following hormones up to the epinephrine. An excess of tyrosine and a scarceness of epinephrine are always present. the deficit of Epinephrine is measurable instanteneously only, in the moments of failure adaptation to the stress when the fits from schizophrenic symptomatology reach their peak because the enzymes have the function of to catalyze the biochemical transformation making her around 200 times faster. For this reason the historical searches around the alterations of the epinephrine, strongly suspect of to be the cause of the schizophrenia, they have given negative result always. The techniques that we can use for centering the diagnosis are two: The first one consists in to effect under stress an opportune test: 1) – test of the enzymes of synthesis of the epinephrine beginning from the Tyrosine: tyrosine-hydroxylase, L-aromatic amino acid decarboxylase, dopamine-α-hydroxylase, phenylethanolamine-N-methyl transferase; while the second, since the geniuses that synthesize the aforesaid enzymes have been already isolated, to use the same procedure to verify the deficit and/or the alteration of such geniuses. The treatment consists in to replacing such geniuses with healthy geniuses and introducing such cells cloned in the human organism to cure.

P46. Psychopharmacology – clinical

P46.01

Pharmacokinetics of psychotropics

S. Tuinier*, W.M.A. Verhoeven, A.E.S. Sijben. *Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands*

Therapeutic Drug Monitoring (TDM) is a well recognized instrument to enhance therapeutic efficacy of psychotropics and to detect pharmacokinetic factors involved in treatment resistance. Over a period of 5 years the results of TDM were analysed yielding a total of 4000 samples.

The first objective was to establish a relationship between dosage and plasma concentration, the second to evaluate the effects of age and sex. From the total group, data were available on the antidepressants: amitriptyline (n=271), clomipramine (n=584), fluvoxamine (n=515), imipramine (n=165) and nortriptyline (n=253), and on the antipsychotics: clozapine (n=93), haloperidol (n=30) and thioridazine (n=41). For the other psychotropics only small groups were present.

With respect to sex, a male-female difference was found for clozapine and nortriptyline in that females appeared to have higher plasma concentrations. Concerning the dose-plasma concentration, a relationship was observed for nortriptyline, fluvoxamine, amitriptyline and clomipramine, but not for clozapine.

Preliminary analysis showed that about 20 percent of the values are outside the more or less established therapeutic range. In addition, major effects of age on the plasma concentrations of various compounds were observed.

P46.02

Valproic acid in unstable mood disorder

S. Tuinier*, W.M.A. Verhoeven. *Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands*

Since the beginning of the last century, cyclic changes in behaviour and mood that do not meet the criteria for bipolar affective disorder, have been reported in patients with developmental disorders. Based on data from factor analytical studies, we recently postulated the concept of unstable mood disorder in mentally retarded patients that is characterized by a cyclic alteration of behaviour associated with an episodic pattern of disturbed mood and/or anxiety.

In the present study including 28 mentally retarded patients with a long history of episodic changes in behaviour and affect, a diagnosis of unstable mood disorder was established. Following a baseline controlled design treatment with valproic acid was started with dosage adjustments according to plasma levels. Treatment period comprised six months (n=7) to one year (n=21). As assessed with the CGIS moderate to marked improvement was observed in 19 patients that included stabilization of behaviour and mood as well as reduction of symptoms belonging to the mood, anxiety and motor domains.

It is concluded that valproic acid is an effective treatment in unstable mood disorder.

P46.03

Atypical antipsychotics in schizophrenia; efficacy and effect on serotonergic parameters

S. Tuinier*, W.M.A. Verhoeven, F.M.M.A. van der Heijden, A.E.S. Sijben. *Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands*

In an ongoing research project the atypical antipsychotics risperidone, olanzapine, sertindole and quetiapine were investigated in patients with an acute episode of schizophrenia. For the various atypical antipsychotics, groups of at least 20 patients who completed the experimental period of 14 weeks were analysed.

The studies followed an open baseline-controlled, prospective design. The compound was administered in a flexible dose during the first 6 weeks to achieve optimal individual dosages and thereafter doses were kept unchanged. As response criterium served in all substudies a reduction of at least 40% on the BPRS total score.

Secondary efficacy measures were PANSS and CGI. Analyses were performed on a intent-to-treat basis and were calculated with a repeated measurement procedure (MANOVA).

For all four atypical antipsychotics a modest treatment response was observed. No specific effects on affective or negative symptoms could be demonstrated.

With respect to serotonergic parameters, at baseline no differences were found between responders and non-responders. In the non-responding group, however, a significant increase of these parameters emerged suggesting the presence of a pre-existing down regulation of the serotonergic receptor system.

P46.04

Citalopram in mentally retarded patients with depression

W.M.A. Verhoeven*, S. Tuinier. *Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands*

Affective disorders in patients with mental retardation should be considered when an episode occurs with changes in affective equivalents, motivational behaviour, motor activity or vital signs. Although the efficacy of several antidepressants in this patient group has been established, various specific risk factors have to be considered such as higher vulnerability for anticholinergic and motor side effects.

In the present study following a baseline controlled, long-term open design, the effect of citalopram was investigated in 20 mentally retarded patients suffering from a depressive disorder characterized by alterations in the domains of affectivity, motivation, motor activity and vital signs. Citalopram was started in a daily dosage of 20 mg that was kept unchanged for six weeks. Thereafter dosage was adjusted to maximally 60 mg per day. Treatment effects were assessed with the CGIS after at least six months.

https://doi.org/10.1016/S0924-9338(02)80812-4 Published online by Cambridge University Press

In 12 patients a moderate to marked improvement in all domains was observed upon treatment with 20–40 mg citalopram daily. Treatment for one year in the effective dose prevented recurrence of depressive symptomatology.

It is concluded that citalopram is a well tolerated, safe, interaction-free and effective antidepressant in mentally retarded subjects with a depressive disorder.

P46.05

Smoking modulates neuroendocrine responses to ipsapirone in patients with panic disorder

A. Broocks[1]*, G. Hajak[2], B. Bandelow[2], K. Koch[1], U. Schweiger[1], F. Hohagen[1]. [1]*Department of Psychiatry and Psychotherapy, University of Lübeck;* [2]*Department of Psychiatry and Psychotherapy, University of Göttingen, Germany*

Objective: Reduced 5-HTIA-receptor responsiveness has been reported in patients with panic disorder and/or agoraphobia (PDA). Although many of these patients are regular smokers, it has not been examined whether psychological or neurobiological effects induced by the highly selective 5-HT1A-receptor agonist, ipsapirone, are affected by the smoking status of the patients.

Methods: In order to clarify this question neuroendocrine challenges with oral doses of ipsapirone (0.3 mg/kg) and placebo were performed in 39 patients with PDA, and results were compared between smokers and non-smokers for at least two years (n=22).

Results: Patients who were smokers (but did not smoke during the challenge procedure) had significantly reduced baseline concentrations of cortisol; they also showed significantly higher cortisol responses to ipsapirone than non-smokers.

Conclusion: Smoking status has to be taken into account when assessing the responsiveness of 5-HTIA receptors in patients with psychiatric disorders.

P46.06

Relation between sexual dysfunctions and CYP 2D6 activity

A. Zourkova*, E. Hadasova. *Masaryk University, Department of psychiatry, Brno, Czech Republic*

The aim of the study was to establish to the difference, as to the frequency and severity of side effects related to sex-life, between patients treated by paroxetine with reduced CYP 2D6 metabolic capacity and patients who showed no such changed capacity. Data were obtained from 30 patients with informed written consent treated by paroxetine for 131.4 days. The average daily dose of paroxetine being 20.8 mg. The effect of treatment on the sexual function was recorded by ASEX and the UKU scale. The difference of sexual dysfunction incidence between extensive and poor metabolizers broken down into the items of the scales used was subjected to statistical evaluation by the Mann-Whitney test. The CYP 2D6 metabolic status was determined with the dextromethorphan test (phenotype) and the allele-specific PCR (genotype). It may be summed up that most patients (24) undergoing long-term treatment by paroxetine reported sexual dysfunction. Subjects with low CYP 2D6 activity probably due to the long-term administration of paroxetine reported statistically significant more frequent sexual dysfunction in the ASEX scale.

Supported by grants IGA MH CR: NF 6169–3/2000 and CEZ: J07/98: 141100001.

P46.07

A rare case of neuroleptic malignant syndrome and the NMS spectrum concept

C. Mantas*, S. Pappas, V. Mavreas. *University of Ioannina Medical School, Department of Psychiatry, Greece*

Neuroleptic malignant syndrome is an uncommon but potentially fatal complication of neuroleptic treatment. We describe a rare case of NMS diagnosed in a18-year old man after a rapid escalation on neuroleptic dose. The patient developed the cardinal features of the syndrome gradually over a period of 15 days. The rather slow presentation was followed by an extremely prolonged course with rigorous treatment, including assisted ventilation in an intensive care unit extending over 3,5 months. The failure of more conventional modes of treatment imposed the use of electro-convulsive therapy. The final outcome was surprisingly positive with complete recovery of the NMS. Furthermore the patient's mental status and functioning remained intact over the last five years. This case raises interesting issues on neuroleptic toxicity lending credence to the spectrum concept of NMS.

P46.08

The effect of olanzapine on dopamine receptor responsivity in schizophrenia

L. Lykouras*, J. Hatzimanolis, M. Markianos, P. Oulis. *Athens University Medical School, Department of Psychiatry, Schizophrenia Research Program, Eginition Hospital, Athens, Greece*

A neuroendocrinological method to cheek the degree of dopamine receptor blocking is by measuring the prolactin (PRL) responses to acute (i.m.) administration of haloperidol (HAL). The authors applied this test in a group of male patients with DSM-IV schizophrenia in the drug-free state. The patients were subsequently treated with olanzapine (OLZ) (mean daily dose: 22.5±5.8) and the test was repeated 6 weeks later. For the Hal-test, 5mg HAL were injected i.m. and blood samples were taken at times 0, 30, 60, 90 and 120 minutes. Fourteen patients enrolled in the study. Psychopathology was assessed by means of the Brief Psychiatric Rating Scale (BPRS).

Six weeks treatment with OLZ resulted in significant decreases in the total BPRS score and on the score of its subscales for positive, negative, and general psychopathology. Comparison of the PRL response patterns, after HAL administration by analysis of variance for repeated measures (ANOVAR) for drug treatment and time, revealed a highly significant time effect (F=28.98, p=0.000) and a significant treatment by time interaction (F=8.27, p=0.000008). Namely, in the drug-free state significant increases were found in the PRL levels after i.m. HAL administration which were significantly reduced during treatment with OLZ, indicating moderate receptor blockade.

P46.09

Psychopharmacotherapy or psychotherapy of anxiety disorders – one year results

D. Ignjatovic*, M. Ignjatovic. *Policlinic Psychiatric Out-patient Department, Banska Bystrica, Slovak Republic*

The purpose of our one-year study was a comparison of psychopharmacotherapy and psychotherapy of acute outpatients with anxiety disorders during crisis periods.

Patients and methods: 20 patients/DSM-IV and ICD-10 classifications used hydroxizin and psychotherapy for 12 weeks.