behavioral sensitization to ETOH's stimulant-like effects in mice, rat studies to date have shown no such sensitization. In fact, given the opportunity, rats will develop tolerance to the rate-increasing or stimulant effects of low dose ETOH treatments, whereas mice will not. Genetic and cross-species limitations have been proposed for this difference. In sum, during the process of tolerance development in the operant situation, rats apparently "actively" learn to compensate for the ETOH-related decrease in reinforcement delivery associated with performance disruptions under schedules of reinforcement sensitive to both the rate-increasing and rate-decreasing effects of ETOH. Additionally, this tolerance to ETOH's disruptive effects appears to subsequently reduce ETOH's usual negative hedonic valence, thereby enhancing its "net" reward properties.

BEHAVIORAL FACTORS INVOLVED IN CONTINGENT TOLERANCE TO BENZODIAZEPINES (BZ). Christine A. Sannerud. NIDA-Addiction Research Center, Baltimore, MD.

The present studies were conducted to evaluate the interactive role of behavioral variables with drug administration in the development of tolerance to benzodiazepine agonists. The first study evaluated the role of behavioral variables in the development of tolerance to the sedative effects of chlordiazepoxide (CDP) and the effect on sensitivity to acute administration of other BZ and non-BZ drugs. Rats received CDP either before (PRE) or after (POST) exposure to the daily experimental session. Large group differences were seen in the rate and degree of tolerance development to CDP. Group PRE showed 3- or 4-fold shifts to the right in the weekly CDP dose-response curves, 10-fold rightward shifts in the midazolam dose-response curves, slight sensitivity to flumazenil, 10-fold increased sensitivity to FG 7142, and cross-tolerance to pentobarbital. Group POST showed no tolerance to CDP, no change in flumazenil, but a 10-fold increased sensitivity to FG 7142. Several ongoing studies are further characterizing the specific behavioral contributions and are evaluating the biochemical correlates underlying CDP contingent tolerance. A second study evaluated the ability of behavioral variables to modify the development of tolerance to the discriminative stimulus (DS) effects of midazolam (MDZ). Rats were trained to discriminate MDZ from no drug in daily sessions consisting of multiple discrete 20-min trials. Tolerance developed to the DS effects of MDZ when it was given while training was suspended: at week 4 chronic MDZ produced 0.5–2 log-unit increases in the minimum discriminable dose of MDZ. In contrast, continued training during chronic MDZ produced no tolerance to MDZ's DS effects: at week 4 chronic MDZ the MDD of MDZ was not different than prechronic or either saline condition. Taken together these data demonstrate that chronic drug administration is necessary but insufficient to produce tolerance to a drug's effect. This emphasizes the need to evaluate interactions between behavioral variables and training contingencies to modify a drug's effects during chronic administration.

BEHAVIORAL PROCESSES IN OPIOID TOLERANCE. Ellen A. Walker and Alice M. Young. Wayne State University, Detroit, MI.

Tolerance to the behavioral effects of repeatedly administered opioids is regulated by both behavioral and pharmacological processes. This discussion will review ways in which behavioral processes can alter the development, progression, and maintenance of tolerance to the effects of opioids in a variety of behavioral paradigms. The discussion will emphasize the interactions of behavioral and pharmacological factors. Opioids exert prominent direct effects on operant behaviors, and sensitivity to such effects can diminish upon repeated drug administration. The development and magnitude of such tolerance can be modulated by a variety of behavioral influences, including prior behavioral conditions, ongoing differential reinforcement contingencies, and stimulus control processes. In addition to exerting direct effects on operant behaviors, opioids can function as discriminative or conditional stimuli, and tolerance to these functional effects can also be modulated by behavioral influences. Finally, opioids can alter reflexive behaviors, and tolerance to such effects can be modulated by behavioral processes, such as respondent conditioning, blocking, extinction, and sensory preconditioning. In each of these behavioral paradigms, the influences of behavioral processes on tolerance can, in turn, be modulated by pharmacological factors, such as agonist efficacy, maintenance dose and treatment regimen. Characterization of such multiple influences on tolerance development will require further study of both pharmacological and behavioral processes.

SYMPOSIUM

Relationship of Problem Severity to Treatment Outcome in Cocaine Dependence.

Chairs: *John Grabowski*, University of Texas Health Science Center, Houston, TX, and *Stephen T. Higgins*, University of Vermont, Burlington, VT.

Discussant: *George Bigelow*, The Johns Hopkins University School of Medicine, Baltimore, MD.

FLUOXETINE DOSE, VISIT FREQUENCY, AND SEVERITY IN COCAINE DEPENDENCE TREATMENT. John Grabowski, Ronith Elk, Howard Rhoades, Kathy Cowan, Joy Schmitz and Kimberly Kirby. University of Texas Health Science Center, Houston, TX.

The antidepressant fluoxetine is one of several medications studied for efficacy in treatment of cocaine dependence. Grabowski et al. (in preparation) describe no clear benefit of fluoxetine (retention or cocaine-free drug screens) in a double-blind study of cocaine-dependent patients. Grabowski et al. (in preparation) describe limited benefit of fluoxetine in a cocaine-using methadone-maintained opiate population, while Batki et al. (1990) reported clear benefit in an open study with a similar population. Reports of other pharmacological interventions have likewise been equivocal. There is a need to examine data from heterogeneous drug-using populations in medication trials to determine if differential effects emerge as a function of patient characteristics or treatment elements.

This double-blind placebo-controlled study examined the joint action of fluoxetine and clinic visit frequency in cocaine treatment (3 × 2). Intake reviewed major areas including drug history, medical status, psychiatric status, and social function. Patients were assigned to fluoxetine doses of 0 mg, 20 mg, or 40 mg and began a 2-week stabilization phase within 3 days. Medication effect was examined in the context of patients receiving either 2 or 5 take-home doses per week (clinic

visits either 5 or 2 times per week). A weekly counselling session addressed patient concerns and included specific behaviorally based recommendations to prevent drug use. Urine drug screens were conducted twice weekly and paper and pencil measures were obtained weekly.

Overall, preliminary analysis indicated no clear differences in drug use as a function of fluoxetine or placebo. Cocaine use continued during treatment. Drop out averaged 50% within the first 2 weeks across all groups for these cocaine-dependent patients. Differences did emerge as a function of required visit frequency. The relationship between other measures (e.g., ASI factors, DSM-III R, POMS, Beck, Drug Use History, medical status) will be described. The general issue of identification of specific treatment elements and patient characteristics will be addressed.

TREATING ALCOHOLIC COCAINE USERS WITH DISULFIRAM AND NALTREXONE. Kathleen M. Carroll,* Doug Ziedonis,* Stephanie O'Malley,* Lynn Gordon,† Tom Kosten* and Bruce Rounsaville.* *Yale University School of Medicine, New Haven, CT, and †APT Foundation, New Haven, CT.

Effective treatments for cocaine abusers who also abuse alcohol have not yet been identified. We evaluated the efficacy of established (disulfiram) and promising (naltrexone) pharmacological treatments for alcoholism in reducing both alcohol and cocaine use. In an open pilot study, eighteen subjects meeting current DSM-III-R criteria for alcohol dependence or abuse and cocaine dependence or abuse were randomly assigned to receive either disulfiram or naltrexone in conjunction with weekly individual psychotherapy. Subjects in the disulfiram group reported significantly fewer days using alcohol (4% versus 26%) and cocaine (4% versus 15%) while in treatment, and longer sustained periods of abstinence from both substances than subjects receiving naltrexone. Attrition was high in both groups, but the disulfiram-treated subjects who dropped out tended to leave treatment after several consecutive weeks of abstinence from both alcohol and cocaine, while dropouts in the naltrexone group generally did so while still using both cocaine and alcohol. Results from this study suggest that effective reduction of alcohol use may lead to corresponding reductions in cocaine use and underscore the importance of the relationship between alcohol and cocaine use.

DRUG CUE REACTIVITY AS A POSSIBLE "SEVERITY" DIMENSION IN COCAINE DEPENDENCE. Anna Rose Childress, Ronald Ehrman, Steve Robbins, Anastasia Droungas, A. Thomas McLellan and Charles P. O'Brien. University of Pennsylvania School of Medicine, Philadelphia, PA.

In general, substance abuse patients who are "more severe" (having more drug and nondrug problems) at the outset of treatment tend to have poorer treatment outcomes. But even the best predictors of treatment outcome (e.g., psychiatric severity) leave substantial outcome variability unexplained. It is possible that variables which are not conventionally measured, such as cue reactivity, may offer a "severity" dimension which can enhance prediction of treatment outcome, particularly drug use/relapse.

For several years our research group at the Penn/VA Addiction Treatment Research Center has studied the conditioned responses associated with chronic drug use on the hypothesis that some of these responses (particularly conditioned craving and arousal) may contribute to relapse in the abstinent patient. According to this hypothesis, stimuli repeatedly associated with drug administration (e.g., drug paraphernalia, the sight of drug-using friends/location, even mood states) can become classically conditioned drug "signals," capable of eliciting subjective and physiological arousal, drug craving, and, potentially, drug-seeking behavior.

We have studied the response to cocaine cues and other comparison cues in several samples of cocaine patients, most of whom were involved in treatment-outcome interventions, including samples who participated in controlled trails of putative "anti-craving" medications (e.g., amantadine, carbamazepine). The studies usually involved assessments of the response to cues prior to treatment, and again at points during treatment or at follow-up from treatment completion. Though these studies have consistently demonstrated group effects of cocaine cues on craving and arousal, there is substantial variability across individuals in the type and degree of differential responsivity to cocaine-related vs. nondrug cues. We are now performing correlative analyses to see how clinical status variables such as psychiatric severity and drug use severity correlate with magnitude of responding to drug cues and to what degree these variables (alone or in combination) can predict treatment outcomes, particularly drug use/relapse. It is possible that the degree of conditioned responding to cues is an individual patient variable which can enhance the prediction of outcome, but which is not linearly related to drug use severity.

By the time of the planned symposium, data will be available for cue reactivity assessments in samples of cocaine patients from a) a passive cue exposure intervention, b) an ambulatory psychotherapy study, c) a double-blind controlled trial of amantadine, and d) a double-blind controlled trial of carbamazepine.

A BEHAVIORAL APPROACH TO OUTPATIENT TREATMENT OF COCAINE DEPENDENCE. Stephen T. Higgins, Alan J. Budney, Florien Foerg, Warren K. Bickel and John R. Hughes. University of Vermont, Burlington, VT.

Cocaine use and dependence are significant public health problems in the United States. At least 22 million individuals in the U.S. have tried cocaine, and estimates indicate 1–2 million are dependent. Because many cocaine-dependent individuals administer the drug intravenously and engage in prostitution and other high-risk behavior, cocaine dependence presents serious problems to be resolved in curtailing the spread of AIDS. Our clinic has been developing an outpatient, behavioral treatment for cocaine dependence. The approach we have taken is based on the theoretical and empirical foundations of the experimential analysis of behavior and operant conditioning. In this presentation we will review the conceptual framework of this approach, describe the behavioral treatment we are using, and describe findings from several investigations conducted in our clinic, assessing predictors of treatment outcome. This clinic has been in existence for less than 2 years and we are still relatively early into our investigations. In our opinion, results obtained thus far are promising and illustrate the strides that can be made toward effective treatment of this disorder with a behavioral approach.