selected from animal data because of the limitations on using human data, mainly the difficulty of identifying sensitive endpoints with noninvasive techniques With optimal data—chronic duration, human subjects, sensitive endpoints—there will be much less uncertainty in the estimates Mathematical approaches focus either on refinements to the existing approach or modeling of the dose-response relationship Refinements under study include statistical estimation of the expected value and variability of the NOAEL, and modeling the probability distribution of the standard scaling factors Other approaches under investigation include dose-incidence and dose-severity models The selection of biologically valid dose-response models is complicated by the multiplicity of endpoints, the varying degrees of severity and the shift of toxic endpoint with dose The presentation will discuss mathematical and biologic considerations in developing models for animal data and extrapolating to humans, limitations of existing models, and utilizing human data in the models

SYMPOSIUM

Severity Issues in Substance Use Disorders
Sunday August 30, 1987 • 1 00 p m –2 50 p m
Marriott Marquis Hotel • Julliard/Imperial Room
Chair *Dace Svikis,* Johns Hopkins University

SEVERITY INDICATORS AS PREDICTORS OF NATURAL HISTORY IN TREATED ALCOHOLICS Thomas E Babor, Ph D University of Connecticut Health Center

This paper begins with a review of treatment evaluation studies with alcoholic patients The literature reveals a remarkable lack of consistency across studies in the significance of various severity indicators in predicting treatment response and natural history of alcoholism The methodological limitations of this research are discussed in terms of sampling bias, statistical artifact and failure to measure relevant variables Data from a prospective, longitudinal study of 321 alcoholics are used to illustrate the relative contributions of different types of variables to the prediction of course over a three-year period Included in an extensive battery of predictor variables are measures of familial alcoholism, psychopathology, life stress, cognitive function, psychiatric diagnoses, lifetime alcohol consumption, recent alcohol and drug use, severity of dependence, blood chemistry abnormalities, and history of institutional treatment for alcohol problems The results indicate that a variety of biological, behavioral and psychosocial indicators contribute to prediction of various outcome measures three years later Although a number of severity indicators predict outcome status, no one domain predominates The methodological and theoretical implications of these findings for alcoholism treatment research are discussed

PSYCHOPATHOLOGY AS A MEASURE OF SEVERITY Thomas McLellan, Ph D VA Medical Center, Philadelphia

This paper discusses the concept of severity and presents the available data relating drug use severity to treatment outcome in one or more forms of treatments and among different classes of drug abusers The case is presented that much of the relationship that has been demonstrated between this variable and outcome depends upon the specific definition of severity, and its relation to the particular outcome criteria measures Part of the difficulty involved in evaluating the relationship between the severity of the drug use disorder and treatment outcome is that there have been several reasonable yet different definitions of severity each involving different degrees of emphasis upon factors such as number and types of drugs used, physical dependence (i e , tolerance-withdrawal), social problems resulting from drug use, loss of control over the use, etc

INHERITANCE OF SEVERITY OF ALCOHOLISM Roy W Pickens, Ph D and Dace S Svikis National Institute on Drug Abuse and Johns Hopkins University

Previously we have shown that genetic factors are involved in the etiology of alcoholism and drug dependence Monozygotic (MZ) twins were found to be about 1 4 times more likely to be concordant for DSM-III diagnosis of Alcohol Abuse/Dependence than were dizygotic (DZ) twins In the present paper we examine the role of genetic factors as determinants of severity of alcoholism The present data were drawn from a twin study of alcoholism currently being conducted at the University of Minnesota Patients entering alcoholism treatment programs are screened to determine twin status Questionnaire and structured personal interview data are being collected on probands and cotwins to determine history of personal and family alcohol use and psychopathological symptomatology Zygosity is being determined by questionnaire items concerning pair similarity (95% accuracy), supplemented when necessary by results from blood group analyses The present report is based on preliminary analyses of questionnaire data from 132 same-sex twin pairs, where at least one member of each pair met DSM-III criteria for Alcohol Abuse/Dependence There was no significant difference in mean age and sex ratio for the 59 MZ and 73 DZ pairs In determining alcoholism severity in probands and cotwins, several measures were used The primary measure was number of pathological use indicators reported by each subject Pathological use indicators were 12 items taken from the DSM-III criteria that included loss of control over alcohol use, drinking of nonbeverage alcohol, etc Other severity measures included reported frequency and quantity of use and admission of previous "heavy" use While MZ and DZ probands reported a similar number of pathological use symptoms (mean 7 6 and 7 5, respectively), concordance rates for greater than 9 symptoms was 40 0 for MZ and 6 2 for DZ, approximately a six-fold difference Concordance rates for quantity of use (drinking at least a pint of alcohol on each drinking occasion) was 14 3 for MZ and 4 8 for DZ, approximately a three-fold difference Concordance rates for admission of previous "heavy" use was 56 0 for MZ and 24 3 for DZ, approximately a two-fold difference Only for frequency of drinking (drinking at least daily) were concordance rates comparable for MZ and DZ twins (41 2 and 44 2, respectively) These results suggest a role for genetic factors in determination of severity of alcoholism, as well as in determination of the transmission of the clinical disorder

DRUG SELF-ADMINISTRATION AS AN INDICATOR OF SEVERITY POTENTIAL Martin Iguchi, Ph D and Roland Griffiths, Ph D Johns Hopkins University, Francis Scott Key Medical Center

While considerable attention has focused upon organis-

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