We suppouse, that the chronification of patient"s psychotic state is followed by the decrease of MM level.

Wed-P43

ZOTEPINE ENHANCES NORADRENALINE LEVELS IN RAT FRONTAL CORTEX MICRODIALYSATES: FURTHER SUPPORT FOR ANTIDEPRESSANT ACTIVITY

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Zotepine is an antipsychotic drug with a marked atypical profile that not only has efficacy for positive and negative schizophrenic symptoms but combines activity in animal models predictive of antidepressant activity (Needham *et al.*, 1997; *Biol. Psychiat.* **42**, 175–176S) with antidepressant properties in patients (Fleischhacker *et al.*, 1989; *Psychopharmacol. Bull.* **25**, 97–100). Since zotepine inhibits ^{3}H-noradrenaline (^{3}H-NA) uptake by rat frontal cortex synaptosomes (Needham *et al.*, 1997), we studied the effects of zotepine and comparator antipsychotics on extracellular NA in the frontal cortex using *in vivo* microdialysis. In freely-moving male CD rats (250–350 g), basal levels of cortical NA were 31 ± 3 fmol/20 µl. Zotepine (0.5, 1.0 or 1.5 mg/kg, ip) evoked biphasic, dose-related rises in cortical NA with peaks at 60 min (+94% to +171% above basal values; $p < 0.001$ by ANOVA with *post hoc* Dunnett's *t*-test) and at 240 min (+142% to +212%; $p < 0.001$) post-zotepine. The increases in NA were sustained for up to 120 min beyond the initial peak. Clozapine (10 mg/kg, ip) increased NA levels by 72% ($p < 0.05$) but only for 20 min. Neither ziprasidone (3 mg/kg, ip) nor olanzapine (1 mg/kg, ip) had any action on cortical NA. The antidepressant, desipramine (a NA uptake inhibitor; 0.3 mg/kg, ip), elevated NA levels 5-fold ($p < 0.001$), an effect which declined over 240 min. Zotepine's elevation of cortical NA probably occurs via NA uptake inhibition. Clozapine's weaker action may derive from α_2-adrenoceptor blockade. This action of zotepine may contribute to its antidepressant profile and its reported superiority *vs* clozapine in improving some cognitive deficits in schizophrenic patients (Meyer-Lindenberg *et al.*, 1997; *Pharmacopsychiatry* **30**, 35–42).

Wed-P44

COGNITIVE AND EMOTIONAL SIDE EFFECTS AND THE EFFICACY OF CLASSICAL AND ATYPICAL NEUROLEPTICS IN ACUTE SCHIZOPHRENIA

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The importance of cognitive emotional side effects of neuroleptics is underestimated in general, but according to the statements of many patients, it is a reason for their noncompliance.

Within various double-blind studies on the efficacy and tolerance of classical and atypical neuroleptics in our hospital we applied a neuro-psychological test battery in order to record the influence of the substances on cognitive and emotional functions.

The results of these investigations were compared quasi-experimentally. The results showed that not only the serotonergic antagonistic atypical neuroleptics clozapine, olanzapine, risperidone and zotepine, but especially also the substituted benzamides remoxipride and amisulpride caused significantly less cognitive emotional side effects than the classical neuroleptics.

The discribed results also found their expression in the contentment with medication of the investigated patients.

The results shall be discussed in context with the problems of methodological measuring.

Wed-P45

PSYCHOPHARMAKOLOGISCHE BEHANDLUNG UND PRÄVALENZ VON EPS BEI PATIENTEN MIT 15JÄHRIGEM VERLAUF EINER AFFEKTIVEN-, SCHIZOAFFEKTIVEN-, SCHIZOPHRENEN- BZW. WAHNHAFTEN PSYCHOSE

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Einleitung: Das Vorkommen von extrapyramidal motorischen Nebenwirkungen (EPS) wird bei bis zu 90% der mit Neuroleptika (NL) behandelten Patienten beschrieben, das von irreversibel auftretenden Spätdyskinesien bei bis zu 40% der Fälle (Möller 1996). Im Rahmen der Münchener 15 - Jahres - Katamnesestudie werden bei Patienten mit der Diagnose einer affektiven-, schizoaffektiven-, schizophrenen- und einer (nicht schizophrenen) paranoiden Psyhose zum Follow-up-Zeitpunkt die gegenwärtige psychopharmakologische Medkation und das Ausmaß unwillkürlicher Bewegungsstörungen nachuntersucht.

Material und Methoden: Bestimmung von EPS und Spätdyskinesien durch: Extrapyramidale Symptom-Skala (Simpson, Angus 1970) und AIMS (abnormal involuntary movement scale).

Ergebnisse: 35% der nachuntersuchten Patienten mit einer funktionellen Psychose erhalten 15 Jahre nach dem ersten stationär psychiatrischen Aufenhalt keinerlei psychopharmakologische Medikation. NL werden von 44% der Patientem eingenommen. 31% der nachuntersuchten Fälle zeigen EPS, ein Drittel davon weisen EPS auf, obgleich sie keine NL einnehmen. 30% der Patienten weisen tardive Dyskinesien auf, 2/3 davon nehmen NL ein. Ausmaß von EPS und Spätdyskinesien bei den betroffenen Patienten werden angegeben.

Diskussion: Bei Betrachtung der Patientem mit EPS zeigt sich, daß die Patienten ohne NL-Einnahme aber mit einer sonstigen psychopharmakologischen Behandlung Lithium erhalten, von welchem bekannt ist, daß es eine neuroleptikainduzierte EPS verstärken une auch selbst EP-Symptome verursachen kann. Die Patienten mit EPS und ohne jegliche psycho-pharmakologische Medikation sind im Durchschnitt um ca. 10 Jahre älter, als die Gruppe mit EPS und NL-Einnahme.

Wed-P46

PHARMACOTHERAPY OF ANXIETY IN SCHIZOPHRENIA

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Nearly 75% of all persons are more of less anxious, which indicates that anxiety normally belongs to human being. At low grade it helps in quick reactions and in "planing" of adaptive activities. But, when anxiety last longer or appear more frequently with hard bearing intensity, we speak about pathological anxiety. In schizophrenia we are faced with syndromes of psychotic anxiety which is very often "intertwine" with other psychopathological features of schizophrenia.

In this research, 80 schizophrenics have been tested (57 male, 23 female) average age of 28–39 years (± 6.3) who were treated in Department for Psychosis of Day Hospital during 1996. The group was divided in two subgroups with 40 patients each who were treated with different pharmacotherapy. First, experimental

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group, has received a combination of antipsychotics with anxiolytics (benzodiazepine group). Control group was treated only with classic antipsychotics (fluphenazine, haloperidol). Testing of psychotic symptoms was realised with the Brief Psychiatric Rating Scale (BPRS) and anxiety was measured by Spielberger's State-Trait Anxiety Index (STAI). Obtained datas were pondered and presented numerically from 1.00 (without anxiety) to 3.00 (very high anxiety). Psychotic behavior was also presented numerically as psychotic index.

In both groups anxiety was at level of 2.96 index points before treatment (very high anxiety). In control group there was no significant improvement (2.38 at the end of examination) which indicates minimal improvement ($p = 0.10$). In experimental group which was treated with combine therapy (antipsychotics and benzodiazepines) there was significant improvement of anxiety, specially psychotic one ($r = 0.059$). This fact indicates very low anxiolytic potential of phenothiazines. Reduction of psychotic features in sense of partial remission of sch phenomenons is significant in both groups (from 178.4 to 46.3 index points, $p = 0.05$).

Hence anxiety in main dynamic force which has great influence at beginning and a development of sch process, polytherapy is necessary in treatment of these patients. It is consisted, in first place, of antipsychotics and anxiolytics, and very often antidepressive because of postschizphrenic depressive syndrome which occurs very often. In that way, it is possible to reach significant reduction of, not only psychotic anxiety but also free floating anxiety which always is present in pre psychotic and post psychotic period in most schizophrenic patients.

Wed-P47

WEIGHT GAIN ASSOCIATED WITH CONVENTIONAL AND NEWER ANTIPSYCHOTICS: A META-ANALYSIS

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A comprehensive literature search of English and non-English articles identified 78 studies which included data on weight change in more than one patient treated with a specific antipsychotic. For each agent, a meta-analysis estimated the effects of 10 weeks of treatment on body weight. The degree of weight change at 10 weeks was estimated by random effects regression. Except for molindone, antipsychotic treatment was associated with weight gain. Placebo was associated with a mean reduction of 1.68 kg. Among conventional agents, mean weight change ranged from a reduction of 0.41 kg with molindone to an increase of 3.25 kg with thioridazine, with an intermediate effect observed for haloperidol, an increase of 1.06 kg. Among newer antipsychotics, mean increases were as follows: clozapine 4.46 kg, olanzapine 4.15 kg, sertindole 2.92 kg, risperidone 2.10 kg and ziprasidone 0.87 kg. Insufficient data were available to evaluate quetiapine. Pairwise tests of differences between newer antipsychotics showed no significant difference between olanzapine and clozapine. Weight gain was significantly lower with ziprasidone compared with clozapine, olanzapine, risperidone and sertindole. There were also significant differences between clozapine and risperidone and olanzapine vs risperidone and vs sertindole. Both conventional and newer antipsychotics are associated with weight gain. Among newer agents, clozapine appears to have the greatest potential to induce weight gain and ziprasidone has the least. The differences among newer agents may impact upon the choice of treatment for some patients. Not only is weight gain undesirable because of associated health risks, but it may also cause non-compliance with antipsychotic therapy which predisposes patients to relapse.

Wed-P48

THE EFFECT OF TREATMENT WITH TYPICAL AND ATYPICAL NEUROLEPTIC DRUGS ON NEUROPSYCHOLOGICAL MEASUREMENTS IN PATIENTS WITH SCHIZOPHRENIA

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Neuropsychological measures (frontal lobe tests, conjugate lateral eye movements) were performed in sixteen patients with paranoid schizophrenia 1) during acute episode, before starting pharmacological treatment (PANSS 126 ± 24) and 2) during improvement, on maintenance dose of neuroleptic drugs (PANSS 62 ± 24). Eight patients were treated with typical neuroleptic (chlorpromazine, levomepromazine, fluphenazine, perphenazine) and eight - with atypical one (clozapine, olanzapine, ziprasidone).

In whole group, after alleviation of psychotic symptoms, the results of frontal lobe tests improved, and in case of Stroop test A and B, significantly so. There were no differences between typical and atypical neuroleptic drug as to the magnitude of such improvement.

During acute episode, schizophrenic patients exhibited excessive activation of left hemisphere in response to emotional and spatial questions (i.e. directed to right hemisphere), measured by CLEM method. During improvement, an increase of activation of right hemisphere was observed in response to these questions, at the expense of left hemisphere activation. Such increase, reflecting a regulatory action on hemispheric activation was significantly greater in patients treated with atypical neuroleptic drugs.

The results obtained suggest a possibility of improvement of some cognitive functions as well as regulation of activational asymmetry in schizophrenic patients with neuroleptic treatment, the latter may be more marked with atypical than typical neuroleptics.

Wed-P49

ZIPRASIDONE: *IN VIVO* EVIDENCE OF CENTRAL $5HT_{1A}$ AGONIST ACTIVITY

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Ziprasidone is a novel antipsychotic with a unique specificity for dopaminergic and serotonergic receptors. *In vitro* studies of cAMP accumulation indicate that ziprasidone is an agonist at $5HT_{1A}$ receptors. Since $5HT_{1A}$ receptor agonism is thought to contribute to reduced extrapyramidal side-effect (EPS) liability and enhanced efficacy against both negative and affective symptoms of schizophrenia, we investigated the *in vivo* $5HT_{1A}$ agonist activity of ziprasidone by measuring its effects on dorsal raphe cell firing and cortical dopamine release in the rat. Ziprasidone inhibited dorsal raphe firing with an ED_{50} of 300 μg/kg intravenous (IV) and its inhibitory effect was blocked by pre-treatment with the $5HT_{1A}$ antagonist WAY-100635 (10 μg/kg IV). Although the $5HT_2/D_2$ antagonist olanzapine also slowed unit activity (ED_{50} = 1000 μg/kg IV), this effect was not attenuated by WAY-100635, but was reversed by pre-treatment with the norepinephrine re-uptake inhibitor, desipramine (5 μg/kg IV). This is consistent with olanzapine's α_1 antagonist activity, low affinity for $5HT_{1A}$ receptors, and

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