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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three baseline uses and less than 20 years of prior use were associated with abstinence rates of 25, 30, and 42 %, respectively. One of the lessons learned was the potential value of assessing cocaine use during the baseline period prior to randomization. Another lesson learned was the use of both standardized assessments across sites and outcome measures that were also employed within individual sites. This allowed exploratory analyses within sites to determine sensitivity of outcome measures.

## S10.04

Behavioural therapies for the treatment of cocaine dependence

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Cocaine, already a significant drug problem in North and South America, has become a more prominent part of the European drug scene. No specific effective pharmacological treatment is available for cocaine addiction, although a number of medications have shown promising results. Behavioural therapies have demonstrated some effectiveness and are currently the standard type of treatment for cocaine addiction. At the present time, Cognitive-Behaviour Therapy (CBT) and Contingency Management (CM) techniques have the strongest empirical support for application with cocaine users. Cognitive behaviour approaches, such as relapse prevention, are grounded in social learning theories and principles of operant conditioning. Several randomised clinical trials have demonstrated the efficacy of cognitive-behaviour therapy (CBT) in the treatment of cocaine-dependent outpatients, particularly more severely dependent cocaine users and depressed. Contingency management approaches are based on principles of behavioural pharmacology and operant conditioning. It is a procedure that decreases the reinforcing efficacy of cocaine via the delivery of reinforcement contingent on abstinence and/or the delivery of punishment contingent on cocaine use. The two most commonly used CM strategies for treating cocaine and stimulant use disorders are voucher-based reinforcement therapy extensively investigated by Higgins and colleagues, and variable magnitude of reinforcement popularized by Petry and colleagues. CBT and/or CM possibly have additive effects when combined with pharmacotherapies.

A variety of other types of behavioural treatment like motivational therapy (MT), community reinforcement and the Matrix model have also been shown to be potent interventions for cocaine addiction. These behavioural interventions, excepted CBT and MT, are not used in France. It seems necessary to evaluate these approaches.

# Symposium: Hallucination in children and adolescents: Risk factors and treatment strategies

## S13.01

Coupling repetitive TMS with functional MRI for the treatment of drug-resistant hallucinations in children with early onset schizophrenia

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To date, there is an absence of curative treatment for very early onset schizophrenia. The antipsychotic drugs that are currently recommended have very little effect and are often badly tolerated by children. We report a case-study which results show a beneficial and significant efficacy of fMRI-guided rTMS in the treatment of pharmaco-resistant hallucinations. Moreover, rTMS applied over several cortical regions provided the means to reveal for the first time a functional dissociation between auditory-verbal hallucinations and agency impairments. These results demonstrate the efficacy of rTMS for young patients suffering from drug-resistant hallucinations but they furthermore question the physiopathology of the hallucinatory process by suggesting that agency and hallucinations may be sub served by different neural networks.

## S13.02

The effectiveness of hallucination focused integrative treatment

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**Background and Aims:** Early intervention in psychosis is considered important in relaps prevention. Limited results of monotherapies prompt to development of multimodular programmes. Presentation concerns Hallucination focused Integrative Treatment (HIT)integrates specific motivational strategies and family treatment with cognitive behavioural treatment, coping training, medication, targeted psychoeducation, crisisintervention and rehabilitation interventions. In patients with chronic schizophrenia effectiveness of HIT appeared significantly greater on subjective burden, control of voices as measured with the AHRS + occurrence of hallucinations, anxiety and depression, global psychopathology as measured with the PANSS, quality of life (WHOqol) and social funcioning (GSDS)compared to treatment as usual. Effects remained significantly better during followup (18 months).

**Method:** Presentation of HIT modules + pilot data of 14 consecutively refferred adolescents with AVH.

**Results:** Good compliance and high satisfaction in most adolescents. 65% free of AVH, substantial improvements on mastery, anxiety, interference with thinking and social functioning.

**Conclusion:** HIT is feasible in community psychiatry, appears to be an acceptable and effective early intervention in adolescents with AVH.

## S13.03

Prevalence and correlates of psychotic-like experiences and other putative antecedents of schizophrenia in children aged 9-12 years

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