It has become increasingly in vogue to state that nicotine is more addictive than heroin, cocaine and other prototypic drugs of abuse. Often used to support the claim are data such as those showing the extraordinarily high likelihood of progression to daily tobacco use following experimentation with a few cigarettes as well as the high percentage of cigarette smokers who appear addicted when compared to users of other addictive drugs. In the context of criteria for addiction or dependence presented by the World Health Organization, the American Psychiatric Association, and the U.S. Surgeon General, we present a review of several lines of evidence including patterns of use, mortality, physical dependence potential, and pharmacologic addiction liability measures. Comparative data from studies in which human and animal subjects have been permitted to self-administer either nicotine, cocaine or heroin are also reviewed. These sets of data provide a rational framework for comparing nicotine to opioids and psychomotor stimulants, and to a lesser extent, to alcohol. We conclude that nicotine is not more addicting than cocaine or heroin. We suggest that these are all highly addicting drugs for which factors such as availability, price, social pressures, regulations, and certain pharmacologic characteristics, strongly influence patterns of use, the development of dependence, and other problems.

BEHAVIORAL TREATMENT OF NICOTINE ADDICTION. Maxine Stitzer, The Johns Hopkins School of Medicine, Baltimore, MD. (Abstract not available)

CLINICAL TRIALS WITH NICOTINE REPLACEMENT THERAPIES. Dorothy Hatsukami. University of Minnesota, Minneapolis, MN.

Several studies have been conducted examining the efficacy of nicotine gum on smoking cessation treatment outcome. In general, the results show that nicotine gum is an effective treatment agent; however, the efficacy diminishes over time. Further, in physician-based trials, the results are not very promising. Treatment efficacy may be maximized by varying the dose, duration and/or route of nicotine replacement. However, only a small number of studies have been conducted examining whether these factors may improve success. Further, very limited research has been conducted examining the effects of nicotine replacement on other tobacco dependence disorders such as smokeless tobacco. This paper will discuss current and new studies examining the effects of dose and duration of nicotine replacement on treatment outcome. In addition, the results from a multicenter trial which found significant effects of a transdermal nicotine system on nicotine withdrawal signs and symptoms and treatment outcome will be covered. Finally, research on the effects of nicotine gum on smokeless tobacco withdrawal symptoms and treatment outcome will be presented.

PRIMARY REINFORCEMENT IN THE MAINTENANCE OF CIGARETTE SMOKING. Jed E. Rose and Edward D. Levin. VA Medical Center, Durham, NC.

Research on smoking cessation has increasingly focussed on pharmacological aspects of nicotine and nicotine withdrawal. However, cigarette smoking also provides a characteristic set of sensory cues. These sensory aspects of smoking are important to address in that they may be potent conditioned reinforcing stimuli linked to the actions of nicotine. The repetition of the smoking act thousands of times per year by a moderately heavy smoker leads to a strong conditioned association between the sensory aspects of smoking (the putative CS) and the pharmacological effects of nicotine (the putative UCS). Strategies for disrupting CS-UCS associations may be useful in developing more effective smoking cessation treatments. These include: counterconditioning of the CS; presenting the CS alone; presenting the CS with the UCS but pharmacologically blocking the UCS; and presenting the CS and UCS in an unconnected fashion. The role of sensory cues in alleviating craving for cigarettes is discussed, and specific techniques for duplicating relevant sensory aspects of smoking without delivering significant doses of nicotine are described. The combination of nicotine and nicotinic antagonists to block primary reinforcement and hasten extinction of conditioned reinforcement is also considered.

NICOTINE AS A TREATMENT FOR MEDICAL AND PSYCHIATRIC DISORDERS. John R. Hughes and Paul A. Newhouse. University of Vermont, Burlington, VT.

Nicotine is one of the major neurotransmitters; thus it is likely to have effects on medical and psychiatric diseases independent of its role in smoking dependence. This presentation reviews several possible therapeutic roles for nicotine therapy. Parkinson's disease is less prevalent in smokers and some positive therapeutic effects of nicotine in Parkinsonism have been reported. Nicotine also may improve motor tics and Tourettes syndrome. Patients with Alzheimer's disease have fewer nicotinic receptors and nicotine appears to produce at least short-term benefit in Alzheimer's. Ulcerative colitis, but not granulomatous colitis, is less prevalent in smokers and patients with ulcerative colitis describe worsening of the disease with smoking cessation and improvement with relapse. The single nicotine therapy trial was negative. Depressed patients are more likely to smoke and smoking cessation may precipitate depression in subjects with a past history of depression. Whether nicotine could be used as a treatment for depression in such patients is unclear. The abovecited information on nicotine therapy is based almost exclusively on case reports; thus results are quite tentative at this time. Before scientific tests of nicotine therapy are indicated, studies of nicotine tolerance, abuse, dependence and safety in nonsmokers and ex-smokers using acute and then chronic dosing are needed.

SYMPOSIUM

Dependence Potential of Caffeine in Humans

Chair: *Stephen J. Heishman,* NIDA Addiction Research Center, Baltimore, MD.

Discussant: *Jack E. Henningfield,* NIDA Addiction Research Center, Baltimore, MD.

CAFFEINE-NICOTINE INTERACTIONS DURING NICOTINE WITHDRAWAL. David Sachs, Palo Alto Center for Pulmonary Disease Prevention, Palo Alto, CA. (Abstract not available)

SUBJECTIVE AND DISCRIMINATIVE STIMULUS EFFECTS OF CAFFEINE. Larry D. Chait. University of Chicago, Chicago, IL.

Studies of the subjective and discriminative stimulus effects of caffeine will be reviewed. Drug discrimination studies with laboratory animals indicate that the stimulus effects of caffeine show at least some drug-class specificity—in most studies theophylline, another methylxanthine, fully substitutes for caffeine, whereas stimulants from other pharmacological classes (e.g.,

d-amphetamine, nicotine) generally do not. However, cocaine and methylphenidate have also been shown in some studies to fully substitute for caffeine. In animals trained to discriminate amphetamine or cocaine from vehicle, studies have consistently found that caffeine partially substitutes for these drugs, usually producing 50–60% drug-appropriate responding. Such partial substitution was also observed in a study in which caffeine was tested in humans trained to discriminate between *d*-amphetamine and placebo. Humans have been trained to discriminate caffeine from placebo at doses as low as 10–56 mg, but to date no generalization testing with the drugs has been performed in caffeine-trained human subjects. A variety of techniques have been used to study the subjective effects of caffeine in humans, including ratings of general stimulus effects, visual analog scales, and standardized questionnaires such as the Addiction Research Center Inventory (ARCI) and the Profile of Mood States (POMS). Significant effects of caffeine on mood have been demonstrated at doses below 100 mg. In general, doses of caffeine in the range of 100–200 mg increase scores on measures indicating stimulation and vigor, whereas doses of 300 mg or higher tend as well to produce aversive symptoms such as increased anxiety and jitteriness. The profile of mood effects produced by caffeine has both similarities and differences compared with those produced by other psychomotor stimulants. The relationship between the subjective and discriminative stimulus effects of caffeine, the effects of level of habitual caffeine use on subjective response to caffeine, and other factors responsible for individual differences in subjective response to caffeine will also be addressed.

REINFORCING EFFECTS OF CAFFEINE IN HUMANS. Roland R. Griffiths and Suzette M. Evans. The Johns Hopkins University School of Medicine and The National Institute on Drug Abuse, Baltimore, MD.

This paper reviews a series of studies that have been conducted in our laboratory which have begun to characterize the reinforcing effects of caffeine in both residential and nonresidential human volunteers. Several of the studies have demonstrated unequivocally that caffeine can function as a reinforcer: Compared to coffee or capsules without caffeine, caffeine-containing coffee and capsules maintained higher levels of self-administration and were preferred in choice tests. Caffeine-containing coffee and capsules were also rated as being better liked than coffee and capsules without caffeine. Data from some studies suggest that the reinforcing effects of caffeine can be potentiated by a history of recent caffeine exposure; however, such a history is not a necessary condition for demonstrating caffeine reinforcement. Other studies have shown that both tolerance to subjective effects and withdrawal upon termination of dosing can be produced by chronic caffeine administration. Both tolerance and physical dependence provide potential mechanisms underlying the potentiation of reinforcement by recent caffeine exposure. While caffeine reinforcement has been reliably demonstrated with subjects with histories of very heavy caffeine use, studies have also documented individual differences in susceptibility to caffeine among normal subjects. There are some data showing that caffeine choice varies inversely with prestudy levels of anxiety, suggesting that trait anxiety may be useful in identifying individuals who are particularly sensitive to the aversive effects of caffeine. Other data indicate that caffeine choosers and nonchoosers show distinctly different profiles of caffeine subjective effects: 1) choosers show "positive" subjective effects of caffeine relative to placebo; 2) nonchoosers show "negative" effects of caffeine relative to placebo and tolerance develops to some of these effects with chronic caffeine administration; and 3) choosers showed "negative" effects of placebo relative to the effects of placebo in nonchoosers. The continued investigation of behavioral and pharmacological mechanisms underlying the reinforcing effects of caffeine, the most widely used behaviorally active drug in the world, should provide valuable insights into the general nature of the drug dependence process.

PHYSICAL DEPENDENCE ON CAFFEINE. Suzette M. Evans and Roland R. Griffiths. The National Institute on Drug Abuse and The Johns Hopkins University School of Medicine, Baltimore, MD.

This paper reviews a series of studies conducted in our laboratory which have examined caffeine physical dependence as manifested by a withdrawal syndrome upon termination of chronic administration. Our first study, which was conducted in residential subjects who had histories of heavy caffeine consumption, examined caffeine withdrawal by substituting decaffeinated for caffeinated coffee for 10 or more days. A withdrawal syndrome, characterized by increases in headache and fatigue, peaked on days 1 and 2 and decreased over the next 5 to 6 days. In our second study, which was conducted in subjects with experimental histories of discriminating caffeine from placebo, withdrawal was examined by substituting placebo for caffeine-containing capsules. The study showed that the incidence of caffeine withdrawal was higher, the daily dose level at which withdrawal occurred was lower (100 mg/day) and the range of symptoms experienced was broader than previously recognized. Our most recent set of studies have extended the generality of these previous observations by parametrically characterizing caffeine withdrawal in normal subjects without idiosyncratic histories of caffeine exposure. Manipulation of three parameters (maintenance dose, within-day dosing interval and number of days of chronic caffeine exposure) has been examined under conditions in which subjects received capsules containing either placebo or low to moderate doses of caffeine. Our studies to date clearly document a clinically significant caffeine withdrawal syndrome upon termination of caffeine doses at and below those habitually consumed by a large portion of the general population.

HOW CAFFEINE DEPENDENCE INFLUENCES THE DIAGNOSIS AND TREATMENT OF BEHAVIORAL DISORDERS. John R. Hughes. University of Vermont, Burlington, VT.

The most common adverse behavioral effects of caffeine are anxiety, difficulty concentrating, insomnia, restlessness and tremulousness. These effects appear at daily dosages as low as 400 mg day, a dosage that 30% of Americans consume. The degree to which tolerance to these effects occurs has not been well-tested. These effects could interfere with the diagnosis and treatment of anxiety disorders, attention deficit disorders, agitated and insomniac depressions, sleep disorders, and alcohol and drug withdrawal and intoxication. Caffeine also can interfere with the therapeutic effects of several psychiatric medications. Cessation of caffeine (e.g., upon admittance to an inpatient ward) can cause drowsiness, fatigue and headaches and thereby mimic side-effects from several psychiatric medications.

SYMPOSIUM

Drug Abuse Treatment: Integration of Behavioral and Pharmacological Approaches