On the other hand, TDM of methadone has shown its usefulness in many situations, such as a non-response due to a rapid metabolism, problems of metabolic interactions or risks of cardiac side effects induced by methadone (i.e. prolongation of the QT interval). This will be discussed in details with practical examples, and the latest data of an ongoing large pharmacogenetic study on methadone examining also the problems of cardiotoxicity of methadone will be presented.

Monday, April 4, 2005

S-41. Symposium: The Addictions: Young Researchers Symposium

Chairperson(s): Falk Kiefer (Mannheim, Germany), Andreas Heinz (Berlin, Germany)
16.15 - 17.45, Holiday Inn - Room 6

S-41-01

Videotapes exposure of delirium tremens reduce the relapse rate in alcohol dependence

A. Mihai. *University Hospital Dept. of Psychiatry, Tg. Mures, Romania*

Objective: Patients with Delirium Tremens (DT) present high relapse rate (more than 80%) in spite of detoxification (Project Match, 1999) Objective of this prospective randomized controlled trials study was to find if individually exposure to videotapes of acute phase of DT could reduce the relapse rate and the amount of alcohol intake comparing with the control group.

Methods: 60 patients with DT were videotaped in acute phase of DT, than randomized in two groups: A - with individually exposure at the videotape after recovery before discharge with explanation of symptoms by the clinician underlying the correlation with alcohol dependence - and B control group. Both groups received the same treatment of acute phase and maintenance phase, not received aversive therapy and psychotherapy. All patients were observed 6 months with monthly - manualized visits. (Project Combine) Informed consent was obtained from all patients.

Results: The results show significant differences in percent of relapse rate after after first month 0% vs 20% $p<0.001$ and also at 6 months 46,66% vs 73,33% $p=0.04$. The patients of group A experienced less severe relapses, consumed fewer units of alcohol than controls and asked for medical help.

Conclusion: Videotapes exposure of Delirium Tremens reduce the relapse rate and proved to be effective in maintaining the abstinence during 24 weeks. The results are comparable with the results of randomized control trials with acamprosate, disulfiram or psychotherapy (Tempesta, 2000; Hammarberg, 2004; Mann, 2004)

S-41-02

Cue-exposure treatment for alcohol dependent patients: Analysis of patients' characteristics associated with beneficial treatment effects

S. Löber, B. Croissant, A. Heinz, H. Flor, K. Mann. *Dept. of Addictive Behaviour, Mannheim, Germany*

Objective: Based on the concept of cue-reactivity, cue exposure treatment techniques have been advocated as potentially effective treatments of addiction and some studies have proved its efficacy compared to standard treatment or relaxation training. In contrast, our results of a controlled treatment trial comparing cue-exposure therapy (CET) to an established cognitive-behavioral treatment approach (CBT), did not support previous findings since we found no beneficial effects of CET on drinking behavior. As cue-reactivity may be necessary for extinction trials to be effective, we addressed in a post-hoc analysis the question whether there are subgroups of patients with special characteristics who show greater effects of CET than the comparison treatment.

Methods: All patients (N = 57) fulfilled the criteria of alcohol dependence (DSM-IV) and had taken part in a 3-week qualified alcohol detoxification program. Patients had been randomly assigned to CET or CBT. Based on theoretical considerations, we classified patients post-hoc according to "urge-reactivity", "psychophysiological responding" and degree of dependence. We compared relapse rates and drinking outcome in the six month following discharge.

Results: We found no beneficial effects of CET for patients who show a higher urge-reactivity or psychopyhsiological responding to alcohol cues. However, our results suggest that patients with severe alcohol dependence show better treatment outcome after CET than CBT.

Conclusion: Due to the small sample size of this subgroup of patients, these results need to be viewed with caution, but they are in line with the results of some other studies, which found beneficial effects of CET for patients with severe dependence.

S-41-03

G. Breen. *Institue of Psychiatry, Kings, London, United Kingdom*

S-41-04

What can imaging studies contribute to illuminate alcohol relapse?

J. Wrase, T. Kienast, T. Siessmeier, P. Bartenstein, D. F. Baus, N. Makris, K. Mann, H. C. Breiter, A. Heinz. *Dept. of Psychiatry, Univ. Hos, Berlin, Germany*

Objective: Animal experiments have provided evidence that the striatum, the amygdalae and medial prefrontal cortex play a predominant role in the acquisition and maintenance of drug seeking behavior. A reduced amygdala volume was found in cocaine dependent subjects. Alcohol stimulates dopamine release in the nucleus accumbens and thus reinforces substance intake. This study sought an association of dopaminergic dysfunction, cue-induced BOLD response, volumetric data, alcohol craving and relapse.

Methods: Functional magnetic resonance imaging (fMRI) and visual alcohol-associated and control cues were used to assess brain activation in abstinent alcoholics and control subjects. The radioligand [18F]DOPA and positron emission tomography (PET) was used to measure presynaptic dopamine production in the striatum and the radioligand 18F]desmethoxyfallypride [18F]DMFP for D2 receptor availability. Amygdalae volumes were assessed via segmentation-based morphometry. Alcohol craving was measured with the Alcohol Craving Questionnaire (ACQ). Patients were followed for six months and alcohol intake was recorded.

Results: We observed a close association of a low availability of D2–dopamine receptors and striatal dopamine production in the nc.accumbens, craving and increased functional activation of fronto-cortical and limbic neurocircuits during the presentation of alcohol-associated cues among abstinent alcoholics. Visual alcohol cues activated the putamen, anterior cingulate and adjacent medial

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prefrontal cortex in alcoholics compared with healthy controls. Cue-induced activation of these brain areas was pronounced in alcoholics who subsequently relapsed during the observation period. The basolateral amygdala was found to have a significantly diminished volume in relapsed subjects relative to controls and abstinent patients. Baseline craving at the time of study was stronger for relapsed than abstinent patients and correlated inversely with amygdala volume, low presynaptic dopamine production and availability of D2 dopamine receptors. No such relationships were observed in healthy control subjects.

Conclusion: Together, these observations point to a relationship between dopaminergic dysfunction, cue-induced BOLD-response, amygdala volume reduction, alcohol craving and eventual relapse into alcohol consumption. A multimodal approach to illuminate alcohol relapse seems to be promising.

S-41-05

A comparative study of young, and elderly patients suffering from "alcoholism"

H. Shahpesandy. *Dept. of Psychiatry, Palucanska, Slovakia*

Objective: The aim was to compare manifestation, and complications of alcoholism in the elderly, and young adults.

Methods: 56 elderly (E) (mean age 70.2), and 59 young (Y) patients (mean age 43), diagnosed by ICD-10, and MALT. We focused on biological markers of alcoholism, (AST, GGT, MCV), and complications of alcoholism. Statistical analysis T-test was used.

Results: The family history (FH) is positive in 17.8 % of E and 47 % of Y. AST was elevated in 53.6 % of E, and 84.7 % ($p<0.05$) of Y, GGT 60.7 % of E, and 91.5 % of Y ($p<0.05$). MCV in 60.7 % of E, and 74.5 % Y. Somatic disease were found in 60.3 % of E, and 25.7% of Y, psychiatric disorders in 34.6% of E, and 18.26% of Y. By MALT, disease of liver was found in 66% of E, and 93.2% of Y ($p<0.05$), polyneuropathy in 48.2% of E, and 5% Y ($p<0.001$), consumption of 300 ml (240 ml for women) once or more a month in 49% of E, and 76.3% of Y ($p<0.01$). MALT supports the diagnosis of Alcohol Dependence in 98.2% of E, and 100% of Y, but ICD-10, in 92.8% of E, and in 79.7% of Y.

Conclusion: Young alcoholics compared to elderly have more often positive FH, drink significantly bigger amounts of alcohol which reflects in elevation of GGT. On the other hand, elderly subjects have more somatic, and psychiatric complications.

Tuesday, April 5, 2005

S-45. Symposium: Genetic analyses of treatment-relevant phenotypes in alcohol dependence

Chairperson(s): Gunter Schumann (Mannheim, Germany), Michael Soyka (Munich, Germany)
08.30 - 10.00, Gasteig – Lecture Hall Library

S-45-01

Candidate genes in alcohol withdrawal process: A relevant phenotype?

P. Gorwood, P. Pickering, C. Boni. *CHU Louis Mourier, Colombes, France*

Objective: Alcohol withdrawal is sometimes associated with severe, life-threatening, symptoms. This may help to pinpoint genetic studies to a more homogenous subgroup of patients that could share common mechanisms.

Methods: We recruited a new sample of 120 male patients with alcohol-dependence, focusing on any lifetime symptoms of severe withdrawal. Two candidate genes were analysed, and compared with their distribution in healthy controls. Two markers in the CB1 gene were analysed, because of the role of the CB1 in the tolerance phenomenum, and one SNPs in the DAT gene, because three studies, including ours, detected a significant role of the A9 allele.

Results: The DAT gene was once again associated with delirium tremens and withdrawal seizure, both symptoms being found in excess when the A9 is present (linear trend, $p=0.08$). When our two samples are considered, the A9 allele has a much more significant role. The CB1 gene was tested for two markers, with low linkage disequilibrium, thus increasing the chance to detect an effect of different haplotypes. Nevertheless, no effect was observed, nor for the previously involved MspI polymorphism, neither for the new XcmI polymorphism.

Conclusion: The DAT gene looks involved in very severe alcohol withdrawal symptoms, with a tendency for an excess of the A9 alle ein patients with these complications. This is now the fourth study showing that the A9 allele could be involved. This does not look the case for the CB1 gene, for both markers tested.

S-45-02

NPY gene in anxiety-related phenotypes and alcohol dependence

M. Heilig. *NIAAA, Bethesda, MD, USA*

Objective: Central expression of NPY is recruited as an adaptive, opposing-process stress response, mimicked by pharmacological actions of exogenous NPY. Stress-reactions are are at the core of negative affect and relapse in alcohol dependence. We have therefore carried out human genetic studies to examine a possible association between variation in the NPY gene and alcoholism; and experimental animal studies to evaluate the potential of this system as a treatment target.

Methods: Human studies: Haplotype based analysis of 5 polymorphic markers for association with diagnosis of alcoholism, or more narrowly defined phenotypes in appr 500 alcohol dependent Swedes and appr 200 healthy volunteers. Experimental studies: Intracranial injections of the NPY-Y2 antagonist BIIE0246 to augment central NPY transmission through blockade of presynaptic receptors, combined with operant alcohol self-administration in animals with or without a history of dependence.

Results: Human: A haplotype-based association between the diagnosis of alcoholism and several of the markers was found. Association was further strengthened when restricted to late-onset alcoholics, characterized by anxious personality traits Experimental: Dose dependent and behaviorally selective suppression of alcohol self-administration by BIIE0246; markedly increased sensitivity to this effect in animals with a history of dependence.

Conclusion: Variation in the preproNPY gene contributes to susceptibility for alcoholism, in particular the late onset type characterized by anxious personality traits. Potentiation of central NPY transmission is a promising novel principle for treatment of alcoholism.

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