to 9.5 and 13.9 (Mann-Whitney U Test, $p < 0.001$). Proportions of sertraline and imipramine patients with reduction of HAMA score $\geq 50\%$, and HAMA ≤ 8 were 66% versus 56% ($p < 0.001$), and 54% versus 38% ($p = 0.014$), respectively. The CGI-I response rate (was higher in sertraline group (76%) than in imipramine group (63%) ($p = 0.028$). The difference in efficacy may have been contributed to by the poorer tolerability of imipramine, leading to many dropouts for adverse event in the imipramine group (24%), relative to the sertraline group (24%) ($p = 0.004$).

Conclusion: Sertraline demonstrated greater effectiveness than imipramine in the acute treatment of depressive and anxiety symptoms in patients with non-melancholic depression

P02.231

24-WEEK PREVENTION OF RELAPSE OF GENERALIZED SOCIAL PHOBIA STUDY IN RESPONDERS TO 20-WEEKS OF SERTRALINE TREATMENT

M. Van Ameringen*, R. Swinson, J.R. Walker, R.M. Lane. *McMasters University Medical Center, Hamilton, Ontario, Canada*

Objective: Demonstrate the efficacy and tolerability of sertraline in the prevention of relapse of generalized social phobia (GSP).

Method: Fifty adult GSP patients with CGI-I much or very much improved after 20-weeks sertraline-treatment (50–200 mg/day) were randomized double-blind in 1:1 ratio to continue sertraline or switch to placebo for 24-weeks. Primary efficacy assessments; number relapsing CGI-S increase of >2 points over continuation baseline and/or discontinuation for lack of efficacy (LOE); CGI-I 1 or 2; mean score changes from continuation baseline on CGI-S, social phobia sub-scale of Marks Fear Questionnaire (MFQ), and Duke Brief Social Phobia Scale (BSPS) at study endpoint.

Results: In ITT, LOCF analyses 1/25 (4%) in sertraline group and 9/25 (36%) in placebo-switch group had relapsed at study endpoint ($p = 0.01$). Mean CGI-S, MFQ social phobia subscale, and BSPS total scores were reduced by 0.07, 0.34, and 1.86 in the sertraline group and increased 0.88, 4.09, and 5.99 in the placebo-switch group ($p < 0.03$), respectively. There was no significant difference in CGI-I responders. Eighty-eight percent of sertraline and 40% of placebo-switch patients completed the study. Discontinuations for LOE were 4% in sertraline and 28% in placebo-switch ($p < 0.05$).

Conclusions: Sertraline is effective in preventing relapse in GSP.

P02.232

IMPACT OF RESIDUAL SYMPTOMS ON OUTCOMES IN GAD: EVIDENCE FROM PLACEBO-CONTROLLED TRIALS OF VENLAFAXINE ER

J.G.C. Rasmussen*, D. Hackett, P. Meoni, C. White. *Chaldon Road Surgery, Caterham; Consulting Statistician, Basingstoke, UK Wyeth Ayerst CR&D, Paris, France*

Background: Residual symptoms are associated with greater risk of relapse and morbidity. Treatment response leaves patients with a significant burden of symptoms and impairment. The goal of treatment for chronic conditions such as GAD should look beyond treatment response to remission.

Methods: Data from 1,129 short-term (8 weeks) and 767 long-term (24 weeks) treatment responders (50% decrease in HAMA total) from placebo-controlled studies of venlafaxine ER in GAD were pooled to compare:

- the number of residual symptoms at the time of first response, and after short-and long-term treatment.
- the effect of residual symptoms on clinical outcomes

Residual symptoms were defined as anxiety symptoms (HAMA items) present at baseline with a score greater than zero at the time of first response.

Results: Regardless of treatment, responders had a similar number of residual symptoms at the time of first response. However, venlafaxine ER was associated with fewer residual symptoms overall at week 8 compared with placebo ($p < 0.001$) for all patients and those with moderate or severe anxiety (HAMA < 25 or ≥ 25) at baseline. In the long term and independent of treatment, patients who responded before week 8 had fewer residual symptoms at end-point than those who responded later. Patients who relapsed (HAMA total ≥ 18 or ≥ 20, EU and US studies, respectively) had the highest number of residual symptoms (9.1 and 9.1 for placebo and venlafaxine, respectively) and those who remitted (sustained HAMA < 8) the lowest number (7.3 and 7.5 respectively) at their first response.

Conclusions:

1. At the time of first response, patients still carry a significant burden of residual symptoms.
2. A higher number of residual symptoms is associated with a poorer outcome.
3. Venlafaxine ER is more effective than placebo in reducing residual symptoms.

P02.233

INFLUENCE OF SELECTED SSRI ON ACTIVITY OF CYTOCHROME P450 2D1 AND ARYLAMINE N-ACETYLTRANSFEARASE IN WISTAR RATS

Z. Justinova*, K. Nerusilova, E. Hadasova, M. Tomandlova[1]. *Masaryk University, Faculty of Medicine, Department of Pharmacology; [1]Department of Biochemistry, Brno, Czech Republic*

(a) Antidepressive therapy includes the use of selective serotonin reuptake inhibitors (SSRI). The elimination of the SSRI proceeds predominantly via oxidation catalyzed by cytochrome P450 in the liver. At our pre-clinical department, interactions on the drug-metabolizing enzyme level have been studied using rodent animal models. Only few data are available on the activities of cytochrome P450 2D1 (CYP2D1) and arylamine N-acetyltransferase (NAT) in Wistar albino rats after pretreatment with SSRI. In the study of Walter et al. (1996), which was performed using liver microsomes of Wistar rats after subacute (7 days) SSRI treatment, only paroxetine inhibited activity of CYP2D1, while citalopram and sertralin did not influence it and fluoxetine even showed stimulatory effect. Fluoxetine and paroxetine also inhibited NAT activity. (b) On the basis of this knowledge the present study was undertaken to characterize changes of the activity of CYP2D1 and NAT in the isolated perfused rat liver after 7 res. 14 days pretreatment of male Wistar rats with fluoxetine (20 mg/kg/day per se) or paroxetine (15 mg/kg/day per se.). Re-circulatory perfusion system by Miller (1951) was used with Williams' medium E as a perfusion medium. As model metabolic reactions was used: O-demethylation of dextromethorphan (DEM) to dextrorphan (DOR) for CYP2D1 and N-acetylation of procainamide (PA) to N-acetylprocainamide (NAPA) for NAT. (c) Concentrations of PA and NAPA was measured spectrophotometrically and those of DEM and DOR by HPLC. Capacity of the isolated liver for O-demethylation of DEM after pretreatment with both of tested antidepressants was significantly ($P < 0.01$) decreased. Fluoxetine (14 days administered) also decreased ($P < 0.01$) concentrations of NAPA in perfusate while paroxetine (14 days admin.) showed stimulatory effect on NAT activity ($P < 0.05$). (d) An inhibitory effect of tested drugs on CYP2D1 was proven. Concerning NAT: slow acetylators seem to preponderate amongst patients with psychiatric disorders. These

https://doi.org/10.1016/S0924-9338(00)94641-8 Published online by Cambridge University Press

persons might have an additional risk of higher plasma levels of arylamine drugs co-administered with fluoxetine.

Supported by the Czech Ministry of Education Project: CEZ: J07/98: 141100001

P02.234

BIPHASIC EFFECTS OF CANNABINOIDS ON LEUKOCYTE PHAGOCYTOSIS IN MICE

J. Vinklerová*, J. Nováková, A. Šulcová. *Masaryk University, Fac. Med., Department of Pharmacology, Joštova 10, 662 43 Brno, Czech Republic*

A biphasic dose dependence of cannabinoid action has been suggested more than two decades ago (Paton W.D. & Pertwee R.G.: in: Marijuana, Academic Press, 1973, 287–333; Dewey W.L.: Pharmacol Rev, 1986, 38, 151–178). We have recently shown that very low doses of the endogenous cannabinoid anandamide counteract or cause the opposite effects of higher doses on behaviour and immune function of leukocyte phagocytosis (Šulcová A. et al.: Pharmacol Biochem Behav, 1998, 59 (2), 347–352). The present study investigated further the relationship between the changes of cannabinoid receptor (CB) activity and leukocyte phagocytosis. In vivo anandamide-induced effects on leukocyte phagocytosis (stimulation at the dose of 0.01 mg/kg and inhibition at the doses of 1.0 and 10.0 mg/kg) were compared with the effects of the synthetic CB receptor agonist HU-210 (0.01 or 0.1 or 0.5 mg/kg), and antagonist AM251 (0.5 or 2.5 or 7.5 mg/kg) Phagocytic activity of mouse leukocytes was measured in chemiluminescence (CL) assay using zymosan induction of phagocytosis and luminol potentiation of CL in vitro. Female mice of the inbred strain C57BL/10 (8 weeks old) were injected prior to the assay with one daily dose of either vehicle or drugs for 7 days. The assay takes place 2 h after the last dose given in blood samples withdrawn from the retro-orbital plexus of mouse in ether anaesthesia. CL was measured every 5th minute during 1 hour. CL curves were analyzed by multifactor analyses of variance: Tukey's honest significant differences test ($p < 0.05$). Cannabinoid HU-210 effects resemble those of anandamide while stimulating leukocyte phagocytosis at the lowest dose tested, and inhibiting it at the higher doses (significantly at the dose of 0.5 mg/kg). All three doses of CB receptor antagonist AM251 used significantly suppressed leukocyte phagocytosis. These results confirm that CB receptors which have been identified on leukocytes (Bouabala M. et al.: Eur J Biochem, 1993, 214, 173–180; Galiegue S. et al.: Eur J Biochem, 1995, 232, 54–61) are active in regulation of their phagocytic function and might be important for immune changes in cannabinoid users.

Supported by the Czech Ministry of Education Project: CEZ: J07/98: 141100001

P02.235

BIOLOGICAL MARKERS OF THE HYPERKINETIC SYNDROME IN CHILDREN OF AGE 6 TO 10 YEARS

I. Paclt*, P. Uhlíková, J. Koudelová, P. Bauer, M. Vaněčková, V. Mat'oška, A. Bóday, Z. Saidl. *Psychiatric Clinic, Prague 2, 128 08, Czech Republic*

Based on our previous studies and references, we can conclude that the children of age 6–10 years suffering from the hyperkinetic syndrome reveal decreased serum levels of dopaminbetahydroxylase, which improve during the treatment by stimulants. The same changes were ascertained in patients with the unsocialized conduct disorder. The genes DBH (dopaminbetahydroxylase), DAT1 (dopamine transporter), DRD2 (dopamine D2 receptor) and DRD4 (dopamine D4 receptor) are counted among the most important, so called candidate genes. The NMR examination demonstrated changes in the size of basal ganglia, especially nucleus caudatus and striatum.

In the present study, results of clinical (Conners' scale, variant for parents), biochemical (serum DBH levels), genetic (occurrence of allele B1 of gene DBH and allele 480 of gene DAT1) and NMR (selected parameters) examinations were collected in children of age 6–10 years with the diagnosis of hyperkinetic syndrome according to DMS-IV. The results of mentioned examinations in untreated uncompensated patients were compared with those in the patients successfully treated with methylphenidate.

P02.236

ECG MAPPING WITH A VIEW TO ISCHEMIC CHANGES OF A MYOCARDIUM IN PATIENTS WITH A PANIC DISORDER

I. Paclt*, K. Pišvejcová, J. Slavíček, O. Kittnar. *Psychiatric Clinic, Prague 2, 128 08, Czech Republic*

In many previous studies, an increased risk of myocardial ischemic changes was demonstrated in patients treated for a panic disorder. Using classic ECG methods, the risk cannot be evaluated in most patients. Our study of 11 patients suffering from a panic disorder without any attacks and pharmacological treatment demonstrated up to this time unpublished changes when compared to the control group. The patients with a panic disorder showed a marked sinus tachycardia, changes of RIAM max., DIAM max. 30 and 40 parameters, less negative DIAM min. 40 and less RIAM max. 35 even in the period free of a panic attack. In patients with a panic disorder, both depolarisation and repolarisation phases of the heart rate were affected. Specific results were ascertained in the parameter RIAM min. 35. This parameter was more negative compared to normal values. An enlargement of the space angle QRS-STT, which is usually interpreted as a result of the myocardial global ischemia, was also determined. This finding could be connected with the predicted increased risk of the ischemic changes of the myocardium in patients with a panic disorder.

Our results will be compared with results of other study evaluating a larger group of patients and also with results of in advance examined patents treated with citalopram (SSRI antidepressant).

P02.237

MIRTAZAPINE: A QUICK AND EFFECTIVE TREATMENT IN PATIENTS WITH DEPRESSION-RELATED ANXIETY SYMPTOMS

J. Ladner*, A.A. Nimmerrichter. *Organon GesmbH, Vienna, Austria*

Background to Study: The aim of the study was to assess clinical efficacy and tolerability of mirtazapine in patients with depression-related anxiety.

Design, Variables Studied: Five-hundred-thirteen depressed patients with associated symptoms of anxiety were treated with mirtazapine for 3 months in an open-label study. Clinical efficacy was assessed after 2 and 9 weeks of treatment by the Clinical Global Impression (CGI) and the Hamilton Anxiety Scale (HAM-A). Tolerability was assessed by registering treatment-emergent adverse events. Only descriptive statistics have been used.

Results: Already in the first two weeks of treatment the magnitude of reduction of the anxiety score was very large and dropped with more than 7 points. Considering that at baseline the mean HAM-A score was 31.5 this improvement indicates a substantial reduction in anxiety symptoms. This was in agreement with the