P46.21

Improvement in general life functioning with venlafaxine versus fluoxetine in outpatients with major depression

N. Kalin[1], C. Nemeroff[2], G. Wan[3], J. Panish[3], M. Cantillon[6]*. [1]*University of Wisconsin;* [2]*Emory University;* [3]*Wyeth-Ayerst Research;* [4]*Wyeth-Ayerst Pharmaceuticals, USA*

The objective of the study was to contrast patient-reported outcomes of patients treated with venlafaxine and fluoxetine with major depression. The study design was a six-week, double-blind, placebo-controlled flexible dose study of venlafaxine (37.5 to 225 mg/day) and fluoxetine (20 to 60 mg/day) in 297 intent-to-treat adult outpatients with major depression. Venlafaxine was significantly superior to placebo based on the total score of the General Life Functioning scale (GLF) ($p<0.01$). Patients treated with venlafaxine reported better social activity, cognitive functioning, general health perceptions, and vitality scores than placebo-treated patients, but this trend did not reach statistical significance. Venlafaxine was also significantly superior to fluoxetine on the GLF ($p<0.05$). No significant differences were found in patient-reported social activity, cognitive functioning, general health, or vitality scores among patients treated with venlafaxine or fluoxetine. Adult outpatients with major depression reported statistically significant superior improvement with venlafaxine vs. fluoxetine and placebo on the GLF. These results are consistent with three other placebo-controlled trials of venlafaxine, which demonstrate that venlafaxine improves GLF.

P46.22

Improvement in social activity level, general life and cognitive functioning with venlafaxine versus fluoxetine in inpatients with melancholic depression

D. Evans[1], C. Nemeroff[2], M. Thase[3], G. Wan[4], J. Panish[4], M. Cantillon[5]*. [1]*University of Pennsylvania;* [2]*Emory University;* [3]*University of Pittsburgh;* [4]*Wyeth-Ayerst Research;* [5]*Wyeth-Ayerst Pharmaceuticals, USA*

The purpose of this study was to compare patient-reported outcomes of patients treated with venlafaxine and fluoxetine with major depression and melancholia. The study design was a six-week, double-blind, placebo-controlled flexible dose study of venlafaxine (75 to 375 mg/day) and fluoxetine (20 to 80 mg/day) in 285 intent-to-treat adult inpatients with melancholic depression. Venlafaxine was significantly superior to placebo based on the total scores of General Life Functioning (GLF) ($p<0.01$), social activity ($p<0.001$), cognitive functioning ($p<0.01$), general health perceptions ($p<0.001$), and vitality ($p<0.05$). Venlafaxine was also significantly superior to fluoxetine on measures such as GLF ($p<0.01$), social activity ($p<0.05$), cognitive functioning ($p<0.05$), and vitality ($p<0.01$). Patients treated with venlafaxine reported better general health than fluoxetine-treated patients, but this difference did not reach statistical significance. Fluoxetine was significantly superior to placebo on only one measure, general health ($p<0.05$). Adult inpatients with melancholic depression displayed statistically significant superior improvement with venlafaxine vs. fluoxetine and placebo on the majority of the patient-reported outcome measures. This data suggest that treatment with venlafaxine may improve GLF, social activity, cognitive functioning, and vitality.

P46.23

Maternal recall bias in the obstetric histories of individuals with and at increased risk of schizophrenia

A.M. McIntosh[1]*, S.-E. Holmes[1], S. Gleeson[1], J.K. Burns[1], A. Hodges[1], M. Byrne[2], R. Dobbie[3], P. Miller[1], S. Lawrie[1], E. Johnstone[1]. [1]*University of Edinburgh, Department of Psychiatry, Scotland, UK*
[2]*National Centre for Register-based Research, Aarhus, Denmark*
[3]*Scottish Office, Edinburgh, Scotland, UK*

Background: The aetiological role of obstetric complications (OCs) in schizophrenia is uncertain1. This study sought to a) test the hypothesis that OCs are an epiphenomenon of genetic liability to schizophrenia contributing no independent additional risk and b) to clarify the role of maternal recall bias2.

Methods: Subjects at high risk of schizophrenia, and two control groups balanced for age and sex were recruited for the study. The first control group comprised subjects in first schizophrenic episodes and the second of healthy volunteers. Consenting mothers of subjects were interviewed using a standardised questionnaire for the recall of OCs, and OCs were also measured from health service records collected at the time of pregnancy and delivery. Total OCs from both sources were compared between the three groups, between high-risk subjects with and without a mother with schizophrenia, and between high risk subjects with at least partial psychotic symptoms and those without such symptoms.

Results: High-risk subjects and first-episode patients had higher rates of OCs recalled by their mother than controls, but no differences in OCs were found between groups when hospital records were used. The number of OCs recalled by mothers of the high-risk group was not related to whether the mother had schizophrenia or not, or whether the individual at high risk was displaying psychotic symptoms. Neither measure of genetic liability was related to the numbers of OCs within the high-risk group. OCs recalled by mother were however related to childhood behaviour at age 11 and 16 as measured by the CBCL.

Conclusions: Subjects at high risk of developing schizophrenia for genetic reasons have higher rates of maternally-rated OCs than controls but, they do not differ when OCs are measured by a more objective method. These results suggest that studies which rely on maternal recall alone may be susceptible to bias and may be related to abnormal behaviour in the child rather than maternal illness, family history or psychotic symptoms.

P47. Psychopharmacology – experimental

P47.01

Steroid-induced granulocytosis in neutropenic patients treated by clozapine

P. Murray[1], A. Laurent[2]*. [1]*Centre Hospitalier Spécialisé, Saint Egrève;* [2] *Department of Psychiatry, University Hospital of Grenoble, France*

Objective: Bone marrow granulocyte reserves or the marrow storage pool can be evaluated by measuring the peripheral blood neutrophil increase following the administration of corticosteroids (Cream JJ, Brit J Haemat, 1968, 15: 259–267). The authors had for goal to investigate 3 schizophrenic patients who had developed a neutropenia (defined as less than 2,000 neutrophils/mm3) when treated by clozapine, to know whether or not this resulted from a bone marrow failure.

Methods: A single intravenous injection of 200 mg of hydrocortisone was given to each subject between 8 and 9 A.M. Blood

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was sampled before and 6 hours after the injection and a WBC count was made.

Results: After administrating hydrocortisone, the increase in the neutrophil count was of at least 2,000 cells/mm3 over the pre-injection value for 2 patients; for 1 patient, the increase was of 1,900 cells/mm3.

Conclusion: Testing marrow granulocyte reserve using hydrocortisone may be helpful in sorting patients with a benign neutropenia from those with an underlying blood dyscrasia. This report must be considered as a new basis for further and longitudinal research.

P47.02

Gene expression profiling of human neuronal cells treated with antipsychotics in vitro

O. von Widdern*, O. Wirths, H. Boenisch, T. Bayer, W. Maier, M. Rietschel. *University of Bonn, Department of Psychiatry, Germany*

Clinical response and patterns of side-effects are different to treatment with "classical" (e.g. haloperidol) and novel (e.g. risperidone) antipsychotic drugs. Both show high affinity to G-protein coupled dopamine D2 receptors, which inhibit adenylyl cyclase. The further molecular mechanism of action however is not well understood yet.

This study aimed to investigate the gene regulating effects of haloperidol vs. risperidone on differentiated human neuroblastoma cells in vitro. Retinoic acid-induced differentiated SKN-SH-SY5Y cells were examined. We studied the differential gene expression profile of "treated" and "untreated" human neuronal cells after short time and long time "treatment" under different pharmacological concentrations. The differential gene expression was assessed by cDNA-microarrays containing 588 genes (ESTs). The expression of selected gene products was confirmed by RT-PCR-methods and Western blotting. Additionally the ProteinChip-technology was used for the protein expression profiling.

We identified differentially expressed genes which are involved in complex signal transduction pathways and in the dopaminergic pathway (e.g. dopamine beta-hydroxylase, MAO, COMT).

P47.03

Differential distribution of (S)- and (R)- pindolol to the rat brain

H. Yan*, T. Lewander. *Department of Neuroscience, Psychiatry, Ulleråker, Uppsala University, Uppsala, Sweden*

Pindolol, a beta blocker and a partial 5-HT1A/1B agonist, accelerates and augments the clinical efficacy of antidepressant drugs. After administration of the racemates (equal parts of two mirror image forms, enantiomers) of pindolol or propranolol in rats, we have found that the concentrations of the (S)-enantiomers are higher than the (R)-enantiomers in brain but lower in plasma. The difference between (S)- and (R)- propranolol, but not (S)- and (R)- pindolol, may be explained by a difference in plasma protein binding between the two molecular conformations. In contrast to the findings in vivo, the passage of the (S)- and (R)- enantiomers of pindolol and propranolol across endothelial cells in a BBB model in vitro were not different. Contrary to expectation, verapamil (calcium channel blocker and P-glycoprotein inhibitor) seems to inhibit the influx of pindolol and propranolol into, rather than the efflux from the rat brain in vivo. These observations indicate that studies of the transport of drugs across the BBB and potential drug-drug interactions at the level of the BBB are important areas for further exploration.

P47.04

Role for the endogenous cannabinoid system in addiction

F. Rodriguez de Fonseca[1]*, I. del Arco[1], A. Bilbao[1], B. Ferrer[1], M. Moreno[2], M. Navarro[2]. *[1]Fundación Hospital Carlos Haya; [2]Universidad Complutense, Spain*

The endogenous cannabinoid system is a new neuromodulatory system composed by several lipid transmitters (anandamide and 2-arachidonylglycerol) and G protein-coupled receptors. This system is the target of the psychoactive constituents of cannabis sativa, termed cannabinoids. The endogenous cannabinoid system has been found to be not only the neurobiological substrate of marijuana addiction, but also a relevant modulatory system of the main neurotransmitters involved in reward circuits such as dopamine, opioid peptides, GABA and glutamate. Animal models have demonstrated that drugs active at brain cannabinoid receptors are able of modulate ethanol, cannabinoid and opiate self-administration. They also modify the acquisition and expression of drug-induced conditioned place preference. Both, anandamide production and the number and efficay of cannabinoid receptors are also relevant for allostatic changes associated with drug dependence. This is reflected in the recent description of the efficacy of cannabinoid receptor antagonists as drugs capable of modify drug intake and relapse in animals with a history of dependence. All these features point to a potential role for the endogenous cannabinoid system as a new source of therapies for drug abuse.

P47.05

Apomorphine induced motility – gender and dopamine-receptor D2-genotypes

U. Havemann-Reinecke[1]*, A. Birke[1], S. Germeyer[2], C. Hiemke[2]. *Departments of Psychiatry, University of [1]Göttingen and [2]Mainz, Germany*

Objectives: In male Wistar rats apomorphine (APO), a dopamine receptor (DRD) agonist, induces individually different motility patterns being differently sensitive to neuroleptics:1. sniffers (stereotyped sniffing and increased locomotor activity) 2. lickers or 3. gnawers (stereotyped licking or gnawing and differently increased locomotor activity). The stereotypies of the sniffers and gnawers are shown to be associated with different DRD2 receptor polymorphism genotypes (Germeyer et al 2001 Brain Res in press). In this study it was examined whether locomotor activation may also correlate with these DRD2 receptor polymorphism genotypes and wether gender may influence DRD-induced stereotyped or locomotor motility, too.

Methods: APO (2mg/kg s.c.)-induced motility patterns of male and female rats were recorded and observed in an Animex-Motility Meter and genotyped to their DRD2 receptor polymorphisms by direct sequencing.

Results: In APO-induced individually different stereotyped behaviour no difference between male and female rat groups was found, but in APO-induced locomotor activation, which also did not correlate with the DRD2 receptor polymorphism genotypes.

Conclusion: DRD-induced individually different locomotor activation seems to be influenced in part by gender, but not by the different DRD2 receptor polymorphism genotypes being associated with the individually different DRD2-induced stereotyped behaviour.

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