contribute to impulsive suicide attempts, as could occur, in cancer or in AIDS patients. However, past work suggested that delirium was a protective factor for suicide.

Symposium: Treatment of cocaine dependence : The state of the science

S10.01

Neurobiology and treatment of cocaine dependence

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Cocaine produces its psychoactive effects primarily by blocking presynaptic transporters for biogenic amine neurotransmitters, especially dopamine and serotonin. This has the effect of increasing activity in the brain's mesocorticolimbic dopaminergic reward circuit. There is no proven medication to treat cocaine dependence. The difficulty in developing an effective medication may derive from cocaine's direct activation of the reward circuit, its ability to generate sensitization with repeated use, and its rapid access to the brain when smoked or injected. Attempts to directly affect the reward circuit, e.g., by blocking the dopamine transporter or dopamine receptors, have not been successful. Attempts to indirectly influence the reward circuit by affecting other neurotransmitters that modulate it have been more promising. These include increasing activity of GABA (an inhibitory neurotransmitter) with baclofen, vigabatrin, or topiramate (which also decreases glutamate activity); and increasing the activity of glutamate (an excitatory neurotransmitter) with N-acetylcysteine. Also somewhat promising are agonist substitution approaches using long-acting amphetamine preparations. Medications that are promising in animal studies, but not yet tested in humans, include dopamine D3 receptor partial agonists and cannabinoid CB1 receptor antagonists. In addition to these pharmacodynamic approaches, pharmacokinetic approaches, which reduce cocaine's access to the brain or enhance its metabolism, are being studied. An anti-cocaine vaccine, which binds cocaine and keeps it from crossing the blood-brain barrier, has been safe and effective in early clinical trials. Administration of cocaine-metabolizing enzymes, e.g., butyrylcholinesterase, has been effective in animal studies, but not yet studied in humans.

S10.02

A Pet imaging study of the effects of modafinil and topiramate on brain mechanisms underlying cue-induced cocaine craving and dependence in cocaine-dependent and methadone maintained cocaine-dependent patients

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Although no pharmacological treatment has proved to be highly effective for reducing cocaine dependence, several medications have been tested over the last decade and have shown promising efficacy. Modafinil (Provigil), known as a treatment for day time sleepiness, and Topiramate (Topamax), an anti-epileptic medication also prescribed for migraine, have been shown to be effective in controlled clinical trials. We have recently started a major study utilizing Positron Emission Tomography (PET) brain imaging to monitor the progress of pharmacotherapy with modafinil or topiramate in cocaine-dependent and methadone-maintained cocaine-dependent patients. Patients will be assessed before treatment, and again after 4 weeks of pharmacotherapy. The aims of the project are to study effects of the two medications on cocaine dependence and craving, and on dopamine binding in the brain. At each assessment session, patients will undergo PET with [11C] raclopride to image the dopamine receptor DRD2. To trigger craving, patients will then be exposed to a videotape showing cocaine use; a questionnaire will be used to record their subjective responses, and a second PET scan will be performed with [18F] fluorodeoxyglucose (FDG) to image cerebral glucose metabolism during craving. This protocol was designed to enable us to study changes resulting from pharmacotherapy on dopamine binding in the brain, and on craving as reflected both in subjective measures and regional cerebral glucose metabolism. In addition, we will investigate the association between subjective measures of craving for cocaine and the level of dopamine DRD2 receptor occupancy in the brain before and after treatment. Notwithstanding the complexity of the clinical and therapeutic reality characterizing cocaine dependence, we hope to present preliminary evidence for the relative efficacy of these two promising medications in treatment for cocaine. dependence. This evidence could also elucidate the brain mechanisms underlying cocaine craving and dependence in cocaine-dependent patients.

S10.03

Cocaine rapid evaluation screening trials: Design, results, and lessons learned

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The development of medications for the treatment of cocaine dependence has been a high priority of the U.S. National Institute on Drug Abuse, National Institutes of Health. One of the main strategies has been to test available, marketed medications that affect CNS function and have a rationale for testing in a cocaine dependent population. The Cocaine Rapid Evaluation Screening Trials (CREST) utilized a randomized, controlled, parallel group, blinded methodology for comparing one or more medications against a placebo. Subjects were evaluated for a 2-4 week baseline and then randomized to a treatment group for 8 weeks. Standardized measures of outcome were used: urinary benzoylecgonine, retention, craving, depression, clinical global impressions, HIV risk behaviors. Counseling and procedures were also standardized across studies to facilitate data comparisons across drug classes. A total of 19 drugs were evaluated in 5 research clinics. Results from the studies suggested that cabergoline and reserpine should be further evaluated. Less robust effects were seen with sertraline and tiagabine although the sample size in each group was small (n= 15/group). Trials were analyzed separately and then a pooled analysis was performed. For example, an analysis of characteristics leading to at least 2 weeks of abstinence was performed. Being female with at most 5 years of prior use and being over 40, being a non-African-American male with at least four baseline uses and more than 4 years of prior use, and males with at most

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