980a). When smokers take more puffs per cigarette, the intercigarette interval increases (Griffiths et al. 1982). When forced to smoke at more frequent intervals, they reduce puff volume (Gritz et al. 1983). Smokers who switched from middle to low tar cigarettes increased their puff size and a mathematically derived exposure index, but not the number of puffs, puff duration, interpuff interval, or butt length (Pawbone et al. 1978). Decreasing the machine-determined nicotine yield of cigarettes increased the number of cigarettes smoked in the 16 studies reviewed by Stepney (1980). Decreasing machine-determined nicotine delivery of cigarettes smoked increases puff volume (Adams 1978; Creighton and Lewis 1978; Herning et al. 1981; Gust and Pickens 1982). Only Dunn and Freiesleben (1978) reported no relationship between puff volume and decreased machine nicotine delivery.

These studies support the nicotine titration hypothesis. That is, smokers adjust their smoking patterns to obtain an optimal dose of nicotine from whatever cigarette they are smoking. Presumably, this dose produces some optimal blood or brain level of nicotine. Had nicotine blood levels been measured in these studies, the titration hypothesis might have been confirmed.

Studies where smokers were given cigarettes of different machine-determined yields and nicotine blood levels were obtained do not appear to support the titration hypothesis. When smokers are switched from mid-nicotine yield cigarettes to high machine yield cigarettes, nicotine blood levels are higher (Ashton et al. 1979,

1981; Benowitz et al. 1982). when smokers are switched from mid- to low-yield cigarettes, the corresponding blood levels decrease (Russell et al. 1972; Ashton et al. 1979 1981; Benowitz et al. 1982). If smokers actually titrate, the nicotine blood levels for the different cigarettes should be similar. However, only Russell et al. (1972) found equal blood levels when cigarettes yielding 1.32 mg and 3.2 mg nicotine were compared. Hill and Marquardt (1980) noted similar nicotine metabolite levels (cotinine) when tar and nicotine machine yield were manipulated.

Thus, these cigarette-switching studies have adequately demonstrated that subjects change puffing patterns in the direction predicted by the titration hypothesis, but they have failed to show that the adjustment leads to similar blood levels. The interpretation of these studies is complicated because high- and low-yield commercial cigarettes contain equivalent amounts of nicotine (Renowitz et al. 1983), and blood nicotine or cotinine levels do not correlate with machine yield of nicotine in large samples of smokers (Russell et al. 1980b; Benowitz et al. 1982; Herning et al. 1983b).

Supplemental nicotine or pharmacological manipulations which modulate nicotine's effects or its excretion alter smoking patterns. Oral doses of nicotine or infusions reduced smoking (Johnston 1942; Lucchesi et al. 1967; Jarvik et al. 1970). Stolerman et al. (1973) found mecamylamine, a nicotine antagonist, increased smoking rate. Naloxone, an opiate antagonist, reduced the number of puffs on a cigarette as well as the number of cigarettes smoked per day (Karras and Kane 1980). The manipulation of urinary pH to alter nicotine excretion modified cigarette smoking (Schachter et al. 1977). Except for a study by Kumar et al. (1977, experimental alterations which either blocked nicotine effects or increased nicotine blood levels produced the expected changes in smoking behavior.

The latter studies provide support for the nicotine titration hypothesis and support the use of supplemental nicotine as adjunct to smoking cessation therapy. Slow release buffered nicotine gum (Nicorette) now available provides the researcher another opportunity to test thenicotine titration hypothesis in controlled laboratory studies. The previous studies giving supplemental nicotine did not measure nicotine blood levels. Although smoking behavior changed, there is no evidence that the experimental manipulation produced similar nicotine blood levels. If subjects are indeed titrating nicotine, blood levels should be equal when supplemental nicotine and placebo are given. The present study evaluates whether smokers given placebo or nicotine gum reduce the intensity with which they smoke as compared with smokers given placebo and whether blood levels are reasonably similar on nicotine and placebo gum test sessions.

METHODS

Subjects

One female and five males served as subjects. They were 31.7 ± 3.3 (mean and standard deviation) years old The subjects smoked 30.8 ± 7.4 cigarettes per day with 6.0 ± 26 of these cigarettes smoked in the morning. All subjects had smoked for at least 10 years and smoked their current brand for 2 years or more. The machine-determined nicotine yield of their current cigarette was 1.14 ± 0.19 mg. They smoked their current brand during each of the two ad lib smoking sessions.

Experimental Procedure

During each of two morning sessions, the subjects smoked their self-selected brand of cigarette while chewing either nicotine or placebo gum in a counterbalanced order. The subjects were asked to remain abstinent from cigarette smoking from the night before. The experimental sessions lasted 4 hours. The subject sat in a comfortable reclining chair during this time and either read or listenedto music. During this period the subject could smoke at anytime. Before and 2 minutes after smoking, blood was drawn for nicotine &terminations. Expired breath samples were collected 10 minutes after each cigarette and tested for carbon monoxide level. During smoking, puff and inhalation patterns were monitored (see below). During the first half hour of each hour the subjects chewed either placebo gum or gum containing 2 mg of nicotine in a buffered slow release resin (Nicorette, supplied by Merrell Dow) according to the instructions in the package insert. Before and 25 minutes after chewing, blood was drawn for nicotine levels. During a given morning session, each subject received four pieces of one type of gum or the other. The gum was administered in a double-blind fashion The lab sessions were separated by 5 or more days. Heart rate and blood pressure were measured at half-hour intervals.

Measurement of Smoking Patterns

Puff volume and duration were measured by a single transducer flow meter. The flow meter consists of a plastic cigarette holder connected via flexible tubing to a Statham pressure transducer (Model PM5TC). Each cigarette smoked was precalibrated with known air flows, as in our previous studies (Herning et al. 1981 1983a,b). Inhaled volume and duration were measured by an Ambulatory Monitoring inductance plethysmograph Respitrace). The plethysmograph was calibrated with a Collins (Model 06031) water spirometer using the method described by Watson (1979).

The analog signals from the flow meter and plethysmograph were digitized every 40 ms from start of the puff for a period of 8 seconds. Puff and inhalation measures were numerically calculated from digital values. We calculated puff volume from flow using numerical integration which involves dividing the area under the flow curve into small trapezoids. These trapezoids are then added

together to obtain volume. Puff duration is the interval from start to end of puff where the flow values are nonxero. Inhaled volume is volume at maximal inhalation after a puff. The duration of inhalation is interval from start of the puff to maximal inhalation. Thus, it is half the actual duration of inhalation. Puff and inhalation duration were measured to the nearest 1/25 of a second while interpuff interval was measured to the nearest second.

Biochemical Measures

Blood samples were drawn from a forearm vein at half-hour intervals, immediately before smoking, and 2 minutes after the last puff. Samples were assayed for nicotine using the gas chromate graphic method described by Jacob et al. (1981). An Ecolyzer (Series 2000) monitor was used to determine the CD levels from the expired breath samples.

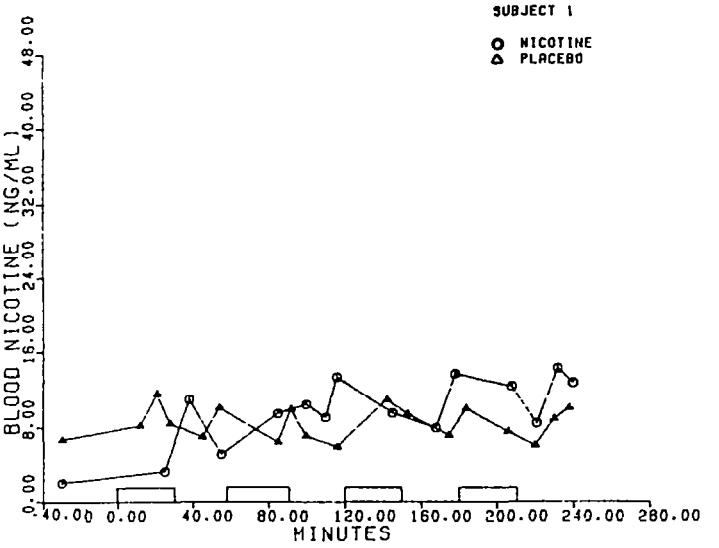
Data Analysis Concerns

We hypothesized that the subjects would reduce the frequency and intensity of smoking when given nicotine gum compared to placebo. Since our hypothesis implied the direction each measure would change when the subjects chewed nicotine gum, one-tail probability values were appropriate for the t-test on these smoking measures. For example, our hypothesis tests especially for reduction in the number of cigarettes smoked on the nicotine gum day as compared to the placebo day.

We also hypothesized that nicotine blood levels would be equal on both test days. Thus, in such a test the area under the nicotine blood level curves (AUC) on both sessions should be equal. This statistical test is a test of the null hypothesis. Such a test presents some statistical problems. The lack of differences, if observed, could be due to excessive variability in the measures or to no actual difference in the means. One cannot be sure. One method to protect against this problem is basing the test against the null hypothesis by adjusting the probability levels to make finding a difference easier. Thus, for the test on nicotine AUC, a probability level of 0.10 was used. An additional problem in testing whether nicotine blood levels are equal revolves around the issue of what is a biologically significant difference in levels. Certain differences in the WC may be found, but are they biologically important? Thus, testing the titration hypothesis has some practical problems.

RESULTS

The area under the curve (AUC) for nicotine tended to be higher during the nicotine gum session (2945 ng•min•ml-1) as compared to the placebo gum session (1925 ng•min•ml-1). This difference was significant (t=2.16, df=l,5, p<.10) at the increased probability level. That is, our test subjects appear not to be titrating. The individual nicotine curves are presented in figures 1, 2, and 3. Before it was concluded that the subjects were not titrating, an unexpected complication was noted. Three of the subjects had



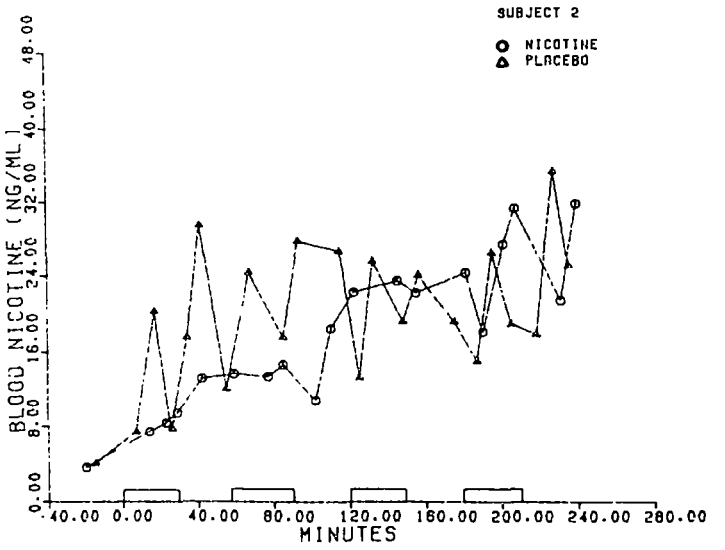
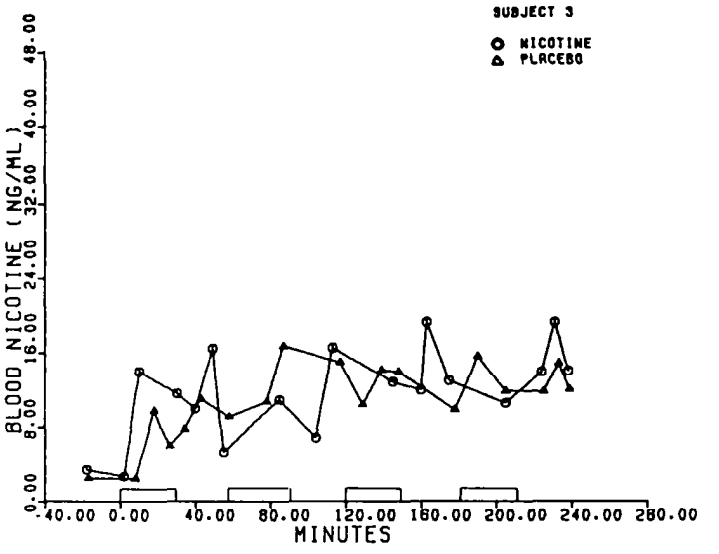


FIGURE 1. Nicotine blood level curves for Subjects 1 and 2. Bars indicate placebo or nicotine gun chewing periods.



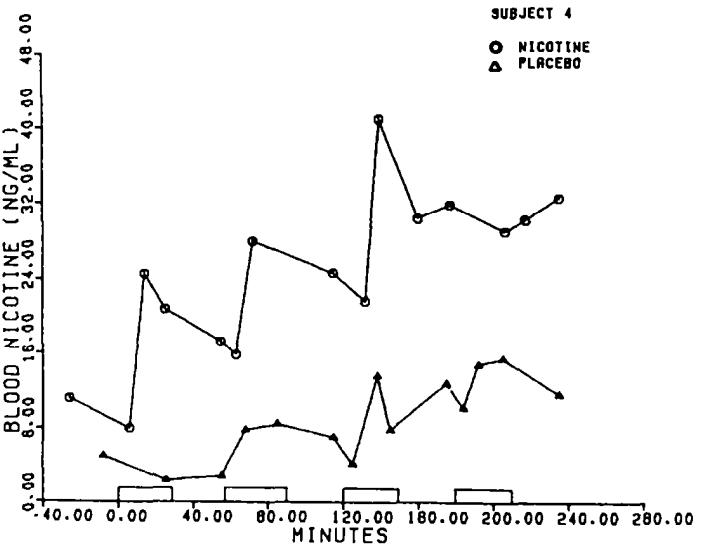
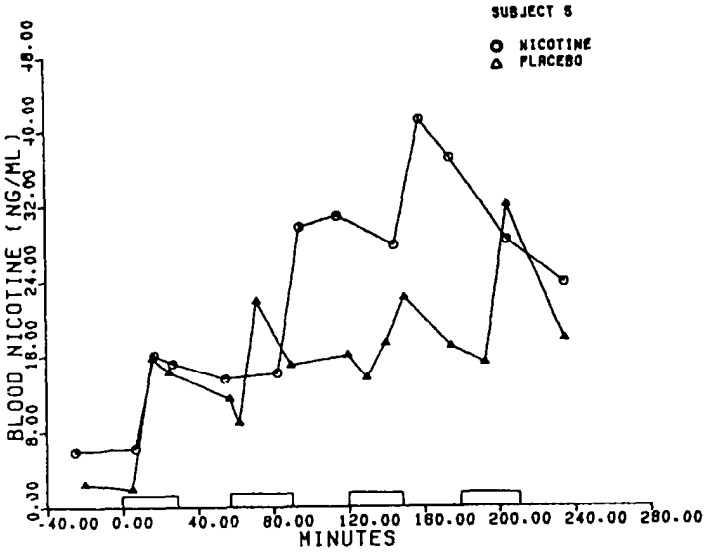


FIGURE 2. Nicotine blood level curves for Subjects 3 and 4. Bars indicate placebo or nicotine gun chewing periods.



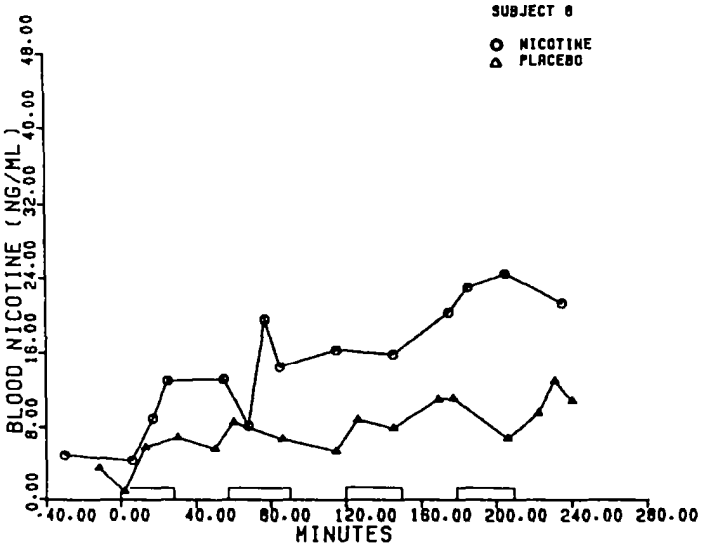


FIGURE 3. Nicotine blood level curves for Subjects 5 and 6. Bars indicate placebo or nicotine gun chewing periods.

higher blood nicotine levels on the gum day. These subjects smoked all or the majority of their cigarettes during the nicotine session while actually chewing the nicotine gum. Both theactive and placebo gum have an alkaline buffer which increases buccal absorption of the nicotine. These subjects were perhaps obtaining more nicotine with the gum than they might have without chewing it We tested for this possibility. A two factor analysis of variance with gum (placebo versus nicotine) and smoking period (chewing versus not chewing) as factors was used to test for any differential increase in nicotine blood levels while chewing gum The increase in nicotine blood levels with smoking was significantly ($F=4.4$, $df=1,53$, $p<.05$) larger when the subjects were chewing gum (8.0 mg/ml) than when they were not chewing (5.1 mg/ml). Thus, regardless of the type of gum, nicotine blood level increased more during periods of gum chewing. Under such unexpected nicotine delivery conditions, titration may have been difficult.

Smoking patterns were modified by the nicotine gum. The mean number of cigarettes smoked during the I-hour session was significantly less ($t=2.23$, $df=5$, $p<.05$, one-tailed) for the nicotine gum (4.3) than the placebo gum session (5.3). Mean interpuff interval, puff volume, puff duration, inhaledvolume, and inhaled duration are listed in table 1 for all subjects on both test sessions. The means are calculated from all puffs during a given session. To simplify the analysis of these measures, a single exposure index (EI) was calculated for each session from equation (1).

$$EI = \sum_{i=1}^{N} EI_i \qquad (1)$$

where N equals the number of cigarettes smoked.

Each EI is calculated by (2) for each cigarette.

$$EI_i=(b_0+b_1 \cdot MDOSE_i+b_2 \cdot NP_i+b_3 \cdot IPI_i+b_4 \cdot PV_I+b_5 \cdot PD_i+b_6 \cdot IV_i+b_7 \cdot IDi) \qquad (2)$$

$MDOSE_i$ = machine determined yield for cigarette i
Np_i = number of puffs for cigarette i
IPI_i = interpuff interval for cigarette i
PV_i = puff Volume for cigarette-i
PD_i = puff duration for cigarette i
IV_i = inhalation volume for cigarette i
ID_i = inhalation duration for cigarette i

The b_0, b_1 . . . b_7 were derived from a multiple regression of the above measures used to predict the increase blood nicotine levels in a large sample (N=104) of smokers used in our previous study (Herning et al. 1983b). Thus, the b_i's were calculated from an independent sample of subjects. The b_i's were 15.35, 8.35, -0.18, -0.25, 0.12, -3.06, -4.46, and 0.59, respectively.

TABLE 1

Mean Smoking Patterns for Placebo and Nicotine Gum Session

Subject Number	Type of Gum	No. of Cigarettes	Smoking Measure: No. of Puffs	Interpuff Interval (sec)	Puff volume (ml)	Puff Duration (sec)	Inhaled Volume (L)	Inhaled Duration (sec)
1	Placebo	6	51	51.5±17.7	49.1±16.1	2.2±0.6	0.68±0.22	2.7±0.5
	Nicotine	4	36	54.1±20.2	58.±20.6	2.4±0.6	0.46±0.16	3.1±0.6
2	Placebo	8	74	37.4±20.0	54.9±15.8	1.8±0.5	0.67±0.15	4.6±1.2
	Nicotine	7	73	29.±15.3	41.7±15.4	1.7±0.7	0.44±0.12	4.4±1.4
3	Placebo	6	43	54.2±35.3	43.8±18.6	1.8±0.7	0.45±0.10	3.2±0.8
	Nicotine	5	38	45.7±27.1	46.2±21.3	2.1±0.9	1.77±0.64	3.9±1.4
4	Placebo	3	34	39.5±25.5	45.7±12.7	1.6±0.7	0.82±0.47	4.0±1.3
	Nicotine	4	48	29.6±17.1	49.2±8.8	1.5±0.4	1.32±0.47	3.4±0.8
5	Placebo	4	22	71.8±28.0	65.8±24.5	2.1±0.7	1.14±0.64	5.0±1.3
	Nicotine	3	20	66.1±42.9	83.2±28.6	2.2±0.6	1.67±0.73	4.8±2.0
6	Placebo	5	46	45.5±28.6	22.1±8.7	1.2±0.4	0.42±.14	4.4±2.0
	Nicotine	3	33	38.1±30.2	18.6± 6.7	1.1±0.4	0.58±0.23	3.3±1.5
	Placebo	5.3± 1.7	45.0± 17.5	49.3±14.8	47.2±14.6	1.8±0.4	0.68±0.35	4.1±1.1
	Nicotine	4.3± 1.5	41.3± 18.0	43.1±16.5	49.9±19.6	1.9±0.5	1.03±0.70	3.8±0.8

The EI for the placebo session (81.6) was significantly larger (t=2.l4, df=5, P<.05) than the corresponding EI (63.6) for the nicotine gum session. The area under the curve for CO tended to be lower on the nicotine session (2222 PPM•sec) than the placebo session (2606 PPM•sec), but the difference in means was not significant. Although CO did not clearly indicate increased smoking on the placebo day, it paralleled the EI measure. The values for each subject are plotted in figure 4. Points below the diagonal line indicate an increase in the intensity of smoking on the placebo day. Points above the diagonal line indicate an increase in the intensity of smoking on the nicotine day. Distance from the diagonal line indicates the magnitude of change. The plots are remarkably similar. Subject 4 is the only smoker not reducing his smoking behavior while on the nicotine chewing gum.

Heart rate (F=4.65, df=9,45, P<.05) increased over the smoking session from a pre mean of 62.9 to a maximum of 69.2. No difference in the increase was observed on the two test sessions. The changes in systolic blood pressure over a given session or over both sessions were not statistically significant from the pre test. Diastolic blood pressure increased with smoking from a pre mean of 69.3 to a maximum level of 75.2. This increase, although significant (F=3.17, df=9,45, p<.05), was similar on both test sessions. The maximal increase for both heart rate and diastolic blood pressure occurred at the 2-hour sample No further increases were observed.

DISCUSSION

Nicotine chewing gum reduced the frequency and intensity of smoking in our subjects. The change in smoking behavior was reflected in a composite index of number of puffs, inter-puff interval, puff volume, puff duration, inhaled volume and duration. A decrease in carbon monoxide was also observed, but the difference in CO AUC between sessions was not statistically different. The composite exposure index appeared to be the more sensitive of the two measures. Since the composite index weights all aspects of smoking behavior, individual differences in regulation can be taken into account. However, a very simple measure of smoking, that is, number of cigarettes smoked, was also significantly reduced. Whether smoking behavior measures were simple or COmplex, our subjects smoked less on the nicotine gum session than on the placebo session.

The reduction in smoking is similar to that found by Johnston (1942) and Lucchesi et al. (1967) with intravenous doses of nicotine and by Jarvik et al. (1970) with nicotine tablets. It is unclear why Kumar et al. (1977) did not find such a reduction in smoking intensity. One possible reason is that the subjects in the Kumar experiment were not abstinent before testing as were the subjects in other studies and thus were relatively nicotine satiated at the time of testing.

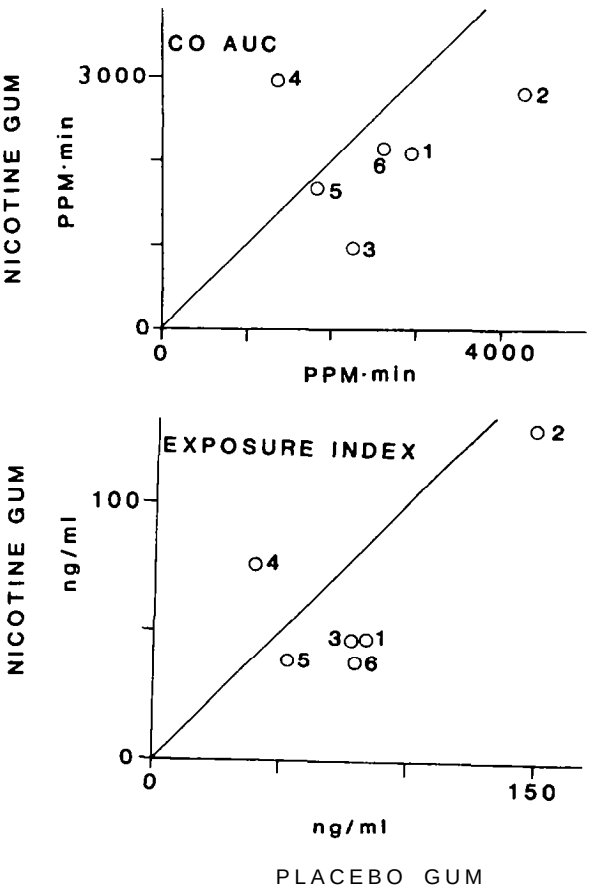


FIGURE 4. The CO AUC values (top) and exposure index values (bottom) are plotted for each subject on both test sessions. The placebo session values are plotted on the x-axis and nicotine session values are plotted on the y-axis. Each point is labeled with a subject number. Values below the diagonal indicate increased smoking intensity on the placebo day.

In previous studies testing the titration hypothesis by administering supplemental nicotine while the subjects were free to smoke, nicotine blood levels were not measured. If subjects are titrating, one might expect the nicotine blood levels to be similar in sessions where supplemental nicotine was given and sessions where no supplemental nicotine was administered. Despite variability, the nicotine levels were higher in the nicotine gum session at the 0.1 level of significance The increase in nicotine levels was due to half the subjects smoking their cigarette while chewing gum on nicotine sessions. The gum (both placeboand nicotine) changed the pH of the mouth which resulted in increased nicotine absorption. The increased nicotine absorption may have made titration more difficult.

Since only six subjects were tested, these results mayor may not generalize to a heterogeneous sample of smokers. Different results might he obtained with less dependent or older, more dependent smokers Cur sample of smokers were in their late twenties and early thirties, had smoked for 10 years, and were now smoking one and a half to two packs a day.

In our study, the nicotine AUC was different between sessions. However, differences in nicotine blood levels between the two experimental sessions did not produce significant cardiovascular changes between sessions. Thus, it could be argued that the differences in blood levels between sessions were not physiologically meaningful. Smokers may have a range of blood levels which are sufficient to produce the cardiovascular andsubjective effects they desire or to reduce the withdrawal symptoms they seek to avoid. Precise titration to identical blood levels may not be necessary.

SUMMARY

Supplemental nicotine gum reduced the intensity of smoking in six one-and-a-half to two-pack-a-day smokers. The study involved two 4-hour self-paced smoking sessions where nicotine and placebo chewing gum were administered in a double-blind fashion. Puff volume, puff duration, inhaled volume, inhaled duration, and interpuff interval were calculated for each puff on each cigarette. Blood was drawn for nicotine levels at regular intervals as well as before and after each cigarette Cardiovascular measures were made at regular intervals. The nicotine gum reducedsmoking frequency and intensity as predicted by the titration hypothesis. Precise titration (i.e., equal nicotine blood levels on both test days) was confounded by changes in smoked nicotine delivery produced by the gum. The gum, whether placebo or active, increased smoked nicotine absorption. However, while nicotine blood levels were slightly higher on nicotine gum day, the differences may not be biologically meaningful since heart rate and blood pressure increases were similar on both days. Difficulties testing the titration hypothesis are discussed.

REFERENCES

Adam, P.I. The influence of cigarette smoke yield on smoking habits. In: Thornton, RR, ed. Smoking Behavior: Physiological and Psychological Influences. London: Churchill-Livingstone, 1978. pp. 349-360.

Ashton, H.; Stepney, R; and Thompson, J.W. Smoking behavior and nicotine intake in smokers presented with a "two-thirds" cigarette. In: Thornton, RR, ed. Smoking Behavior: Physiological and Psychological Influences. London: Churchill-Livingstone, 1978. pp.315-329.

Ashton, H.; Stepney, R.; and Thompson, J.W. Self-titration by cigarette smokers. Brit Med J 279:357-360, 1979.

Ashton, H.; Stepney, R.; and Thompson, J.W. Should intake of carbon monoxide be used as a guide to intake of other smoke constituents? Brit Med J 282:10-13, 1981.

Benowitz, N.L.; Hall, S.M.; Herning, RI.: Jacob, P.; Jones, R.T.; and Osman, A-L Smokers of low yield cigarettes do not consume less nicotine. New Eng J Med 309:139-142, 1983.

Benowitz, N.L; Kuyt, F.; and Jacob, P. III. Circadianblood nicotine concentrationduring cigarette smoking. Clin Pharmacol Ther 32:758-764, 1982.

Creighton, RR, and Lewis, P.H. The effect of different cigarettes on human smoking patterns. In: Thornton, R.E., ed. Smoking Behavior: Physiological and Psychological Influences. London: Churchill-Livingston, 1978. pp. 76-86.

Dunn, P.J. The effects of reduced draw resistance on human smoking parameters and alveolar carbon monoxide levels. In: Thornton R.E., ed. Smoking Behavior: Physiological and Psychological Influences. London: Churchill-Livingstone, 1978. pp. 203-207

Dunn, P.J., and Freiesleben, E.R. The effects of nicotine enhanced cigarettes on human smoking parameters and alveolar carbon monoxide levels. In: Thornton. R.E., ed. Smoking Behavior: Physiological and Psychological Influences. London: Churchill-Livingstone, 1978. pp. 195-202.

Goldfarb, T., and Jarvik, M. Accommodation to restricted tobacco smoke intake in cigarette smokers. Intl J Addictions 7:559-565, 1972.

Griffith, RR; Henningfield, J.E.; and Bigelow, GE Human cigarette smoking: Manipulation of number of puffs per bout, interbout interval and nicotine dose. J Pharmacol Exp Ther 220:156-265, 1982.

Gritz, E.R.; Baer-Weiss, B.; and Jarvik, M.E. Titration of nicotine intake with full-length and half-length cigarettes. Clin Pharmacol Ther 20:552-556, 1976.

Gritz, E.R.; Rose, J.E.; and Jarvik, M.E. Regulation of tobacco smoke intake with paced cigarette presentation Pharmacol, Biochem Behavior 18:457-462, 1983.

Gust, S.W., and Pickens, R.W. Does cigarette nicotine yield affect puff volume? Clin Pharmacol Ther 32:4l8-422, 1982.

Henningfield, J.E., and Griffiths, R. Effects of ventilated cigarette holders on cigarette smoking by humans. Psychopharmacology 68:115-119, 1980.

Herning, R.T.; Jones, R.T.; Bachman, J.; and Mines, A.H. Puff volume increases when low nicotine cigarettes are smoked. Brit Med J 283:187-193, 1981.

Herning, RI.; Jones, R.T.; Benowitz, N.L.; and Mines, A.H. How a cigarette is smoked determines nicotine blood levels. Clin Pharmacol Ther 33:84-91, 1983a.

Herning, RI.; Jones, R.T.; Hall, S.M.; Benowitz, N.L.; Hunt, J.S.; and Jacob, P. III. How cigarette smokers regulate nicotine dose. Submitted, Ann Rev Respiratory Respiratory Dis, 1983b.

Hill, P., and Marguardt, H. Plasma and urine changes after smoking different brands of cigarettes. Clin Pharmacol Ther 17:652-658,1980.

Jacob, P. III; Wilson, M.; and Benowitz, N.L. Improved gas chromatographic method for thedetermination of nicotineand cotinine in biologic fluids. J Chromatogr 222:61-70, 1981.

Jarvik, M.E.; Glick, S.D.; and Nakamara, R.K. Inhibition of cigarette smoking by orally administered nicotine. Clin Pharmacol Ther 11:574-576, 1970.

Johnston, L.M. Tobacco smoking and nicotine. Lancet 2:742, 1942.

Karras, A, and Kane, J.M. Naloxone reduces cigarette smoking. Life Sci 27:1541-1545, 1980.

Kumar, R.; Cooke, E.C.; Lader, M.H; and Russell, M.A.H Is nicotine important in tobacco smoking? Clin Pharmacol Ther 21:520-529,1977.

Lucchesi, B.R.; Schuster, C.R.; and Emley, G.S. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. Clin Pharmacol Ther 8:789-796, 1967.

Rawbone, R.G.; Murphy, K.; Tate, M.E.; and Kane, S.J. The analysis of smoking parameters, inhalation and absorption of tobacco smoke in studies of human smoking behavior. In: Thornton, R.E., ed. Smoking Behavior: Physiological and Psychological Influences, London: Churchill-Livingstone, 1978. pp. 171-194.

Russell, M.AH.; Jarvis, M.; Iyer, R; and Feyerabend, C. Relation of nicotine yield of cigarettes to blood nicotine concentrations in smokers. Brit Med J 1:972-976, 1980b.

Russell, M.A.H.; Sutton, S.R.; Feyerabend, C.; and Saloojee, Y. Smokers response to shortened cigarettes: Bose reduction without dilution of tobacco smoke. Clin Pharmacol Ther 27:210-218, 1980a.

Russell, M.A.H.; Wilson, C.; Patel, U.A.; Cole, P.V.: amd Feyerabend, C. Comparison of effect on tobacco consumptionand carbon monoxide absorption of changing to high and low nicotine cigarettes. Brit Med J 4:512-516, 1972.

Schachter, S.; Kozlowski, LT.; and Silverstein, B. Effects of urinary pH on cigarette smoking. J Exp Psychol: General 106:3-40, 1977.

Stepney, R. Consumption of cigarettes of reduced tar andnicotine delivery. Brit J Addictions 75:81-88, 1980.

Stolerman, I.R.; Goldfarb, T.; Fink, R; and Jarvik, M.E. Influencing cigarette with antagonists. Psychopharmacolgia 28:247-259, 1973.

Sutton, S.R.; Feyerabend, C.; Cole, P.V.; and Russell, M.A.H. Adjustment of smokers to dilution of tobacco smoke by ventilated cigarette holders. Clin Pharmacol Ther 24:395-405, 1978.

Watson, H. The technology of inductive plethysmography. Proceedings of Third International Symposium on Ambulatory Monitoring, Middlesex, U.K., 1979.

ACKNOWLEDGMENTS

Research supported in part by Grants No. DA02088, DA00053 and DA01696 from the National Institute on Drug Abuse and funds provided by Merrell Dow pharmaceuticals, Inc.

AUTHORS

Ronald I. Herning, Ph.D.*
Assistant Professor of Medical Psychology
Langley Porter Psychiatric Institute
University of California, San Francisco
San Francisco, California 94143

Reese T. Jones, M.D.
Professor of Psychiatry
Langley Porter Psychiatric Institute
University of California, San Francisco
San Francisco, California 94143

Patricio Fischman, M.D.
Resident, Langley Porter Psychiatric Institute
University of California, San Francisco
San Francisco, California 94143

* Current Address:

NIDA Addiction Research Center
P.O. Box 5180
Baltimore, Maryland 21224

Cardiovascular Effects of Nicotine Gum and Cigarettes Assessed by ECG and Echocardiography

Janine Krivokapich, M.D., and Nina G. Schneider, Ph.D.
John S. Child, M.D., and Murray E. Jarvik, M.D., Ph.D.

INTRODUCTION

Cigarette smoking is one of the most firmly established risk factors for coronary heart disease (Kannel 1981). This risk can be dramatically reduced by discontinuation of cigarette smoking (Doll and Peto 1976; Hammond and Garfinkle 1969; Kannel 1981). Unfortunately, smoking cessation programs have low long-term success rates (Evans and Lane 1980; Raw 1978; Schwartz 1979). Several investigators attribute the maintenance of smoking behavior to a dependence upon nicotine (Gritz 1980; Jarvik 1970; Russell 1980). Nicotine induced withdrawal symptoms and nicotine seeking may account for cessation difficulty and high relapse rates. Nicotine chewing gum was introduced as a means of treating the pharmacological dependence during cessation of smoking (Ferno et al. 1973). The 4 mg dose results in blood levels of nicotine similar to a cigarette although without the "bolus" effect (see Russell and Jarvis in this volume). The 2 mg dose results in even lower blood levels. The purpose of using nicotine gum is to prevent abrupt withdrawal from nicotine and consequent symptoms and craving while supplying a substitute oral activity. Several recent studies attest to its efficacy in the alleviation of withdrawal (Hughes et al. 1984; Schneider et al. 1984; West 1984). Enhanced success rates in smoking cessation have been demonstrated in a number of recent placebo-controlled trials (Fagerstrom 1982: Hjalmarson 1984; Jarvis et al. 1982; Killen et al. 1984; Schneider et al. 1983). Since its introduction in the United States in 1984, this preparation is now widely available by prescription for the treatment of smoking dependence.

The purpose of this study was to examine and compare the acute effects on the cardiovascular system of nicotine delivered by smoking cigarettes versus chewing nicotine gum. Low and high nicotine cigarettes (0.2 mg and 2 mg) and 2 mg and 4 mg nicotine gum formed the four treatment conditions with each subject serving as his own control for all conditions. Cardiovascular evaluation included blood pressure, heart rate, electrocardiographic monitoring, and N-mode echocardiography, performed before and at

intervals up to 90 minutes after nicotine was introduced in eith form to healthy male smokers. Psychological responses wer elicited to determine whether there were any subjective response to treatment.

MATERIALS AND METHODS

Subjects

Fourteen paid volunteers were obtained through advertisements i the UCLA school newspaper. Subjects selected were males wh smoked at least one pack a day for two years or more and who wer healthy and active. Exclusion criteria included any history o cardiac, respiratory, gastrointestinal, or peripheral vascula disease. Subjects were required to be free of medications. On th first day of the study, a brief medical history was taken and pertinent physical examination was performed on each subject by cardiologist. This was followed by obtaining a resting bloom pressure (BP) measurement, a 12-lead electrocardiogram (ECG), an an M-mode echocardiogram (ECHO). If these tests were all withi normal limits and the echocardiogram was easily obtainable and o good quality technically (i.e. the subject was echogenic), the subject was recruited for an additional four days of study. Si males, ages 23 to 32 (mean age 27.3 ± 3.6 years), formed the final study group. Subjects smoked an average of 26 ± 5 cigarettes pe day for an average of 8.8 ± 5.1 years. Results of the cardiovascular tests were available to subjects' physicians upo request.

Materials

High nicotine (2.0 mg) and low nicotine (0.2 mg) cigarettes were provided by the National Cancer Institute. Merrell Dow Pharmaceuticals of Indianapolis, Indiana, provided 2 mg and 4 mg nicotine gum which was manufactured by A.B. Leo in Sweden. The gum (Nicorette) contained nicotine bound to an ion exchange resin which permitted the controlled release of nicotine. The gum was buffered to allow for rapid absorption through the buccal mucosa. Chewed gum was sealed in plastic containers and returned to Merrell Dow Pharmaceuticals for determination of residual nicotine. The residual amount was then subtracted from the initial dose to estimate the nicotine dose delivered.

Measurements

Cardiovascular measurements were taken in the supine position. A sphygmomanometer was used to obtain the systolic and diastolic blood pressure (BP) from the right arm in mm mercury (Hg). The mean BP was calculated as the difference between the systolic and diastolic BP, divided by three, and added to the diastolic BP. Electrocardiograms were taken with a Hewlett-Packard electrocardiograph. Standard echocardiographic techniques were used to obtain M-mode echocardiograms. The following measurements from the echocardiogram were made in triplicate and averaged wing a mini-computer (ECHO COMP by Digisonics, Inc., Houston, Texas):

1) left ventricular end-diastolic dimension (LVEDD) in mm at the onset of the R wave of the simultaneously recorded electrocardiographic lead II; 2) left ventricular end-systolic dimension (LVESD) in mm; 3) left ventricular ejection time (LVET) in seconds from the duration of aortic valve systolic opening; and 4) heart rate. From these measurements the left ventricular fractional shortening percent (FS%=LVEDD-LVESD/LVEDD) and velocity of circumferential fiber shortening (VCF=FS%/LVET) were calculated.

Carbon monoxide levels were measured by having the subject hold his breath for 20 seconds and then exhale into a carbon monoxide (CO) collection bag. The CO level was measured in parts per million on an Ecolyzer. A baseline CO level was taken on the first day of the study before the subjects were asked to abstain from smoking after 12 am on the day of study. On the following four treatment days, CO levels were obtained prior to treatment after abstinence from cigarettes for at least 11 hours and at 10 and 90 minutes after the beginning of each treatment.

psychological measures were obtained to determine whether subjects experienced subjective state changes over time and across treatments. Four items were tested on a lo-point verbal scale. The four items were: Are your hands shaky? Is your heart beating faster? Do you feel more alert? and Do you feel lightheaded? This scale was used previously and found sensitive to subjective changes from pre- to post-smoking (Schneider 1978). On the 10-point scale 1 represented “not at all" and 10 represented “very much.” In order to reduce random error and give the subject an opportunity to respond as exactly as possible, the immediately preceding response was read to the subject just before he gave his cur rent response.

Protocol

After informed consent was obtained, potential subjects who were still smoking were individually screened at 11:00 AM on Mondays. Six subjects were recruited for an additional four days of study. Subjects underwent testing of the four conditions (2 mg and 4 mg nicotine gum and 0.2 mg and 2 mg nicotine cigarettes) from 11:00 AM to 1:00 PM on the next four days in a randomly assigned order. Subjects were asked to abstain from smoking after 12:00 AM on each test day but not prior to the initial Monday visit. In addition, they were to abstain from caffeine in any form after 9:00 AM on each treatment day. Smoking abstinence was verified by testing the exhaled carbon monoxide levels. The dose of nicotine in the gum or cigarette was unknown to the investigator at the time of testing and the echocardiograms and ECG’s were read by two observers without knowledge of subject identity or of test condition.

On each test day, baseline heart rate (HR), BP, ECG, and ECHO were performed with the subject supine in a hospital bed prior to smoking a test cigarette or chewing a gum. Following the baseline measurements, repeat RR, BP, ECG leads 1, aVF, and V5, and ECHO of

the left ventricle and aortic root were performed at 5, 10, 20, 30, 45, 60, and 90 minutes after the test condition was started. The test questions were repeated at 5, 30, 60, and 90 minutes after the beginning of a treatment and carbon monoxide measurement was made at 10 and 90 minutes.

Smoking and chewing procedures were strictly controlled as follows: The cigarette was lit and held by the subject, who was instructed to take one puff every 30 seconds, hold each puff in for 5 seconds, exhale, and relax for 25 seconds. The timing was monitored and 10 puffs were completed in 5 minutes. For the gum treatment the subject chewed hard for 5 seconds and then held the gum in the cheek (for absorption) for 25 seconds. This cycle was timed and repeated every 30 seconds for 30 minutes. This procedure maximized and controlled the nicotine release while minimizing side effects.

Design

The design of the study was a 2x2x8 factorial for HR, BP, and echocardiographic measures, The first factor was type of treatment (gum vs. cigarettes); the second factor was dose (high vs. low nicotine); and the third factor was the 8 time periods at which measurements were taken. Psychological testing results made up a 2x2x5 factorial and CO measurements a 2x2x3 factorial.

Statistics

Repeated measures analysis of variance (ANOVA) with trends were performed on the data using a BMDP Statistical Software Program. One-way analysis of variance was used to compare baseline values across treatments for each measure. F tests for repeated measures were used to compare differences between baseline and 5 minute values and baseline and 30 minute values for heart rate and mean BP. These analyses were pre-planned and based on data for peak blood levels of nicotine reported after cigarette smoking (5 minutes) and after gum chewing (30 minutes) (Russell et al. 1980). Level of significance was chosen as $p < 0.05$ unless otherwise stated.

RESULTS

Nicotine Content in Chewed Gum

The average amount of nicotine absorbed by the subjects from the 2 mg and 4 mg nicotine gum was 1.1 ± 0.2 mg and 2.7 ± 0.4 of nicotine, respectively. These were estimated from values obtained for nicotine remaining in chewed gum. Thus, the high dose nicotine gum appeared to supply at least twice as much nicotine as the low dose nicotine gum. Five of six subjects reported an aversive or burning taste with the 4 mg gum and two of six subjects reported a burning taste with the 2 mg gum. Additional side effects consisted of nausea and belching in two subjects, and soreness of the throat in two others.

Carbon Monoxide Levels

Baseline levels of CO obtained before the subjects were asked to abstain from smoking are listed in table 1. CO levels obtained immediately prior to each treatment and at 10 minutes and 90 minutes after the treatment began are also listed in table 1 with ANOVA statistics presented in table 2. A main effect of condition ($p=0.02$) was noted which can be attributed to the significant rise in CO at 10 minutes for the cigarettes compared to the gum. The condition x time interaction was significant at the $p<.005$ level. There was no significant main effect of dose or dose x treatment interaction.

Heart Rates

The baseline and post-treatment HR responses are listed in table 3 as means ± SD for each condition with ANOVA statistics listed in table 2. The means are plotted in figure 1. There were no

TABLE 1. Carbon Monoxide Levels (ppm)

Sub	1	2	3	4	5	6	X ± SD
Base	25.0	26.0	5.0	26.0	57.0	40.0	29.8±17.4
C1							
Pre	17.0	14.0	4.5	11.0	10.0	21.0	12.9±5.8
10'	*	*	7.5	22.0	19.0	33.0	20.4±10.5
90'	13.0	14.0	6.0	16.0	14.0	27.0	15.0±6.8
CH							
Pre	6.5	17.0	4.0	11.0	8.5	21.0	11.3±6.5
10'	*	25.0	10.0	20.0	19.5	30.0	20.9±7.4
90'	9.0	18.0	6:0	16.0	13.5	23.0	14.2±6.2
GL							
Pre	17.5	12.5	3.0	11.0	8.0	21.0	12.2±6.5
10'	*	14.5	4.0	12.0	9.0	20.0	11.9±6.0
90'	15.0	11.5	3.5	9.0	7.0	14.0	10.0±4.4
G H							
Pre	19.5	10.5	4.0	11.0	8.0	24.0	12.8±7.5
10'	*	12.0	5.0	16.0	9.0	25.0	13.4±7.6
90'	12.5	10.5	4.0	13.0	8.0	19.0	11.2±5.1

Base, CO levels on Day 1 of study prior to abstention; CL, cigarettes containing low (0.2 mg) nicotine; CH, cigarettes containing high (2 mg) nicotine; GL, gum containing low (2 mg) nicotine; GH, gum containing high (4 mg) nicotine; Pre, immediately prior to intervention after at least 11 hours abstention from cigarettes: ppm, parts per million: Sub, subject; *, 10 minute CO measurement had not been added to protocol at the time of study.

TABLE 2. Analysis of Variance Statistics (p values)

	CO	HR	SBP	DBP	MBP	LVEDD	LVESD	FS%	VCF
Cond	0.02	0.61	0.74	0.54	0.57	0.92	0.76	0.69	0.95
Dose	0.18	0.01	0.01	0.06	0.31	0.11	0.20	0.88	0.87
Time	0.005	0.001	0.001	0.0009	0.0001	0.08	0.0004	0.0008	0.09
Cond X Dose	0.12	0.67	0.71	0.26	0.30	0.78	0.87	0.54	0.16
Cond x Time	0.0005	0.003	0.001	0.10	0.01	0.37	0.11	0.46	0.99
Dose x Time	0.77	0.29	0.96	0.43	0.61	0.51	0.33	0.61	0.43
Cond x Dose x Time	0.70	0.16	0.57	0.53	0.85	0.91	0.50	0.24	0.11

Cond, condition of cigarette vs gum; dose, low vs high nicotine; CO, carbon monoxide; HR, heart rate; SBP, systolic blood pressure (BP); DBP, diastolic BP: MBP, mean BP; LVEDD, left ventricular (LV) end diastolic dimension; LVESD, LV end systolic dimension; FS%, fractional shortening; VCF, velocity of circumferential fiber shortening; n=6 for all measures except n=4 for CO.

significant differences among the baseline values. A main effect of time (p=0.001) was observed with an increase in heart rate from baseline for all conditions with a return to near baseline values by 90 minutes. The significant dose effect (p=0.01) indicated that the higher doses of nicotine regardless of condition had a greater effect on heart rate than the lower doses. This dose effect was not interactive with time or condition. A significant condition x time interaction (p=0.003) revealed different peaks in time dependent on treatment (i.e., cigarettes vs. gum). The peak HR for the 90-minute study period was recorded at 5 minutes after the intervention began for the 0.2 mg and 2 mg nicotine cigarettes with an increaseover baseline of 7% and 28%, respectively. The increase in HR noted with the 2 mg nicotine cigarettes was significant (p<0.001). There was an insignificant 6% increase in baseline HR with the 2 mg nicotine gum observed at 5, 20, and 60 minutes. The peak HR for the 4 mg nicotine gum recorded at 30 minutes post-treatment represented a 12% increase which was also not significant (p=0.18).

Electrocardiograms

No changes occurred in the QRS complexes, ST segments, or T waves in leads 1, avF, or V_5 at any time during the various interventions. In addition, no ectopy was detected.

TABLE 3. Cardiovascular Measures

	CL	CH	GL	GH	CL	CH	GL	GH
	Heart Rate				Mean BP			
Baseline	67±9	64±7	64±9	67±7	72±3	73±8	7l±7	73±7
5 min	72±9	82±10	68±lO	71±9	74±2	8O±8	7O±5	73±8
10 min	70±11	74±l0	65±ll	72±8	7l±6	75±4	71±5	74±8
20 min	7O±9	73±7	68±ll	75±6	68±7	73±8	70±4	73±5
30 min	66±ll	69±9	66±7	75±9	67±5	7l±6	7O±4	73±7
45 min	65±9	71±7	65±lO	72±7	67±5	69±7	72±2	73±6
60 min	62±10	70±11	68±11	69±8	67±6	7l±6	70±3	70±6
90 min	66±9	66±8	60±5	65±11	68±6	73±3	7l±3	73±5
	Systolic BP				Diastolic BP			
Baseline	101±7	103±10	103±10	106±8	57±3	58±8	56±7	57±8
5 min	103±9	112±7	lOl±7	lO1±12	60±3	64±7	55±5	59±7
10 min	lOO±12	l04±7	lO2±7	103±9	57±6	60±5	56±7	59±9
20 min	97±ll	lO2±lO	98±7	103±6	53±8	58±7	57±4	58±7
30 min	96±10	lOl±7	99±8	102±9	52±6	55±6	56±4	59±7
45 min	97±7	99±10	99±6	l01±10	53±6	55±7	58±2	58±7
60 min	96±l2	lOO±7	97±5	lO2±1O	52±5	57±6	57±3	54±8
90 min	97±ll	l00±9	99±9	104±11	53±6	60±2±57+4		58±7

CL, low (0.2 mg) nicotine cigarettes; CH, high (2 mg) nicotine cigarettes: GL, low (2 mg) nicotine gum; GH, high (4 mg) nicotine gum; heart rate in beats/min; BP in mm Hg; values are means ±SD.

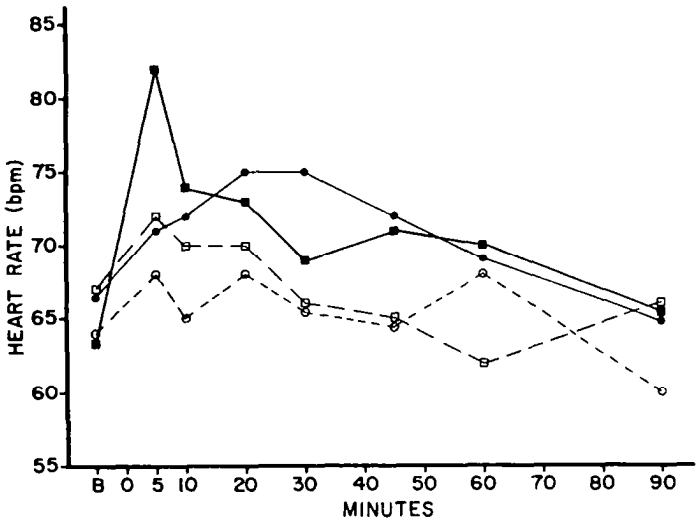


Figure 1. Mean heart rate in beats/min plotted versus time (minutes) for the four test treatments: □, low (0.2 mg) nicotine cigarettes; ■, high (2 mg) nicotine cigarettes; ○, low (2 mg) nicotine gum; ●, high (4 mg) nicotine gum. n=6. B, baseline.

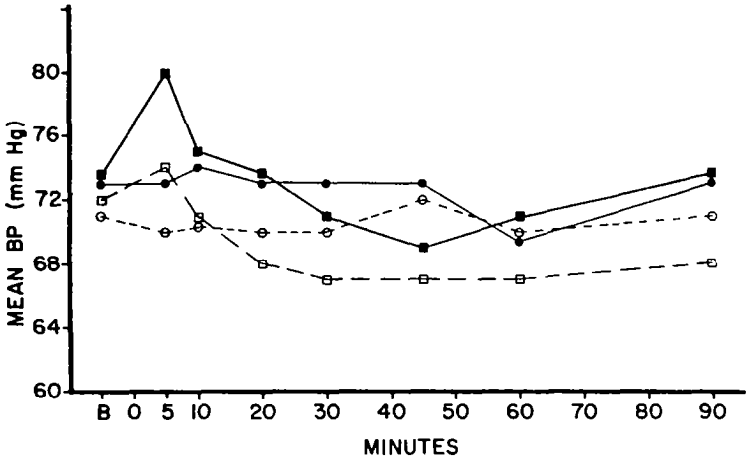


Figure 2. Mean blood pressure in mm Hg plotted versus time (minutes) for the four test treatments: □, low (0.2 mg) nicotine cigarettes: ■, high (2 mg) nicotine cigarettes: ○, low (2 mg) nicotine gum; ●, high (4 mg) nicotine gum. n=6. B, baseline.

Blood Pressure

The systolic, diastolic, and mean blood pressurevalues for the four conditions are listed in table 3. The mean BP is plotted in figure 2. No significant differences among baselinevalues for treatment conditions for systolic, diastolic, or mean BP's were noted. There was a significant condition x time interaction for systolic ($p=0.001$) and mean ($p=0.01$) BP. 'Ibis is attributed to an increase in both of these measures for cigarettes at 5 minutes in contrast to a decrease or no change in these measures after gum treatment (table 3). A peak rise in systolic BP of 2% and 9% and peak rise in diastolic BP of 4% and 12% were recorded at 5 minutes for the 0.2 mg and 2 mg nicotine cigarettes, respectively. The systolic BP did not rise above baseline for the 2 mg and 4 mg nicotine gum, and the diastolic BP rose less than 4% at anytime interval for both the 2 mg and 4 mg nicotine gum. The mean blood pressure rose a maximum of 3% and 10% for 0.2 mg and 2 mg nicotine cigarettes, respectively, at 5 minutes. The mean BP did not rise more than 1% above baseline at any time for the nicotine gum.

Echocardiographic Measures

The mean values for LVEDD and LVESD from ECHO are listed in table 4 in mm. No significant differences among baselines for the 2 variables were observed. A significant time effect for LVEDD of 0.08 and for LVESD of 0.0004 was present. However, there were no significant effects on LVEDD or LVFSD by dose or condition, and no significant interactions (table 2). The normal range for LVEDD in our laboratory is 38 - 57 mm and the normal LVESD is 21-39 mm. No value for the LVESD or LVEDD was out of the normal range during any part of the study.

The fractional shortening (FS) per cent is normally between 28% and 488. The values obtained in this study appear in table 4 and were all within the normal range. There was a significant ($p=0.0008$) main effect of time. The maximum change from baseline values was recorded over the first 10-20 minutes post-treatment and was a decrease of 3%, 3%, 11% and 9% for 0.2 mg and 2 mg nicotine cigarettes and 2 mg and 4 mg nicotine gum, respectively. By 90 minutes, FS% was within 3% of baseline values. There were no significant condition or dose effects or any significant interactions between or among condition, dose, and time (table 2).

Finally, the velocity of circumferential fiber shortening (VCF) was within the normal range of 0.89 - 1.60 at all times for all 4 conditions (table 4). No significant time, dose, or condition effects or any significant interactions were found (table 2).

Psychological testing

The only significant change ($p<0.05$) in subjective state reported for the 4 questions was for "Do you feel lightheaded?" . For this question there was a significant condition x time interaction ($p<O.004$) manifested by a significant increase in perceived lightheadedness at 5 minutes for the 2 mg nicotine cigarettes, only.

TABLE 4. Echocardiographic Measures

	CL	CH	GL	GH	CL	CH	GL	GH
	LVEDD				LVESD			
Baseline	50±2	50±l	49±2	51±5	33±2	33±l	32±l	33±2
5 min	49±2	51±4	49±2	50±4	33±2	34±3	32±l	33±2
10 min	50±2	51±3	49±2	51±5	34±3	34±2	34±2	34±2
20 min	50±2	51±3	48±2	52±5	33±2	34±3	32±2	34±2
30 min	49±1	51±3	49±2	52±5	32±2	34±2	33±2	34±3
45 min	49±3	51±3	49±2	5l±5	32±2	33±2	33±l	34±3
60 min	50±1	50±5	49±2	51±4	32±2	32±4	32±l	33±3
90 min	48±2	50±2	50±3	51±6	32±2	33±2	32±2	34±3
	FS				VCF			
Baseline			35±1	35±3	l.l5±0.06	1.09±O.10	1.13±O.11	1.12±0.03
5 min	33±3	34±2	34±3	34±3	1.07±0.13	1.13±0.10	1.07±O.09	1.14±0.11
10 min	33±4	33±2	31±3	33±3	l.O8±0.11	l.O4±0.08	l.O2±0.14	1.07±0.10
20 min	33±3	34±2	33±3	32±4	1.08±0.13	l.lO±0.12	1.10±0.10	1.05±0.13
30 min	35±3	33±3	33±3	34±3	1.14±O.12	1.03±0.11	1.05±O.09	l.O5±O.13
45 min	34±3	34±2	33±3	34±2	1.08±0.12	1.08±0.12	l.96±O.lO	1.12±0.14
60 min	35±3	37±2	34±3	35±1	1.06±0.14	1.15±0.12	l.ll±O.09	l.ll±0.06
90 min	34±2	33±2	34±4	34±3	l.lO±0.lO	1.07±0.10	1.08±0.10	1.06±0.16

CL, low (0.2 mg) nicotine cigarettes; CH, high (2 mg) nicotine cigarettes: GL, low (2 mg) nicotine gum; GH, high (4 mg) nicotine gum; LVEDD, left ventricular end diastolic dimension in mm; LVESD, left ventricular end systolic dimension in mm; FS, fractional shortening in %; values are means ±SD.

DISCUSSION

This study was designed to compare the cardiovascular effects of smoking a 0.2 mg or 2 mg nicotine cigarette with chewing a 2 mg or 4 mg nicotine gum and to begin to examine the safety of using nicotine gum as a method of smoking cessation.

The work of the heart, or oxygen demand, is dependent on four major factors: RR, preload, afterload, and contractility. RR can easily be directly measured. A significant increase in RR above baseline was noted only for the 2 mg nicotine cigarettes and consisted of a 28% increase from 64 ± 7 to 82 ± 10 beats/min noted at 5 minutes. Tachmes et al. (1978) reported heart rate and BP responses in eight healthy smoking subjects (five men and three women) before and after smoking low nicotine (0.3 mg) and high nicotine (2.0 mg) cigarettes. Their plotted mean values recorded at baseline and at 5 minutes after smoking agree almost precisely with our data, although S.D's were not reported. The increase in AR from baseline to 5 minutes for both low and high nicotine cigarettes was significant at $p<0.05$ in their study. The difference in sample size (n=8 vs. n=6) may account for the difference. Aronow et al. (1971) performed a similar study in male patients with a history of angina and found an increase in HR from 71.0 ± 11.0 to 86.8 ± 9.2 after smoking a high nicotine cigarette (2 mg) and an increase from 72.4 ± 11.1 to 81.0 ± 9.4 after smoking a low nicotine cigarette (0.3 mg). Both of these increases were significant.

The peak HR for the 4 mg nicotine gum was recorded as a 12% increase at 20 and 30 minutes, but this change was not significant. The timing of the peak HR correlates with previously reported peak plasma nicotine levels after chewing gum (McNabb et al. 1982; Russell et al. 1980). Wyberg et al. have reported a 15% increase in HR at 30 minutes after chewing nicotine gum containing 4 mg of nicotine for 30 minutes using a similar protocol (NYberg et al. 1982). This corresponded with peak whole blood nicotine levels which were also recorded by them at 30 minutes. Thus, a single dose of nicotine gum resulted in no significant change in HR in contrast to the significant increase observed with a single high nicotine cigarette over the 90 minutes studied. However, it is noteworthy that the peak HR achieved with 4 mg nicotine gum was greater than that observed with 0.2 mg nicotine cigarettes.

The mean BP, which is dependent on both the systolic and diastolic pressures, provides an indirect measure of afterload on the heart. The only significant changes ($p<0.05$) observed in the systolic, diastolic, and mean BPS were a 9%, 12%, and 10% increase from baseline noted at 5 minutes for the 2 mg nicotine cigarettes. The systolic and diastolic BPs recorded after gum chewing began were all less than the baseline, although not significantly less, indicating no effect of nicotine gum on BP. We did not observe the 7% increase at 30 minutes in systolic BP reported previously with 4 mg nicotine gum (Nyberg et al.). Their protocol differed from ours in that their subjects chewed the gum for 10 seconds instead of 5 seconds every 30 seconds. This may have been

responsible for the higher absorption of nicotine that they reported of 3.3 mg (range 2.9-4.0 mg) and may have resulted in the increase in systolic BP at 30 minutes.

The two remaining determinants of cardiac work are the preload (or stretch on the left ventricle) and contractility. The echocardiographically derived LVEDD provides a measure of preload, and FS% and VCF provide measures of contractility. None of these echocardiographic measures showed treatment effects. Thus, nicotine gum in a single dose given to healthy males with no known cardiovascular disease does not increase the work of the heart or adversely affect its function.

Raeder et al. (1979) assessed cardiac contractility using PEP, (pre-ejection period corrected for HR) and PEP/LVET in healthy male smokers and found no significant changes related to smoking low nicotine (0.1 mg) and high nicotine (2.6 mg) cigarettes. Our data is in agreement with this study but is in slight variance with a study by Rabinowitz et al. (1979) in 16 subjects (14 smokers). They reported an increase in LVEDD of 6% (cf. our 2% increase), in LVESD of 3% (cf. our 3% increase), and an increase in VCF of 13% from 1.12 ± 0.06 to 1.26 ± 0.09 (cf. our 4% increase) after smoking a high nicotine (2.5 mg) cigarette.

The experimental studies were performed after subjects had abstained from cigarettes for at least eleven hours. Mean baseline CO values for our six subjects were 29.8 ± 17.4 while smoking, and 12.4 ± 6.2 after abstaining for at least 11 hours. This average 58% reduction in CO levels is similar to data for 27 subjects previously studied with CO levels of 43.3 ± 15.3 while smoking and 16.4 ± 6.7 after abstinence for less than 1 day (unpublished data). This represented a 62% reduction in CO levels and was consistent with abstinence.

As expected, CO levels increased for both cigarette conditions immediately post-treatment, and such differences were not observed for the gum conditions. The results are similar to previously reported values (Aronow et al. 1971). No significant difference in the increase in CO levels at 10 minutes between the 0.2 mg and 2 mg nicotine cigarettes indicated that the differential increase in HR seen with the 0.2 mg vs. 2 mg nicotine cigarettes was likely due to the nicotine content and could not be ascribed to a variation in CO levels.

The only significant change in subjective state was an increase in lightheadedness reported at 5 minutes for the 2 mg nicotine cigarettes. The value for 0.2 mg nicotine cigarettes was increased at 5 minutes but not significantly. This subjective sensation may have been related to the increased CO and/or the rapid delivery of nicotine by cigarette smoking. It is unlikely that the increase in HR noted would be perceived as an increase in lightheadedness.

In summary, our study has shown no significant effect of 2 mg or 4 mg nicotine gum after a single dose on HR, BP, electrocardio-

graphic parameters, or echocardiographic measures of left ventricular function. This suggests that this modality may be a safe method from a cardiovascular perspective to use as an adjunct in smoking cessation therapy. We did not, however, examine the cardiovascular effects after multiple doses of gum as would be used clinically or give the gum to patients with significant cardiovascular or pulmonary disease. Both of these issues will require further study of nicotine gum.

REFERENCES

Aronow, W.S.; Dendinger, J.; and Rokaw, S.N. Heart rate and carbon monoxide level after smoking hi h-, low-, and non-nicotine cigarettes. Ann Intern Med 74:697-702, 1971.

Doll, R.; and Peto, R Mortality in relation to smoking: 20 ears observation in male British doctors. Br Med J 2:1525-1536, 1976.

Evans, D.; and Lane, D.S. Long-term outcome of smoking cessation Am J Public Health 70:725-727, 1980.

Fagerstrom, K-G. A comparison of psychological and pharmacological treatment in smoking cessation. J Behav Med 5:343-351, 1982.

Ferno, O.; Lichmeckert, S.J.A; and Lundgren, C.E.G. A substitute for tobacco smoking. Psychopharmacologia 31:201-204, 1973.

Gritz, E.R. Smoking behavior and tobacco abuse. In: Mello, N.K., ed. Advances in in Substance Abuse. Greenwich CT: JAI Press, 1980. pp. 91-158.

Hammond, E.C.; and Garfinkle, L. Coronary heart disease, stroke and aortic aneurysm. Factors in etiology. Arch Environ Health 19:167-182, 1969.

Hjalmarson, RI. Effect of nicotine chewing gum in smoking cessation: a randomized, placebo-co JAMA 252:2835-2838, 1984.

Hughes, J.R.: Hatsukami, D.K,: Pickens, R.W.: Krahn, D.: Malin, S.; and Luknic, A. Effects of nicotine gum on the tobacco withdrawal syndrome. Psychopharmacology 83:82-87, 1984.

Jarvik; M./E. The role of nicotine in the smoking habit. In: Hunt, W.A., ed. Learning Mechanisms in Smoking. Chicago: Aldine publishing Company, 1970. pp. 155-190.

Jarvis, M.J.; Raw, M.; Russell, M.A.H.; and Feyerabend, C. Randomised controlled trial of nicotine chewing-gum. Br Med J 285:537-540 1982.

Kannel, W.B. Update on the role of cigarette smoking in coronary artery disease. Am Heart J 101:319-328, 1981.

Killen, J.D.; Maccoby, N.: and Taylor, C.B. Nicotine gum and self-regulation training in smoking relapse prevention. Behavior Therapy 15:234-248 1984.

McNabb, M.E.; Ebert, R.V.; and McCusker, K. Plasma nicotine levels produced by chewing nicotine gum. JAMA 248:865-868, 1982.

Nyberg, G.; Panfilov, V.; Sivertsson, R.; and Wilhemsen, L. Cardiovascular effects of nicotine chewing in healthy non-smokers. Eur J Clin Pharmacol 23:303-307, 1982.

Rabinowitz, B.D.; Thorp, K.; Hube, G.L.; and Abelmann, W.H. Acute hemodynamic effects of cigarette smoking in man assessed-by systolic time intervals and echocardiography. Circulation 60:752-760, 1979.

Raeder, E.A.; Burckhardt, D.; Perrachoud, A.; Blum, P.; Amrein, P.; and Herzog, H. Effects of smoking and inhalation of carbon monoxide on systolic time intervals and blood pressure. Chest 75:136-140, 1979.

Raw, M. The treatment of cigarette dependence. In: Israel, Y.; Glaser, F.B.; Kalant, R.E.; Popham, W.; Schmidt, W.; and Smart, R.G, eds. Research Advances in Alcohol and Drug Problems. New York: Plenum, 1978. pp. 441-485.

Russell, M.A.H. Nicotine intake and its regulation. J Psychosom Res 24:253-264, 1980.

Russel, M.A.H.; Raw, M.; and Jarvis, M.J. Clinical use of nicotine chewing-gum. Br Med J 280:1599-1602, 1980.

Schneider, N.G. The effect of nicotine on learning and short-term memory. University Microfilms (#79-06196), Ann Arbor, Michigan, 1978.

Schneider, N.G.; Jarvik, M.E.; Forsythe, A.B.; Read, L.L.; Elliott, M.L.; and Schweiger, A. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. Addict Behav 8:253-262, 1983.

Schneider, KG; Jarvik, M.E.; and Forsythe, AR Nicotine versus placebo gum in the alleviation of withdrawal during smoking cessation. Addict Behav 9:149-156, 1984.

Schwartz, J.L. Smoking cures: Ways to kick an unhealthy habit. In: Jarvik, M.E.; Cullen, J.W.; Gritz, E.R.; Vogt, T.M.; and West, L.J., eds. Research on Smoking Behavior. National Institute on Drug Abuse, Research Monograph 17. DHEW Pub. No. (AMD) 78-581. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979. pp. 122-146

Tachmes, L.; Fernandez, R.J.; and Sackner, M.A. Hemodynamic effects of-smoking cigarettes of high and low nicotine content. Chest 74:243-246, 1978

West R.J. Psychology and pharmacology in cigarette withdrawal. J. Psychosom Res 28:379-386, 1984.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of Stephanie Thessomboon in obtaining echocardiograms, Stacey Posner in administering the treatments, and Laura Read in data analysis. Alan B. Forsythe, Ph.D, provided statistical assistance in the analyses of the data This work was supported by a grant from Merrell Dow Pharmaceuticals.

AUTHORS

Janine Krivokapich M.D.
John S. Child, M.D.
Department of Medicine
University of California,
Los Angeles
Los Angeles, CA 90024

Nina G. Schneider Ph.D.
Murray E. Jarvik M.D., Ph.D.
Department of Psychiatry and
Biobehavioral Sciences
University of California,

Los Angeles, CA 90024;
and Psychopharmacology Unit,
V.A. Medical Center, Brentwood
Los Angeles, CA 98073

Characterization of Tobacco Withdrawal: Physiological and Subjective Effects

Dorothy Hatsukami, Ph.D., John R. Hughes, M.D., and Roy Pickens, Ph.D.

Tobacco deprivation has been found to produce many symptoms in chronic smokers. While increased craving for tobacco is most commonly reported, a wide variety of other symptoms have also been reported, including changes in physiological, psychomotor and subjective functioning (see Jaffe and Jarvik 1978; USDHEW 1979; Shiffman 1979). This observation has led to the belief that a tobacco withdrawal syndrome exists which implies a physical dependence to tobacco. However, at the present time, it is unclear if all or any of the reactions following tobacco deprivation are in fact indicators of physical dependence. This uncertainty exists in part because of the lack of systematic and comprehensive studies of tobacco withdrawal similar to the classical studies such as those which have examined opiate withdrawal symptoms (Himmelsbach 1942). The classical studies of withdrawal phenomena have tended to examine a variety of signs and symptoms in a prospective fashion with measurements obtained on repeated occasions both during baseline and drug deprivation. In contrast, most previous investigations on tobacco withdrawal symptoms have been either retrospective, employed only a limited number of measures, employed no baseline period or failed to include control groups. Furthermore, in order to define reactions to tobacco deprivation as a true withdrawal syndrome, it is necessary to rule out the possibility that these symptoms are attributable to removal of drug action, to a loss of a reinforcer, or a disruption of a habit. A careful examination of tobacco withdrawal is important not only to better understand factors which maintain smoking, but also to develop more effective smoking treatment procedures. For example, if specific signs and symptoms after tobacco deprivation are due to pharmacological withdrawal, then pharmacological intervention to treat these symptoms may provide the best treatment outcome.

Over the past few years we have been conducting studies to determine reliable and valid indicators of tobacco withdrawal. We have also attempted to determine if nicotine replacement can reduce the number or intensity of tobacco withdrawal symptoms. Two studies have been completed describing the characteristics of tobacco withdrawal, and one study has been completed determining if withdrawal symptoms can be alleviated with nicotine replacement. This paper will describe the results of these studies, as well as investigations currently underway.

TOBACCO WITHDRAWAL SYMPTOMS IN A CONTROLLED ENVIRONMENT

In the first study (Hatsukami et al. 1984), a prospective examination of tobacco withdrawal symptoms was undertaken while subjects (chronic smokers) lived in a controlled environment. Subjects were hospitalized in the General Clinical Research Center of the University of Minnesota Hospitals. This Center is a federally funded unit established to support clinical research, and contains its own staff of physicians, nurses, and dieticians as well as its own biochemical laboratory and kitchen facilities. In the study, subjects (N=27) were hospitalized for seven consecutive days. For the first 3 days, they were allowed to smoke ad lib while a battery of tests (see table 1) was administered 1-2 times a day. For the next 4 days, subjects in the experimental group (N=20) were required to abstain from all tobacco use, while subjects in the control group (N=7) were allowed to continue to smoke ad lib. Compliance was monitored by random carbon monoxide breath samples and observations by the nursing staff.

The study has yielded several interesting findings. First, few of the measures changed significantly after tobacco deprivation. Of the 37 measures examined, significant effects were found with only 9. Physical measures that changed significantly were a decrease in heart rate, and increases in caloric intake and body weight. Subjective measures increasing significantly were craving for tobacco, confusion and depression-dejection scores on the POMS, and reports of number of awakenings and duration of awakenings during the sleep period. The only other significant change was reports by observers that the subject had difficulty concentrating (table 2). The remaining 28 measures in table 2 did not change following tobacco deprivation.

As part of the study, the time course of withdrawal measures was examined over the 4 days of tobacco deprivation. Self-report symptoms such as craving for tobacco, confusion, number of awakenings and duration of the awakenings, and depression-dejection peaked within 24 to 72 hours after tobacco deprivation and then declined. Caloric intake increased over the first 72 hours of tobacco deprivation and decreased after 96 hours, while weight continued to increase. Similarly heart rate decreased initially with a slight increase after 96 hours of deprivation. This finding would indicate that some of these symptoms may not solely be due to the removal of a pharmacological effect.

There may be several reasons for our failure to find significant changes in measures that other studies have reported following tobacco deprivation. One reason may be our inclusion of a control group. We found that addition of the control group eliminated findings that would have been significant if only a baseline/deprivation comparison had been made. For example, restlessness increased significantly from baseline to the deprivation period for subjects in the experimental group. However, there was also an increase in this measure for subjects in the control group over the same period of time. Thus, the inclusion of a control prevented an erroneous

485-874 0 - 85 - 3

Table 1

Measures Employed in the Studies on Tobacco Withdrawal Symptoms and Effects of Nicotine Gum on Tobacco Withdrawal Symptoms

Measures	Study I (Inpatient)	Study II (Outpatient)	Study III (Nicotine Gum)	Study IV (Recent Investigation)
Objective Measures				
Vital Signs				
Heart Rate				
Supine	X	X	X	X
Orthostatic		X	X	X
Blood Pressure				
Supine Systolic	X			X
Supine Diastolic	X			X
Orthostatic Systolic	X			X
Temperature	X			X
Respiratory Rate	X			X
Appetitive Behavior				
Body Weight	X	X	X	X
Caloric Intake/Eating	X	X	X	X
Fluid Input	X			
Fluid Output	X			
Psychomotor Behavior				
Level of Activity	X			
Reaction Times				
Simple	X			X
Choice	X			X
Errors	X			X
Tremor	X	X	X	X
Self-Report Measures				
Shiffman-Jarvik Tobacco Withdrawal Questionnaire[1]	X			X
Profile of Mood States Scale[2]	X	X	X	X
Self-Rating Checklist[3]		X	X	
Stanford Sleep Scale[4]	X	X	X	X
Behavioral Observation Checklist[5]	X	X	X	

[1] Includes scores on craving for tobacco, stimulation/sedation, appetite, psychological discomfort, physical symptoms scales.
[2] Includes scores on anxiety-tension, anger-hostility, depression-dejection, fatigue, confusion. vigor scales.
[3] Incluses ratings of cigarette craving, irritability, anxiety, difficulty concentrating, restlessness. headache, drowsiness, gastrointestinal disturbances, fatigue, impatience, hunger, eating, somatic complaints.
[4] Includes reports on number of awakenings. durations of awakening, duration of sleep. quality of sleep, latency of sleep.
[5] For Study I, includes observations on restlessness, argumentativeness, slow movements, drowsiness, poor concentration. For Study II. includes observations on irritability, anxiety, restlessness and impatience.

Table 2

Significant Changes Following Tobacco Deprivation
and Effects of Nicotine Gum on Tobacco Withdrawal Symptoms

Measures	Study I (Inpatient)	Study II (Outpatient)	Study III (Nicotine Gum)	Study IV (Recent Investigation)
Objective Measures				
Heart Rate				
Supine	-	-		-
Drthostatic	a	-		-
Body Weight	+			
Caloric Intake/Eating	+	+		+
Tremor		-		
Self-Report Measures				
Shiffman-Jarvik				
Craving	+	a	a	+
POMS				
Tension-Anxiety		+	*	
Depression-Dejection	+			
Confusion	+	+	*	+
Anger-Hostility		+	*	+
Vigor		-		-
Self-Rating Checklist				
Craving	a	+		a
Irritability	a	+	*	a
Anxiety	a	+	*	a
Difficulty Concentrating	a	+	*	a
Restlessness	a	+	*	a
Impatience	a	+	*	a
Hunger	a	+		a
Somatic Complaints	a	+	*	a
Sleep Problems	a	+		a
Standard Sleep Scale				
Number of Awakenings	+	+		+
Duration of Awakenings	+			
Behavioral Observation Checklist				
Difficulty Concentrating	+	a	a	a
Irritability	a	+	*	a
Anxiety	a	+	*	a
Restlessness		+	*	a
Impatience	a	+	*	a

a measure not employed in study
+ increase
- decrease
* significant effect of nicotine gum on tobacco withdrawal symptoms

conclusion from being drawn, as would have happened if data from only the experimental group had been analyzed.

A second reason we found few tobacco withdrawal symptoms may be related to the type of environment in which the study was conducted. In a controlled hospital environment, subjects are not exposed to many of the stimuli that are typically associated with their smoking. If environmental factors play a role in determining the intensity of tobacco withdrawal symptoms (Pomerleau 1981), then hospitalization may have minimized the intensity of those symptoms.

The third reason for our failure to find withdrawal symptoms that others have reported may be the large between-subject variability in our data. This would reduce the likelihood of our obtaining a statistically significant effect. For example, for blood pressure and temperature, some subjects showed an increase, other showed no change, while still others showed a decrease on these measures. Across subjects, such effects tend to cancel out, leaving no net change for the group.

TOBACCO WITHDRAWAL SYMPTOMS IN THE NATURAL ENVIRONMENT

In the first study, lack of environmental stimuli typically associated with smoking was suggested as one reason for relatively few withdrawal symptoms being found. A second study was therefore conducted to examine tobacco withdrawal symptoms as they occur in the natural environment. This study was part of a larger investigation designed to examine the effects of nicotine gum on tobacco withdrawal symptoms (Hughes et al. 1984). The project was conducted with outpatients who returned to the smoking clinic for measurement of withdrawal symptoms. After two evenings of baseline measurement, subjects were randomly assigned to either nicotine or placebo gum groups in a double-blind manner. Subjects were then asked to stop smoking, chew nicotine gum or placebo gum ad lib, and return to the smoking clinic for measurements on the first, second, and fourth evenings of tobacco deprivation.

For our present purposes, only data from the placebo group (N=49) will be examined. (The effect of nicotine gum on tobacco withdrawal symptoms will be described in a later part of this paper.) Since the study was double-blind, the effects of subject and experimenter expectancy on tobacco withdrawal symptoms were controlled. The measures employed in this study are shown in table 1.

In this study, the physiological measures that changed significantly following tobacco deprivation were supine and orthostatic heart rate. Both decreased with tobacco deprivation. Measures on the self-rating checklist that changed significantly were craving for tobacco, irritability, anxiety, impatience, difficulty concentrating, and restlessness. All increased with tobacco deprivation. The results obtained with the Profile of Mood States (POMS) were similar to the results obtained with the self-rating checklist, where significant increases in the anger-hostility, anxiety-tension, and confusion scores, and decreases in the vigor score were

obtained. Behavioral observations by others tended to confirm the self-report results, where significant increases in irritability, anxiety, restlessness, and impatience were obtained. Other significant changes reported by subjects included decreased tremulousness, increased hunger, increased eating, increased somatic complaints, and increased number of awakenings during sleep and sleep problems. As in the first study, most of these withdrawal symptoms began shortly after onset of tobacco deprivation and peaked 24-48 hours later.

Compared to the inpatient study, the outpatient study found a greater number of significant changes following tobacco withdrawal (see table 2). The symptoms found in common in the two studies were a decrease in heart rate and increases in craving for tobacco, difficulty concentrating, eating behavior, and number of awakenings during sleep. Unlike the previous study, however, the outpatient study results included no statistically significant increase in body weight, duration of awakening during sleep, or depression-dejection score on the POMS. On other common measures, a decrease in tremulousness, an increase in anger-hostility and tension-anxiety scores, and a decrease in vigor score on the POMS were found in the outpatient study but not in the inpatient study.

EFFECTS OF NICOTINE ADMINISTRATION ON TOBACCO WITHDRAWAL SYMPTOMS

Do tobacco withdrawal symptoms result from nicotine deprivation? Other studies attempting to answer this question have focused on whether frequency of smoking cigarettes is related to severity of withdrawal and have obtained equivocal results (Shiffman 1979). In the present study, however, we attempted to determine whether nicotine gum relieves tobacco withdrawal symptoms. This study is important not only in determining whether physiological dependence on nicotine can occur, but also for clinical reasons. If relapse to smoking is related to the appearance of aversive nicotine withdrawal symptoms following tobacco deprivation, then attenuation of withdrawal symptoms by other forms of nicotine administration could improve smoking cessation success rates (Russell et al. 1980).

Subjects were 100 smokers who met the criteria for Tobacco Dependence and who had a history of Tobacco Withdrawal as defined by the DSM III criteria (APA 1981). Subjects were randomly assigned to either a nicotine (2 mg) gum or placebo gum group. Following 2 days of smoking baseline, all subjects were required to undergo 4 days of tobacco deprivation, during which time they were instructed to chew the gum (either nicotine or placebo) on a PRN basis. Measures employed are shown in table 1. Only those symptoms that changed signficantly following tobacco deprivation in the placebo group were examined in the analysis.

The nicotine gum group reported significantly less irritability, anxiety, difficulty concentrating, restlessness, impatience, and somatic complaints after smoking cessation than the placebo gum group on the self-rating checklist. Reductions in these withdrawal symptoms were confirmed by subjects' scores on the Profile of Mood

States and by observer ratings. Nicotine did not reduce the increase in cigarette craving, hunger, eating, and insomnia, or the decrease in tremulousness and supine heart rate that occurred after smoking cessation. The effect of the nicotine was evident on the first day of deprivation and throughout the 4-day tobacco deprivation period.

In summary, it appears the nicotine relieves some, but not all, of the symptoms of tobacco deprivation. There are a number of factors which may account for the failure of the gum to relieve all tobacco withdrawal symptoms. For example, the gum dose that was used in the study may have been inadequate. Second, it may be that nicotine must be given in a bolus form (i.e., as delivered in smoking) to relieve some symptoms of withdrawal (Russell and Feyerabend 1978). Third, there may be other psychoactive ingredients in tobacco in addition to nicotine which are correlated with physiological dependence on tobacco (Jarvik 1981). Fourth, tobacco withdrawal symptoms may be controlled by behavioral or psychological as well as a pharmacological factors (Falk 1971; Jaffe and Jarvik 1978).

CURRENT INVESTIGATIONS

A study is currently being undertaken to determine the within-subject reliability of tobacco withdrawal symptoms. The study employs a modified single-subject A-B-A-B experimental design. Following an intial 48-hour period during which baseline measures are obtained while subjects smoke ad lib, subjects are required to undergo a 96-hour period of tobacco deprivation. After the deprivation period, subjects are asked to resume smoking for a 96-hour period (during the latter half of which additional baseline measures are obtained). This second baseline period is followed by a second 96-hour tobacco deprivation period. Preliminary analysis of the data from three subjects showed that decreases in supine heart rate and in vigor score on the POMS, and increases in caloric intake, anger-hostility, and number of awakenings during sleep occurred consistently both within and across subjects during both periods of deprivation. In five out of six measurement periods, craving and confusion score on the POMS also increased. Measures which showed consistent effects of tobacco deprivation within but not across subjects include orthostatic heart rate change. All other variables showed inconsistent changes between and within subjects over the two tobacco deprivation periods.

SUMMARY

In total, our studies show that changes which occur reliably and consistently in chronic smokers after tobacco deprivation include: (1) decreased heart rate, (2) increased caloric intake/eating, (3) increased number of awakenings during sleep, (4) increased craving for tobacco, and (5) increased confusion, as measured by the POMS. Other changes that were found to occur after tobacco deprivation in some but not all of our studies include decreased orthostatic heart rate, increased irritability, and decreased vigor score on the POMS.

Previous investigators have found a consistent effect of tobacco deprivation on heart rate (Gilbert and Pope 1982; Knapp et al. 1963; Parsons and Hamme 1975; Weybrew and Stark 1967; Glauser et al. 1970; Myrsten et al. 1977; Murphee and Schultz 1968). Although decreased blood pressure (Knapp et al. 1963; Murphee and Schultz 1968) and changes in other vital signs such as temperature (Gilbert and Pope 1982; Myrsten et al. 1977; Ague 1974) have been reported, our present studies and studies by others (Weybrew and Stark 1967; Glauser et al. 1970) failed to find a significant deprivation effect on these measures. Perhaps the contradictory findings are a function of the reliability of the measures themselves or of the population tested.

Caloric intake has been found to increase in both animals and humans after nicotine or smoking cessation (Gruneberg 1982; Myrsten et al. 1977; Wack and Rodin 1982). These results are consistent with studies which have found that smoking cessation causes an increase in body weight (Wack and Rodin 1982). However, previous studies disagree on how smoking cessation causes weight gain. Our inpatient study is believed to be the first to simultaneously measure changes in caloric intake, fluid retention, and physical activity after tobacco deprivation. In the study, caloric intake increased but fluid retention and physical activity did not change. The increases in weight may not be accounted for solely by increases in caloric intake. There may be other factors such as decreased basal metabolic rate which cause the increase in weight.

Other studies have also reported sleep disturbance or insomnia among tobacco-deprived smokers (Larson et al. 1961; Weybrew and Stark 1967). Studies directly monitoring sleep have found a decrease in duration awake (Soldatos et al. 1980), increased REM sleep (Soldatos et al. 1980; Kales et al. 1970; Parsons et al. 1975), and increased Stage IV (>50% delta waves) sleep (Parson et al. 1975; Parsons and Hamme 1975). Thus, objective data indicate that after tobacco deprivation smokers actually sleep longer, which contradicts subjective reports of insomnia.

Difficulty concentrating after tobacco deprivation has also been reported by other investigators (Weybrew and Stark 1967; Frankenhauser et al. 1971; Myrsten et al. 1977; Wynder et al. 1967). The difficulty may be reflected in poor performance shown by tobacco-deprived smokers on driving simulation (Heimstra et al. 1973) and vigilance (Ashton and Stepney 1982) tasks. Furthermore, smokers deprived of tobacco have shown an increase in slow wave activity (Ulett and Itil 1969) and slower dominant alpha frequency (Knott and Venables 1977) which are associated with a hypoexcitation state and perhaps a decrease in attention (Knott and Venables 1977; Ashton and Stepney 1982).

Subjective reports of craving for tobacco, increased irritability, and decreased vigor have been widely cited in other studies (Shiffman 1979). Craving for tobacco has been found to be the most prevalent withdrawal symptom reported by exsmokers, with up to 90 percent of smokers who quit reporting a craving for tobacco (Guil-

ford 1966). While most of these mood changes have been obtained by self-report, two studies have employed objective measures of irritability or anger. Hutchinson and Emley (1973) found that masseter muscle contraction increased in frequency in 7 of 8 subjects withdrawn from tobacco. Schechter and Rand (1974) found higher aggression scores in chronic smokers on the Buss Aggression Machine when subjects were deprived of cigarettes than when allowed to smoke.

The time course for symptoms that were examined after tobacco deprivation would suggest that some of the symptoms are not primarily due to the removal of a pharmacological effect and consequently a return to values prior to the onset of smoking. The onset of most symptoms was rapid (within 24 hours of onset of deprivation), reached a peak in 36 to 72 hours, and then gradually declined. Other investigators have also noted that the peak in tobacco withdrawal symptoms based on subjective reports occurs between 24 and 48 hours (Shiffman and Jarvik 1976). If these symptoms would have been due to return to baseline, symptoms would not have shown the "overshoot" or "rebound" pattern that has been found in the opiate withdrawal syndrome (Himmelsbach 1942).

Our study indicates that nicotine appears to affect the occurrence of some but not all symptoms of tobacco withdrawal. Previous studies have also found that administration of nicotine minimizes tobacco withdrawal symptoms (Hughes and Hatsukami, this volume). The only symptom that has been consistently found to be reduced by the administration of nicotine has been irritability.

Another method of determining whether tobacco withdrawal symptoms are a result of nicotine deprivation is by examining the signs and symptoms after nicotine gum deprivation. In a recent study, West and Russell (in press) have shown that symptoms occur after cessation of long-term nicotine gum use. They found that among individuals who have been using 2 mg gum for at least a year, cessation from gum use led to increases in reported irritability, depression, hunger, tiredness and restlessness, and decrease in ability to concentrate and ability to cope. In addition, they found significant decreases in heart rate. Interestingly, these symptoms are similar to those we found among smokers undergoing tobacco deprivation (i.e., irritability, hunger, decrease in ability to concentrate, and decreased heart rate).

Inevitably, attempts to clarify the characteristics of tobacco withdrawal generate questions that need to be addressed in further investigations. More research is necessary to determine which changes observed following tobacco withdrawal are specifically the result of removal of the pharmacological effects of the drug and subsequent return to baseline, the result of interrupting a positively reinforced behavior (Falk 1971), the occurrence of a disruptive event, or true pharmacological withdrawal symptoms. In addition, further research is required to determine which symptoms of tobacco withdrawal result from deprivation from nicotine. Determination of the symptoms which are a result of behavioral dependence or physical dependence on nicotine can lead to more

directed treatment approaches. For example, craving for tobacco does not seem to be affected by nicotine replacement, therefore behavioral management may be necessary for symptoms of craving rather than pharmacological intervention with nicotine.

REFERENCES

Ague, C. Cardiovascular variables, skin conductance and time estimation: Changes after the administration of small doses of nicotine. Psychopharmacologia, 37:109-125, 1974.

Ashton, H., and Stepney, R. Smoking: Psychology and Pharmacology. New York: Travistock Publications, 1982.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder; 3rd Ed. Washington: APA, 1981.

Burns, B.H. Chronic chest disease, personality, and success in stopping cigarette smoking. Brit J Prev Soc Med, 23:23-37, 1969.

Falk, J.L. The nature and determinants of adjunctive behavior. Physiol Behav, 6:577-588, 1971.

Frankenhaeuser, M.; Myrsten, A-L; Post, B.; and Johansson, G. Behavioral and physiological effects of cigarette smoking in monotonous situation. Psychopharmacologia, 22:1-7, 1971.

Gilbert, R.M., and Pope, M.A. Early effects of quitting smoking. Psychopharmacology, 78:121-127, 1982.

Glauser, S.C.; Glauser, E.M.; Reidenberg, M.M.; Rusy, B.F.; and Tallarida, R.J. Metabolic changes associated with the cessation of cigarette smoking. Arch Environ Health, 20:337-381, 1970.

Grunberg, N.E. The effects of nicotine and cigarette smoking on food consumption and taste preferences. Addict Behav, 7:317-331, 1982.

Guilford, J.S. Factors Related to Successful Abstinence from Smoking. Pittsburgh, PA: American Institute for Research, 1966.

Hatsukami, D.; Hughes, J.; and Pickens, R. Tobacco withdrawal symptoms: An experimental analysis. Psychopharmacology, 84:231-236, 1984.

Heimstra, N.W. The effects of smoking on mood change. In: Dunn, W.G., ed. Smoking behavior: Motives and Incentives. Washington, D.C.: Winston and Sons, 1973, pp. 197-207.

Himmelsbach, C.K. Clinical studies of drug addiction: Physical dependence, withdrawal and recovery. Arch Intern Med, 69:776-782, 1942.

Hughes, J.R.; Hatsukami, O.K.; Pickens, R.W.; Krahn, D.; Malin, S.; and Luknic, A. Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacology, 83:82-87, 1984.

Hutchinson, R.R., and Emley, G.S. Effects of nicotine on avoidance, conditioned suppression, and aggression response measures in animals and man. In: Dunn, W.L., ed. Smoking Behavior: Motives and Incentives. Washington, D.C.: Winston and Sons, 171-196, 1973.

Jaffe, J. H., and Jarvik, M.E. Tobacco use disorder. In: Lipton, M.A.; DiMascia, A.; and Killam, K.F., eds. Psychopharmacology:

A Generation of Progress. New York: Raven Press, 1978, pp. 1665-1675.

Jarvik, M.E. Biological factors underlying the smoking habit. In: Jarvik, M.E.; Cullen, J.W.; Gritz, E.R.; Vogt, T.M.; and West, L.J., eds. Research on Smoking Behavior. National Institute on Drug Abuse Research Monograph No. 17 DHEW Pub. No. (ADM) 78-581. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981, pp. 122.

Kales, J.D.; Allen, C.; Preston, T.A; and Tan, T-L. Changes in REM sleep and dreaming with cigarette smoking and following withdrawal. Psychophysiol, 7:347-348, 1970.

Knapp, P.H.; Bliss, C.M.; and Wells, H. Addictive aspects in heavy cigarette smoking. Am J Psychiatry, 119:966-972, 1963.

Knott, V.J., and Venables, P.H. EEG alpha correlates of nonsmokers, smokers, smoking, and smoking deprivation. Psychophysiol, 14(2): 150-156, 1977.

Larson, P.S.; Haag, H.B.; and Silvette, H. Tobacco: Experimental and Clinical Studies. Baltimore, MD: The Williams and Wilkins Co., 1961.

Murphee, M.E., and Schultz, R.E. Abstinence effects in smokers. Fed-Proc, 27:220, 1968:

Myrsten, A-L.; Algerot, A.; and Edgren, B. Effects of abstinence from tobacco smoking on physiological and psychological arousal levels in habitual smokers. Psychosom Med, 39(1):25-38, 1977.

Parsons, L.D., and Hamme, S. The effects of nicotine withdrawal on the sleep awake cycle. VA J of Science, 27:86, 1975.

Parsons, L.C.; Luttrell, N.; Gabe, J.; and Pollock, P. The effect of 48 hour nicotine withdrawal on all night sleep patterns in adult females. VA J of Science, 26:192, 1975.

Pomerleau, O.F. Underlying mechanisms in substance abuse: Examples from research on smoking. Addict Behav, 6:187-196, 1981.

Russell, M.A.H., and Feyerabend, C. Cigarette smoking: A dependence on high nicotine boli. Drug Metab Rev, 8:29-57,1978.

Russell, M.A.H.; Raw, M.; and Jarvis, M.J. Clinical use of nicotine chewing gum. Br Med J, 1:1599-1602, 1980.

Schechter, M.D., and Rand, M.J. Effect of acute deprivation of smoking on aggression and hostility. Psychopharmacologia, 35:19-28, 1974.

Shiffman, S.M. The tobacco withdrawal syndrome. In: Kransegor, N.A., ed. Cigarette Smoking as a Dependence Process, National Institute on Drug Abuse Research Monograph No. 23. DHEW Pub. No. (ADM)79-800, Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979, pp. 158-185.

Shiffman, S.M., and Jarvik, M.E. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology, 50:35-39, 1976.

Soldatos, C.R.; Kales, J.D.; Scharf, M.B.; Bixler, M.B.; and Kales, A. Cigarette smoking associated with sleep difficulty. Science, 207:551-553, 1980.

Ulett, J.A., and Itil, T.M. Quantitative electroencephalogram in smoking and smoking deprivation. Science, 164:969-970, 1969.

U.S. Department of Health, Education, and Welfare, PHS. The Health Consequences of Smoking: Reference Edition. Washington, D.C.: Pub. No. (CDE) 78-8357, 1979.

Wack, J.T., and Rodin, J. Smoking and its effects on body weight

and the system of caloric regulation. Am J Clin Nutr, 35:366-380. 1982.
West. R., and Russell, M.A.H. Effects of withdrawal from long-term nicotine gum use. Psychol Med, in press.
Weybrew, B.B., and Stark, J.D. Psychological and Physiological Changes Associated with Deprivation from Smoking. U.S. Naval Submarine and Medical Center Report No. 490, 1967.
Wynder, E.L.; Kaufman, P.L.; and Lesser, R.L. A short-term follow-up study on ex-cigarette smokers, with special emphasis on persistent cough and weight gain. Am Rev Resp Dis, 96:645-655. 1967.

AUTHORS AND ADDRESSES

Dorothy Hatsukami, Ph.D.
University of Minnesota
Department of Psychiatry
Box 393 Mayo
Minneapolis, MN 55455

Roy Pickens, Ph.D.
University of Minnesota
Department of Psychiatry
Box 392
Minneapolis, MN 55455

John R. Hughes, M.D.
University of Vermont. College of Medicine
Department of Psychiatry
Burlington, VT 05408

Short-Term Effects of Nicotine Gum

John R. Hughes, M.D., and Dorothy Hatsukami, Ph.D.

Pharmacological treatments of drug dependence vary in their approach. Medications may make drug administration aversive (e.g., disulfiram). block the reinforcing effects of the drug (e.g., naltrexone), substitute for the drug (e.g., methadone), or relieve the discomfort of drug withdrawal (e.g., benzodiazepines).

Based on these approaches, several types of medications, such as taste adulterants, stimulants, and tranquilizers have been tested as aids to smoking cessation (Kozlowski, in press; Raw 1978; Grabowski and Hall, this volume). Most of these medications have not been efficacious. Nicotine chewing gum is the exception (Hughes and Miller 1984). The major hypotheses to explain the efficacy of nicotine gum are that the gum substitutes for the reinforcing effects of cigarettes or that the gum relieves tobacco withdrawal symptoms.

This article will review studies of the short-term effects of nicotine gum that test these two hypotheses. Although we will attempt some conclusions, the reader should be aware that, as with most drugs (Thompson and Johanson 1981), the effects of nicotine depend on several conditions. For example, differences in dose, duration and route of administration, drug history, external stimuli, genetics, personality, rate of ongoing behavior, schedule, time since drug ingested and tolerance can produce marked differences in nicotine's actions (Aston and Stepney 1982; Emley and Hutchinson 1984; Gilbert 1979; Goldberg et al. 1983; Henningfield 1984; Henningfield and Goldberg 1983; Hughes, in press; Mangan and Golding 1984). For example, differences in external stimuli (Goldberg et al. 1983). instructional set (Hughes et al., in press-a). and schedule (Goldberg et al. 1983) can determine whether nicotine will serve as a reinforcer or a punisher. Thus, when we summarize "the" short-term effects of nicotine gum, the reader should realize the results obtained in laboratory studies may not generalize to those obtained in medical practice.

EFFECT ON SMOKING BEHAVIOR

The effects of nicotine on smoking vary widely both between and even within studies (Brantmark et al. 1973; Ebert et al. 1984; Kozlowski et al. 1975; McM Turner et al. 1977; Ohlin and Westling 1975; Russell et al. 1976; Westling 1976). Of the 16 comparisons in these studies, 7 showed nicotine gum decreased smoking and 9 did not.

These contradictory results may be due to differences in subjects (those who were vs. were not trying to quit), sample size (8 vs. 92 Ss), design (within- vs. between-group design), dose (1 vs. 2 vs. 4 mg). schedule of dosing (e.g.. single vs. ad-lib administrations). duration (30 min vs. 2 wks). and dependent measures (self-report vs. objective measures and frequency vs. topographical vs. biochemical measures). Whether any of these differences do, in fact, control whether nicotine gum influences smoking might be determined by looking for an association between positive results and a methodological procedure (e.g.. use of smokers trying to quit) across the studies. Unfortunately, the small number of studies and the fact that the different methods are confounded with each other prohibits such an analysis. About the only conclusion that can be reached is that, at this time, a conclusion cannot be reached.

EFFECT ON CIGARETTE CRAVING

Perhaps the major hypothesis to explain the efficacy of nicotine gum is that the gum relieves craving for cigarettes during abstinence. Tests of this hypothesis have thus far been restricted to examining the effects of nicotine gum on subjects' endorsements of descriptions of craving, such as desire to smoke, thoughts about cigarettes, difficulty refraining from smoking, urges to smoke, hunger for a cigarette, and awareness of not having a cigarette. Nicotine gum decreased some of these measures of craving in some subjects in three small studies (Russell et al. 1977; Ryden 1975; Schneider et al. 1977). However, nicotine gum did not decrease these measures of craving in large, placebo-controlled trials of the gum (Hughes et al. 1984; Jarvis et al. 1982; Ohlin and Westling 1975; Schneider et al. 1984; West et al. 1984). Thus, the weight of the evidence does not support the hypothesis that the efficacy of nicotine gum is due to its ability to relieve craving.

There are several reasons why nicotine gum might not reduce cigarette craving. First, the route of administration (oral vs. inhalation) might be crucial. Oral nicotine produces low levels of nicotine (Hughes and Miller 1984) that might be insufficient to reduce craving. However, previous studies have shown that nicotine via other routes of administration, e.g.. capsules (Jarvik et al. 1970) or intramuscular (Johnston 1942) and intravenous (Henningfield et al. 1983; Lucchessi et al. 1967) injections decrease smoking and cigarette craving. Unfortunately, none of these studies reported examining self-reported craving during abstinence. Oral nicotine also does not reproduce the "bolus" injection of nicotine from smoking. Bolus injections may be essential to replicate the effects of smoking (Russell and Feyerabend 1978). However, Kumar et al. (1977) found that intravenous bolt of nicotine did not decrease smoking frequency. Second, other ingredients in tobacco may control the desire for a cigarette. Although there are several reasons to believe nicotine is the major psychoactive ingredient in tobacco, the psychopharmacological properties of several thousand other compounds in tobacco have not been tested (Jarvik 1977). Third, craving may be controlled by environmental factors. Smoking occurs many times per day, in a variety of situations, and produces a psychoactive effect quite rapidly (i.e.. within 7 seconds); thus, the opportunities for environmental conditioning are great. Recent studies with

amphetamines suggest that once a conditioned drug response is established, the response may no longer be influenced by agonists or antagonists of the drug (Benninger and Hahn 1983). If this is true, then once tobacco craving is conditioned to environmental cues, nicotine alone may no longer reduce craving.

A fourth possibility is that nicotine reduces craving only in the more "dependent" smoker (Hughes. in press-b). The results of Russell's study (1977) are consistent with this hypothesis in that they suggest the reduction in cigarette craving by nicotine gum varies widely across smokers. To test this hypothesis we divided smokers in our study into a dependent and nondependent group according to their scores on the Tolerance Questionnaire (Fagerstrom 1978). We then compared the reduction in cigarette craving from nicotine and placebo gum between the two groups. The reduction in craving was the same for dependent and nondependent smokers; thus, the hypothesis that nicotine reduces craving only in the more dependent smoker was not supported.

Finally, there is the possibility that self-reported craving is a poor measure. Perhaps better measures would be direct, objective tests of nicotine self-administration during abstinence such as concurrent access (Hughes et al., in press) to tobacco and non-tobacco cigarettes or the amount of work to obtain nicotine or tobacco (Griffiths et al. 1982).

The inability to document that nicotine gum reduces craving during abstinence may have clinical implications. At present, when smokers are prescribed nicotine gum, they are told the gum will reduce cigarette craving. Perhaps instead smokers should be told not to rely on the gum to relieve all craving and be encouraged to develop a plan to deal with craving that does not respond to the gum (e.g., engaging in alternative behaviors or avoidance of cues). When smokers are prescribed nicotine gum, they are also told to use the gum whenever craving for a cigarette occurs. If nicotine gum does not reduce craving, perhaps they could be told to use the gum on a fixed time schedule instead of a PRN schedule. Fixed time schedules might be preferable to PRN schedules as the former schedule helps extinguish conditioned craving responses and decreases the probability that use of nicotine gum itself will become conditioned to craving cues. Another alternative is that smokers should be told to use the gum not when cigarette craving occurs, but rather when withdrawal symptoms occur (see below).

EFFECT ON TOBACCO WITHDRAWAL

Abstinence from smoking induces a variety of withdrawal symptoms (Hatsukami, this volume; Shiffman 1979). Several double-blind, placebo-controlled studies have tested the effect of nicotine gum on tobacco withdrawal. Some studies correlated withdrawal symptom ratings into a total withdrawal discomfort score. These withdrawal scores consisted of a single global self-report rating (Russell et al. 1976; Westling 1976). number of symptoms reported (Puska et al. 1979). or a cumulative score based on the sum of intensity ratings for individual symptoms (Fagerstrom 1982; Hughes et al. 1984; Killen et al. 1984: Schneider et al. 1984). In all but one of these

studies (Puska et al. 1979). nicotine gum reduced total withdrawal discomfort (see figure for an example).

In terms of individual withdrawal symptoms, the only effect of nicotine that was consistent across studies was a reduction in irritability, anger, and frustration (table 1). Depression was also reduced by nicotine gum in two of the four studies.

Abstinence from cigarettes produces behavioral as well as self-report changes (Hatsukami et al. this volume). Our study examined the effects of nicotine gum on such behavioral changes by collecting observer ratings of abstinent smokers. Observers (e.g., spouse or employer) rated subjects who received nicotine gum less irritable, anxious, restless, and impatient than subjects who received placebo gum (table 2). Thus, nicotine gum produced behavioral changes that occurred in the natural environment and were apparent to persons near the smoker.

Abstinence often produces weight gain. Post cessation weight gain may be due to several factors, e.g.. increased hunger, increased consumption of sweets, decreased resting metabolic rate, or decreased motor activity (Grunberg. in press; Hatsukami et al. this volume; Hughes et al. 1982; Wack and Rodin 1981). Nicotine decreases appetite, increases resting metabolic rate, and increases physical activity (Grunberg, in press); thus, nicotine gum could be expected to counteract the weight gain associated with smoking cessation. Two double-blind placebo-controlled trials reported that subjects who received nicotine gum reported less hunger (Jarvis 1982) and gained less weight (Bantmark et al. 1973) at 6-month followup than subjects who received placebo gum. In contrast, similar trials by Puska et al. (1979). Hall et al. (in press) and Hjalmarson (1984) found no difference in weight gain or hunger between those on nicotine gum and those on placebo. Also, both West et al. (1984) and we (Hughes et al. 1984) found that nicotine did not reduce hunger during the first few days of abstinence.

Although this evidence suggests nicotine gum does not decrease post cessation weight gain, clinical trials of nicotine gum may not be fair tests. This is because some subjects in a clinical trial will relapse to smoking. Since nicotine gum keeps people from smoking and since abstinence increases weight. then nicotine gum will appear to <u>increase</u> weight gain due to its-therapeutic efficacy. To truly test the effect of nicotine gum on post cessation weight gain. a study must prevent attrition-back to smoking and study the effect of nicotine gum on weight gain only in abstinent smokers.

Another less well-documented effect of abstinence from smoking is analgesia. Milgrom-Friedman et al. (1983) examined whether nicotine gum would influence abstinence-induced analgesia. They studied nonsmokers, smokers smoking ad lib, abstinent smokers who chewed nicotine gum, and abstinent smokers who did not chew nicotine gum. Each group had a tourniquet applied to one arm and then reported the time to onset of pain and the time until the pain was intolerable. Abstinent smokers who chewed nicotine gum reported pain onset similar to that of abstinent smokers who did not chew gum. Both these groups had a pain onset longer than that of smokers smoking and

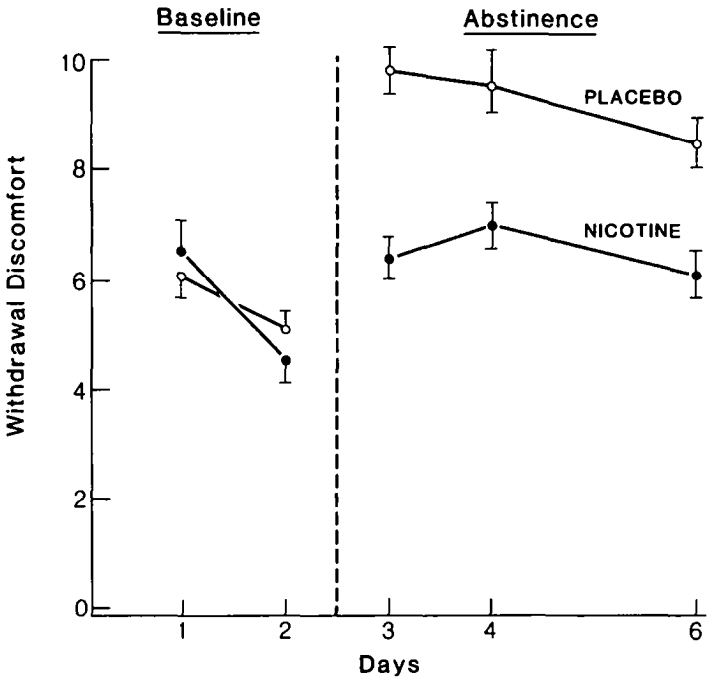


Figure. Mean and standard error of daily discomfort score by experimental condition and drug group for our nicotine gum study (Hughes et al. in press). Open circles = placebo, closed circles = nicotine.

Table 1. Effects of nicotine gum on the commonly reported symptoms of tobacco withdrawal

	Brantmark et al. 1973	Puska et al. 1979	Jarvis et al. 1982	Hughes et al. 1984	West et al. 1984
DSM-III Criteria					
Irritability/Anger/Frustration	None	None	Reduced	Reduced	Reduced
Anxiety/Tension	None	None	None	Reduced	
Difficulty Concentrating	None	None		Reduced	None
Restlessness/Impatience				Reduced	None
Headache	None	None			
Drowsiness/Alertness			Reduced		
Gastrointestinal Problems		None			
Other Criteria					
Depression	None	None	Reduced		Reduced
Fatigue	None	None			
Hunger			Reduced	None	None
Insomnia		None		None	

Table 2. Behavioral effects of nicotine gum[a]

Variable	Group	Baseline	Abstinence	F value for Nicotine < Placebo[b]
Irritability	Placebo	0.4	0.9	10.7**
	Nicotine	0.5	0.6	
Anxiety	Placebo	0.6	1.1	4.7*
	Nicotine	0.6	0.7	
Restlessness	Placebo	0.4	0.9	7.5*
	Nicotine	0.6	0.8	
Impatience	Placebo	0.5	1.0	10.5**
	Nicotine	0.7	0.7	

[a] All ratings based on scale of 0=not present, 1=mild, 2=moderate, and 3= severe. All standard errors <0.15.
[b] F value for the interaction that the increase in the behavioral rating would be less for the nicotine group than for the placebo group, df=(1,79).
* p<.05
** p<.01

nonsmokers. Thus, nicotine gum did not reverse abstinence-induced analgesia.

In summary, nicotine gum decreases both self-reported and observed symptoms of tobacco withdrawal. The most consistent effect of nicotine gum is to decrease irritability/anger/frustration. Whether the gum reduces other withdrawal phenomena, such as weight gain, is unclear.

BIOCHEMICAL/PHYSIOLOGICAL EFFECTS

One hypothesis to explain the ability of nicotine gum to decrease withdrawal symptoms is that the gum dampens the arousal associated with tobacco withdrawal. The only biochemical effects of nicotine gum that have been tested are its effects on serum glucose and excreted catecholamines. Gennser et al. (1975) and Manning and Feyerabend (1976) reported that neither the 2 mg nor the 4 mg gum changed the blood glucose of pregnant women. West et al. (1984) reported that the fall in excreted catecholamines during abstinence was similar in nicotine (2 mg) and placebo groups.

The physiological effects of nicotine gum that have been examined are its effects on cardiovascular function, tremor, and, in one study, evoked potentials. Most studies of the cardiovascular effects of nicotine gum on nonsmokers and nonabstinent smokers report that the 4 mg gum, but not the 2 mg gum, increases heart rate (Fredholm and Sjorgen 1979; Gennser et al. 1975; Jarvik 1982; Manning and Feyerabend 1976; Nyberg et al. 1982). Neither dose of gum influenced EKG measures or blood pressure (Fredholm and Sjorgen 1979; Nyberg et al. 1982). A report that the 4 mg gum decreases skin temperature (Fredholm and Sjorgen 1979) was not replicated (Nyberg et al. 1982). Among the studies of the effect of nicotine gum on the cardiovascular response of abstinent smokers, two reported that nicotine gum 2 mg dampened the fall in heart rate during abstinence (Schneider et al. 1984; West et al. 1984); however, our study (Hughes et al. 1984) failed to replicate this finding. In addition, our study (Hughes et al. 1984) found that nicotine gum tended to reduce the increase in orthostatic response (i.e., the increase in heart rate upon standing) after abstinence.

The two other physiological responses that have been studied are tremor and evoked potentials. The 4 mg, but not the 2 mg, dose of gum increased hand tremor in nonabstinent smokers (Shiffman et al. 1983). The 2 mg dose also failed to counteract the decrease in tremor after abstinence in our study. Finally, nicotine gum has been reported to have the same effect as smoking on visual evoked potentials (Milgrom-Friedman et al. 1981).

In summary, the effects of the gum on biochemical and physiological indices of arousal appear to be dose-dependent; i.e., the 4 mg gum does cause some changes, but the 2 mg gum does not appear to have any significant effects.

TIME COURSE OF NICOTINE EFFECTS

The time course of a drug's effects may be crucial to its ability to produce therapeutic effects. The onset of nicotine gum's effects appears quite rapidly (see figure). In two studies, the gum reduced total withdrawal discomfort within 24 hours (Hughes et al. 1984, West et al. 1984) and in a third study within 48 hours (Schneider et al. 1984).

The duration of the effects of nicotine gum has not been well studied. In our study, the effect of the gum tended to decrease over four days (see figure) and a similar effect appeared to occur in the study of Schneider et al. (1984). Unfortunately, no studies have tracked gum effects over longer periods.

Schneider and Jarvik (1984) also demonstrated an interaction between time of day and the effect of the gum such that the nicotine gum reduced withdrawal symptoms later in the day more than it reduced withdrawal symptoms earlier in the day. Whether this interaction was due to diurnal variation in the intensity of withdrawal symptoms or in the intensity of nicotine effects is unclear.

NICOTINIC VS. EXPECTANCY EFFECTS

Subjects in "double-blind" studies of psychoactive drugs can often tell if they are receiving active drug (e.g., Brownell and Stunkard 1982, Johnson and Hughes 1976). There is anecdotal evidence that smokers (Schneider et al. 1977) and their therapists (Fagerstrom 1982; Westling 1976) are able to discriminate nicotine from placebo gum. Such knowledge of drug receipt may produce expectancies that will influence tobacco withdrawal symptoms (Gritz 1980) and the efficacy of nicotine gum (Fagerstrom and Strom 1981); thus, it is particularly important to verify that any effects of nicotine gum are not actually expectancy effects.

In our study we directly tested whether the reduction in withdrawal symptoms by nicotine gum could have been due to subjects' identification of whether they received nicotine or placebo gum (Hughes and Krahn, in press). Although many subjects in our study could identify their drug assignment, the effect of nicotine gum on withdrawal discomfort was present independent of identification of drug assignment (table 3).

SIGNIFICANCE

The studies reviewed indicate that nicotine gum does relieve withdrawal discomfort. This fact might be interpreted to support the hypothesis that tobacco withdrawal is due to nicotine deprivation (e.g.. Schachter 1978); however, the logic of this interpretation can be questioned. Demonstration that a drug relieves a syndrome is consistent with, but not equivalent to, a demonstration that the syndrome is due to deprivation of the drug or class of drugs. Morphine relieves congestive heart failure but congestive

Table 3. Analysis of variance of withdrawal discomfort score by drug group and belief of drug assignment

Drug Group	Identification of Drug Assignment: Correct	Incorrect	Uncertain
Placebo	5.34 (n=19)	2.14 (n=15)	3.03 (n=16)
Nicotine	1.10 (n=34)	0.03 (n=6)	0.74 (n=9)

F for main effect of drug group (1,90)=14.8, p<.001
F for interaction between drug group and belief (2,89)<1.0, p>.10

t for nicotine < placebo within correct identification group (14)=14.4, p<.001
t for nicotine < placebo within incorrect identification group (16)=1.7, p=.06
t for nicotine < placebo within uncertain (24)=2.1, pp.04

heart failure is not due to morphine deprivation. Several alternative explanations are available. Perhaps nicotine relieves irritability, etc., regardless of its source.

Another interpretation of the finding that nicotine reduces withdrawal discomfort is that this indicates the efficacy of nicotine gum is due to its ability to relieve withdrawal. However, none of the previous studies have directly related reduction in withdrawal discomfort by nicotine to improved long-term cessation success.

In summary, many of the short-term effects of nicotine gum are consistent with theories that nicotine dependence plays a role in maintaining smoking. However, other results directly contradict this hypothesis and crucial tests of the hypothesis (e.g., does nicotine gum relieve withdrawal which then improves cessation?) have not been reported.

FUTURE RESEARCH

In the introduction we mentioned that several nonpharmacologic factors can control nicotine's actions (e.g., instructional set). Thus, one explanation for the many inconsistent results of studies of nicotine gum is that nonpharmacologic factors that control nicotine's actions varied across the studies. If this is true, then empirical studies are needed to determine those factors that are necessary and sufficient for nicotine gum to have beneficial effects. For example, studies that contrast different doses (1 vs. 2 vs. 4 mg). durations of administration (1 vs. 3 vs. 6 months), schedules (fixed time vs. ad-lib) or subjects ("dependent" vs. "nondependent" smokers) must be more useful than simple outcome studies pitting nicotine gum vs. a standard treatment.

REFERENCES

Ashton. H., and Stepney, R. Smoking: Psychology and Pharmacology, New York: Travistock Publications, 1982.

Benninger, R.J., and Hahn B.L. Pemozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. Science, 220:1304-1306, 1983.

Brantmark, B.; Ohlin, P.; and Westling, H. Nicotine-containing chewing gum as an antismoking aid. Psychopharmm 31:191-200, 1973.

Brownell. K.D., and Stunkard. A.J. The double-blind in danger: Untoward consequences of informed consent. Am J Psychiat, 139:1487-1489, 1982.

Ebert, R.V.; McNabb, M.E.; and Snow, S.L. Effect of nicotine chewing gum on plasma nicotine levels of cigarette smokers. Clin Pharmacol Ther, 35:495-498.

Emley, G.S., and Hutchinson, R.R. Behavioral effects of nicotine. In: Thompson, T., ed. Advances in Behavioral Pharmacology, No. 4. New York: Academic Press, pp. 105-129. 1984.

Fagerstrom, K-O. A comparison of psychological and pharmacological treatments in smoking cessation. J Behav Med. 5:343-351, 1982.

Fagerstrom, K-O. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav, 3:235-241, 1978.

Fagerstrom, K-O, and Storm, H.G. The effect of instructions on smoking cessation for individuals with different degrees of dependence. Behav Psychother, 9:310-315, 1981.

Fredholm, B., and Sjogren, C. The Effects of Chewing Nicorette and Smoking Cigarettes on the Heart Rate and Skin Temperature in Healthy Smokers. Helsingborg, Sweden: Leo Laboratories, 1979.

Gennser, G.; Marsal, K.; and Brantmark, B. Maternal smoking and fetal breathing movements. Am J Obstet Gynecol, 123:861-867, 1975.

Gilbert, D.G. Paradoxical tranquilizing and emotion-reducing effects of nicotine. Psychol Bull, 86:643-662, 1979.

Goldberg, S.R.; Spealman, R.D.; Risner, M.E.; and Henningfield. J.E. Control of behavior by intravenous nicotine injections in laboratory animals. Pharmacol Biochem Behav, 19:1011-1020, 1983.

Griffiths, R.R.; Henningfield. J.E.; and Bigelow, G.E. Human cigarette smoking: Manipulation of number of puffs per bout. interbout interval and nicotine dose. J Pharmacol Exp Ther, 220:256-265, 1982.

Gritz, E.R. Smoking behavior and tobacco abuse. In: Mello, N.K., ed. Advances in Substance Abuse, Vol. 1. Greenwich, CT: JAI Press, pp. 91-158, 1980.

Grunberg, N.E. Behavioral and biological factors in the relationship between tobacco use and body weight. In: Katkin, E.S. and Manuck, S.E., eds. Advances in Behavioral Medicine, Vol. 2. Greenwich, CT: JAI Press, in press.

Hall. S.M.; Ginsberg, D.: and Jones. R.T. Smoking cessation and weight gain. J Consult Clin Psychol, in press.

Henningfield. J.E. Behavioral pharmacology of cigarette smoking. In: Thompson, T., ed. Advances in Behavioral Pharmacology. New York: Academic Press, pp. 131-210. 1984.

Henningfield, J.E.; and Goldberg', S.R. Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav, 19:887-890, 1983.

Hjalmarson, A.I.M. Effect of nicotine chewing gum in smoking cessation: A randomized, placebo-controlled, double-blind study. J Am Med Assoc. 252:2835-2838, 1984.

Hughes, J.R. Genetics of smoking: A brief review. Behav Ther, in press-a.

Hughes, J.R. Identification of the dependent smoker: Validity and clinical utility. Behav Med Abs, in press-b.

Hughes, J.R.; Hatsukami, D.K.; Carroll, K.; and Pickens, R.W. Effects of smoking cessation on weight, eating and activity. Paper presented at Annual Meeting of the American Psychological Association, 1982.

Hughes, J.R.; Hatsukami, D.K.; Pickens, R.W.; Krahn, D.; Malin, S.; and Luknic, A. Effect of nicotine on the tobacco withdrawal syndrome. Psychopharm, 83:82-87, 1984.

Hughes, J.R., and Krahn, D. Blindness and the validity of double-blind drug trials. J Clin Psychopharm, in press.

Hughes, J.R.; Pickens, R.W.; Spring, W.; and Keenan, R. Instructions control the ability of nicotine to serve as a reinforcer. J Pharm Exp Ther, in press.

Hughes, J.R., and Miller, S. Nicotine gum to help stop smoking. J Am Med Assoc. 252:2855-2858, 1984.

Jarvik, M.E. Biological factors underlying the smoking habit. In: Jarvik, M.E.; Cullen, J.W.; Gritz, E.R.; Vogt, T.M.; and West, L.J., eds. Research on Smoking Behavior. National Institute on Drug Abuse Research Monograph No. 17. DHEW Pub. No. (ADM)78-581. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., pp. 122, 1977.

Jarvik. M.E.; Glick, S.D.; and Nakamura, R.K. Inhibition of cigarette smoking by orally administered nicotine. Clin Pharm Ther, 11:574-575, 1970.

Jarvis. M.J.; Raw, M.; Russell, M.A.H.; and Feyerabend, C. Randomized controlled trial of nicotine chewing gum. Clin Pharm Ther, 11:537-540, 1982.

Johnson, W.G., and Hughes, J.R. Mazindol: Its' efficacy and mode of action in generating weight loss. Addict Behav, 4:237-244. 1979.

Johnston, L. Tobacco smoking and nicotine. Lancet, 2:742, 1942.

Killen, J.D.; Maccoby, N.; and Taylor, C.B. Nicotine gum and self-regulation training in smoking relapse prevention. Behav Ther, 15:234-248, 1984.

Kozlowski, L. Pharmacological approaches to smoking modification. In: Matarazzo, J.; Miller, N.; Weiss, S.; Hurd, J.; and Weiss, S. Wiley and Sons: New York, in press.

Kozlowski, L.T.; Jarvik, M.E.; and Gritz, E.R. Nicotine regulation and cigarette smoking. Clin Pharm Ther, 17:93-97, 1975.

Kumar, R.; Cooke, E.C.; Lader, M.H.; and Russell, M.A.H. Is nicotine important in tobacco smoking? Clin Pharm Ther, 21:520-529, 1977.

Lucchessi, B.R.; Schuster, C.R.; and Emley, A.B. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. Clin Pharm Ther, 26:789-796, 1967.

Mangan, G.L., and Golding, J.F. The Psychopharmacology of Smoking. New York: Cambridge University Press, 1984.

Manning, F.A., and Feyerabend, C. Cigarette smoking and fetal breathing movements. Br J Obstet Gyn, 83:262-270, 1976.

McM Turner, J.E.; Sillett, R.W.; Taylor, D.M.; and McNicol, M.W. The effects of supplementary nicotine in regular cigarette smokers. Postgrad Med J, 53:683-686, 1977.

Milgrom-Friedman, J.; Meares, R.; and Penman, R. Smoking, cortical evoked potentials and habituation: A placebo effect. Unpublished manuscript, 1981. Cited in Milgrom-Friedman, J., et al. 1983

Milgrom-Friedman, J.; Penman, R.; and Meares, R. A preliminary study in pain perception and tobacco smoking. Clin Exp Pharm Physiol, 10:161-169, 1983.

Nyberg, G.; Panifelov, V.; Silvertsson, R.; and Wilhemsen, L. Cardiovascular effects of nicotine chewing gum in healthy non-smokers. Eur J Clin Pharmacol, 23:303-307, 1982.

Ohlin, P., and Westling, H. Nicotine containing chewing gum as a substitute for smoking. In: Richardson, R.G., ed. The Second World Conference on Smoking and Health, London: Pittmen, pp. 171-174, 1975

Puska, P.; Bjorkqvist, S.; and Koskela, K. Nicotine containing chewing gum in smoking cessation: A double blind trial with half year followup. Addict Behav, 4:141-146, 1979.

Raw, M. The treatment of cigarette dependence. In: Israel, Y.; Glaser, F.B.; Kalant, H.; Popham, R.E.; Schmidt, W.; Smart, R.G., eds. Research Advances in Alcohol and Drug Problems, Vol. 4. New York: Plenum Press, 1978. pp. 441-485.

Russell, M.A.H., and Feyerabend, C. Cigarette smoking: A dependence on high-nicotine boli. Drug Metab Rev, 8:29-57, 1978.

Russell, M.A.H.; Feyerabend, C.; and Cole, P.V. Plasma nicotine levels after cigarette smoking and chewing nicotine gum. Br Med J, 1:1043-1046, 1976.

Russell, M.A.H.; Sullen, S.R.; Feyerabend, C.; Dole, P.V.; and Saloojie, Y. Nicotine chewing gum as a substitute for smoking. Br Med J, 1:1060-1063, 1977.

Ryden, cited in Axeisson, A., and Brantmark, B. The antismoking effect of chewing gum with high and low bioavailability. In: Steinfield, J.. Griffiths, W., Ball, K. and Taylor, R.M., eds. Smoking and Health II: Health Consequences, Education, Cessation Activities and Governmental Action. Proceedings of the Third World Conference on Smoking and Health. DHEW Pub. No. (NIH) 77-1413, Washington, D.C.: Supt. of Docs., U.S. Government Printing Office, p. 550, 1975.

Schachter, S. Pharmacological and psychological determinants of smoking. Ann Int Med, 88:104-114, 1978.

Schneider, N.G., and Jarvik, M.E. Time course of smoking withdrawal as a function of nicotine replacement. Psychopharm, 82:143-144, 1984.

Schneider, N.G.; Jarvik, M.E.; and Forsythe, A.B. Nicotine versus placebo gum in the alleviation of withdrawal during smoking cessation. Addict Behav, 9:149-156, 1984.

Schneider, N.G.; Popek, P.; Jarvik, M.E.; and Gritz, E.R. The use of nicotine gum during cessation of smoking. Am J Psychiat, 134:439-440, 1977.

Shiffman, S.M. The tobacco withdrawal syndrome. In: Krasnegor, N.A.. ed. Cigarette Smoking as a Dependence Process, National Institute on Drug Abuse Research Monograph No. 23. DHEW Pub. No. (ADM) 79-800, Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., pp. 158-185. 1979.

Shiffman. S.M.; Gritz, E.R.; Mallese. J.; Lee, M.A.; Schneider, N.G.; and Jarvik, M.E. Effects of cigarette smoking and oral nicotine on hand tremor. Clin Pharm Ther, 33:800-805, 1983.

Thompson, T., and Johanson. C.E., eds. Behavioral Pharmacology of Human Drug Dependence. National Institute on Drug Abuse Research Monograph No. 37. DHHS Pub. No. (ADM) 81-1137. Washington, D.C.: Supt. of Dots., U.S. Govt. Print. Off., p. 280, 1981.

Wack, J.T., and Rodin. J. Smoking and its effects on body weight. Am J Clin Nutr, 35:366-380. 1982.

West, R.; Jarvis, M.J.; Russell, M.A.H.; Carruthers, M.E.; and Feyerabend. C. Effect of nicotine replacement on the cigarette withdrawal syndrome. Br J Addict, 79:215-219. 1984.

nestling, H. Experience with nicotine-containing chewing gum in smoking cessation. Lakartidningar, 73:2549-2552. 1976.

ACKNOWLEDGMENTS

Work included in this review was supported by grants from the National Institute on Drug Abuse (2 ROl DA 02988 and DA 03728) and Merrell Dow Pharmaceuticals and by funds from the State of Minnesota to the University of Minnesota for psychiatric research. Steve Miller of Merrell Dow Pharmaceuticals provided many of the manuscripts reviewed.

AUTHORS

John R. Hughes, M.D.
Neuroscience Research Unit
Department of Psychiatry
University of Vermont College of Medicine
Burlington, Vermont 05405

Dorothy Hatsukaml, Ph.D.
Department of Psychiatry
Box 393 May Memorial Building
University of Minnesota
Minneapolis, Minnesota 55455

Nicotine Gum vs. Placebo Gum: Comparisons of Withdrawal Symptoms and Success Rates

Nina G. Schneider, Ph.D., and
Murray E. Jarvik, M.D., Ph.D.

Until recently, the importance of nicotine in smoking and the existence of nicotine-specific withdrawal have been hard to demonstrate empirically. Several investigators succeeded in focusing attention on nicotine and presenting a strong case for nicotine as the critical factor in smoking dependence (Gritz 1980b; Jarvik 1970; Russell 1980; Russell and Feyerabend 1978). However, smoking is a complex dependence in which pharmacological and psychosocial reinforcement systems are confounded. What we have needed is a direct means of testing the relative contributions of these factors to why people smoke, to variations in individual habit patterns, and to why cessation is difficult and relapse rates high.

The introduction of nicotine gum and its placebo counterpart (Ferno et al. 1973) has provided a means of manipulating nicotine intake independent of the behaviors associated with the habit. The idea of varying nicotine levels and studying withdrawal is not new. Manipulation of nicotine was reported as early as 1942 by Johnston using repeated doses of nicotine in injections. Johnston (1942) administered the injections to himself and several volunteers and reported dysphoric reactions upon their abrupt cessation. In laboratory settings, intravenous nicotine studies provide basic Information for the role of nicotine in smoking (Henningfield et al. 1983; Feyerabend et al. 1985). For application in cessation studies, the intravenous method is impractical.

Surprisingly, snuff has not been used to vary nicotine levels in the study of withdrawal nor in any formal cessation procedure. Given that there are snuff users and absorption of nicotine is rapid (Russell et al. 1980a). nasal snuff use may approximate the nicotine delivery in a cigarette best while eliminating the habit reinforcers. Gritz et al. (1981) have noted that comparable levels of nicotine can be achieved using chewing tobacco as with cigarettes. In our own laboratory experience, we have found smokers reluctant to switch to snuff in attempting cessation. Similarly, another means of separating nicotine from the other reinforcers of smoke would be in the use of nicotine-free cigarettes. These could be used in a long-term cessation study and would allow alteration in nicotine intake with controls for psychological variables. Unfortunately, nicotine-free cigarettes have also been unacceptable to smokers even for short periods in an experimental context.

Finally, one of the most promising tools for the study of the role of nicotine in withdrawal and cessation may come with a transdermal nicotine patch (Rose et al. 1984). This would allow, as does nicotine gum, the testing of withdrawal and cessation in a potentially acceptable form and for prolonged periods of time.

For the present, we have access to nicotine gum in several doses. Nicotine gum is both easily self-administered and well received by smokers. It allows for the manipulation of nicotine intake during smoking abstinence while holding psychosocial and sensory factors constant. Russell et al. (1976a). Russell et al. (1977); Russell et al. (1980b); and McNabb et al. (1982) have demonstrated that nicotine in gum can theoretically produce blood levels sufficient to prevent nicotine withdrawal. In addition, the slow buccal absorption does not produce the peak nicotine "boll" delivered in smoke. Controlling nicotine withdrawal and nicotine seeking should enhance success rates if nicotine is important in cessation. In effect, the active and placebo gums allow for systematic testing of the role of nicotine in the appearance and alleviation of withdrawal and in the cessation process.

The specific questions we addressed in testing may be summarized for outcome as follows: 1) Will use of nicotine gum enhance success rates over placebo? 2) Under what conditions (dispensed, clinic-support) will this occur?

The specific questions regarding withdrawal are: 1) Is there nicotine-specific withdrawal? 2) Can nicotine replacement with gum be effective in alleviating or preventing withdrawal? 3) Are certain symptoms or emotional states more responsive to nicotine replacement than others?

While there are many questions concerning selection of smokers (see Jarvik and Schneider 1984) and parameters for proper use, the present article will focus on outcome and withdrawal data. Results are summmarized for two studies (clinic and dispensary) in which outcome and withdrawal have been tested. Both published and previously unpublished findings are reported.

OUTCOME

In several of the initial gum studies, titration was the focus of study (Brantmark et al. 1973; Russell et al. 1976b; Turner et al. 1977). In the first two studies, active gum reduced tobacco consumption compared to placebo controls. However, the efficacy of nicotine gum is best studied when total smoking abstinence is required. Several efforts to study total cessation with nicotine gum were marred by lack of chemical verification (e.g., Puska et al. 1979). absence of long-term followup (e.g., Malcolm et al. 1980) or inadequate controls. Raw et al. (1980) found improved cessation rates with nicotine gum but compared those results to a "psychological" control tested 2 years earlier.

Prior to our study, several investigators reported the advantage of nicotine gum over placebo, depending, in part, upon the support

conditions. Jarvis et al. (1982) implemented a cessation study in which clinic support was provided and cessation was verified with carbon monoxide. Nicotine gum significantly elevated success rates at 1 year compared to a lower dose "placebo" control. The placebo in that study was an unbuffered 1 mg nicotine gum which could produce an active effect if enough was chewed (20 pieces). However, conceptualized as a dose-response study, the results suggest that the more nicotine replacement, the greater the success. Jarvis et al. (1982) also reported that success rates were elevated for nicotine gum when restarts were included. For a detailed description of this study, see Russell and Jarvis, this volume.

Fagerstrom (1982) reported striking success rates in a Swedish clinic for both nicotine and placebo groups with a significantly higher success rate for the active gum subjects at 6 months. This significant effect, however, disappeared at 1 year although the trends still favor the active gum. In this study, as in Jarvis et al. (1982). success is attributed to the interaction between active gum use and clinic support.

In the above studies, the subjects were studied by researchers knowledgeable in the effects and appropriate use of gum. In a study reported by the British Thoracic Society (1983). nicotine gum plus advice and a smoking dangers booklet did not improve success rates over advice alone, advice plus the booklet, or placebo gum plus advice and the booklet. Rates were low (between 8-12%) across groups. The authors attribute their poor findings to the population (chest clinic patients who may have been unmotivated) and to poor instructions but concluded that their study reflects instructed use in the real world. In a critique of that study, Jarvis and Russell (1983) take issue with that conclusion and point out additional flaws in the study. To those criticisms it should be added that nicotine gum in the British Thoracic Society study (1983) was given with "instructions to substitute it for a cigarette when there was an urge to smoke." From our own pilot work, we have found that allowing any smoking with chewing undermines cessation.

The issue of what conditions of support may be necessary for success with nicotine gum was the focus of our outcome testing (Schneider et al. 1983). Two studies had been designed to test the efficacy of nicotine vs. placebo gum use. In one, clinic support was provided for both groups; in the other, gum was "dispensed" with minimal intervention. The latter was intended to mimic administration of, gum by physician prescription where little support and/or followup may be provided. The most recent clinical replications (Hall et al. 1984; Hjalmarson 1984; Killen et al. 1984) and recent physician studies (Jamrozik et al. 1984; Russell et al. 1983) are discussed later.

Method

In both studies, subjects were heavy smokers (30-35 cigarettes a day) in good health who had tried repeatedly to quit smoking. The studies were double-blind, and subjects were allowed to chew the gum ad lib both in terms of daily number of pieces and length of time on gum. The clinic study included measures of withdrawal which are

described in the next section. Baseline questionnaires and repeated measures testing are listed in table 1. The tests listed under repeated measures were all given at baseline with the exception of the questionnaires on side effects and gum use.

TABLE 1

Materials

Baseline Materials - All Subjects

1. Consent Forms
2. Subject Bill of Rights
3. Health Screening
4. Smoking and Quitting History
   (includes demographics)
   Motivation Questionnaire
5. Expectations Questionnaire
   Why I Smoke
8. Smoking Occasions
9. Why I Want to Quit
10. Fagerstrom Tolerance Questionnaire
11. Weight Questionnaire
12. Gum Instructions
13. Address Sheet
14. Subject Comments and Questions

Repeated Measures - Clinic Groups

1. Pulse Rate
2. Weight
3. Daily Abstinence - 2 Scales:
   Schneider Smoker Complaint Scale (SCS)
   Shiffman-Jarvik Scale
4. Mood Checklist
5. Carbon Monoxide
   (as verification in all groups;
   as feedback in clinic groups)
6. Side Effects
7. Gum Use - Satisfaction and Open-Ended Remarks

Treatment

Treatment consisted of either 2 mg nicotine gum or placebo gum. The low dose (2 mg) was chosen to avoid side effects associated with 4 mg gum although eventually mixed use of both doses may prove advantageous (see Schneider et al. 1977). Subjects were instructed to chew each piece slowly for 20 to 30 minutes to insure the release of nicotine. Buccal absorption was explained. Weaning from nicotine may be said to begin with the switch from cigarettes to gum in terms of both the slower absorption and reduced speed of reinforcement. With 2 mg gum the immediate blood levels are reduced compared to

4 mg gum or a 1.2 mg cigarette as noted earlier. Three-month prolonged use of 2 mg gum has also recently been shown to produce significantly less nicotine than cigarettes or 4 mg gum (McNabb 1984). The oral-manipulative component of gum use was expected to aid cessation while not disrupting extinction of smoking behaviors.

Procedure

Subjects were given the baseline questionnaires for survey purposes and for assessment of their selective and predictive value. Baseline scores were obtained for all repeated measures and tests (see table 1).

Sixty subjects participated in the clinic study - 30 subjects in the nicotine group and 30 subjects in the placebo group. Total abstinence was required and was verified at all test intervals (including daily the first week) with carbon monoxide expired air analyses. Following baseline testing (always on a Friday), clinic subjects were instructed to quit the next Monday morning and were given pieces of gum to take home. Subjects then came to the laboratory dally for 1 week for testing (withdrawal, CO, pulse rate, gum use, weight) and for individual support sessions with the experimenter. The sessions lasted between l/2 and 1 hour. Clinic subjects were also asked to fill out withdrawal scales at home in the morning and evening for the first week of abstinence (see withdrawal section). Followup test intervals (including ail measures and support) occurred weekly for 4 additional weeks and then at 3 months, 6 months, and 1 year. Not counting baseline, this amounted to a total of 12 visits for subjects completing the study.

The dispensary groups consisted of 13 nicotine gum subjects and 23 placebo gum subjects. Testing at baseline was identical for clinic and dispensary groups. However, subjects in the dispensary groups did not return to the laboratory for first-week testing and support. One appearance was required (on Thursdays) for gum supplies and CO verification of abstinence in the first week. Thereafter, subjects appeared once a week for 4 more weeks and at 3 months, 6 months, and 1 year for verification and supplies. No testing (besides CO) was allowed at any of the followup intervals. Thus, the baseline testing and abstinence checks served as minimal intervention compared to the clinic groups.

Results

Results of the clinic study and dispensary study appear in Schneider et al. (1983). A survival analysis was performed on outcome curves for both groups in the clinic study. The success rates are presented in figure 1. The nicotine group was significantly more successful than the placebo group in abstinence over time ($p<.03$).

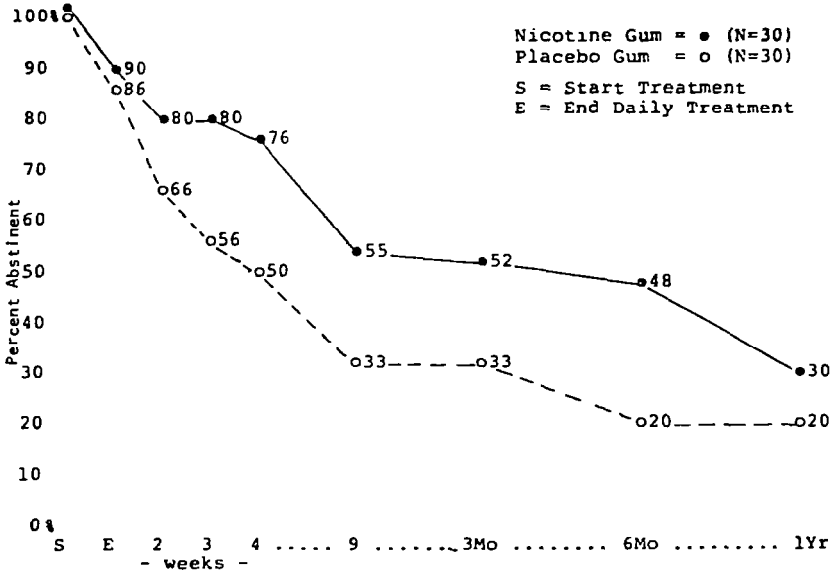


FIGURE 1

Clinic Group Success Rates: Nicotine vs. Placebo Gum

Adapted from Schneider et al. (1983). Copyright 1983, Pergamon Press, Ltd.

As can be seen from figure 1, the differences between groups are most apparent at 3-4 weeks and at 6 months. The groups are fairly equivalent during first-week treatment and separate by the second week with a peak difference at 6 months (28%). Between 6 months and 1 year, relapse in the nicotine group reduces the difference to 10%.

Success curves for the two dispensary groups are presented in figure 2. The data in figure 2 indicate that neither 2 mg nor placebo gum was effective in cessation when no support or guidance was offered. After 1 week, both groups had dropped to the same level and by 1 year, low rates of 8% for nicotine and 13% for placebo were observed. It should be noted that subjects stopped using gum in the dispensary groups within the first few days to 1 week of the study. The only difference in the clinic and dispensary groups following baseline testing and instructions was the first-week support and testing provided for the clinic groups. It is assumed that the clinic appearances indirectly and directly encouraged the subjects to continue gum use.

With support, nicotine gum clearly enhanced short-term (6-month) success rates over placebo (Schneider et al. 1983). These clinic results are consistent with the placebo-controlled findings of

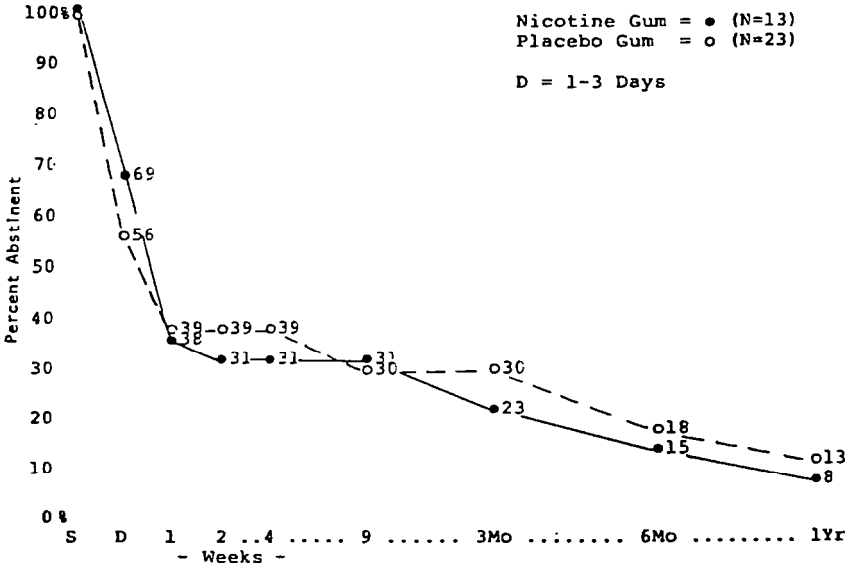


FIGURE 2

Success Rates: Dispensary Study

Adapted from Schneider et al. (1983). Copyright 1983, Pergamon Press, Ltd.

Fagerstrom (1982) and Jarvis et al. (1982), although in the latter success rates between treatments were still significant at 1 year. The differences between the groups in the Jarvis et al. (1982) study were as high as 47% with nicotine gum vs. 21% treated with an unbuffered 1 mg nicotine placebo. When a stricter criterion of outcome was used in which no relapses between the initial assessment and end assessment were allowed, these figures remained significant at 31% in the active group vs. 14% in the placebo group.

In a study comparing nicotine gum to placebo gum (Hjalmarson 1984), success rates were also doubled at 1 year, with 29% abstaining in the active gum group vs. 16% in the placebo group. In Hall et al. (1984) and Killen et al. (1984), the value of clinic support in combination with active gum use was demonstrated in a different format. In Hall et al. (1984), subjects were assigned to either nicotine gum with minimal intervention, intensive behavioral treatment by itself, or to a combination of the intensive behavioral treatment plus nicotine gum. The combination of the nicotine gum plus the intensive treatment produced better success rates than the other two conditions. This was significant at the 3-month and 6-month intervals, but not at 1 year. This was validated with blood cotinine levels and those with the higher levels appear to be helped

485-874 0 - 85 - 4

more by nicotine gum than those with lower levels at the start of the study. Interestingly, and in contrast to the physician studies to be discussed below, the low contact nicotine gum group did better than the behavioral only group; however, the low contact group did meet four times over a 3-week period, which in itself constitutes some intervention.

In Killen et al. (1984) the subjects were assigned to one of three conditions: nicotine gum only, skills training only, or a combination of skills training and nicotine gum. There was some intervention in the nicotine gum only group in that they attended a clinic weekly for 7 weeks to receive gum and complete assessments. Abstinence rates at 10-l/2 month followup were 23% for nicotine gum only, 30% for skills training only, and 50% for a combination of the skills training plus nicotine gum. Carbon monoxide and thiocyanate levels verified the subjects' reports of abstinence. In this study a combined treatment doubled the rates obtained with nicotine gum alone.

The studies which look at some form of dispensary tactic show mixed results. In our study, simply dispensing nicotine or placebo gum resulted in early failure and in no differences between the groups. Similar findings were observed in the British Thoracic Society (1983) and Jamrozik et al. (1984) studies. The British study has been correctly critiqued by Jarvis and Russell (1983) and, in general, problems with dispensing may be due to inadequate instruction and training in proper gum use.

While the clinical studies clearly show that support systems are instrumental in producing successful cessation, we cannot conclude that dispensing cannot be successful. It may be that variables involving the carefully instructed use of the active gum may play a part in its viability as a smoking cessation tool. For example, Russell et al. (1983) reported a study in which there was a nonintervention group; a second group receiving advice to stop smoking, a booklet, and a warning of followup; and a third group receiving the same as the second group but with the offer of nicotine chewing gum. The results showed that the overall rate of cessation is lower than anything observed in clinics. For the no-advice group there was a 3.9% success rate, for advice only a 4.1% success rate, and for advice plus nicotine gum an 8.8% success rate. However, when the data were analyzed by the amount of gum used, those subjects who used more than one box of gum had a long-term success rate of 24% after validation. This is a surprisingly high success rate considering the very minimal intervention in this study. It suggests that if we can identify the use variables which enhance success, we can increase success rates with the dispensing of gum. This is particularly important in that physicians can prescribe this preparation and have the opportunity to help in the treatment of cigarette smoking.

In a variation of the low contact physician studies, Fagerstrom (1985) looked at short- vs. long-term followup with nicotine gum vs. no gum. He found significant differences between nicotine gum and

no gum groups at 1 year with validation. Again, the rates were lower than in any of the clinical studies, but differences were still observed. At 12 months the following was reported for four groups: a group given advice, long-term followup, and nicotine gum showed a 27% success rate. Advice, short-term followup, and nicotine gum yielded a 22% success rate. Advice, long-term followup, and no gum reduced success to 15%. Finally advice, short-term followup, and no gum produced a low 3% success rate.

The clinic and physician studies taken together show that success rates can be enhanced 1) with active gum compared to no gum or placebo, and 2) with support vs. minimal or no behavioral intervention. It should be noted that in the present study it is not necessarily known which aspects of the support system contributed to success. On the one hand, individual attention and problem-solving were offered by the experimenters. Lowered carbon monoxide levels served as positive feedback. Test taking, in itself, may have helped by allowing the subject an outlet for dysphoria and the difficulty of quitting. Thus, strong psychological support was provided in the first week and ensuing followup visits. On the other hand, by coming to the laboratory daily, the subject was encouraged to continue using the gum. Side effects and fears associated with use could be allayed and increased use tested in a "safe" setting. It may be this initial monitoring of use per se that accounts for success.

One final issue that also has not been systematically tested is that of length of use. Several investigators have observed post hoc that longer use (3 to 4 months) may be a significant factor in outcome (Russell et al. 1980b, 1983; Wilhelmsen and Hjalmarson 1980) and that by extending use past at least one box, success rates can be elevated.

In summary, initial use and prolonged use of nicotine gum may both figure prominently in outcome. We cannot conclude from the present work that the enhancement of success with clinical support is due to psychological factors alone. Use variables (dose, number of pieces, length of time on gum, instructions) must be defined through controlled evaluation. We suggest that appropriate dose and carefully instructed use are critical and that intervention should focus on long-term relapse prevention. Ultimately, a combination consisting of physicians advising patients to stop, treatment of pharmacological dependence, and long-term behavioral training and support could provide the most valuable smoking cessation intervention to date.

WITHDRAWAL

Underlying the development of nicotine gum and its use in cessation are the assumptions that nicotine withdrawal occurs and that its alleviation through a replacement procedure will improve success rates. The questions are 1) Can nicotine-specific withdrawal be demonstrated? and 2) If so. will replacement other than in bolus smoke delivery be effective? If nicotine gum alleviates or prevents

symptoms compared to placebo, then it is effective. By inference, withdrawal symptoms (to the degree they are relieved) can be attributed to the removal of nicotine per se. Ultimately, symptom relief should correlate with short-term and/or long-term success in cessation.

In the early studies using nicotine gum, titration effects, by combining gum and smoking and continued partial reinforcement with smoking, precluded the assessment of withdrawal. Brantmark et al. (1973) acknowledged that their attempts to measure withdrawal were rendered "meaningless" because of the simultaneous use of gum and smoking. In Puska et al. (1979) the same problem is encountered. In a recent and interesting study by West et al. (1984), smokers' baseline blood levels were taken and compared in one group with a switch to an ultra-low nicotine cigarette. It was observed that plasma nicotine concentrations dropped 60% when they were switched to the ultra-low cigarette. A slight drop in heart rate and an increase in hunger were observed with the lowered levels. However, it was not paralleled by typical withdrawal symptoms such as irritability. Ironically, this is consistent with the concept of a lesser replacement of nicotine with nicotine gum. That is. in both instances the partial amount of nicotine obtained provides enough nicotine to alleviate irritability. Although some physiological changes were observed in this study, nicotine-specific withdrawal will probably be best demonstrated by comparing nicotine replacement to no replacement.

In Jarvis et al. (1982). withdrawal symptoms were measured in nicotine and placebo groups during total abstinence from smoking. Ratings of withdrawal were taken once a week and averaged across 6 weeks. Unfortunately, abstinence was confirmed with carbon monoxide breath analyses only at 1 year and not at earlier intervals. It should also be noted that not all subjects attended all sessions, although this probably occurred for both groups. The authors used an unbuffered 1 mg nicotine gum as their placebo which, as they point out, can produce a pharmacological effect when enough is chewed (20 pieces). In this sense, the study is a dose-response comparison. Given these qualifications, this remains one of the few early tests of withdrawal during total abstinence. Jarvis et al. (1982) reported significantly "less irritability" and "less hunger" for the 2 mg group compared to the 1 mg unbuffered controls. Several other symptoms were reduced in the 2 mg group but these differences were not significant.

In our clinic study, withdrawal measures were obtained daily for 5 days for 50 subjects remaining abstinent. Twenty-six subjects formed the nicotine group and 24 formed the placebo group. To insure completion of scales, the scales were given in the laboratory (in-lab) each day. Carbon monoxide tests were also taken daily to confirm self-reported abstinence.

Pulse rate was taken as a physiological measure of withdrawal. Subjective responses were obtained using a Smoker Complaint Scale (SCS), the Shiffman-Jarvik (1976) Scale, and a mood checklist.

Ratings were obtained for four physical symptoms associated with withdrawal from smoking (Shiffman 1979). Because of item wording and scaling problems in the Shiffman-Jarvik Scale, the study focus was on the SCS. This scale was derived from smokers' reports on the nature of withdrawal symptoms experienced in previous cessation attempts. These reports were obtained from pilot subjects and subjects in a "cold turkey" study. Responses were scaled so that I represented "very definitely not" and 7 represented "very definitely." The SCS consisted of the following 14 items: anxiety, irritability, fluctuations in mood, craving for cigarettes, concern about weight, trouble sleeping, disorientation, impaired concentration, depression, feeling left out, restlessness, hostility, annoyance, and frustration. Where items overlapped with the Shiffman-Jarvik Scale (e.g., irritability), responses were checked for consistency between the scales. The mood checklist is described in the following section along with those results. The four physical items included: nausea, constipation, diarrhea, and headache.

Results

Pulse rate and SCS total scores appear in Schneider et al. (1984). Pulse rates decreased significantly for placebo subjects (15 bpm over 5 days) compared to a slight reduction in those using active gum (4 bpm over 5 days). For SCS totals a repeated measures ANOVA with trends was performed on the data. A significant effect of treatment was observed ($p<.03$) as well as a significant quadratic treatment x time interaction ($p<.Ol$). The pattern was as follows: baselines did not differ between groups (separate ANOVA); for both groups there was a rise from baseline to Day 1; thereafter, withdrawal in the placebo group continued to increase in severity while symptom reduction occurred in the nicotine group. Differences between groups were significant for Days 2, 3, and 4, By Day 5, the group scores tended to merge. When baselines were covaried, the results were the same except that the quadratic component became linear. Figures for the pulse rate and withdrawal findings by treatment are presented in Schneider et al. (1984).

We also attempted to look at which items were more sensitive to nicotine replacement than others (previously unreported data, table 2). As can be seen from table 2. almost every symptom on the SCS scale except for weight concern and craving showed a significant increase from baseline smoking levels to abstinence days. In addition, annoyed, hostile, irritable, and fluctuations in mood showed significant changes between groups with frustration and depression showing borderline effects.

Craving and weight concern showed no effects on the SCS. From the Shiffman-Jarvik Scale, craving was assessed by asking the question differently in two ways: Do you have an urge to smoke right now? and do you miss a cigarette? On that questionnaire those two items showed significant quadratic treatment effects at the $p<.05$ level. Given that craving is one of the most important issues, these three items taken together suggest that semantics are going to be a key

TABLE 2

Item Analyses for the SCS Scale*

Withdrawal Symptom	Main Effect Time	Main Effect Treatment	Interaction
Annoyed	p<.001**	p<.OO8	
Hostile	p<.001**	p<.03	p<05**
Irritable	p<.OOl	p<.05	P<.03
Fluctuations in Mood	p<.Ol	p<.05	P<.04
Frustration	p<.001**	p<.O6	ns
Depression	p<.002**	p<.07	ns
Left Out	p<.02**	ns	ns
Anxiety	p<.OOl	ns	ns
Concentration	p<.001	ns	ns
Disorientation	p<.OOl	ns	ns
Restlessness	p<.OOl	ns	ns
Trouble Sleeping	ns	ns	P<.01
Concern About Weight	ns	ns	ns
Craving	ns	ns	ns

*Analyses of Variances were performed on each item and included baseline and 5 days of abstinence.

**These differences disappeared when baseline was used as a covariate. Thus, there was an initial rise from baseline (still smoking) to abstinence days but no additional differences in temporal course beyond that rise.

issue in assessing "craving." These data represent a preliminary analysis of the item-by-item data for this study. Hunger on the Shiffman-Jarvik Scale was significantly reduced with nicotine gum (p<.05) compared to placebo gum, whereas for the item measuring weight concern no differences were found.

It should be kept in mind that with ad lib use we are not certain to what degree differences in amount of chewing accounted for the results. For example, where there are no differences between groups, it may be that more pieces of 2 mg gum or a higher dose is indicated, particularly in the first week. In a current uncontrolled clinical trial it has been observed that lethargy, spaciness, and disorientation respond to the 4 mg dose of gum where the 2 mg dose is less effective. Also, consistent and minimal use of 2 mg gum (10 to 15 pieces daily) helped reduce symptoms such as anxiety, irritability, and restlessness better than low level (5 to 6 pieces daily). A dose-response study should define the extent to

which symptoms can be alleviated with nicotine gum (Schneider, unpublished data; manuscript in preparation).

An ANCOVA was also performed on the withdrawal data described above for treatment x sex. Thus, these results are the same as the SCS totals described above except that conditions are subdivided into male and female. The treatment x sex findings are graphed in figure 3. The number of subjects within each category were as follows: nicotine gum female (12); nicotine gum male (14); placebo gum female (14); placebo gum male (10).

The main effect of treatment was significant ($p<.05$), and there is little overlap between treatments (both placebo groups vs. both nicotine groups in figure 3). The pattern (with baselines covaried) showed a significant quadratic component ($p<.01$) with all groups reporting withdrawal at Day 1. separating during the middle 3 days, and merging at Day 5. No main effect of sex was observed and there were no interactions between treatment and sex over time. This may have been a consequence of the small sample size when groups are divided in this manner. It is tempting to explore possible gender effects further in a larger sample. As Gritz (1980a) has noted, male/female differences have received little attention.

The pattern of responding suggests that nicotine gum may not be effective in first-day withdrawal. This could be a consequence of anticipation factors, of inadequate dose (including the initial

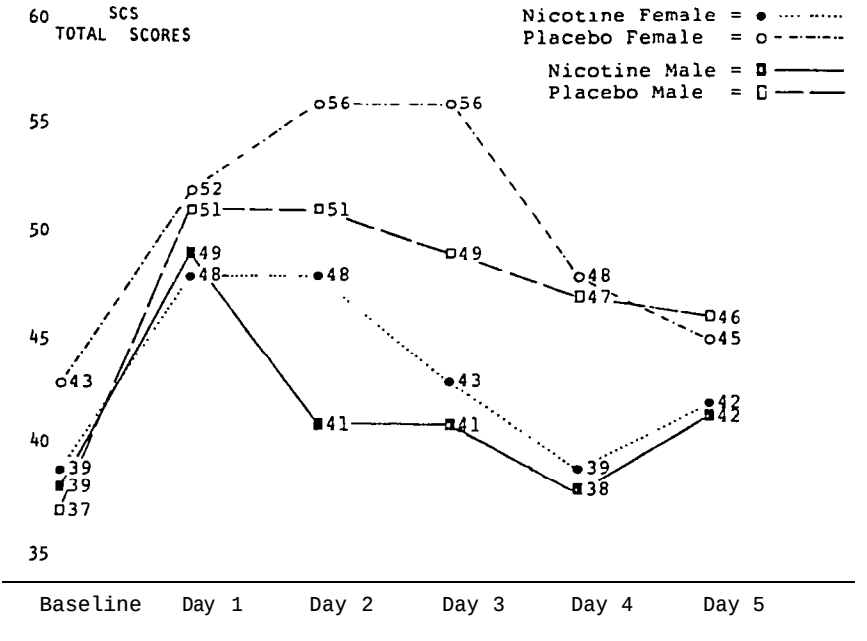


FIGURE 3

SCS Withdrawal Responses by Treatment and Gender

change from inhalation bolus to gum). improper gum use (subjects may have waited for first clinic visit). or may be attributable to changes with cessation (e.g., loss of ritual behaviors). The effectiveness of the gum becomes apparent as cessation progresses. A dose-response study should clarify whether symptoms can be alleviated entirely with replacement.

In addition to totals, specific items, and sex differences, we looked at a time-of-day effect in compliant subjects. Subjects were asked to fill out the withdrawal scales at home in the morning and evening. Of the 50 abstinent subjects providing the in-lab data, 3.2 cooperated in filling out the home scales. These results have been reported in Schneider and Jarvik (1984). The basic finding was a treatment x time-of-day effect. For placebo subjects, the severity of withdrawal symptoms was significantly higher than nicotine subject responses and increased in the evenings compared to a more stable withdrawal level in the nicotine group. The results indicate that withdrawal varies within a given day as well as across days and that nicotine is implicated in these fluctuations.

Mood Effects

A mood checklist (items were taken from the POMS mood scale) included 27 items reflective of positive and negative states. Thirteen items were positive: active, alert, carefree, cheerful, clear-headed, considerate. efficient, friendly, full-of-pep, lively, optimistic. proud, and relaxed. Thirteen items were negative: angry, bad-tempered, confused, hopeless, miserable, muddled, nervous, sad, shaky, spiteful, tense, unworthy, and worn-out. One item was dropped (ready-to-fight) because some subjects perceived this as positive and others as negative. In responding, the subject checked as many of the adjectives as applied at the moment. There was no mandatory responding on a scale as required with the SCS items. Responses were recorded as total number checked for the 13 positive items and total checked for the 13 negative items. These totals were obtained for baseline scores and for each of the 5 days of abstinence. For the positive items, the results (previously unreported) are presented in figure 4.

A repeated measures ANOVA with trends was performed on the positive item totals for all days. The results showed a significant effect of treatment ($p<.01$) as well as a significant quadratic treatment x time effect ($p<.02$). Subjects on nicotine gum showed only a slight decrease in positive responses checked. For placebo subjects, the drop from baseline to Day 1 is fairly sharp and stays lowered through the first few days. Note that for the SCS scores, the effects are also quadratic but the separation between groups does not occur until Day 2.

The results for negative items (also previously unreported) are consistent with the positive affect pattern by treatment. Placebo gum subjects showed a greater increase in negative responses than nicotine subjects. The repeated measures ANOVA with trends showed no significant main effects or overall interactions, so a

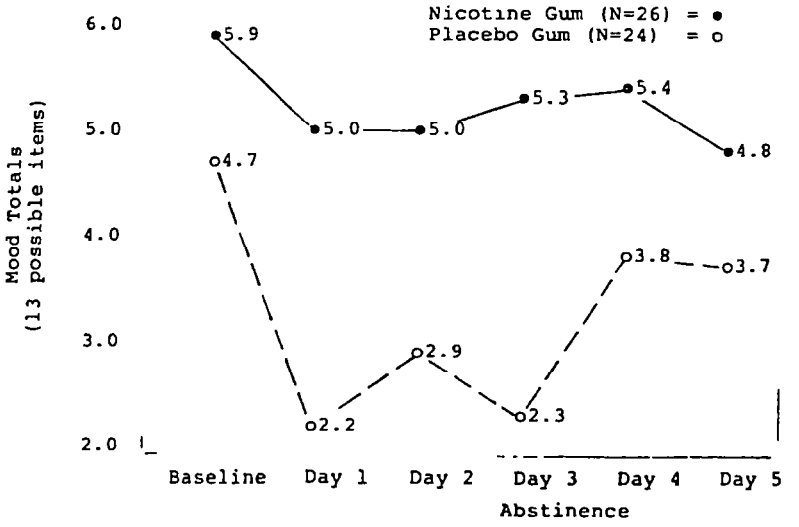


FIGURE 4

Positive Items Checked During
5 Days of Abstinence From Smoking

significant quadratic treatment x time effect was ignored. The problem with the negative item testing was that a floor effect occurred. Out of the 13 possible responses, mean responding ranged from 0.50 to 1.70 for the placebo group and 0.53 to 1.11 for the nicotine group. A review of the items suggests that a social desirability effect may have been operating. The items are very strongly negative and tend to go against feelings of self-worth that a smoker trying to quit may be seeking. Because the items are checked, there is no qualifying of the response. By contrast, we were able to assess negative changes in state with the SCS through use of scaled responding and through use of specific complaints associated with smoking cessation.

The withdrawal findings for 5 days of first-week abstinence provide support for the proposed mechanism of action with gum use during cessation. Nicotine replacement alleviated or prevented symptoms compared to nonreplacement with placebo. These findings have been supported by recent reports in the literature of nicotine-alleviated withdrawal (Hughes et al. 1984; West et al. 1984).

In the Hughes et al. (1984) study, symptoms of withdrawal were measured in 100 smokers. After baseline measurement subjects received either nicotine or placebo gum in a double-blind study and were tested in the first, second, and fourth evenings of abstinence. Hughes et al. (1984) report reductions in irritability. anxiety, difficulty concentrating, restlessness, and impatience between groups, with nicotine gum alleviating the symptoms. The

nicotine replacement did not reduce increases in craving. hunger, eating, insomnia, tremulousness, or supine heart rate after cessation.

In West et al. (1984) 48 smokers were either given 2 mg nicotine gum or a .5 mg unbuffered nicotine gum "placebo" for 24 hours of cigarette deprivation. In that study, the 2 mg gum alleviated irritability, depression, and difficulties with social interaction, but not hunger or ability to concentrate. As in our study, the drop in heart rate was reduced with active gum. In West et al. (1984) and Hughes et al. (1984) the authors conclude that nicotine replacement reduces symptoms of withdrawal and that nicotine deprivation plays a significant role in producing these effects.

In a recent paper, West (1984) has summarized the four studies representing tests of withdrawal during total abstinence. In conclusion, we suggest that with proper dosage we may reduce most, if not all, symptoms of withdrawal. Maintenance of higher blood levels will be important while the person is already reducing levels of nicotine from cigarettes. As the person adjusts to changing levels, relief should require less and less replacement with gum. However, we cannot view nicotine dependence and withdrawal as operating only in the short term. Urges to smoke long after cessation may represent conditioned nicotine-seeking and coping behavior.

SUMMARY

Our data and that of researchers in the area clearly provide evidence for nicotine-specific withdrawal and its relief with nicotine gum. In addition, outcome efficacy is enhanced when nicotine gum is combined with behavioral treatment.

Nicotine gum appears to be valuable both as a systematic tool and as a means of combatting short- and long-term nicotine seeking that contribute to maintenance of smoking and the inability to quit.

REFERENCES

Brantmark, B.; Ohlin, P.; and Westling, H. Nicotine-containing chewing gum as an anti-smoking aid. *Psychopharmacologia* 31:191-200, 1973.

British Thoracic Society. Comparison of four methods of smokings withdrawal in patients with smoking related diseases. *Br Med J,* 286:595-597. 1983.

Fagerstrom, K.O. Tobacco smoking, nicotine dependence and smoking cessation. Acta Univ Upsaliensis. Sweden: Uppsala, 1981.

Fagerstrom, K.O. A comparison of psychological and pharmacological treatment in smoking cessation. J Behav Med 5:343-351. 1982.

Fagerstrom. K.O. Effects of nicotine chewing gum and followup appointments in physician-based smoking cessation. Prev Med 13(5):517-527, 1984.

Ferno, 0.; Lichtneckert, S.; and Lundgren, C. A substitute for tobacco smoking. Psychopharmacologia 31:201-204. 1973.

Feyerabend, C.; Ings. R.M.J.; and Russell, M.A.H. Nicotine pharmacokinetics and its application to intake from smoking. Brit J Clin Pharmacol 19:239-247, 1985.

Gritz, E.R. Problems related to the use of tobacco by women. In: Kalant, O.J., ed. Alcohol and Drug Problems in Women. New York: Plenum, 1980a., pp. 487-544.

Gritz. E.R. Smoking behavior and tobacco abuse. In: Mello, N.K., ed. Advances in Substance Abuse. Greenwich, CT: JAI Press, 1980b. pp. 91-158.

Gritz. E.R.; Baer Weiss, V.; Benowitz, N.L.; Van Vunakis, H.; and Jarvik, M.E. Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. Clin Pharmacol Ther 30(2):201-213. 1981.

Hall, S.M.; Tunstall, C.; Rugg, D.; Jones, R.T.; and Benowitz, N. Nicotine gum and behavioral treatment in smoking cessation. J Consult Clin Psychol, in press.

Henningfield, J.E., and Goldberg, S.R. Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav 19:989-992. 1983.

Hjalmarson, A.I.M. Effect of nicotine chewing gum in smoking cessation: A randomized, placebo-controlled, double-blind study. JAMA 252:2835-2838. 1984.

Hughes, J.R.; Hatsukami, D.K.; Pickens, R.W.; Krahn, D.; Malin, S.; and Luknic, A. Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacology 83:82-87, 1984.

Jamrozik, K.; Fouler, G.; Vessey, M.; and Wald, N. Placebo controlled trial of nicotine chewing gum in general practice. Br Med J 289:794-797, 1984.

Jarvik, M.E. The role of nicotine in the smoking habit. In: Hunt, W.A., ed. Learning Mechanisms in Smoking. Chicago: Aldine Publishing Company, 1970, pp. 155-190.

Jarvik, M.E., and Schneider, N.G. Degree of addiction and effectiveness of nicotine gum therapy for smoking. Am J Psychiat 141(6):790-791, 1984.

Jarvis, M.J.; Raw, M.; Russell. M.A.H., and Feyerabend. C. Randomised controlled trial of nicotine chewing-gum. Br Med J 285:537-540. 1982.

Jarvis, M.J., and Russell, M.A.H. Correspondence: Smoking withdrawal in patients with smoking related diseases. Br Med J 286:976, 1983.

Johnston, L.M. Tobacco smoking and nicotine. Lancet 2:741, 1942.

Killen, J.D.; Maccoby, N.; and Taylor, C.B. Nicotine gum and self-regulation training in smoking relapse prevention. Behav Ther 15:234-248, 1984.

Malcolm, R.E.; Sillett, R.W.; Turner, J.A. McM.; and Ball, K.P. The use of nicotine chewing gum as an aid to stopping smoking. Psychopharmacology 70:295-296. 1980.

McNabb, M.E.; Ebert, R.V.; and McCusker, K. Plasma nicotine levels produced by chewing nicotine gum. JAMA 248:865-868, 1982.

Puska, P.; Bjorkvist, S.; and Koskela. K. Nicotine-containing chewing gum in smoking cessation: A double-blind trial with half year followup. Addict Behav 4:141-146. 1979.

Raw, M.; Jarvis, M.J.; and Russell, M.A.H. Comparison for nicotine chewing-gum and psychological treatments for dependent smokers. Br Med J 281:481-482, 1980.

Rose, J.E.; Jarvik, M.E.; and Rose, K.D. Transdermal administration of nicotine. Drug Alcohol Depend 13:209-213, 1984.

Russell, M.A.H. Nicotine intake and its regulation. J Psychosom Res 24:253-264, 1980.

Russell, M.A.H., and Feyerabend. C. Cigarette smoking: A dependence on high-nicotine boll. Drug Metab Rev 8:29-57, 1978.

Russell, M.A.H.; Feyerabend, C.; and Cole, P.V. Plasma nicotine levels after cigarette smoking and chewing nicotine gum. Br Med J 1:1043-1046, 1976a.

Russell. M.A.H.; Jarvis. M.J.; and Feyerabend. C. A new age for snuff? Lancet 1:474-475, 1980a.

Russell, M.A.H.; Merriman. R.; Stapleton, J.; and Taylor, W. Effect of nicotine chewing gum as an adjunct to general practitioner's advice against smoking. Br Med J 287:1782-1785. 1983.

Russell, M.A.H.; Raw, M.; and Jarvis, M.J. Clinical use of nicotine chewing-gum. Br Med J 280:1599-1602, 1980b.

Russell, M.A.H.; Sutton, S.R.; Feyerabend. C.; Cole, P.V.; and Saloojee. Y.K. Nicotine chewing gum as a substitute for smoking. Br Med J 1:1060-1063. 1977.

Russell, M.A.H.: Wilson, C.; Feyerabend. C.; and Cole, P.V. Effect of nicotine chewing-gum on smoking behaviour and as an aid to cigarette withdrawal. Br Med J 2:391-393, 1976b.

Schneider, N.G. An uncontrolled clinical trial of 2 mg and 4 mg nicotine gum in 100 subjects. Unpublished data.

Schneider, N.G., and Jarvik, M.E. Time course of smoking withdrawal symptoms as a function of nicotine replacement. Psychopharmacology 82:143-144. 1984.

Schneider, N.G.; Jarvik, M.E.; and Forsythe, A.B. Nicotine vs. placebo gum in the alleviation of withdrawal during smoking cessation. Addict Behav 9:149-156, 1984.

Schneider, N.G.; Jarvik, M.E.; Forsythe, A.B., Read, L.L.; Elliott, M.E.; and Schweiger, A. Nicotine gum in smoking cessation: A placebo-controlled, double-blind trial. Addict Behav 8:253-262. 1983.

Schneider, N.G.; Popek, P.; Jarvik, M.E.; and Gritz, E.R. The use of nicotine gum during cessation of smoking. Am J Psychiat 4:439-440, 1977.

Shiffman, S.M. The tobacco withdrawal syndrome. In: Krasnegor, N.A., ed. Cigarette Smoking as a Dependence Process. National Institute on Drug Abuse Research Monograph 23. DHEW Pub. No. (ADM)79-800. Washington, D.C.: Supt. of Dots., U.S. Govt. Print. Off., 1979. pp. 158-184.

Shiffman. S.M., and Jarvik, M.E. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology 50:35-39. 1976.

Turner, J.A.McM.; Sillett, R.W.; Taylor, D.M.; and McNicol, M.W. The effects of supplementary nicotine in regular cigarette smokers. Postgrad Med J 53:683-685, 1978.

West, R.K. Psychology and pharmacology in cigarette withdrawal. J Psychosom Med 28:379-386. 1984.

West, R.J.; Jarvis, M.J.; Russell, M.A.H.; Carruthers. M.E.; and. Feyerabend. C. Effect of nicotine replacement on the cigarette withdrawal syndrome. Br J Addict 79:215-219, 1984.

West, R.J .; Russell, M.A.H.; Jarvis. M.J.; and Feyerabend, C. Does switching to an ultra-low nicotine cigarette induce nicotine withdrawal effects? Psychopharmacology 84:120-123. 1984.

Wilhelmsen, L.. and Hjalmarson, A. Smoking cessation experience in Sweden. Can Fam Physician 26:737-743. 1980.

AUTHORS

Nina G. Schneider, Ph.D.*
Murray E. Jarvik. M.D., Ph.D.
Department of Psychiatry and Biobehavioral Sciences
The Neuropsychiatric Institute
University of California
Los Angeles, California 90024

and

Veterans Administration Medical Center
West Los Angeles, Brentwood Division
(691/BlSlD)
Los Angeles, California 90073

*Program Director, Smoking Cessation
Mark Taper Center for Health Enhancement
University of California Medical Center
University of California
Los Angeles, California 90024

Nicotine Chewing Gum in Smoking Cessation: Efficiency, Nicotine Dependence, Therapy Duration, and Clinical Recommendations

Karl-Olov Fagerstrom and Bo Melin

This paper will deal with four topics pertinent to nicotine gum: (1) A review of the placebo-controlled trials of the nicotine gum; (2) An analysis of how nicotine dependence interacts with nicotine gum therapy; (3) An analysis of duration of nicotine gum therapy; and (4) Experiences and recommendations derived from clinical practice.

REVIEW OF CONTROLLED TRIALS WITH NICOTINE GUM

The review covers smoking cessation studies that satisfy the criteria of (a) placebo control, (b) blindness, (c) randomization of subjects, and (d) long-term followup.

Table 1 shows the studies that meet the above requirements. The studies are characterized in terms of additional therapy format, number of subjects, time of followup and abstinence rates.

TABLE 1 Outcome from Placebo-Controlled Cessation Studies

Trial		% nonsmokers Active	Placebo	Follow-up at	Additional therapy	N
Fee, Stewart *+	1982	13	9	1 year	Lectures	352
Puska et al. *	1979	35	28	6 months	Group	160
Fagerstrom	1982	49	37	1 year	Individ.	96
Jarvis et al.	1982	47	21	1 year	Group	116
Malcolm et al.	1980	23	5	6 months	Individ.	210
BTS	1983	10	14	1 year	None	802
Hjalmarson	1984	29	16	1 year	Group	205
Schneider et al.	1983	30	20	1 year	Group	60
Jamrozik	1984	10	8	6 months	Indlvid.	200

* No CO-verification of claims
+ Only 18% of subjects were followed up

Eight of the nine studies show an advantage for the nicotine gum, although it does not, in most cases, reach statistical significance. When the studies are analyzed in terms of setting and the therapist's profession, it is evident that the best results are obtained by psychologists experienced in smoking cessation therapy and working in a cessation clinic with probably more motivated and dependent patients (Fee and Stewart 1982; Fagerstrom 1982; Jarvis et al. 1982; Hjalmarson 1984; and Schneider et al. 1983). That does not mean that psychologists' interventions are inherently better. Rather, physicians and other health care professionals would obtain the same effects if they used it in the same ways as it is used within a special cessation clinic.

NICOTINE DEPENDENCE

The concept behind the nicotine gum is that, while substituting nicotine gum for cigarettes, the need for nicotine can be satisfied while the psychosocial part of tobacco dependence may first be addressed. In the next step the pharmacological dependence of nicotine should gradually be dealt with. The smoker's dependence on nicotine is, thus, a crucial factor in the therapeutic rationale of the nicotine gum. Nicotine dependence varies considerably from smoker to smoker, and a hypothesis would be that the more the smoker is dependent on nicotine, the better the effect of the gum should be relative to placebo or a non-gum condition. In Table 2 is a scale (Fagerstrom Tolerance Questionnaire) for measuring the dependence of nicotine among smokers (Fagerstrom 1978).

The questions are individually scored and summed to provide a composite score in the range from 0 to 11, in which the higher values reflect greater dependence. The results from the published studies, where nicotine dependence has been related to nicotine or placebo gum are presented in table 3.

The Fagerstrom (1982) study defines high dependence as 8 points and above and low dependence as up to 6 points. In the second Fagerstrom report (1984), as in the rest of the studies, the patients have been divided into halves, split by the median value 6 or 7 points. The followup times are for Fagerstrom (1984) and Jarvik et al. (1984) 12 months, for Fagerstrom (1982) 6 months, and for Christen et al. (1984) 6 weeks. As can be seen from table 3, the increased likelihood among high nicotine dependent smokers to reach long-term abstinence with the help of nicotine gum is greatly enhanced.

DURATION OF NICOTINE GUM THERAPY

When smokers who are trying to quit are offered nicotine gum without any instructions concerning how long they should use it, the duration of use varies considerably. Some will only use a few pieces of gum throughout the whole therapy, while 5-10% will have difficulties in terminating nicotine gum use. How long then should nicotine gum treatment be continued in order to secure the best

TABLE 2 The Fagerstrom Questionnaire

Questions	Answers	Points	Score
1 How soon after you wake do you smoke your first cigarette?	Within 30 min	1	–
	After 30 min	0	–
2 Do you find it difficult to refrain from smoking in places where it is forbidden; e.g., in church, at the library, in cinemas, etc?	Yes	1	–
	NO	0	–
3 Which cigarette would you hate most to give up?	The first one in the morning	1	–
	Any other	0	–
4 How many cigarettes a day do you smoke?	15 or less	0	–
	16-25	1	–
	26 or more	2	–
5 Do you smoke more frequently during the early morning than during the rest of the day?	Yes	1	–
	No	0	–
6 Do you smoke if you are so ill that you are in bed most of the day?	Yes	1	–
	No	0	–
7 What is the nicotine level of your usual brand of cigarettes?	0.9 mg or less	0	–
	1.0 mg - 1.2 mg	1	–
	1.3 mg or more	2	–
8 Do you inhale?	Never	0	–
	Sometimes	1	–
	Always	2	–

long-term abstinence rates? At the moment there are few scientific data on which to draw. Russell et al. (1980) suggest that "it might be worth encouraging smokers to persist with the gum for at least 4 months." To support their view they rely on clinical experiences and a finding from a trial by Raw in 1980, where 67% of the patients using the gum for 3 months or longer were abstinent at 12 months in contrast to the overall figure of 38%. Another figure, cited by Russell et al. (1980). is a 68% 4-year abstinence rate obtained by Wilhelmsen and Hjalmarson (1980) for the subjects who had used nicotine gum for at least the first 4 months. However, the abstinence rate at 4 years was the same for those persons who were neither smoking nor chewing gum at 4 months after stopping smoking (Hjalmarson 1982). In a placebo-controlled trial from the Addiction Research Unit, Maudsley Hospital, some data pertinent to the length

TABLE 3 Abstinence Rates in Relation to Nicotine or Placebo Gum and Nicotine Dependence

	High dependent Nic. gum	Placebo gum	N	Less dependent Nic. gum	Placebo gum	N
Fagerstrom (1982)	71%	39%	35	75%	65%	40
Fagerstrom (1984)	26	5*	67	32	13	76
Christen et al. (1984)	46	9	80	28	12	113
Jarvik et al. (1984)	41	8	17	0	30	8

* No gum

of chewing were reported by Jarvis et al. (1982). The l-year abstinence rate for the subjects chewing for 3 months was 75% for nicotine chewing and 62% for placebo gum. In another controlled trial (Fagerstrom 1982), no difference in long-term abstinence rates could be seen as a function of time on nicotine gum.

The fact that long-term chewers of nicotine gum generally have good or excellent abstinence rates should not be surprising and may not be caused by gum use. Both longer use and abstinence may be modulated by a third variable such as motivation. A long-term chewer is a former smoker who has managed to terminate, and maintain non-smoking for a number of reasons. Nicotine chewing gum is one of several factors in obtaining and maintaining abstinence, and it may serve as both a dependent and an independent variable.

At the Smoking Cessation Clinic in Uppsala, Sweden, a prospective study has been completed (Melin 1984). "Time on gum" has been deliberately manipulated for 121 consecutive patients. They were randomized into 1 (n=61) or 6 (n=60) months of nicotine gum use. They were given access to the gum for their respective time without instructions to continue chewing until the deadline. In addition to nicotine gum, they received the standard, individual, cognitive behavioral-oriented counseling offered at the clinic. The number of sessions varied according to the subjects' need. Both 2 and 4 mg doses of the gum were used, according to the need of the subject. Figure 1 shows that the 6-month group is somewhat superior to the one-month group at 3 and 6 months. However, the long-term abstinence rates are equal, since many of the 6-month subjects relapsed when gum therapy was discontinued at 6 months. Thirty-nine percent were abstinent in the l-month group at 12 months follow-up and 32% in the 6-months group.

Many subjects, forced to cease chewing nicotine gum at 1 month, relapsed. Since their treatment protocol allowed for individual variation in the number of sessions given each patient, a post hoc analysis of number of sessions given the groups was made to determine if the nonpharmacological part of the treatment compensated for discontinuing chewing. No significant difference was seen during the first month. However, when the whole length of treatment was reviewed, 5-7 months after quitting, the l-month group

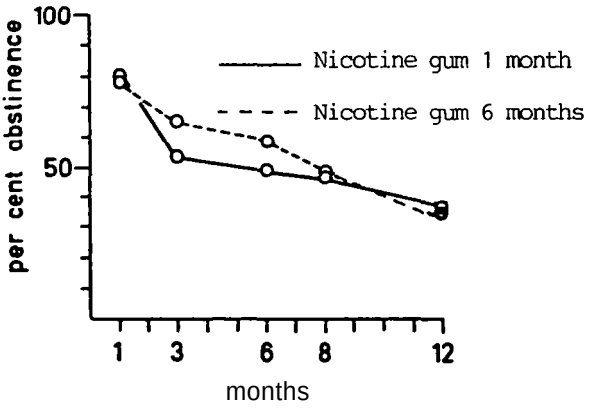


Figure 1: Abstinence Rates Over Time for 1 Months and 6 Months Nicotine Gum Treatment

had significantly more treatment sessions than the 6-month group (8.5 compared to 7.2, $t=2.0$, $p<.05$). It appears that time on nicotine gum was unintentionally traded for more nonpharmacological treatment sessions.

Optimal time on nicotine gum may therefore interact with the degree of psychological support given. The less support, the more the ex-smoker has to rely on nicotine gum, and vice versa. At the moment, no hard scientific evidence exists for recommending any specific duration of nicotine gum therapy. The best advice available today is to keep in close contact with the ex-smoker and let him or her determine the duration.

EXPERIENCES AND RECOMMENDATIONS FROM CLINICAL PRACTICE

Many smokers feel anxious about terminating smoking. Smokers seeking help often expect and are afraid of physiological and psychological reactions that they have encountered in earlier unsuccessful attempts. Describing the nicotine gum's effect on physiological abstinence and concurrently conveying a skilled and experienced therapist's commitment to giving psychological support, usually creates a therapeutic effect on patients' anxiety and instills a sense of optimism despite several prior cessation attempts. Naturally, a warm and accepting attitude may increase the likelihood of a favorable outcome. The therapeutic atmosphere with renewal of nicotine gum prescription as well as other methods of nonpharmacological support does motivate the patients to come to scheduled appointments.

Consumption of gum is likely to vary across patients. Most patients chew about 8-10 pieces of gum per day, but there are considerable individual differences. The patients usually chew the gum for 2-3 months. After 3 months most of the patients cease chewing. About 5-10% will have difficulties in stopping using the gum and need strong psychological support to finally break their addiction to

nicotine. One way to handle the patients who find it difficult to give up using nicotine gum may be to have them switch to a nicotine-free chewing gum. Sometimes patients may simply have developed a new habit (gum chewing) and may be quite able to stop using nicotine.

At the clinic in Uppsala. where the authors have been working, the abstinence rate rose by about 15% when nicotine gum was introduced in the treatment. However, it should also be kept in mind that nicotine gum alone -is seldom sufficient. Nicotine gum is a complement to psychosocial treatment for helping people to stop smoking (see Hall and Killen, this volume). We have not observed any severe side effects in the 6 years during which nicotine gum has been used in our clinic. As long as chewing instructions are appropriately given, the adverse reactions usually involving taste and irritation in throat and stomach can be well controlled. It is found that nicotine gum is tolerated by approximately 90% of the smokers.

Recommendations

* Nicotine gum should be used only when smoking is completely terminated and not in conjunction with successive reduction of smoking.

* When nicotine gum is prescribed, it should be in sufficient quantity and for a sufficiently long time period. The exact quantity and time period are best judged by the patient. The more nicotine-dependent smokers usually chew more pieces per day, need nicotine gum for a longer period, and also tend to prefer the 4 mg strength more often than the less dependent smokers.*

* Nicotine dependence should be assessed. If the smokers' dependence score is in the upper half of the distribution (usually about 7 points and above), it is a strong indication for prescribing nicotine gum.

* It is firmly recommended that a sample of nicotine gum should be kept in the therapist's office. Let the patients chew a piece of gum while instructed and supervised. This will facilitate the acceptance of nicotine gum and the choice between 2 and 4 mg dosage.*

* Since many patients are at high risk for relapse when nicotine gum therapy is discontinued, it is suggested that an appointment be made with the patients after nicotine gum chewing has terminated.

*Note: The 4 mg gum is not currently available in the U.S. Dosage must be adjusted by number of pieces chewed.

REFERENCES

British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. British Medical Journal, 286:595-597. 1983.

Christen, A.G., et al. Efficacy of nicotine chewing gum in facilitating smoking cessation. JADA, 108:594-597, 1984.

Fagerstrom. K.O. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addictive Behavior, 3:235-241, 1978.

Fagerstrom, K.O. A comparison of psychological and pharmacological treatment in smoking cessation. Journal of Behavioral Medicine, 5:343-351, 1982.

Fagerstrom, K.O. Effects of nicotine chewing gum and follow-up appointments in physician-based smoking cessation. Preventive Medicine, 13:517-527, 1984.

Fee W.M., Steward, M.J. A controlled trial of nicotine chewing gum in a smoking withdrawal clinic. The Practitioner, 226:148-151. 1982.

Hjalmarson, A.I.M. Effect of nicotine chewing gum in smoking cessation. JAMA, 252;20;Nov 23/30:2835-2838, 1984.

Hjalmarson, A.I.M. Personal communication, 1982.

Jamrozik, K., et al. Placebo controlled trial of nicotine chewing gum in general practice. British Medical Journal, 289;29;Sept. 1984.

Jarvik, M.E., Schneider, N.G. Degree of addiction and effectiveness of nicotine gum therapy for smoking. Am. J. Psychiatry, 141:6. June 1984.

Jarvis. M.J., et al. Randomized controlled trial of nicotine chewing gum. British Medical Journal, 285:537-540, 1982.

Malcolm, R.E., et al. The use of nicotine chewing gum as an aid to stopping smoking. Psychopharmacology 70:295-296. 1980.

Melin, 8. Effekter av tva ollka administrationstider vid nikotin-tuggummi 1 rokavvanjnlngsbehandling. Institutionen for till-lampad Psykologi. Uppsala University, Sweden, 1984.

Puska, P., et al. Nicotine-containing chewing gum in smoking cessation: A double-blind trial with half-year follow-up. Addictive Behaviors, 4:141-146, 1979.

Raw, M., et al. Comparison of nicotine chewing gum and psychological treatments for dependent smokers. British Medical Journal, 281:481-482. 1980.

Russell, M.A.H., et al. Clinical use of nicotine chewing gum. British Medical Journal, 281:1599-1602, 1980.

Schneider, N.G., et al. Nicotine gum in smoking cessation: A placebo-controlled double-blind trial. Addictive Behaviors. 8:253-261. 1983.

Wilhelmsen. L. and Hjalmarson, A. Smoking cessation experience in Sweden. Canadian Family Physician, 26:737-747, 1980

AUTHORS

Karl Olov Fagerstrom. Ph.D.
Leo Research Laboratory and Medicine Clinic
Helsingborg Hospital
Sweden

Bo Melin, B.A.
Department of Applied Psychology
University of Uppsala
Sweden

Theoretical Background and Clinical Use of Nicotine Chewing Gum

M. A. H. Russell, FRCP, FRCPsych., and
M. J. Jarvis, MPhil.

> If we accept the fact that the use of tobacco in its various preparations is a form of drug addiction, even though a pleasant one not affecting criminal statistics, we can more readily help our patient when he finds that his problem has gotten out of hand.
>
> John L. Dorsey, MD, FACP, Baltimore, Maryland, 1936.

INTRODUCTION

For many years campaigns and treatments to promote smoking cessation have had disappointing results. In our view, this is because for most smokers cigarette smoking is a form of drug dependence and our programmers have failed because they have not taken this sufficiently into account. But the prospects are now brighter for more successful intervention in the future.

Firstly, there is more widespread appreciation of the addictive nature of smoking and, secondly, the development of nicotine chewing gum has provided the first effective aid to overcoming the pharmacological problem of withdrawal. But it is crucial that the pendulum does not swing too far towards over-reliance on pharmacological treatments and neglect of the important social and psychological factors which are a fundamental part of all addictive disorders. It is also important that the labelling of smoking as an addiction does not lead to the belief that permanent cessation is therefore impossible for smokers who are addicted. An addictive state is in no way impossible to overcome, although it is likely to be difficult and therefore to require commitment, planning, and possibly support as well.

Another significant recent advance that gives grounds for expecting more success in the future is the recognition of the value and cost-efficacy of minimal intervention or self-help, and the potential role of physicians in applying this approach. Most

important of all, perhaps, is the possibility that physician advice could be combined synergistically with the use of nicotine gum. Besides enhancing the efficacy of brief advice to stop smoking, it is likely that the availability of nicotine chewing gum will in turn encourage physicians to be more active in advising and helping their patients to give up smoking.

It is our purpose first to discuss briefly the nature of smoking as a form of drug dependence. This provides the theoretical basis for developing pharmacological approaches to cessation. We then focus on nicotine chewing gum as the first pharmacological approach with proven efficacy and discuss the theoretical rationale for its use, its mode of action, and various practical aspects necessary for effective use in different settings. Finally, besides its use as an effective aid to cessation, it has provided a means for advancing knowledge of the role of nicotine in smoking.

SMOKING AS A FORM OF DRUG DEPENDENCE

People smoke cigarettes for many reasons - social, psychological, sensory, behavioural, and pharmacological. But of all these the pharmacological motives are the most powerful and the most fur&mental. If tobacco contained no nicotine, there would be no problem. People wouldn't smoke it, nor would they snuff it or chew it.

Although people begin to smoke for social and psychological reasons, pharmacological motives gradually take over as the smoker learns to inhale and a regular dependent smoking pattern becomes established. This escalation to dependence usually takes two or three years but sometimes occurs far more quickly. Other factors such as taste, smell, sensory irritation, and behavioural components such as handling also become important. This is mainly through frequent and close association with the pharmacological effects of nicotine. In other words, they are secondary. Without the presence of nicotine few people would develop a strong taste for tobacco.

Many surveys have shown that at least three out of every four smokers want to stop smoking or have tried to stop - some of them many times. Surveys also show that only about one in three smokers succeeds in stopping permanently before the age of 60. Thus most people smoke not because they really want to, but because they cannot easily stop. In other words, they smoke because they are hooked and dependent on nicotine. Blood nicotine levels of smokers vary widely, from 5 ng/ml to over 70 ng/ml, with an average level for heavy smokers of about 35 ng/ml. The distribution of peak blood nicotine concentrations just after a cigarette is shown in figure 1 for a sample of heavy smokers. Although the curve for smokers in the general population would be somewhat to the left, measurable pharmacological effects are produced with blood nicotine levels of 10 ng/ml or less. It is thus apparent that most regular smokers inhale and absorb sufficient nicotine to produce pharmacological effects.

FIGURE 1

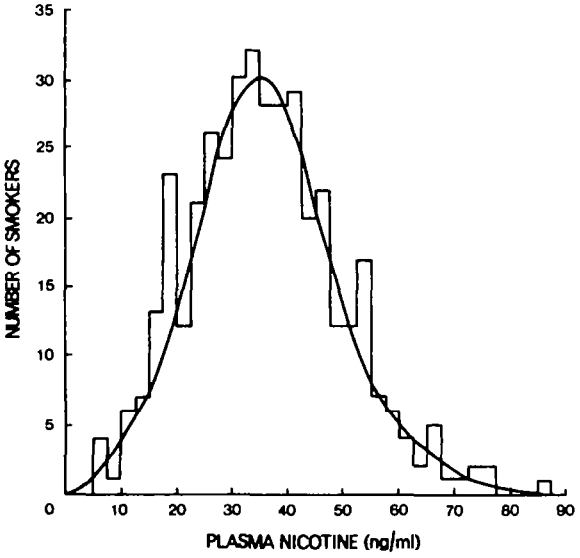


Figure 1. Distribution of peak plasma nicotine concentrations in a sample of 393 heavy smokers (250 women, 143 men) with a mean cigarette consumption of 30.1 per day. Blood was taken 2 minutes after completing a cigarette during the afternoon of a day of usual smoking. The average plasma nicotine concentration was 35.8 ng/ml (SD 13.7) and was not significantly different between men and women.

It is not our brief here to go into all the pharmacological effects of nicotine or into the details of the evidence for its role in smoking and the tobacco withdrawal syndrome. But it should be emphasised that the modern cigarette is a highly efficient device for getting nicotine to the brain. The smoke is mild enough to be inhaled deeply into the alveoli of the lungs from where nicotine is rapidly absorbed into the bloodstream to reach the brain within about 7 seconds. This means that the inhaling cigarette smoker receives a rapid intravenous-like "shot" or bolus of nicotine to the brain after each inhaled puff. This contrasts with the slower steady rate of absorption from chewing tobacco or non-inhaled cigar smoking. Furthermore, the nicotine concentrations in the post-inhalation boli must be many times higher than those measured in mixed venous blood after completion of a cigarette. The pattern of pharmacological effects is no doubt correspondingly different following the different forms of intake.

PHARMACOLOGICAL APPROACHES

The concept of pharmacological approaches to smoking cessation is not new. In 1936, Dorsey suggested the use of lo&line as a

substitute for nicotine because of some putative pharmacological similarities (Dorsey 1936). But the pharmacological effects of lobeline are weak. It does not substitute for nicotine in animal experiments, and clinically it has never proved superior to placebo. The story is similar for other potential substitutes. Amphetamine, for example, increases smoking behaviour rather than diminishing it, and sedatives have no effect in tranquillizing doses. The subtle dual stimulant and sedative actions of nicotine appear to be unique. Animals discriminate these actions from those of all other drugs that have been tested (Hendry and Rosecrans 1982), and there is evidence for its effect on specific nicotine receptors in the brain (Abood et al. 1981) in addition to its classical effects on aceylcholine receptors.

Receptor blockade is another potential pharmacological approach. A drug that blocks the rewarding effects of nicotine could theoretically be used as an agent of extinction. Beta-adrenergic blockade by propranolol has been shown to block the peripheral effects of smoking on heart rate and blood pressure (Carruthers 1976). However it has no effect on reducing subjective satisfaction from smoking and has no potential, therefore, as a means to produce extinction. Mecamylamine, on the other hand, is a blocker of the nicotinic receptors of acetylcholine and appears to effectively block some of the subjective effects of nicotine (Henningfield and Jasinski 1983). Its short-term effect is to increase smoking behaviour (Stolerman et al. 1973), possibly in an attempt on the part of smokers to overcome the receptor blockade. But this is not an appropriate test of its potential as an aid to smoking cessation. More prolonged use would be necessary to test its capacity to produce extinction. It is our view, however, that cognitive factors and the capacity of humans to discriminate between conditions of smoking with and without mecamylamine make it unlikely that an extinction model based on old-fashioned learning theory would work. For similar reasons pharmacological aversion therapy with drugs such as emetine and apomorphine is unlikely to be effective. There is no punishment-model drug for smoking, such as disulfiram for alcohol abuse. There is also no prospect of one, since none of the known metabolites of nicotine are aversive in realistic concentrations. All this leaves nicotine substitution as the only feasible potentially effective pharmacological approach to smoking cessation.

NICOTINE SUBSTITUTION

There are many potential routes for administering nicotine. Besides the rate of absorption and other issues relating to bioavailability, the therapeutic potential of a particular route will also depend on factors such as safety and social acceptability. A number of routes can be excluded immediately. In the case of ingestion, absorption is slow and most of the nicotine is metabolised by the liver to metabolites which are

pharmacologically inert. Nicotine suppositories or pessaries would be inconvenient and unacceptable. Injections would need to be repeated too frequently to be practical, and would not be feasible for widespread use. Transdermal delivery certainly has potential but has not yet been developed in the case of nicotine. This leaves the three routes - lungs, buccal and nasal mucosae - which have been used for tobacco for over 500 years.

Of these three routes, the rate of absorption through the lungs is, as mentioned earlier, far and away the most rapid. This is simply a matter of surface area, that of the lungs being roughly equivalent to the size of a tennis court. Although it is technically possible to produce aerosols with particles small enough to reach the alveoli, to our knowledge no satisfactory nicotine aerosol has yet been developed. We have seen and tested four. They have been either too clumsy or have failed to produce potentially useful blood nicotine concentrations. Irritancy to the throat has been another major problem. A notable exception has been the development of a vaporiser shaped like a cigarette (Jacobson et al. 1982). Inhalation through this device enables nicotine in vapour form to be taken into the lungs. It is not excessively irritating and is capable of producing therapeutically useful blood nicotine concentrations. If a problem of safety can be overcome, such a device would be well worth further study.

The historical fact that tobacco has been chewed and taken as "wet" snuff in the north and "dry" snuff in the nose suggests that absorption of nicotine by either route is sufficient to produce pharmacological effects. Blood nicotine concentrations after "wet" and “dry” snuff have been shown to be equivalent to those produced by cigarette smoking (Gritz et al. 1981; Russell et al. 1981). Various nicotine-containing lozenges and tablets have been produced from time to time for help with smoking cessation, but they have never been systematically tested, and in most cases their nicotine delivery has been inadequate for therapeutic value. Nicotine-containing chewing gum, on the other hand, has been extensively tested (see below). One possible limitation of nicotine gum is that the rate of nicotine absorption is slow compared with inhaled cigarette smoking. Preliminary study with a nasal nicotine solution (NNS) used as a kind of liquid snuff shows that nicotine is absorbed more rapidly and efficiently through the nose than through the lining of the mouth (Russell et al. 1983a, see figure 2). With refinements in flavour and acceptability, it is possible that a form of NNS could be clinically useful for those smokers who get insufficient help from nicotine gum or who have problems with dyspeptic symptoms.

Finally, as a general principle, it is likely that more therapeutic success might be expected from those forms of nicotine substitution which also provide a sensory experience and a socially acceptable behavioural component to act as substrates for conditioning as acquired secondary reinforcers.

FIGURE 2

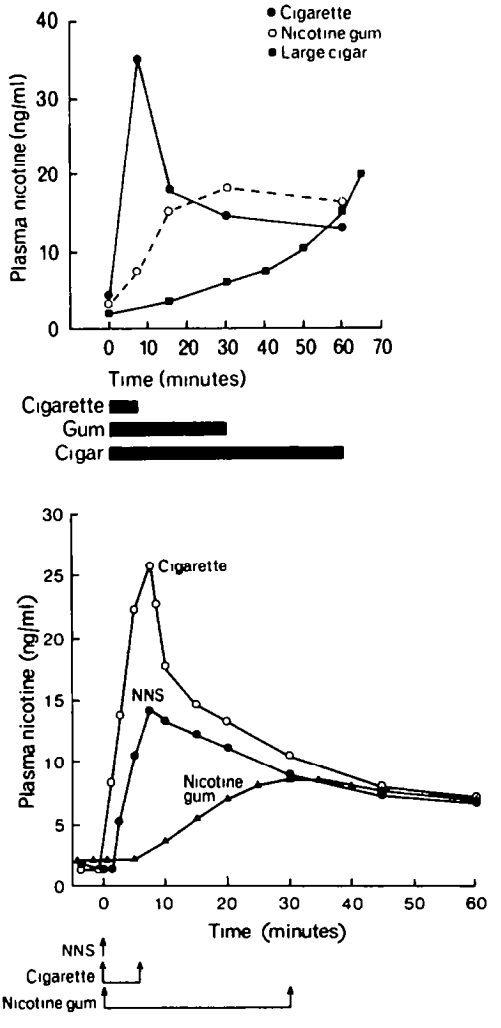


Figure 2. Plasma nicotine concentrations before, during, and after chewing a single piece of nicotine chewing gum containing 4 mg (top) and 2 mg nicotine (bottom). The plasma nicotine concentrations produced by smoking a cigarette are also shown as are those produced by the non-inhaled smoking of a large Havana cigar (top) and use of a single 2 mg dose of nasal nicotine solution (NNS) (bottom). (Top is from Russell et al. Brit Med J, 280:1599-1602, 1980, and bottom from Russell et al. Brit Med J, 286:683-684, 1983). Copyright 1980 and 1983, The British Medical Association.

NICOTINE CHEWING GUM

A nicotine-containing chewing gum was first developed more than 10 years ago by Ove Ferno in Sweden for use as an aid to smoking cessation (Ferno et al. 1973). Its purpose is to ease withdrawal symptoms by providing an alternative source of nicotine and, in addition, a substitute oral activity. It enables the smoker to break the habit in two stages. In the first stage, the smoker is able to focus on overcoming the behavioural and psychological components of dependence without at the same time having to cope with nicotine withdrawal. The dependence on nicotine is overcome at a later stage when there is no longer any urge to smoke.

It should be stressed, however, that the slower rate of nicotine absorption through the buccal mucosa and the absence of puff-by-puff high-nicotine boli (see above) make the gum an incomplete nicotine substitute for smokers who inhale. For the same reason cigarette smokers who inhale deeply gain little satisfaction from cigars unless they too are inhaled. The purpose of nicotine gum, therefore, is to relieve nicotine related withdrawal symptoms rather than provide the same positive pleasure as inhaled smoking.

The product

Since the early days of its development the nicotine-containing chewing gum (Nicorette) has been considerably refined and improved. It is available in two strengths, each piece containing either 2 mg or 4 mg of nicotine (only the 2 mg strength is available in the United States). The nicotine is bound to a resin and its release depends on the rate and vigour of chewing. About 90% of the nicotine is released after 30 minutes of normal chewing (Ferno et al. 1973). The gum also contains a buffer to maintain the pH in the mouth at about 8.5, at which the nicotine is well absorbed through the buccal mucosa. Swallowed nicotine is absorbed and rapidly metabolized in its first passage through the liver (Russell and Feyerabend 1978).

Pharmacology

The rate of absorption of nicotine from the gum is relatively slow (see figure 2). The peak plasma concentration is reached 15-30 minutes after starting to chew the gum, compared with 1-2 minutes after completion of a cigarette. However, a 4 mg piece of gum chewed every hour for 2-3 hours produces plasma nicotine concentrations similar to those in heavy cigarette smokers (McNabb et al. 1982; Russell et al. 1976a and 1977; see figure 3). Cardiovascular effects, such as increase in heart rate and blood pressure, produced by 4 mg gum match those after cigarette smoking, but the 2 mg gum has less effect (Fredholm and Sjogren 1979; Nyberg et al. 1982).

Effect on Ad Libitum Smoking Behaviour

In two short-term studies in subjects who were instructed to smoke freely without making any deliberate attempt to reduce their

FIGURE 3

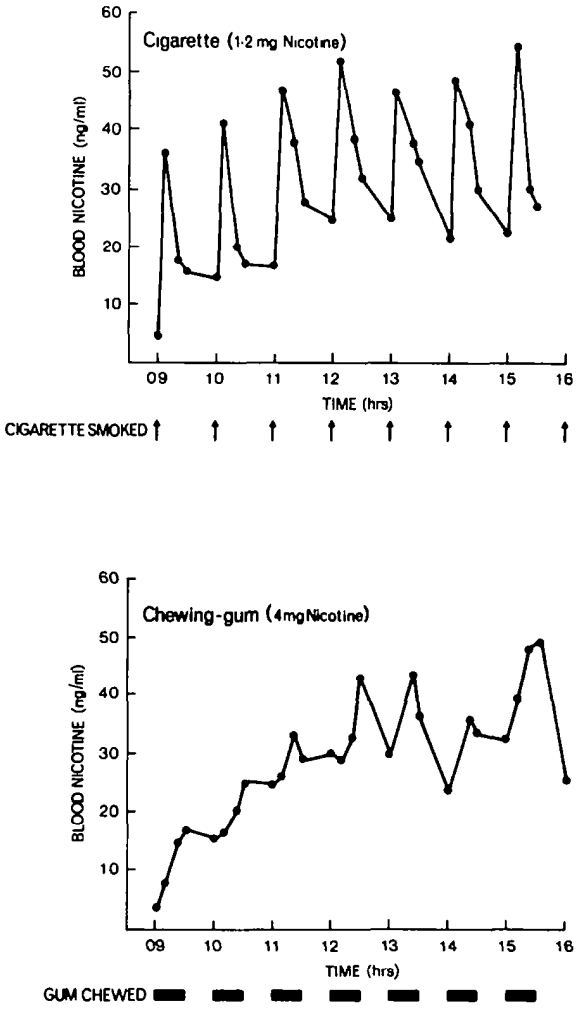


Figure 3. Plasma nicotine concentrations in the same subject when smoking one cigarette per hour ad when chewing a piece of 4 mg nicotine gum every hour. (From Russell et al. Brit Med J, 1:1043-1046, 1976). Copyright 1976, The British Medical Association.

smoking, nicotine chewing gum had a modest inhibitory effect on smoking behaviour (Kozlowski et al. 1974; Russell et al. 1976b). While chewing active gum, the subjects smoked fewer cigarettes, smoked them less intensively, and inhaled less deeply (as measured by COHb) than when chewing a placebo gum.

Effect on Withdrawal Symptoms

In an early short-term crossover study (Russell et al. 1976b), nicotine chewing gum was rated as more satisfying than a placebo. It was also rated as significantly more effective at putting the subjects off cigarettes and as more helpful after stopping smoking. In more recent clinical studies (see below), besides being more effective than placebo in helping smokers to give up cigarettes, active gum was significantly more effective than placebo at relieving irritability, hunger, and sleepiness during the first 6

TABLE 1

Significance levels of changes in mood and other ratings before and after 24 hours abstinence in subjects receiving active nicotine chewing gum or placebo

	Placebo (n=21)	Active Gum (n=27)	Difference between groups
Depressed	.06	NS	.025
Irritable	.001	NS	.025
Less sociable	.025	NS	.05
Less composed in company	.05	NS	.01
At a loose end	.05	NS	NS
Restless	.05	NS	NS
Dizzy	.05	NS	NS
Reduced concentration	.025	.001	NS
Hunger	.001	.001	NS

Note: Ratings of all the withdrawal symptoms listed above changed significantly in those on placebo gum. In those on active gum, the only ratings to show significant change were reduced concentration and increase in hunger. Comparison of the changes in the two groups (3rd column) shows that nicotine replacement provided by 2 mg nicotine gum alleviated symptoms of depression, irritability, reduced sociability and composure in company. (See West et al., Brit J Addict, 79:215-219, 1984).

weeks of treatment (Jarvis et al. 1982). However, the active and placebo groups differed in abstinence rates during this period, and this may have partially accounted for the differences in withdrawal symptom ratings.

In a study designed specifically to test the effect of partial nicotine replacement on withdrawal symptoms during the first 24 hours of abstinence from smoking, 48 smokers were randomly assigned to chew either active 2 mg nicotine gum or a placebo (West et al. 1984). Subjective ratings were recorded &fore and during abstinence. The results in table 1 show that those who received placebo gum experienced a number of withdrawal symptoms during abstinence, whereas those given active gum experienced very few. In other words, the active gum was successful in alleviating some but not all the withdrawal symptoms. Similar findings have been reported in other studies (Hughes et al. 1984; Schneider and Jarvik 1984). It is noteworthy that these results were achieved despite the fact that plasma nicotine concentrations on the active 2 mg gum averaged only 8.3 ng/ml compared with base-line smoking concentrations of 31 ng/ml and 25 ng/ml for peaks and troughs respectively (West et al. 1984). More effective nicotine replacement with 4 mg gum and/or more experience of chewing could lead to greater relief of withdrawal symptoms.

In view of the capacity of nicotine chewing gum to produce blood nicotine levels comparable to smoking, albeit more slowly, in view of its capacity to produce some of the pharmacological effects of smoking, to inhibit ad libitum smoking, and to relieve tobacco withdrawal symptoms, in addition to providing an oral substitute, it would be suprising indeed if it were not also to prove a useful aid to cessation.

CLINIC-BASED TREATMENT

Over the past 20 years, many kinds of treatment methods have been tried to help people to give up smoking. These include hypnosis, group treatment, acupuncture, aversion therapy, and other psychological methods. None of these has been shown to give better results than an equivalent amount of simple attention and support which produces success rates ranging from about 10% - 25% abstinent at l-year follow up. Drugs such as lobeline and tranquillizers are no better than placebos, probably because they are inadequate substitutes for nicotine (see above). In our view, the main obstacle to success is the addictive nature of smoking. This is the root of the problem and, until recently, none of the cessation methods have been applied directly to it. However, since the development of nicotine chewing gum, the situation has changed.

In a comparative study at our clinic (Raw et al. 1980), those treated with nicotine gum had a success rate of 38% at l-year follow up, compared with only 14% for those who had intensive psychological treatments. More recently, in a double-blind placebo-controlled trial (Jarvis et al. 1982) we obtained a success rate of 47% not smoking at l-year follow up, compared with 21% for those on placebo gum (see table 2). The active gum was also

significantly more effective than the placebo at relieving withdrawal symptoms. In both these studies abstinence from smoking was confirmed by carbon monoxide measures. Adverse side-effects were limited to gastrointestinal symptoms such as nausea, indigestion, and hiccups. These were minor and transient and in no case warranted discontinuance of gum use. About 7% of the subjects became dependent on active gum (none on placebo). Probably because absorption of nicotine is less rapid than from smoking, the dependence was also less severe and was usually overcome without relapse to smoking. Similar results have been obtained in placebo-controlled trials in Sweden and the U.S.A. (Fagerstrom 1982; Hjalmarson 1984; Schneider et al. 1983).

TABLE 2

Treatment with nicotine chewing gum (% abstinent)

	Placebo Gum (n=58)	Active Gum (n=58)	Statistical Significance
Abstinent at 1 month	33%	62%	p<.01
Abstinent at 1 year	21%	47%	P<.01
Lapse-free abstinence throughout 1 year	14%	31%	P<.025

Jarvis et al. Brit Med J, 285:537-540, 1982. Copyright 1982, Medical Association.

LIMITATIONS OF INTENSIVE METHODS

Intensive treatment and support at specialised smoking withdrawal clinics can achieve l-year abstinence rates of up to 40%, but the average is nearer 20%. Even if higher success rates could be obtained, the clinic-based approach has two major limitations. Firstly, only a minority of smokers will ever attend a clinic and, secondly, if they did attend, there are simply too many smokers for clinics to cope with. Few clinics in Britain attract as many as 200-300 clients a year, and many of these attend only once and so do not avail themselves of the treatment offered. A relatively busy and effective clinic is unlikely to achieve more than 100 long-term ex-smokers per year and the yield of the average clinic is probably below 50 per year.

THE MINIMAL INTERVENTION STRATEGY

The rationale behind this strategy is that the yield of long-term ex-smokers will be greater if the therapist/counsellor/advisor spends less time with more smokers rather than focusing on intensive effort with a few. A method with a low but proven success rate, achievable with minimal effort and readily applicable to large numbers of smokers, could be more useful in terms of public health than a time-consuming intensive method with a far higher success rate. In this respect we have been impressed by the powerful role that physicians could exercise. In the course of their everyday work physicians have face-to-face access to the majority of the 17 million cigarette smokers in Britain. Some 95% of the British population attend their family physician at least once in a 5-year period, and about 75% attend at least once in a year. Attendance rates in other developed countries are unlikely to be very different.

In a previous study we showed that brief advice against smoking given by family physicians in their own style, together with a leaflet and warning of follow-up, achieved a success rate of 5.1% who stopped smoking within the first month and were still abstinent at 1 year, compared with 0.3% in non-intervention controls (Russell et al. 1979). It is emphasised that these results were based on all cigarette smokers who attended the physicians' offices, irrespective of whether they wanted to stop at the time or whether they had or had not already got a smoking-related disease. Although small, this effect was highly significant statistically, and for the reasons stated above has the potential for creating more ex-smokers than is ever likely to occur via intensive methods.

PHYSICIAN INTERVENTION WITH NICOTINE CHEWING GUM

We have recently completed a further study designed to see whether the offer and prescription of nicotine chewing gum (2 mg Nicorette) would enhance the efficacy of brief routine advice by physicians (Russell et al. 1983b).

The target sample comprised all cigarette smokers, aged 16 or more, who attended the offices of 34 family physicians in six group practices during a 3 1/2-week period. They were assigned by week of attendance (in a balanced design) to one of three groups. Group 1 were non-intervention controls. Group 2 received advice to stop smoking plus a booklet and a warning of follow up. Group 3 received the same as Group 2 but, in addition, were offered nicotine chewing gum. If the offer was accepted, a prescription and instruction booklet were also given, A postal follow-up was done after 4 months and again after 1 year. Expired-air carton monoxide was checked in two-thirds of those claiming abstinence at 1 year. The results are based on the 1,938 (89%) who had not moved to an unknown address or died during the year. Among these 1,938 there were 327 who did not provide adequate data. They were counted as continuing smokers. The main results are shown in table 3.

485-874 0 - 85 - 5

TABLE 3

Minimal intervention by family physicians

	No Advice (N=584)	Advice Only (n=675)	Advice and Nicotine Gum (n=679)
Tried to stop	36.6	46.1	61.1
Abstinent at 4 months	10.3	14.1	20.2
Still abstinent at 1 year			
Self-report	6.0	6.4	11.9
Adjusted for non-validation	3.9	4.1	8.8

Note: The results are showrr as percentages based on all subjects in each group. All comparisons between the nicotine gum and the other groups were significant at the p<.OO5 level. (Russell et al. Brit Med J, 287:1782-1785, 1983). Copyright 1983, The British Medical Association.

As with the clinic based studies, use of the gum in a family physician setting doubled the success rate achieved by advice alone. Further analyses, which can be found in the full report (Russell et al. 1983b), showed that the offer and availability of the gum achieved its overall effect in three ways. It motivated more smokers to try to give up smoking (p<.OOl), it increased the success rate among those who tried (p<.05), and reduced the relapse rate among those who had stopped at 4 months (p<.05) .

The greater efficacy of Group 3 intervention was achieved despite the fact that the results are based on all subjects and that only 53% actually tried the gum. There was a complex relation between initial cigarette consumption, gum use, and success rate. Heavier smokers tended to use more gum, and heavy gum use was associated with a higher success rate. In particular, the self-selected subgroup (8% of Group 3) who used more than a box of gum (105 pieces) had a long-term success rate of 34.6% (24% after adjustment for failed validation). These successes had had an initial cigarette consumption prior to intervention averaging 23 cigarettes per day compared with 13 and 12 per day for the successes in Groups 1 and 2 respectively and 12 per day for the remaining successes in Group 3.

An 8.8% success rate may at first seem unimpressive compared with rates of 40% obtained with intensive methods at specialised clinics. It may help to get it in perspective. We calculated that if the 34 physicians in this study were to continue the Group 3 procedure routinely, the net yield of long-term ex-smokers (over and above the spontaneous cessation rate in the non-intervention controls) mold average about 38 per physician in the first year. Extrapolated to all 28,000 family physicians in Britain, and assuming they could achieve similar results, the initial yield would be around 1 million w-smokers a year, and possibly similar results could be obtained for several ensuing years.

Finally, although higher success rates could undoubtedly be achieved if physicians had the time for more intensive support and follow up, we suggest that the overall yield of ex-smokers would be greater if physicians allocated their time by spending a little of it with many smokers rather than a longer time with a few. Ideally, physicians should know, by enquiring if necessary, the current smoking status of every patient they see, advise all cigarette smokers to stop, and offer nicotine gum and an instruction booklet to all those who want to stop but have little confidence in being able to succeed without help. Such activity by physicians could achieve more than most other approaches to smoking cessation.

PRACTICAL ASPECTS OF GUM USE

Success rates achieved with the use of nicotine chewing gum depend on many factors, including the degree of motivation and dependence of clients, the intensity of psychological support in the short term, and in the longer term the degree of care given to follow-up. However, one factor is essential if the gum is to be used successfully in any setting. This is adequate information on what the gum will and will not do, and careful instruction on its use. As mentioned previously, the gum is at best a partial substitute for cigarettes and does not provide as much positive satisfaction. It follows that it is a treatment aid rather than a complete treatment. Smokers who approach it naively, hoping, as many do, that it will somehow magically stop their smoking without the need for any effort on their own part, are inevitably disappointed and may wrongly conclude that the gum has nothing at all to offer. It is therefore vital that clients be made aware of the positive and negative aspects of the gum in order to gain maximum benefit from its use. The failure of a recent multicentre trial of nicotine chewing gum to achieve even a placebo effect may reflect among other things inadequate attention to the crucial aspects of subject instructions (British Thoracic Society 1983; Jarvis and Russell 1983). We summarise in appendix 1 the main points that we have found helpful to communicate to clients.

Management of treatment with nicotine gum is relatively straightforward. The main issues are firstly whether all patients need the gum, and secondly whether long-term dependence on it is a matter for serious concern. Motivation to give up cigarettes is a prerequisite for success, and it is sensible to seek evidence of this in serious unaided attempts to quit before considering the offer of nicotine chewing gum. Light smokers are more likely than heavy to stop without any formal help, but present evidence suggests that their success rates, like those of heavy smokers, are enhanced by use of the gum. The main point to resolve therefore should be whether the client's history suggests that dependence as opposed to lack of motivation has been the main block to achieving smoking cessation.

Most people do not find it difficult to stop using the gum, but a small minority do become dependent on it and may continue to use it for a year or longer. While long-term use of the gum should be discouraged, both because continuing dependence on nicotine increases the risk of relapse to smoking and because of possible health risks of gum use per se, in our view it is not advisable to refuse to continue to prescribe to a client who is not smoking. This is almost guaranteed to produce relapse to smoking, which is far more harmful to health. We summarize in appendix 2 the main issues of treatment management.

THEORETICAL IMPLICATIONS

Like most new treatments, nicotine chewing gum given with enthusiasm no doubt has a strong placebo effect. Some people dismiss this quality with scorn. In our view, this is mistaken. As a principle, a safe placebo may be turned to better use than an active treatment that carries a risk. Placebo response is a valid and potentially useful psychological effect. It would seem preferable in treatment situations to view it as an asset to be used positively to enhance results rather than negatively as a reason for undermining the value of treatment.

There is no doubt, however, that nicotine chewing gum has an effect over and above that of the attention-placebo response. Besides achieving higher success rates than placebo, it significantly alleviates withdrawal symptoms, as has been discussed already. There is one further point. In our placebo-controlled trial (Jarvis et al. 1982) we found that among those who were abstinent at 1 month, gum consumption (number of pieces per day) correlated with pretreatment blood nicotine concentration in the active group ($r = .48$) but not in the placebo group ($r = .17$). Pretreatment cigarette consumption, on the other hand, correlated with gum use in the placebo group ($r = .47$) but not in the active gum group ($r = .ll$). These findings were statistically significant and point to different processes underlying the use of nicotine gum and placebo gum. The evidence for the specific efficacy of nicotine chewing gum over and above that of attention-placebo factors is summarized in table 4.

TABLE 4

SUMMARY OF EVIDENCE FOR SPECIFIC EFFICACY OF NICOTINE CHEWING GUM

1. Can produce blood nicotine levels similar to cigarette smoking.
2. Produces some pharmacological effects equivalent to smoking.
3. Inhibits ad libitum smoking.
4. Clinical efficacy: doubles long-term abstinence rates.
5. Subjectively helpful to smokers.
6. Reduces withdrawal symptoms.
7. Gum use correlates with pretreatment blood nicotine; placebo does not.
8. About 7% become dependent on nicotine gum, none on placebo.

Besides its use as an effective aid to smoking cessation, nicotine chewing gum has already proved a useful tool for research. Firstly, it has stimulated a new wave of clinical trials in which far more rigour has been applied than previously to important methodological issues such as biochemical validation and success criteria. Only recently, for example, has a clear distinction been made between abstinence at 1 year follow-up and lapse-free abstinence throughout the year.

Secondly, and more importantly, its effect compared with placebo in enhancing smoking cessation success rates, in alleviating withdrawal symptoms, and in inhibiting ad libitm smoking has provided new evidence for the role of nicotine in smoking.

SUMMARY AND CONCLUSIONS

In our view, nicotine chewing gum is the most significant single advance achieved so far in the whole field of smoking cessation. It is the only treatment that has yet been shown to have a specific effect over and above that of attention-placebo factors, and this has been demonstrated repeatedly by several research groups in different countries. It is suitable for use as an adjunct both to intensive psychological methods of treatment and to minimal and largely self-help types of intervention. In either case, it approximately doubles the success rates achieved by intervention without the use of gum. It can be administered effectively by psychologists and family physicians and no doubt by other adequately trained health professionals too.

The efficacy of nicotine chewing gum is not limited to the smokers who use it. Its incorporation into a treatment or intervention programme revitalises and maintains the morale of therapists. Until the advent of nicotine gum it has required either a research interest, financial reward, or a degree of masochism to remain for long at the sharp end of the business of helping people to give up smoking. Without a treatment capable of reducing withdrawal symptoms, therapists became drained by having constantly to give out encouragement and support to help their clients to tolerate withdrawal long enough for the difficulties gradually to wane. The rapid and tangible effect of the gum in relieving withdrawal symptoms is a boost to the morale and confidence of client and therapist alike. It is perceived as helpful even by those who fail. This encourages people who relapse to return for further therapy. A discouraging feature with other treatments has been the tendency for those who relapse to avoid contact with their therapists even to the extent of not responding to data collection at long-term follow up.

In view of its efficacy, its potential for use in many settings, its minimal demands on therapists' time, and its synergistic effect in encouraging and boosting the confidence of clients and therapists alike, it is possible that over a period of years nicotine chewing gum could have a significant impact on national smoking prevalence. But to achieve this, it is essential that it be used correctly.

APPENDIX 1

INFORMATION FOR CLIENTS ABOUT NICOTINE CHEWING GUM
AND INSTRUCTI0NS ON ITS USE

* The gum is not a magic cure. Personal commitment and effort are still necessary for success.

* The gum contains nicotine which is released as it is chewed and absorbed through the lining of the mouth.

* Absorption of nicotine is slower than from cigarettes; therefore the gum does not give the same positive pleasure as smoking.

* The gum does not stop the smoker from smoking, but it does make it easier to cope without cigarettes after stopping.

* The gum reduces craving for cigarettes and makes withdrawal symptoms less severe.

* Its use should be started after quitting cigarettes.

* Each piece should be chewed for 20-30 minutes to allow all the nicotine to be released.

* The gum should be chewed gently, with frequent pauses. Too vigorous chewing causes excessive salivation. Nicotine which is swallowed is destroyed and wasted. It may also cause indigestion.

* A piece of gum should be chewed whenever the urge to smoke is very strong. On average pack-a-day smokers use about 7 gums per day.

* The gum may taste unpleasant at first and irritate the throat. Most people adapt to it after persisting for a day or two, but it may take up to a week to get used to it.

* The gum should be used for up to 3 months before attempting to discontinue its use. Even then it is a good idea to carry a few pieces in case of emergencies.

APPENDIX 2

MANAGEMENT OF TREATMENT WITH NICOTINE CHEWING GUM

* Offer only to smokers who seriously want to quit, and have tried previously without success or have little confidence in succeeding without help, including light smokers who meet these criteria.

* Give usual guidelines on quitting - e.g., setting a target day for stopping, avoiding difficult situations, etc. The gum is probably less suitable for gradual cessation, but can be readily incorporated into most other programs.

* Give verbal and written instructions to all clients, along the lines suggested in appendix 1. In most countries a manufacturer's booklet is available.

* Discontinue the gum if the client continues to smoke. We usually warn clients who have not quit by 2 weeks that they will get no more if they have not quit by their next visit.

* Consider 4 mg gum if the client uses more than 15 per day of the 2 mg strength. (4 mg gum is not yet available in the U.S.A.)

* Encourage gradual withdrawal from gum after 3 months abstinence from smoking. Most will not find this difficult. Longer term dependence develops in a few, but may be preferable to relapse to smoking, which is the probable alternative if the gum is withheld from clients who feel they cannot do without it.

* Unwanted effects such as sore mouth, hiccups, and gastric symptoms are relatively common initially but are rarely a cause for discontinuance. They are often a sign of excessively vigorous chewing.

* In our view the following conditions are cause for caution but do not exclude use of the gum: pregnancy, peptic ulcer, coronary heart disease, hypertension, peripheral vascular disease. In all these conditions continued smoking is probably more harmful than moderate gum use.

REFERENCES

Abood, L.G.; Reynolds, D.T.; Booth, H.; and Bidlack, J.M. Sites and mechanisms for nicotine's action in the brain. Neurosci and Biobehav Reviews, 5:479-486, 1981.

British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. Brit Med J, 286:595-597, 1983.

Carruthers, M. Modification of the noradrenaline related effects of smoking by beta-blockade. Psychol Med, 6:251-256, 1976.

Dorsey, J.L. Control of the tobacco habit. Ann Int Med, 10:628-631, 1936.

Fagerstrom, K-O. A comparison of psychological and pharmacological treatment in smoking cessation. J Behav Med, 5:343-351, 1982.

Ferno, 0.; Lichtneckert, S.J.A.; and Lundgren, C.E.G. A substitute for tobacco smoking. Psychopharmacologia, 31:201-204, 1973.

Fredholm, B., and Sjogren, C. The effects of chewing Nicorette and smoking cigarettes on the heart rate and skin temperature in healthy smokers. Leo Laboratories, Div Utredningar No 260, Helsingborg, Sweden, 1979.

Gritz, E.R.; Baer-Weiss, V.; Benowitz, N.L.; Van Vunakis, H.; and Jarvik, M.E. Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. Clin Pharmacol Ther, 30: 201-209, 1981.

Hjalmarson, A.I.M. The effect of nicotine chewing gum in smoking cessation: a randomized, double-blind study. JAMA, 252:2835-2838, 1984.

Hendry, J.S., and Rosecrans, J.A. Effects of nicotine on conditioned and unconditioned behaviors in experimental animals. Pharmacol and Therapeutics, 17:431-454, 1982.

Henningfield, J.E., and Jasinski, D.R. Human pharmacology of nicotine. Psychopharmacol Bulletin, 19:413-415, 1983.

Hughes, J.R.; Hatsukami, D.K.; Pickens, R.W.; Krahn, D.; Malin, S.; and Luknic, A. Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacol, 83:82-87, 1984.

Jacobson, N.L.; Jacobson, A.A.; and Ray, J.P. Non-combustible cigarette: Alternative method of nicotine delivery. Chest, 76: 355-356, 1979.

Jarvis, M.J.; Raw, M.; Russell, M.A.H.; and Feyerabend, C. Randomised controlled trial of nicotine chewing gum. Brit Med J, 285:537-540, 1982.

Jarvis, M.J., and Russell, M.A.H. Smoking withdrawal in patients with smoking related diseases. (Letter). Brit Med J, 286:976, 1983.

Kozlowski, L.T.; Jarvik, M.E.; and Gritz, E.R. Nicotine regulation and cigarette smoking. Clin Pharmacol Ther, 17:93-97, 1975.

McNabb, M.E.; Ebert, R.V.; and McCusker, K. Plasma nicotine levels produced by chewing nicotine gum. JAMA, 248:865-868, 1982.

Nyberg, G.; Panifilov, V.; Sivertsson, R.; and Wilhelmsen, L. Cardiovascular effects of nicotine chewing gum in healthy non-smokers. Eur J Clin Pharmacol, 23:303-307, 1982.

Raw, M.; Jarvis, M.J.; Feyerabend, C.; and Russell, M.A.H. Comparison of nicotine chewing gum and psychological treatments for dependent smokers. Brit Med J, 281:481-482, 1980.

Russell, M.A.H.; Feyerabend, C.; and Cole, P.V. Plasma nicotine levels after cigarette smoking and chewing nicotine gum. Brit Med J, 1:1043-1046, 1976a.
Russell, M.A.H.; Wilson, C.; Feyerabend, C.; and Cole, P.V. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal. Brit Med J, 2:391-393, 1976b.
Russell, M.A.H.; Sutton, S.R.; Feyerabend, C.; Cole, P.V.; and Saloojee, Y. Nicotine chewing gum as a substitute for smoking Brit Med J, 1:1060-1063, 1977.
Russell, M.A.H., and Feyerabend, C. Cigarette smoking: a dependence on high-nicotine boli. Drug Metab Reviews, 8:29-57, 1978.
Russell, M.A.H.; Wilson, C.; Taylor, C.; and Baker, C.D. Effect of general practitioners' advice against smoking. Brit Med J, 2: 231-235, 1979.
Russell, M.A.H.; Raw, M.; and Jarvis, M.J. Clinical use of nicotine chewing gum. Brit Med J, 280:1599-1602, 1980.
Russell, M.A.H.; Jarvis, M.J.; Devitt, G.; and Feyerabend, C. Nicotine intake by snuff users. Brit Med J, 283:814-817, 1981.
Russell, M.A.H.; Jarvis, M.J.; Feyerabend, C.; and Ferno, 0. Nasal nicotine solution: a potential aid to giving up smoking? Brit Med J, 286:683-684, 1983a.
Russell, M.A.H.; Merriman R.; Stapleton, J.; and Taylor, W. Effect of nicotine chewing gum as ah adjunct to general practitioners' advice against smoking. Brit Med J, 287:1782-1785, 1983b.
Schneider, N.G.; Jarvik, M.E.; Forsythe, A.B.; Read, L.L.; Elliott, M.L.; and Schweiger, A. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. Addictive Behaviors, 8: 253-261, 1983.
Schneider, N.G., and Jarvik, M.E. Nicotine vs. placebo gum in the alleviation of withdrawal during smoking cessation. Addictive Behaviors, 9:149-156, 1984.
Stoleman, I.P.; Goldfarb, T.; Fink, R.; and Jarvik, M.E. Influencing cigarette smoking with nicotine antagonists. Psychopharmacologia, 28:247-259, 1973.
West, R.J.; Jarvis, M.J.; Russell, M.A.H.; Carruthers, M.E.; and Feyerabend. C. Effect of nicotine replacement on the cigarette withdrawal syndrome. Brit J Addict, 79:215-219, 1984.

ACKNOWLEDGEMENT

We thank the Medical Research Council for continued support over many years.

AUTHORS

M.A.H. Russell, FRCP, FRCPsych. Psychiatrist
M.J. Jarvis, MPhil. Clinical Psychologist

Addiction Research Unit
Institute of Psychiatry
The Maudsley Hospital
London SE5 8AF, England

Psychological and Pharmacological Approaches to Smoking Relapse Prevention

Sharon M. Hall, Ph.D., and Joel D. Killen, Ph.D.

This paper reports data from two studies which examined the effects of smoking treatments combining psychological and pharmacologic treatment methods. Nicotine chewing gum (Nicorette) was used as a pharmacologic aid to help achieve nonsmoking and maintain abstinence. Aversive smoking procedures were used to produce rapid cessation. Cognitive behavioral skills training was included to help subjects develop strategies for identifying and coping with high risk episodes.

NICOTINE CHEWING GUM: A PHARMACOLOGIC THERAPY

The use of nicotine gum as a therapeutic agent is based on the assumption that smokers smoke for nicotine. The evidence supporting nicotine as the dependency-producing agent is suggestive but inconclusive. The dependency premise has led to proposals of nicotine regulation or "titration." That is. it has been assumed that smokers. once dependent, regulate nicotine through relatively stable patterns of self-administration. Data supporting the nicotine regulation model come mostly from experiments showing variation in smoking rates accompanying experimental manipulation of nicotine levels (for example, e.g., Mangan and Golding, 1978; Herning et al. 1981). However, the regulation in most studies is imprecise. Some investigations. especially those correlating nicotine yield and nicotine blood levels, have failed to demonstrate a regulation effect (Kumar et al. 1977).

Initial trials with nicotine gum conducted in Great Britain and other European countries produced mixed results. Russell et al. (1976) compared 2 mg nicotine chewing gum with placebo in a double-blind cross-over trial during which 43 smokers were either smoking "as inclined" or were attempting cessation. Use of the gum signficantly reduced smoking during the ad lib period, but differences between the two conditions disappeared when subjects attempted to quit smoking. At 6-month followup, Puska et al. (1979) found 35% abstinence for nicotine gum treatment subjects and 25% for placebo. Malcolm et al. (1980) found 23% abstinence for gum treated subjects, 5% for placebo, and 14% for a no-drug control. Recent studies reported by Russell have produced higher abstinence rates, probably due to improvements in the formulation of the gum and to better instructions in its use. One year COH_b validated abstinence rates

of 38% have been reported (Russell et al. 1980). These may be increased to 67-68% for subsample which continue to use the gum for at least four months (Russell et al. 1980; Wilhelmson and Hjalmarsson 1980).

However, at least one recent placebo-controlled trial has failed to demonstrate an effect for the active gum (British Thoracic Society 1983). and two others reported failures to maintain initial significant differences at 1-year assessments (Fagerstrom 1982; Fee and Stewart 1982). a negative result replicated in a sample from the United States (Schneider et al. 1983).

ADVANCED PSYCHOLOGICAL TREATMENTS

Multicomponent psychological interventions represent "state-of-the-art" efforts in psychosocial approaches to smoking cessation the relapse prevention (e.g.. Hall 1984). Treatments typically combine aversive smoking strategies to produce quitting with behavioral skill training. The skill training gives clients skills to successfully overcome high risk situations.

Results from controlled investigations of multicomponent programs have been mixed. Although some have reported 12-month abstinence rates above 50% (Delahunt and Curran 1976; Lando 1977), the data from most of these studies are less than persuasive. Rates are either lower (e.g., Danaher 1977). or they are based on self-reported abstinence without biochemical verification.

COMBINING PSYCHOLOGICAL AND PHARMACOLOGICAL APPROACHES

Most investigators agree that both psychological and pharmacologic factors maintain smoking (Jaffe and Kanzler 1979). Therefore, procedures enabling quitters to cope with the psychological factors precipitating relapse combined with pharmacological management of withdrawal symptoms may enhance long-term treatment outcomes. In one such trial. Fagerstrom (1982) reported a 12-month abstinence rate of 49%.

The two trials reported in this paper combined nicotine gum with similar multicomponent psychological interventions. The studies were designed and executed independently. One was Implemented at Stanford University (Killen), the other at the University of California, San Francisco (Hall).

THE STANFORD TRIAL

Sixty-four subjects were assigned to one of three maintenance treatment conditions: (1) nicotine gum (n=22); (2) skills training (n=20); (3) combined. The latter included gum plus skills training (n=22). Abstinence was assessed at 6 and 15 weeks and 10.5 months following cessation. Expired air carbon monoxide levels were measured at all three points. Serum thiocyanate levels were collected at 6 weeks.

Subjects

Subjects met the following criteria: (1) did not present cardio-vascular cr pulmonary disease symptoms; (2) were not pregnant; (3) paid a 50 dollar deposit; and (4) obtained physician's consent to participate. Subject characteristics are presented in table 1.

TABLE 1

The Stanford Trial - Demographics

Mean number of cigarettes per day	31.7
Mean age	44.1
Mean number of years smoked	23.8
Mean (SD) expired air CO (PPM)	28.2 (12.5)
Mean (SD) blood cotinine (NG/ML)	192.9 (100.0)
Mean (SD) serum thiocyanate (UMOL/L)	165.9 (53.1)

Cessation Phase

A 7-week treatment program consisting of cessation and maintenance phases was developed. The cessation phase occurred during week 1. Maintenance training was conducted during weeks 2-7.

All subjects participated in the cessation phase, designed to produce rapid quitting. Therapists met with participants in groups of 10-12 in four consecutive 1.5-hour sessions. All smoking was expected to cease after the third session so that subjects would have achieved abstinence for 24 hours at session four.

During the first hour of each session, a four-step skills training procedure was used to help participants develop strategies for coping with the multiple determinants of smoking. In Step 1. self-efficacy scales developed by Condiotte and Lichtenstein (1981) were used to target high-risk situations. In Step 2, therapists led group members in a discussion of potentially effective coping strategies. In Step 3, therapists demonstrated how strategies for selected target situations might be implemented. In Step 4. participants rehearsed responses specific to personal high-risk situations in front of the group. Therapists and group members provided feedback following each rehearsal.

During the final 30 minutes of each session participants engaged in an aversive smoke holding procedure. Imagery training with home practice was used with smoke holding to promote more potent, self-regulated use of aversion effects.

Maintenance Phase

Condition 1: nicotine gum. Subjects in this condition used nicotine gum (2 mg) for 7 weeks. Nicotine gum was begun on day 1 of the cessation phase. Participants were informed that-a variety of psychophysiological withdrawal symptoms accompany cessation and may increase the chance of relapse. They were instructed to chew nicotine gum at each occurrence of an urge, craving, or other symptom; they were told that symptoms would diminish within 10 to 15 minutes of onset. Participants were also told that the gum was only viewed as an adjunct to cessation, and that skill development and practice were essential to continued abstinence. They were instructed to reduce gum usage beginning in week 3 in order to terminate gum use completely at the end of treatment. Gum was not available beyond week 7.

During the maintenance phase, participants in Condition 1 attended a drop-in clinic for 20 minutes once a week beginning in week 2. At each session participants received new gum supplies if desired and returned unused portions of gum allotments distributed at the previous session. Carbon monoxide levels were measured and self-regulatory efficacy scales were completed.

Portions of the $50 deposit were returned for attending weekly sessions.

Condition 2: skills training. Participants in Condition 2 met in small, therapist-led groups during weeks 2 and 3 for additional skills training designed to strengthen nonsmoking skills. Nicotine gum was not administered.

In weeks 4-7 they directed their own maintenance program and received performance feedback during weekly drop-in clinic sessions. Participants used efficacy scales to target high-risk situations and wrote treatment plans detailing the (a) problem situation; (b) appropriate coping strategies; (c) change plan implementation procedures; and (d) outcomes. Portions of the deposit were returned for completion of weekly homework assignments.

Condition 3: combined. During the maintenance phase, participants in Condition 3 received the skills training program developed for those in Condition 2 (ST). They also began; nicotine gum on day 1 and discontinued use at the end of treatment (week 7).

RESULTS

Abstinence rates are presented in table 2.

At 6 weeks, the rate for the combined group was significantly higher than the rate achieved by the skills training condition only format

TABLE 2

Stanford Trial - Abstinence Rates

	NG (n=22)	ST (n=20)	NG+ST (n=22)
6-week followup			
N	14	11	19
% Quit	64	55	86
15 week followup			
N Quit	11	9	16
% Quit	50	45	73
10.5 month followup			
N Quit	5	6	11
% Quit	23	30	50

(ST) (X^2=3.63, p<.05, one-tailed), but not different from the gum only format (NG). At 10.5 months, differences between the gum formats were not significant at (p<.O5) but were in the predicted direction (X^2=2.46, p<.10, one-tailed). Carbon monoxide values were used to verify self-report: at each assessment. Thiocyanate was used to verify reports at 6 weeks. Ninety percent agreement was obtained between biochemical measures.

Withdrawal Symptoms

A Tobacco Withdrawal Scale, developed by Bachman (unpublished) was used to assess the frequency and severity of withdrawal symptoms associated with cessation. Subjects rated the severity of each of 24 symptoms on a scale ranging from 0 (no symptom) to 4 (extremely severe). Withdrawal symptoms were collected daily during weeks 2-4. At week 3. gum users reported significantly less severe symptoms t(48)=2.39, (p<.O5). Differences at weeks 2 and 4 were not significant but in the predicted direction.

Physical Dependence Predictors

A stepwise logistic regression analysis was conducted to examine the utility of seven factors (Fagerstrom Tolerance Questionnaire, reported cigarette consumption, withdrawal symptom severity, urge severity, cotinine, expired-air carbon monoxide and serum thiocyanate) in predicting resumption of smoking. Urge severity accounted for about 14% of the relapse variance (X^2=10.93,p<.009) at the 15-week followup. Symptom severity accounted for about 3% of

the variance (X^2=3.95,p<.05). Suprisingly. cotinine failed to predict relapse at any assessment.

Side Effects of Gum Use

Most users reported some side effects, but only three discontinued use due to personal discomfort. Table 3 presents the most frequently reported side effects.

TABLE 3

The Stanford Trial - Reported Side Effects

Side Effect	Percent Reporting
oral soreness	
hiccups	32
nausea	11
lightheadedness	20
mouth sores	14
jaw muscle ache	36
appetite loss	9
headache	23
heartburn	5

THE UNIVERSITY OF CALIFORNIA - SAN FRANCISCO TRIAL

Subjects

Subjects were 120 smokers who attended an orientation meeting and (1) did not have cardiovascular or pulmonary disease; (2) were not pregnant; (3) were between the ages of 21 and 55; (4) paid a $75 deposit; and (5) obtained physicians' concurrence about their health status. Demographic and smoking characteristics of these subjects at pretreatment are in table 4.

Subjects were assigned by order of entrance into treatment to one of three treatment conditions. These were nicotine gum in a low contact group, entensive behavioral, or combined.

All subjects were told to stop smoking on the first day of treatment and were precautioned against smoking outside the sessions thereafter. All meetings lasted 75 minutes.

TABLE 4

UCSF Trial - Sample Description (N=l20)

		N	%
SEX:	Male	64	53
	Female	56	47
Treatment Completion:			
	Treatment Completers	114	95
	Dropouts	6	3
Years Smoked:	l-5 Years	5	4
	6-10 Years	15	13
	11-20 Years	52	46
	>20 Years	42	37

Pretreatment Blood X = 186.55
Cotinine Level SD = 92.94
(NG/ML) Range = 15-469
AGE X = 38
SD = 7.6
RANGE = 24-56

Intensive Behavioral Treatment

This treatment was modeled on that studied earlier in the senior author's laboratory. In that trial, it produced 50% abstinence rate at 6 months. and 39% at 1 year (Hall et al. 1982). The treatment had two phases, a quitting phase and a relapse prevention phase. The quitting phase consists of eight aversive smoking sessions held during the first 3 weeks. Subjects puffed and inhaled every 30 seconds. Videotape feedback of the smoking sessions was used to provide negative images for the smoker to use when tempted to smoke outside the session. Carbon monoxide feedback was given before and after each treatment session, to emphasize the physical effects of smoking.

The relapse prevention phase had three components. These were relaxation training, smoking situation training, and structured feedback. Subjects were taught a modification of Benson's (1974) relaxation method. They made a commitment to use this technique or another of their choosing to combat feelings of tension and irritability. Subjects role-played typical relapse situations and learned ways of rethinking responses to urges. Structured feedback consisted of paper and pencil exercises with group discussion on the costs of smoking and the benefits of quitting. CO levels were also used as feedback during this phase of treatment.

Nicotine Gum plus Low Contact Group

Four treatment sessions were held over a 3-week period. Subjects were given detailed instructions in use of nicotine gum, including when and how to taper off the gum. During treatment sessions, use of the gum was monitored, reading materials were discussed, and individual plans to quit smoking were formulated. As part of that plan, subjects made a commitment to the group to use specific strategies. Materials presented included three booklets: a tip sheet taken from the American Cancer Society, information on the American Lung Association Tel-Med Phone line, and a magazine article on nicotine gum. Gum was available for 6 months from study start.

Combined Treatment

The combined treatment was identical to the behavioral treatment except that nicotine gum and instructions in its use were provided and gum was available for 6 months from study start.

Assessments were held at weeks 0 (pretreatment), 3 (posttreatment). 12, 26. and 52. Abstinence was verified by CO. Plasma thiocyanate analyses were used to verify abstinence at 26 and 52 weeks. Blood cotinine and Tolerance Scores were collected at pretreatment.

RESULTS

Abstinence rates are shown In table 5.

TABLE 5

UCSF Trial - Abstinence Rates

	Treatment Group		
	Low Contact (N=43)	Combined (N=41)	Behavioral (N=36)
3-Week Assessment			
N Abstinent	35	39	28
% Abstinent	81	95	78
12-Week Assessment			
N Abstinent	25	30	17
% Abstinent	58	73	47
26-Week Assessment			
N Abstinent	20	24	11
% Abstinent	47	59	31
52-Week Assessment			
N Abstinent	16	18	10
% Abstinent	37	44	28

Differences between the Combined condition and the two single modality treatment conditions considered together were significant at weeks 3 ($X^2(1)=5.00$, $p<.02$), 12 ($X^2(1)=4.50$, $p<.03$), and 26 ($X^2(1)=4.05$, $p<.04$), but not at week 52 ($X^2(1)=1.40$, $p<0.24$).

Hierarchial logistic regression indicated significant treatment condition by cotinine level interventions. For subjects above the median, differences in abstinence rates between gum and no gum conditions were significant at all assessments at week 3 ($X^2(1)=3.89$, $p<.05$, 26 ($X^2(1)$-4.71, $p<.03$), and 52 ($X^2(l)=5.31$, $p<.05$). A nonsignificant trend in the same direction was noted at week 12 ($X^2=2.97$, $p<.08$).

There were no significant differences between gum and no gum conditions for subjects below the cotinine median. Results for the Tolerance Scale followed a similar pattern, but differences between gum and no gum for subjects above the median were significant only at weeks 12 ($p<.026$) and 26 ($p<.027$). Cigarettes per day showed a similar pattern, but differences were significant only at week 26 ($p<.034$).

Abstinence rates at each assessment for both gum and no gum conditions for subjects above and below the median on cotinine are shown in table 6.

TABLE 6

Number (and Percent) Abstinent at each Assessment for Subjects High and Low on Blood Cotinine in Gum and No Gum Treatment

	Above Cotinine Median		Below Cotinine Median	
	Gum (n=37)	No Gum (n=17)	Gum (n=40)	No Gum (n=l9)
Week 3	37 (93)	13 (68)	30 (al)	15 (88)
Week 12	27 (67)	7 (37)	23 (62)	10 (58)
Week 26	21 (53)	3 (16)	18 (49)	8 (47)
Week 52	16 (40)	2 (11)	15 (41)	8 (47)

DISCUSSION

The two studies produced similar outcomes. In both, the intensive behavioral treatment combined with nicotine chewing gum produced some of the highest longer term abstinence rates ever reported,

especially in relatively early assessments. Biochemical verification of self-reported abstinence strengthens the persuasiveness of the findings.

The results suggest that nicotine gum should be combined with considerable psychological support. While the short-term performance of subjects in Killen's gum-only format was encouraging, only 23% remained abstinent at 45 weeks. Relapse rates for the other conditions were not nearly so marked. Subjects in the gum-only format may have been less prepared to cope with psychological factors, since their exposure to the behavioral intervention was brief. Hall's low contact condition did not produce nearly so sharp a relapse rate. Of these subjects, 37% were abstinent at 1 year. Several factors may have contributed to differences between the two studies, including the long period of gum availability for Hall's subjects, or the emphasis on self-reliance in the low contact groups, or the formulation of a plan and commitment to use it. It should be noted, however, that in both studies even the low contact conditions provided more support than patients will probably receive when the gum is administered as a prescription drug.

Physicians should be cautioned that mere prescription of the gum cannot be expected to produce optimal performance. Psychological and behavioral factors clearly influence outcomes and must be addressed if treatments are to produce durable results. How the gum will be combined with behavioral treatments in clinical practice is unclear, and is likely to be neglected unless considerable effort is directed to physician education. Research designed to develop and evaluate physician-administered treatments combining both nicotine and psychological interventions is clearly needed.

Controlled placebo comparison trials testing the effects of the gum and standardized psychological treatments are essential to clarify the importance of different mechanisms in the change process. Fagerstrom (1982) has reported 6-month abstinence rates of 63% and 45% for active and placebo gum combined with psychological therapy. Fee and Stewart (1982) reported posttreatment rates of 46% and 33% for active and placebo gum respectively. Given their sample sizes, the 18% difference reported by Fagerstrom and the 13% difference reported by Fee and Stewart were statistically significant.

However, the so-called placebo effect of the gum would appear to be important, since abstinence rates in both placebo conditions were respectable. Thus, as Russell notes (this volume), the placebo effect can be used to advantage. It should also be noted that significant differences between the active and placebo gums vanished at 12-month followups in both reports.

Periods of gum availability have ranged from 5 weeks (Fee and Stewart, 1982) to 1 year (Schneider et al. 1984). Research on different gum administration schedules is also needed. Russell (1980) suggested that nicotine gum be available for at least 4 months. The data are mixed, but relapse may be, in part, a function

of the effects of tobacco dependence. However, we know very little of the process by which presumed psychological and pharmacological manifestations of dependence promoted relapse (Jarvik 1979).

The Stanford and UCSF trials examined several biochemical and self-report measures of physical dependence. Previous work suggests that cotinine may be a useful measure of chronic tobacco dependence and might serve to identify those smokers most likely to relapse following smoking cessation (Hall et al. 1984b; Zeidenberg et al. 1977). Findings from Hall's study support the earlier work. Subjects above the median cotinine level did poorly without nicotine gum. Availability of the gum had little effect for subjects below the median. Killen's data showed no correlation between cotinine levels and abstinence. Reasons for differences in outcome are unclear. Blood samples were drawn in Hall's study after an 8- to 12-hour cigarette fast. Thus, the levels reported represent constant levels, unconfounded by length of time since last cigarette. This was not the case in Killen's sample, where time since last cigarette was not controlled. However, this procedural difference cannot entirely account for the differences between the two studies, since Hall et al. (1984b) used procedures similar to those of Killen in earlier work, and were able to predict outcome. In Hall's sample, cotinine was an especially good predictor when a median split was used, suggesting measurement at some points of the distribution may be more reliable than at others.

The Fagerstrom Tolerance Questionnaire was also examined in both trials. Prediction of relapse was reasonably good only in the UCSF study.

Killen also examined measures of withdrawal symptoms severity and urge severity. Reported urge severity accounted for about 14% of the relapse variance at the 15-week followup. This is one of the first studies to demonstrate a relationship between urge, strength and relapse. Although modest, the level of prediction achieved with this measure compares well with the predictive power of measures such as self-efficacy or cotinine which typically account for between 10% and 15% of the variance in treatment outcome. The results suggest that further efforts to develop measures of smoking urge may be warranted.

REFERENCES

Bachman. J. Tobacco withdrawal symptoms inventory. Unpublished, University of California, 1980.

British Thoracic Society. Comparing four methods of smoking withdrawal in patients with smoking related diseases. Brit Med J, 286:595-597, 1983.

Condiotte, M.M., and Lichtenstein, E. Self-efficacy and relapse in smoking cessation programs. J Consulting & Clinical Psychology, 49:648-658. 1981.

Danaher, B.G. Rapid smoking and self-control in the modification of smoking behavior. J of Consulting & Clinical Psychology, 2(5):1068-1075.

Delahunt, J. and Curran. J.P. Effectiveness of negative practice and self-control techniques in the reduction of smoking behavior. J Consulting & Clinical Psychology, 44:1002-1007, 1976.

Fagerstrom. K.O. A comparison of psychological and pharmacological approaches in smoking cessation. J Behavioral Med. 5:343-352, 1982.

Fee, W.M., and Stewart, J.J. A controlled trial of nicotine chewing gum in a smoking withdrawal clinic. Practitioner, 226:148-151. 1982.

Hall, S.M.; Rugg, D.L.; Tunstall, C.D.; and Jones, R.T. A comparative study. Third Annual Society of Behavioral Medicine Conference, Chicago, 1982.

Hall, S.M.; Rugg, D.L.; Tunstall, C.D.; and Jones, R.T. Preventing relapse by behavioral skill training. J Consulting Psychology, 52(3):372-382. 1984.

Herning. R.I.; Jones, R.T.; Bachman, J.; and Mines, A.H. Puff volume increases when smoking low nicotine cigarettes. Brit Med J, 283:187-193, 1981.

Jaffe, J.H., and Kanzler. M. Smoking as an addictive disorder. In: Krasnegor, N.A. (ed.) Cigarette Smoking as a Dependence Process. National Institute on Drug Abuse Research Monograph No. 23. DHEW Pub. No. (ADM) 79-800, Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979.

Jarvik, M.E. Biological influences on cigarette smoking. In: Smoking and Health: A Report of the Surgeon General. Washington, D.C.: U.S. Govt. Print. Off., DHEW Publication No. (PHS) 79-50066, 1979.

Killen, J.D.; Maccoby, N.; and Taylor, C.B. Nicotine gum and self-regulation training in smoking relapse prevention. Behavior Therapy, 15:234-248, 1984.

Killen, J.D.; Taylor, C.B.; Maccoby. N.; Fong, T.; and Bachman, J. Investigating predictors of relapse: An analysis of biochemical and self-report measures of tobacco dependence. (unpublished)

Kumar. R.; Cooke, E.C.; Lader, M.H.; and Russell, M.A.H. Is nicotine important in tobacco smoking? Clinical Pharmacology and Therapeutics, 21:520-529. 1977.

Lando, H.A. Successful treatment of smokers with a broad-spectrum behavioral approach. J Consulting and Clinical Psychology, 45:361-366, 1977.

Malcolm, R.E.; Sillett, R.W.; Turner, J.A.; and Ball, K.P. The use of nicotine chewing gum as an aid to stop smoking. Psychopharmacology, 70(3):295-296. 1980.

Mangan, G.L., and Golding, J. An enhancement model of smoking maintenance. In: Thornton, R.E. (ed.) Smoking Behavior. London: Churchill, Livingston, 1978.

Puska, P.; Bjorkvist, S.; and Koskela, K. Nicotine-containing chewing gum in smoking cessation: A double-blind trial with half-year followup. Addict Behav. 4:141-146. 1979.

Russell, M.A.H. Tobacco smoking and nicotine dependence. In: Gibbons, R.J., et al. (eds.) Research Advances in Alcohol and Drug Problems, New York: Wiley and Sons, 1976.

Russell, M.A.H.; Raw, M.; and Jarvis, M.J. Clinical use of nicotine chewing gum. Brit Med J, 1559-1602, 1980.

Schneider, N.G.; Jarvik, M.E.; Forsythe, A.B., et al. Nicotine gum in smoking cessation: A placebo controlled double blind trial. Addictive Behaviors, 10:253-261.

Wilhelmson, L.. and Hjalmarsson, A. A smoking cessation experience in Sweden. Canadian Family Physician, 26:737-743, 1980.

Zeidenberg. P.; Jaffe, J.H.; Kanzler. M.; Levitt, M.D.; Langone, J.L.; and Van Vunakis, H. Nicotine: Cotinine levels in blood samples during cessation of smoking. Comprehensive Psychiatry, 18:93-101, 1977.

ACKNOWLEDGMENTS

Preparation of this manuscript and research described in it funded in part by Research Grant Number Da 03538 and ADAMHA Research Scientist Development Award Number DA 00065. both from the National Institute on Drug Abuse.

AUTHORS

Sharon M. Hall, Ph.D.
Center for Social and Behavioral Sciences
University of California, San Francisco
San Francisco, California 94143

Joel D. Killen, Ph.D.
Stanford University
Stanford, California 94305

National Institute on Drug Abuse

Research MONOGRAPH SERIES

While limited supplies last, single copies of the monographs may be obtained free of charge from the National Clearinghouse for Drug Abuse Information (NCDAI). Please contact NCDAI also for information about availability of coming issues and other publications of the National Institute on Drug Abuse relevant to drug abuse research.

Additional copies may be purchased from the U.S. Government Printing Office (GPO) and/or the National Technical Information Service (NTIS) as indicated. For the most recent monographs, stock numbers and prices may not be shown because they had not been assigned when this monograph went to press. NTIS prices are for paper copy. Microfiche copies, at $4.50, are also available from NTIS. Prices from either source are subject to change.

Addresses are:

NCDAI
National Clearinghouse for Drug Abuse Information
Room lOA-43
5600 Fishers Lane
Rockville, Maryland 20857

GPO
Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

NTIS
National Technical Information Service
U.S. Department of Commerce
Springfield, Virginia 22161

1 FINDINGS OF DRUG ABUSE RESEARCH. NCDAI out of stock
Vol. 1: GPO out of stock — NTIS PB #272 867/AS $32.50
Vol. 2: GPO out of stock — NTIS PB #272 868/AS $29.50

2 OPERATIONAL DEFINITIONS IN SOCIO-BEHAVIORAL DRUG USE RESEARCH 1975. Jack Elinson, Ph.D., and David Nurco, Ph.D., eds. NCDAI out of stock GPO out of stock — NTIS PB #246 338/AS $16

3 AMINERGIC HYPOTHESES OF BEHAVIOR: REALITY OR CLICHE? Bruce J. Bernard, Ph.D., ed. NCDAI out of stock
GPO out of stock — NTIS PB #246 687/AS $16

4 NARCOTIC ANTAGONISTS: THE SEARCH FOR LONG-ACTING PREPARATIONS. Robert Willette. Ph.D., ed.
GPO out of stock NTIS PB #247 096/AS $8.50

5 YOUNG MEN AND DRUGS: A NATIONWIDE SURVEY. John A. O'Donnell, Ph.D., et al. NCDAI out of stock
GPO out of stock NTIS PB #247 446/AS $16

6 EFFECTS OF LABELING THE "DRUG ABUSER": AN INQUIRY. Jay R. Williams, Ph.D. NCDAI out of stock
GPO out of stock NTIS PB #249 092/AS $8.50

7 CANNABINOID ASSAYS IN HUMANS. Robert Willette. Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-01151-l $5 NTIS PB #251 905/AS $14.50

8 Rx: 3x/WEEK LAAM - ALTERNATIVE TO METHADONE. Jack Blaine, M.D., and Pierre Renault, M.D., eds.
Not available from GPO NTIS PB #253 763/AS $14.50

9 NARCOTIC ANTAGONISTS: NALTREXONE PROGRESS REPORT. Demetrios Julius, M.D., and Pierre Renault, M.D., eds. NCDAI out of stock
GPO out of stock NTIS PB #255 833/AS $17.50

10 EPIDEMIOLOGY OF DRUG ABUSE: CURRENT ISSUES. Louise G. Richards, Ph.D., and Louise B. Blevens. eds. NCDAI out of stock
GPO out of stock NTIS PB #266 691/AS $22

11 DRUGS AND DRIVING. Robert Willette, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-00576-2 $5.50 NTIS PB #269 602/AS $16

12 PSYCHODYNAMICS OF DRUG DEPENDENCE. Jack D. Blaine. M.D., and Demetrios A. Julius, M.D., eds. NCDAI out of stock
GPO out of stock NTIS PB #276 084/AS $17.50

13 COCAINE: 1977. Robert C. Petersen, Ph.D., and Richard C. Stillman. M.D., eds. NCDAI out of stock
GPO out of stock NTIS PB #269 175/AS $19

14 MARIHUANA RESEARCH FINDINGS: 1976. Robert C. Petersen, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #271 279/AS $22

15 REVIEW OF INHALANTS: EUPHORIA TO DYSFUNCTION. Charles Wm. Sharp, Ph.D., and Mary Lee Brehm, Ph.D., eds.
GPO out of stock NTIS PB #275 798/AS $28

16 THE EPIDEMIOLOGY OF HEROIN AND OTHER NARCOTICS. Joan Dunne Rittenhouse, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #276 357\AS $20.50

17 RESEARCH ON SMOKING BEHAVIOR. Murray E. Jarvik, M.D., Ph.D., et al., eds. NCDAI out of stock
GPO out of stock NTIS PB #276 353/AS $29.50

18 BEHAVIORAL TOLERANCE: RESEARCH AND TREATMENT IMPLICATIONS. Norman A. Krasnegor, Ph.D., ed.
GPO out of stock NTIS PB #276 337/AS $16

19 THE INTERNATIONAL CHALLENGE OF DRUG ABUSE. Robert C. Petersen, Ph.D., ed.
GPO out of stock NTIS PB #293 807/AS $28

20 SELF-ADMINISTRATION OF ABUSED SUBSTANCES: METHODS FOR STUDY. Norman A. Krasnegor, Ph.D., ed.
GPO out of stock NTIS PB #288 471/AS $22

21 PHENCYCLIDINE (PCP) ABUSE: AN APPRAISAL. Robert C. Petersen, Ph.D., and Richard C. Stillman, M.D., eds.
GPO out of stock NTIS PB #288 472/AS $25

22 QUASAR: QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS OF ANALGESICS, NARCOTIC ANTAGONISTS, AND HALLUCINOGENS. Gene Barnett, Ph.D.; Milan Trsic, Ph.D.; and Robert Willette, Ph.D.; eds. NCDAI out of stock
GPO out of stock NTIS PB #292 265/AS $35.50

23 CIGARETTE SMOKING AS A DEPENDENCE PROCESS. Norman A. Krasnegor, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-00895-8 $6 NTIS PB #297 721/AS $19

24 SYNTHETIC ESTIMATES FOR SMALL AREAS: STATISTICAL WORKSHOP PAPERS AND DISCUSSION. Jos. Steinberg, ed. NCDAI out of stock
GPO out of stock NTIS PB #299 009/AS $23.50

25 BEHAVIORAL ANALYSIS AND TREATMENT OF SUBSTANCE ABUSE. Norman A. Krasnegor. Ph.D., ed.
GPO ouf of stock NTIS PB #80-112428 $22

26 THE BEHAVIORAL ASPECTS OF SMOKING. Norman A. Krasnegor, Ph.D., ed.
GPO out of stock NTIS PB #80-118755 $17.50

27 PROBLEMS OF DRUG DEPENDENCE, 1979: PROCEEDINGS OF THE 41ST ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. L.S. Harris, Ph.D., ed. NCDAI out of stock
GPO Stock #017-024-00981-4 $9 NTIS PB #80-175482 $37

28 NARCOTIC ANTAGONISTS: NALTREXONE PHARMACOCHEMISTRY AND SUSTAINED-RELEASE PREPARATIONS. Robert Willette, Ph.D., and Gene Barnett, Ph.D., eds. NCDAI out of stock
GPO out of stock NTIS PB #81-238875 $23.50

29 DRUG ABUSE DEATHS IN NINE CITIES: A SURVEY REPORT. Louis A. Gottschalk, M.D., et al. NCDAI out of stock
GPO Stock #017-024-00982-2 $6.50 NTIS PB #80-178882 $17.50

30 THEORIES ON DRUG ABUSE: SELECTED CONTEMPORARY PERSPECTIVES. Dan J. Lettieri, Ph.D.; Mollie Sayers; and Helen Wallenstein Pearson. eds. NCDAI out of stock
GPO Stock #017-024-00997-l $10 Not available from NTIS

31 MARIJUANA RESEARCH FINDINGS: 1980. Robert C. Petersen, Ph.D., ed.
GPO out of stock NTIS PB #80-215171 $20.50

32 GC/MS ASSAYS FOR ABUSED DRUGS IN BODY FLUIDS. Rodger L. Foltz. Ph.D.; Allison F. Fentiman, Jr., Ph.D.; and Ruth 8. Foltz.
GPO out of stock NTIS PB #8l-133746 $19

33 BENZODIAZEPINES: A REVIEW OF RESEARCH RESULTS, 1980. Stephen I. Szara, M.D., D.Sc., and Jacqueline P. Ludford, M.S., eds.
GPO Stock #017-024-01108-8 $5 NTIS PB #82-139106 $13

34 PROBLEMS OF DRUG DEPENDENCE, 1980: PROCEEDINGS OF THE 42ND ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #8l-194847 $34

35 DEMOGRAPHIC TRENDS AND DRUG ABUSE, 1980-1995. Louise G. Richards, Ph.D., ed.
GPO out of stock NTIS PB #82-103417 $13

36 NEW APPROACHES TO TREATMENT OF CHRONIC PAIN: A REVIEW OF MULTI-DISCIPLINARY PAIN CLINICS AND PAIN CENTERS. Lorenz K.Y. Ng, M.D., ed.
GPO out of stock NTIS PB #8l-240913 $19

37 BEHAVIORAL PHARMACOLOGY OF HUMAN DRUG DEPENDENCE. Travis Thompson, Ph.D., and Chris E. Johanson. Ph.D., eds.
GPO Stock #017-024-01109-6 $7 NTIS PB #82-136961 $25

38 DRUG ABUSE AND THE AMERICAN ADOLESCENT. Dan J. Lettieri. Ph.D., and Jacqueline P. Ludford, M.S., eds.
GPO Stock #017-024-01107-O $4.50 NTIS PB #82-148198 $14.50

39 YOUNG MEN AND DRUGS IN MANHATTAN: A CAUSAL ANALYSIS. Richard R. Clayton, Ph.D., and Hat-win L. Voss, Ph.D.
GPO out of stock NTIS PB #82-147372 $19

40 ADOLESCENT MARIJUANA ABUSERS AND THEIR FAMILIES. Herbert Hendin, M.D., Ann Pollinger, Ph.D., Richard Ulman, Ph.D., and Arthur Carr, Ph.D. NCDAI out of stock
GPO out of stock NTIS PB #82-133117 $13

41 PROBLEMS OF DRUG DEPENDENCE, 1981: PROCEEDINGS OF THE 43RD ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
Not available from GPO NTIS PB #82-190760 $41.50

42 THE ANALYSIS OF CANNABINOIDS IN BIOLOGICAL FLUIDS. Richard L. Hawks, Ph.D., ed.
GPO Stock #017-024-01151-7 $5 NTIS PB #83-136044 $16

43 PROBLEMS OF DRUG DEPENDENCE, 1982: PROCEEDINGS OF THE 44TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed. NCDAI out of stock
GPO out of stock NTIS PB #83-252-6927AS $40

44 MARIJUANA EFFECTS ON THE ENDOCRINE AND REPRODUCTIVE SYSTEMS. Monique C. Braude. Ph.D., and Jacqueline P. Ludford, M.S., eds.
GPO Stock #017-024-01202-S $4 NTIS PB #85-150563lAS $14.50

45 CONTEMPORARY RESEARCH IN PAIN AND ANALGESIA, 1983. Roger M. Brown, Ph.D.; Theodore M. Pinkert, M.D., J.D.; and Jacqueline P. Ludford, M.S., eds.
GPO Stock #017-024-01191-6 $2.75 NTIS PB #84-18467O/AS $11.50

46 BEHAVIORAL INTERVENTION TECHNIQUES IN DRUG ABUSE TREATMENT. John Grabowski, Ph.D .; Maxine L. Stitzer, Ph.D., and Jack E. Henningfield, Ph.D., eds.
GPO Stock #017-024-01192-4 $4.25 NTIS PB #84-184688/AS $16

47 PREVENTING ADOLESCENT DRUG ABUSE: INTERVENTION STRATEGIES. Thomas J. Glynn, Ph.D.; Carl G. Leukefeld, D.S.W.; and Jacqueline P. Ludford, M.S., eds.
GPO Stock #017-024-01180-l $5.50 NTIS PB #85-1596637AS $22

48 MEASUREMENT IN THE ANALYSIS AND TREATMENT OF SMOKING BEHAVIOR. John Grabowski, Ph.D., and Catherine S. Bell, M.S., eds.
GPO Stock #D17-024-01181-9 $4.50 NTIS PB 84-145184 $14.50

49 PROBLEMS OF DRUG DEPENDENCE, 1983: PROCEEDINGS OF THE 45TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01198-3 $12 NTIS PB 85-1515537AS $22

50 COCAINE: PHARMACOLOGY, EFFECTS, AND TREATMENT OF ABUSE. John Grabowski, Ph.D., ed.
GPO Stock #017-020-01214-9 $4 NTIS PB 85-1503817AS $14.50

51 DRUG ABUSE TREATMENT EVALUATION: STRATEGIES, PROGRESS, AND PROSPECTS. Frank M. Tims, Ph.D., ed. NCDAI out of stock
GPO Stock #017-020-01218-l $4.50 NTIS PB 85-150365/AS $17.50

52 TESTING DRUGS FOR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. Joseph V. Brady, Ph.D., and Scott E. Lukas, Ph.D., eds.
GPO Stock #017-024-01204-l $4.25 NTIS PB 85-150373/AS $16

53 PHARMACOLOGICAL ADJUNCTS IN SMOKING CESSATION. John Grabowski, Ph.D., ed.

54 MECHANISMS OF TOLERANCE AND DEPENDENCE. Charles Wm. Sharp, Ph.D., ed.
GPO Stock #017-024-01213-1 $8.50

55 PROBLEMS OF DRUG DEPENDENCE, 1984. PROCEEDINGS OF THE 46TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01242-4 $9.50

56 ETIOLOGY OF DRUG ABUSE: IMPLICATIONS FOR PREVENTION. Coryl LaRue Jones, Ph.D., and Robert J. Battjes, D.S.W., eds.
GPO Stock #017-024-01250-S $6.50

57 SELF-REPORT METHODS OF ESTIMATING DRUG USE: MEETING CURRENT CHALLENGES TO VALIDITY. Beatrice A. Rouse, Ph.D., Nicholas J. Kozel, M.S., and Louise G. Richards, Ph.D., eds.
GPO Stock #017-024-01246-7 $4.25

58 PROGRESS IN THE DEVELOPMENT OF COST-EFFECTIVE TREATMENT FOR DRUG ABUSERS. Rebecca S. Ashery, D.S.W., ed.
GPO Stock #017-024-01247-5 $4.25

59 CURRENT RESEARCH ON THE CONSEQUENCES OF MATERNAL DRUG ABUSE. Theodore M. Pinkert, M.D., J.D., ed.
GPO Stock #017-024-01249-l $2.50

IN PRESS

60 PRENATAL DRUG EXPOSURE: KINETICS AND DYNAMICS. C. Nora Chiang, Ph.D., and Charles C. Lee, Ph.D.. eds.

61 COCAINE USE IN AMERICA: EPIDEMIOLOGIC AND CLINICAL PERSPECTIVES. Nicholas J. Kozel, M.S., and Edgar H. Adams, M.S., eds.

62 THE NEUROSCIENCE OF DRUG ABUSE. Roger M Brown, Ph.D., and David P. Friedman, Ph.D., eds.

63 PREVENTION RESEARCH: DETERRING DRUG ABUSE AMONG CHILDREN AND ADOLESCENTS. Catherine S. Bell, M.S.; and Robert J. Battjes, D.S.W., eds.

U.S. GOVERNMENT PRINTING OFFICE : 1985 O - 485-874

DHHS Publication No. (ADM) 85-1333
Printed 1985