mic variables (e g , psychopathology) that may influence severity of drug dependence, much less has been directed toward examining environmental variables (e g , types of drug, schedule of reinforcement) as indicators of severity This paper reviews drug self-administration model which has been developed and refined over the last 15–20 years In this model, animals are given access to a manipulandum, and responding on the manipulandum results in drug delivery to the subject The model has been established across species (e g , rats, cats, humans), types of responses (e g , lever press, panel press), and routes of drug self-administration (e g , intravenous, oral, intragastric, inhalation) In general drugs which are self-administered by animals are the same drugs abused by humans The purpose of this paper is to examine the evidence for environmental factors as indicators of severity using the animal model of drug self-administration, and to discuss how this relates to human studies of severity of drug dependence

SYMPOSIUM

Nicotine Replacement in Tobacco Dependence Pharmacology, Therapeutics, and Policy

Monday August 31, 1987 • 9 00 a m –10 50 a m
Marriott Marquis Hotel • Empire/Hudson/Chelsey Room

Chair *Jack Henningfield,* Biology of Dependence and Abuse Potential Assessment Laboratory, MIDA Addiction Research Center, Baltimore, MD, and *Gregory Connolly,* Division of Dental Health, Massachusetts Department of Public Health, Boston, MA

PHARMACOLOGIC AND NEUROENDOCRINE BASIS OF NICOTINE REPLACEMENT, Jack E Henningfield, Ph D and Ovide F Pomerleau, Ph D Johns Hopkins University and University of Michigan

This presentation will provide an overview of recent data supporting the biologic basis for using nicotine replacement approaches to treat tobacco dependence A simple, but not entirely satisfactory, view of the dependence process entailed by the compulsive use of tobacco products is as follows when tobacco products are used as advertised by manufacturers, nicotine is delivered to the central nervous system, repeated use leads to tolerance, physiologic and behavioral dependence, treatment may be attempted in which the nicotine usually obtained by tobacco self-administration is replaced with another source to facilitate behavioral change, then the nicotine replacement is gradually removed In fact, however, the process of tobacco dependence is no less complex than dependence to opium, sedative, alcohol, or stimulant derived products Dependence to any of these substances is a confluence of pharmacologic and nonpharmacologic factors The nonpharmacologic factors include social and other non-drug environmental factors Among the pharmacologic factors, the control over behavior is also complexly mediated For instance, nicotine may serve as a positive reinforcer in its own right, its reinforcing efficacy may be sharply increased or decreased depending on situational factors such as stress and performance demands, intake of other drugs, food deprivation, and prior level of nicotine intake, nicotine may even serve as a punisher at higher dose levels and thereby restrain levels of tobacco self-administration which otherwise might occur A further complexity among pharmacologic factors is that nicotine, like other drugs of abuse, produces a cascade of neurohormonal responses which mediate many of the effects commonly ascribed simply to the taking of the primary substance Since the nicotine dose which is obtained when tobacco serves as the vehicle for delivery is easily and rather precisely regulated by the experienced tobacco user, a high degree of "fine-tuning" of neuroregulatory systems is possible Recent data suggest that the powerful control exerted by nicotine over the behavior of the tobacco user, is not simply due to the reinforcing properties of nicotine in its own right, or to the avoidance of short term withdrawal effects, but is also a function of the multitude of individually- and situationally-specific benefits in the regulation of mood, in performance enhancement, and for weight control It is plausible that the potential utility of nicotine for certain individuals is due to vulnerability factors which are either (1) common to those which may predispose individuals to other forms of drug abuse, (2) specific to nicotine, (3) are due to long term chronic exposure to nicotine beginning in adolescence or earlier (nearly 90% of cigarette smokers), or (4) represent a protracted withdrawal syndrome Recent data from a residential withdrawal study, studies of neuroendocrine effects of nicotine, and the potential utility of nicotine for therapeutic application other than as a short term tobacco detoxification agent relevant to the above described issues and will be reviewed

RECENT FINDINGS ON BEHAVIORAL AND PHYSICAL DEPENDENCE TO NICOTINE GUM Dorothy K Hatsukami, Ph D and John R Hughes, M D University of Minnesota and University of Vermont College of Medicine

Previous studies have shown that nicotine gum replacement improves smoking cessation rates, particularly when combined with behavioral treatment However, the results from double-blind placebo-controlled studies indicate that improvement of smoking cessation with nicotine gum fades over time Even the most successful nicotine gum treatment studies show smoking cessation rates no greater than 50% These results have led to the impetus to market a higher dose of nicotine gum The use of a higher dose of nicotine gum may have associated problems such as a potential physical or behavioral dependence on the gum We have conducted two studies in which these issues were examined The first study was an evaluation of the incidence of use of the gum beyond the prescribed period In addition, the incidence of withdrawal symptoms from the gum and the relationship between duration of gum use and severity of withdrawal symptoms was determined In the study, 315 smokers (seen in a family practice clinic) who wanted to stop smoking were randomly assigned to receive either placebo or 2 mg nicotine gum in a double-blind manner The smokers were instructed to chew the gum for up to three months according to Food and Drug Administration approved instructions The main findings were the following (1) The incidence of persistent gum use, that is use of gum beyond the recommended period, among all those who were prescribed gum, was 8% among placebo gum users, and was 12% for nicotine gum users (2) The incidence of persistent gum use among those who had quit smoking was 35%, whether nicotine-delivering or placebo gum had been prescribed Thus, persistent use of gum may not be solely dependent on the pharmacological properties of

the gum The results also showed that there were no significant differences in signs and symptoms of withdrawal between placebo gum and 2 mg nicotine gum The second study involved a comparison of signs and symptoms of withdrawal from placebo, 2, and 4 mg gum, and a comparison of these findings to those obtained in studies of tobacco cigarette withdrawal We also examined whether the dose of gum or severity of withdrawal subjects experienced following abstinence from gum use was a determinant of whether subjects continued to use the gum or relapsed to cigarette smoking Subjects were withdrawn from cigarettes for four days during which previously validated signs and symptom of withdrawal were measured Subjects were then randomly assigned to either placebo, 2 or 4 mg nicotine gum in a double-blind manner for a period of one month They were then withdrawn from the gum and signs and symptoms of withdrawal were measured again over the course of four days Gum was made available to subjects if they chose to continue use of gum, and follow-up was conducted at one, three and six months to determine smoking and gum use status Thus far, the results indicate that subjects experienced more severe withdrawal symptoms during cigarette deprivation that nicotine gum deprivation Interestingly, there were no differences in severity of withdrawal between those subjects who were prescribed placebo, 2 and 4 mg gum with exception of a measure of craving for tobacco No differences were found in spite the fact that we asked all subjects to chew at least six pieces of gum per day Preliminary results also showed that the dose of the gum did not predispose further use of the gum Data regarding relapse to smoking is pending In summary, the results show that among subjects who quit smoking, there is a relatively high prevalence of persistence of gum use However, this continued use may not be a simple function of avoiding signs and symptoms of withdrawal from nicotine gum or dose of the gum

OPTIMAL COMBINATIONS OF NICOTINE DOSAGE FORM AND BEHAVIORAL INTERVENTION John Grabowski, Ph D Tufts University

Tobacco dependence constitutes a prototypic form of drug dependence but also represents well the most complex form of biobehavioral and behavioral medicine disorder There is ample evidence from the behavioral pharmacology laboratory and clinic that the use of nicotine polarcrilex, gum, can effectively produce the pharmacological effects that are also obtained when tobacco cigarettes are smoked Behavioral and physiological abstinence symptoms can be reversed by readministration of nicotine in this form Maintenance of tobacco cessation can thus be assisted with this pharmacological adjunct Behavioral intervention techniques have been implemented to reduce tobacco use As in the case of nicotine polarcrilex, some advantage emerges in the maintenance of smoking cessation, even when nicotine replacement is also maintained In combination, behavioral and pharmacological strategies have proven variably effective at reducing smoking The results to date suggest that there is a need to reexamine the basic behavioral-pharmacological models and common strategies in treatment and to determine whether improved combinations of pharmacological adjuncts and behavioral intervention strategies will improve success rates A three-stage model of cessation is proposed Consideration is given to the natural history of acquisition of tobacco use, duration of treatment, optimal behavioral strategies and optimal dosage preparation forms of pharmacological adjuncts

PROBLEMS AND CHALLENGES FOR NICOTINE REPLACEMENT John D Slade, M D University of Medicine and Dentistry of New Jersey St Peters Medical Center

The basis for our knowledge of the clinical utility of nicotine replacement has depended upon studies of volunteers participating in controlled trials These settings sometimes differ from typical clinical settings in a number of ways which may have important effects on the efficacy of the nicotine replacement in clinical practice The level of motivation and expectations about therapy are obvious patient variables which may be different The interest level, understanding and support of the provider has both positive and negative influences upon the probability of achieving a stable abstinence, and these are expecteed to vary in important ways as well These issues can be specifically addressed in post-marketing surveillance programs and focused studies which consider problems such as the following Most people who try to quit fail What factors improve the chances of their making further quit attempts? Is failure after nicotine replacement more likely to lead to postponing the next quit attempt than failure after other therapies? Consideration of the over-the-counter (OTC) availability of nicotine raises additional questions about efficacy and safety, including possible increase in the use of nicotine gum by people who continue to smoke Might pharmacist prescription of nicotine provide better results than either physician prescription or OTC availability because of convenience and better follow-up? Pharmacist prescription could also form the basis of sound post-marketing surveillance, while this would be difficult with OTC marketing Other challenges for nicotine replacement include questions about nicotine maintenance versus nicotine withdrawal, and the general policy question of nicotine's regulatory status, and the possible implications of regulatory status of nicotine replacement modalities for therapeutic intervention

PUBLIC POLICY ISSUES ASSOCIATED WITH NICOTINE Gregory N Connolly, D M D , M P H Division of Dental Health, Massachusetts Department of Public Health

This presentation will discuss public policy issues associated with the promotion and sale of three types of non-smoked nicotine replacement products that have been recently developed The products include low-nicotine containing pouches of moist snuff, nicotine vapor inhalers (smokeless cigarettes or nicotine tubes), and nicotine polacrilex (gum) All of these products have been recently developed and have been marketed in different ways as nicotine replacement devices Marketing practices including product design, distribution, promotion and advertising will be reviewed, and comparisons made among the products The target audiences for the devices will also be described, and, to the extent that data are available, user demographics will be discussed Based on industry marketing strategies and trends in product use, it appears that the pouches of moist snuff have become popular among young males and serve as initiating devices into nicotine use by persons with no previ-