cost-benefit-relation on the one hand and the adequacy for acute psychosis versus relapse prevention on the other hand. Although atypical antipsychotics possess a positive image with regard to several dimensions there are still important dimensions in which they are not regarded as effective as conventional antipsychotics. The appraisal of the cost-benefit relations reveals inconsistencies to prior estimations, particularly the atypical antipsychotics were judged rather unfavourable.

Conclusion: The attitudes of German psychiatrists towards the usage of different antipsychotic treatment strategies appear concordant with treatment guidelines and empirical evidence in many domains. However, in some aspects occur inconsistencies. Some of the latter may be attributed to economic pressure.

O-08-07

Psychosis in an inpatient unit: Types of patients and treatment

B. Perez Ramirez, M. Marin Olalla. *Inmaculada Hospital Mental Health, Huercal Overa. Almeria, Spain*

Objective: Analyse the links between different dates and the type of treatment in patients with psychotic disorders

Methods: Cross study Population: The patients admitted in our Hospital between january to december of 2003, with diagnosis of psychotic disorder (schizophrenia, brief psychotic episode, schizoaffective disorder, delusional disorder). Dates: type of treatment-typical, atypical or both-; socio-familiar situation (living with their own families, in a public center, with their original families, alone); numbers of admissions, diagnosis and psychiatric comorbility. Statistic Analysis: descriptive and univariant study crossing type of treatment and the rest of dates.

Results: 59% out of the patients live with their families, 48.5% out of the patients had an additional diagnosis and the most important was substance misuse-29.5% of the cases-. 38.1% out of the patients were taking atypical antipsychotics(a.a.), 18.1% were taking typical drugs(t.a), and 43.8% were takink both treatments.

Conclusion: We found statistic differences-p<0.000-regarding to the treatment when we consider first episodes, so 60% out of these patients were under (a.a.). On the contrary, patients with more episodes were mostly under both type of treatment simultaniosly. We did not find differences between the treatment and other dates like the average time admitted in the Hospital and the number of admissions.

O-08-08

Structure of complementary care of schizophrenic patients

V. Lambolez. *Nancy, France*

Objectives: at the conclusion of the lecture, the participant should be able to describe how psychiatric rehabilitation and stucture of complementary care are necessary to help people with chronic schizophrenic disorder.

Methods: this is a cohort study of 179 patients followed over a period of 23 years, the population have an average age of 45 years, and consists of 35% of women. The group of patients with chronic schizophrenic disorder is living on their own in the community,in specialized common flats, with at home mental health care.

Results: During the lasts years we've established that this ambulatory home care in the community is very important in the overall care of chronic patients and help them to live independantly.

O-08-09

Cognitive-behavioural treatment for schizophrenic patients in routine care: Results of a RCT

G. Wiedemann, S. Klingberg, A. Wittorf, A. Fischer, K. Jakob-Deters, G. Buchkremer. *University of Frankfurt/Main Psychiatry and Psychotherapy, Frankfurt, Germany*

Objective: In order to further establish the clinical relevance of CBT for patients suffering from schizophrenic disorders we investigated the efficacy of a cognitive-behavioural treatment (CBT) program under conditions of routine care. We analysed the short- and medium-term treatment effects in a randomised clinical trial. The treatment program, the study design and the process of patient selection are briefly described. The presentation will focus on the effects of the inpatient treatment phase and the six-month follow-up after discharge from hospital.

Methods: Firstly we analysed effects of the inpatient treatment phase in a pre-post control-group design with a treatment as usual (TAU) condition as control group. We assessed the Positive and Negative Syndrome Scale (PANSS) and self-rating-data. Patients were assessed by independent raters. Secondly we compared relapse rates regarding the period of 6 months after discharge from hospital. Relapse was defined as an increase of 6 points on both positive and negative symptoms.

Results: CBT and TAU resulted in improvement regarding positive and negative symptoms during inpatient treatment. At the six-month follow-up CBT-Patients had significantly less relapses.

Conclusion: CBT is effective in reducing relapse rates even in routine care.

O-08-10

Effect of a adherence counselling training package for case managers on relapse for patients with schizophrenia: cluster randomised controlled trial

R. Gray, D. Robson. *Institute of Psychiatry Denmark Hill, London, United Kingdom*

Objective: To assess the effectiveness of an adherence counselling training package for case managers in reducing relapse rates in patients with schizophrenia.

Methods: Pragmatic cluster randomised controlled trial. Forty-six case managers (the cluster) were assigned randomly to adherence counselling training or a control training intervention. Five patients were randomly selected from each case managers caseload and were assessed at baseline and again after twelve months. The primary outcome of interest was relapse of psychosis. Secondary outcome measures included: compliance; substance use; and functioning

Results: Forty-four case managers and 203 patients were followed up at the trial end point.

Conclusion: Training was acceptable and well evaluated by case managers.

Sunday, April 3, 2005

P-02. Poster session: Psychotic disorders II

Chairperson(s): Cyril Höschl (Prag 8, Czech Republic), Kenneth Kaufman (New Brunswick, NJ, USA)
11.15 - 12.15, Gasteig - Foyers

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P-02-01

The monitoring of cognitive processes in patients with schizophrenia treated with amisulpride during a 12 month period

A. Klasik, I. Krupka-Matuszczyk, K. Krysta, I. Ziajka. *Medical University of Katowice Psychiatry and Psychotherapy, Katowice, Poland*

Objective: The effect of II-nd generation neuroleptics on cognition in patients with schizophrenia has been described in detail with regard to most of the substances in this group. Following a review of current literature it was noted that there is insufficient data regarding the long term impact of amisulpride use on cognition in patient with a diagnosis of schizophrenia.

Methods: Therefore a 12 month research was performed describing the influence of amisulpride on cognitive functioning in patients with schizophrenia. The research was carried out as part of the European Long and Short–Term Studies On The Efficiency Of Amisulpride(Solian) E.L.S.A in the Departament of Psychiatry and Psychotherapy of the Medical University of Silesia in Katowice, (Poland).

Results: The study group consisted of 11 patients with schizophrenia selected according to the criteria outlined in the above mentioned research. The patients were examined neuropsychologically with the Vienna Test System – computer version. The following series of tests were performed: CORSI - attention span test (S4 module: UBS and SBB version for clinical patients) RT – reaction test (module S6:diagnostic version, effect of medication on the attention processes in clinical patients),SIGNAL – test for signal detection (module S1:diagnosing the attention selectivity in clinical patients).The examination of cognitive functions was performed seven times, on the day before the administration of the first dose, on the 7-th day after, on the 14-th day, on the 28–th day, on the day of discharge from hospital, 6-months after the initial dose, 12-months after the initial dose.

Conclusion: Based on the results it was significantly proven that amisulpride had a positive effect on cognitive functioning in patients with schizophrenia.

P-02-02

Efficacy of quetiapine in schizophrenic patients: A retrospective real-life study

M. Tafalla. *AstraZeneca Medical, Madrid, Spain*

Objective: Most data used to aid clinical decisions originate from clinical trials. Normal clinical practice, however, differs from controlled conditions. This study has been designed to evaluate outcome among real-life schizophrenic patients treated with quetiapine

Methods: A retrospective analysis of patients diagnosed with schizophrenia (DSM-IV) and treated with quetiapine was conducted by 239 psychiatrists in Spain.

Results: A total of 1238 patients were included (57.7% males, mean age 37.4 years). Mean time since diagnosis was 10.27 years; 89.1% had received previous antipsychotic treatment, most commonly with risperidone, olanzapine and haloperidol, and were switched to quetiapine because of tolerability issues (72%), lack of efficacy (23%) or low compliance (5%). The most common adverse events associated with the previous treatment that caused the switch to quetiapine were sexual dysfunction (44%) and extrapyramidal symptoms (43.4%). Mean dose of quetiapine at the review period was 586.8 mg (SD:270.8). Compliance was quite good: 65.8% of the patients reached a compliance rate of 80% or more. Clinical Global Impression of change (CGI-C) scale assessment show that two thirds (65.2%) of patients were "very much or much improved", and 93% were improved to some extent. The doctors rated the overall therapeutic effect of the medication on patient's condition to be marked or moderate in 71% of patients. With regards to tolerability, 42.5% of patients reported no adverse event, and 52.6% had no clinically significant ones.

Conclusion: Although uncontrolled and retrospective design, this analysis demonstrated strong compliance, therapeutic benefit, and an excellent tolerability profile with quetiapine in Spanish schizophrenic patients.

P-02-03

A Naturalistic Study of Aripiprazole Treatment in a General Psychiatric Setting in Europe

J.-N. Beuzen, M. Pans, S. Modell, P. Hagens, R. McQuade, T. Iwamoto, W. Carson. *Bristol-Myers Squibb Pharmaceutical Research Inst, Paris, France*

Objective: To examine the overall effectiveness of aripiprazole treatment in a naturalistic setting in 14 European countries.

Methods: This multicentre, open-label study of aripiprazole was conducted in outpatients with schizophrenia for whom a switch or initiation of antipsychotic medication was required. A total of 833 patients were randomized in a 4:1 ratio to aripiprazole treatment (n=680) or a safety-control group (n=153) who were prescribed an antipsychotic other than aripiprazole (primarily ziprasidone, amisulpride, quetiapine, olanzapine or risperidone). Aripiprazole treatment was initiated at a 15 mg/day dose, with an option to adjust within a range of 10–30 mg/day. The treatment period was 8 weeks. Effectiveness was evaluated using the CGI-Improvement scale (CGI-I). Patients' and caregivers' medication preference was assessed using the preference of medication scale (POM).

Results: At study endpoint, the mean aripiprazole dose was 19.1 mg/day, with 49.8% of patients receiving the 15 mg dose. The effectiveness of aripiprazole treatment was demonstrated as early as week 1. Among patients completing the study, 52% of those in the aripiprazole group responded to treatment (CGI-I score of 1 or 2) with a mean CGI-I score of 2.71. Sixty-eight per cent (68%) of aripiprazole-treated patients and 66% of caregivers rated aripiprazole as slightly better or much better than prior antipsychotic therapy (score of 1 or 2). The only two adverse events reported with aripiprazole treatment with an incidence of 10% or above were nausea (10.2%) and insomnia (16%).

Conclusion: Aripiprazole demonstrated overall effectiveness in patients with schizophrenia in a general psychiatric setting.

P-02-04

Ziprasidone induced priapism requiring surgical treatment

K. Kaufman, L. Stern, A. Mohebati. *UMDNJ-RWJMS Psychiatry, New Brunswick, NJ, USA*

Objective: Priapism is defined as persistent erection of the penis, usually painful, not associated with sexual desire or stimulation. Priapism is a urologic emergency; if not evaluated and treated appropriately, long-term sequelae include erectile dysfunction and impotence. Both typical and atypical antipsychotic psychotropics have

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been reported to cause this adverse effect (AE) secondary to alpha-adrenergic blockage. Only two cases of ziprasidone induced priapism have been reported; neither required surgical intervention. This paper addresses the first case of priapism secondary to ziprasidone that required surgical intervention.

Methods: Case analysis with PUBMED literature review.

Results: 31-year-old black male transferred from a community hospital with intense penile pain (10/10) associated with a 4-day priapism non-responsive to initial treatments with phenylephrine injections, Winter procedure, and corporal irrigation. Further aggressive medical intervention (leuprolide, bicalutamide, and pseudoephedrine) failed necessitating definitive surgery with Al-Ghorab corpora cavernosum to spongiosum shunt. By 9th day from initiation of priapism (4th post-operative day), pain and priapism had resolved. Both Sickle Cell Screen and hemoglobin electrophoresis were negative. The patient was previously diagnosed by DSM-IV criteria with schizoaffective disorder, bipolar type. Prior psychiatric treatments included electroconvulsive therapy, divalproex sodium and olanzapine. Ziprasidone monotherapy was initiated and titrated to 160 mg total daily dose one month prior to his priapism. Ziprasidone was discontinued in the community hospital; post-shunt procedure, aripiprazole was initiated.

Conclusion: Ziprasidone can induce irreversible priapism requiring surgical intervention. Though a rare atypical antipsychotic AE, priapism requires emergency intervention. Clinicians and patients should be educated regarding this potential AE.

P-02-05

Course of weight & metabolic benefits 1 year after switching to Ziprasidone

A. Berntsson, P. Weiden, A. Loebel, S. Murray, R. Yang, H. Lebovitz. *Danderyds Syukhus Psykiatriska Kliniken, Danderyd, Sweden*

Objective: To determine time course of weight and lipid reductions in outpatients switched to ziprasidone from other antipsychotics.

Methods: Three open-label, flexible-dose, 1-year extensions enrolled stable completers of 6-week trials switched from conventionals (n=71), olanzapine (n=71), or risperidone (n=43) to ziprasidone. Follow-up to 1 year of ziprasidone monotherapy permitted longitudinal assessment of improvement in weight and metabolic side effects. Mixed-model regression analysis was used to estimate LS mean change over time (58 weeks total).

Results: Mixed-model analysis showed that subjects switched from olanzapine or risperidone demonstrated progressive, sustained weight loss and BMI reduction. In pre-switch olanzapine group, estimated LS mean weight loss was –3.4 (±0.6 SE) lb at 6 weeks (P<0.0001) and –21.6 (±3.6) lb at 58 weeks (P<0.0001). In pre-switch risperidone group, loss was –2.1 (±0.8) lb at 6 weeks (P<0.05) and –15.2 (±4.5) lb at 58 weeks (P<0.005). Statistically significant improvements in triglycerides and total cholesterol occurred rapidly during initial 6 weeks of ziprasidone monotherapy, and were sustained through extension endpoints. In pre-switch olanzapine group, estimated LS mean triglyceride reductions were –78.0 (±11.7) mg/dL (P<0.0001) at 6 weeks and –54.5 (±15.5) mg/dL (P<0.0005) at 58 weeks. In pre-switch risperidone group, respective improvements were –39.2 (±14.6) mg/dL (P<0.05) and –36.7 (±18.9) mg/dL.

Conclusion: Subjects switched from olanzapine or risperidone to ziprasidone demonstrated progressive, sustained weight loss and BMI reduction for up to 58 weeks. Lipid improvements were substantial, occurred rapidly, and were sustained during long-term ziprasidone monotherapy.

P-02-06

Neuropsychological outcome before administration atypical and classical antipsychotic treatment. A pilot study.

O. Pino, J. E. Rojo, D. Carmona, G. Guilera, J. Gómez. *Bellvitge Hospital Psychiatry, Barcelona, Spain*

Objective: To asses changes in cognitive function in patients with stable schizophrenia treated with conventional antipsychotics when 80 mg ziprasidone are added to the treatment

Methods: We asses 10 patients in 4 cognitive domains (including working memory and attention, learning and verbal memory, executive functions and speed of information processing), pre-morbid QI and psychopathological symptomatology (PANSS scale), during the basal visit. After 3 or 4 weeks of the treatment it was performed the same exploration in order to compare ziprasidone effects into cognitive domains and results obtained by PANSS scale

Results: Working memory in long-delay recall in the category of Fluency Test and the speed of information processing seems to show a positive tendency after ziprasidona treatment. Moreover, similar improvement tendency can be observed in post-treatment PANSS scale results

Conclusion: Our preliminary data show a positive tendency onto cognitive and psychopathological domains we explored, when administration and antipsychotic association treatment

P-02-07

Ziprasidone vs Olanzapine: Contrasts in CHD risk

A. Cheli, D. Harrison, A. Loebel, S. Murray. *Pfizer Inc., New York, USA*

Objective: This analysis was conducted to examine differences in coronary heart disease (CHD) risk arising from short-term treatment with ziprasidone and olanzapine.

Methods: Hospitalized schizophrenic adults underwent 6 weeks' randomized, double-blind treatment with ziprasidone or olanzapine, with data collected at baseline and endpoint for fasting lipids and weekly for blood pressure. A Framingham algorithm was used to calculate percentage CHD risk over 10 years in subjects ≥30 years (per algorithm). Baseline-to-endpoint mean changes in age-adjusted risk by sex were compared using ANCOVA (baseline adjusted).

Results: In men ≥30 years, there was a significant difference in mean changes in total cholesterol for olanzapine versus ziprasidone (+18.5 mg/dL [n=53] and -8.5 mg/dL [n=44], respectively; P=0.0006). A significant difference was also seen in mean changes in low-density lipoprotein cholesterol for olanzapine versus ziprasidone (+13.0 mg/dL [n=45] and -7.2 mg/dL [n=40], respectively; P=0.004). Mean CHD risk in men increased by 0.6% (baseline 8.1%) with olanzapine (n=53) and decreased by 1.1% (baseline 9.6%) with ziprasidone (n=42). In women ≥30 years, between-group differences were trending toward significance for lipid changes and CHD risk. Neither treatment had significant effects on blood pressure.

Conclusion: The findings indicate that in short-term treatment of men, olanzapine was associated with significant changes in lipid

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profile versus ziprasidone, with a consequent increase in CHD risk versus ziprasidone. These findings, coupled with those of significant weight gain with olanzapine versus ziprasidone, warrant investigation in longer-term trials.

P-02-08

Olanzapine-treated patients with psychotic disorders improved after changing to risperidone long-acting injectable

W. Chrzanowski, M. Latif, M. Masiak, R. Medori, M. Gastpar. *Klinika Psychiatrii AM, Choroszcz, Poland*

Objective: Maintained efficacy and safety of a direct transition from olanzapine to risperidone long-acting injectable without an oral risperidone run-in in adults with schizophrenia or other psychotic disorders requiring a change of treatment.

Methods: Patients clinically stable on olanzapine for ≥ 1 month were changed to risperidone long-acting (25 mg, increased to 37.5 mg or 50 mg, if necessary) injected every 14 days for 6 months.

Results: The analysis included 192 patients (63% male) of mean age of 38 years; 134 patients (70%) completed the study. The mean daily olanzapine dose was 15.22 ± 7.63 mg. Insufficient response (43%) and non-compliance (44%) were the main reasons for a treatment change. Mean total PANSS score at baseline was 74; this was significantly reduced after 1 month (mean -5 points) with further improvement until endpoint (mean -8 points) ($p<0.001$). At endpoint, 32% of patients had a ≥ 20% improvement from baseline in PANSS total score. By CGI-S (Disease Severity), 10% of patients were classified as 'not ill/borderline ill' at baseline vs 21% at endpoint. Patient satisfaction with treatment improved significantly; 31% of patients rated their treatment 'very good' at endpoint vs 6% at baseline. The ESRS total score was reduced significantly ($p<0.001$) from baseline to 1 month, and these improvements continued until endpoint. The most frequently reported AEs were anxiety (14.1%) and insomnia (10.9%). Patients' weight did not change during the trial.

Conclusion: Schizophrenic patients previously considered clinically stable on olanzapine showed significant improvements in symptom control and functioning after changing directly to risperidone long-acting injectable.

P-02-09

Intramuscular olanzapine in acutely agitated manic or schizophrenic patients. A naturalistic study

L. San, B. Arranz, R. Dueñas, J. de la Gandara, V. Perez. *Barcelona, Spain*

Objective: Agitation is commonly seen in acute manic and schizophrenic patients and it requires rapid and effective treatment approaches in order to protect patient and caregiver from potential injury. We performed a multicenter, open label, naturalistic study including 32 agitated patients attending to psychiatric emergency services (PES) and receiving treatment with intramuscular olanzapine.

Methods: . The study subjects were male and female patients (mean age 36,4±13,8 years, age range 19-75 years), attending to PES, who had a DSM-IV-TR diagnosis of schizophrenia (n=18), manic bipolar disorder (n=8), and Psychotic disorder non otherwise specified (n=6). The primary outcome of efficacy was the excited component of the PANSS (PANSS-EC) (tension, uncooperativeness, hostility, poor impulse control, and excitement), which was completed before starting treatment and at 2 and 24 hours following treatment with 10 mg intramuscular olanzapine. The CGI-S was used to record the severity of illness at baseline.

Results: Basal PANSS excited component was 25,7±6,1 (range 13-35). Basal CGI-S frequencies were: moderately ill in 9,4% of the patients, markedly ill in 28,1% severely ill in 46,9, and among the most severely ill 15,6%. Two hours after the olanzapine injection a statistically significant reduction in the PANSS-EC was noted (25,7±6,1 vs 15±8,5; p=0,002; Student's t test, paired). This reduction in the score was observed in all five items from the PANSS-EC. At 24 hours, 87,5% of the patients only needed one injection, with two injections needed in 12,5% of the patients.

Conclusion: This naturalistic study confirms the results obtained in the pivotal clinical trials in real-world agitated patients.

P-02-10

Olanzapine velotab 20 mg.: an experience of SPDC - USL 7 of Siena

A. Giovannoni. *Italy*

P-02-11

QT changes associated to treatment with clozapine.

A. Pons, V. Valls, A. Romero, G. Massana, M. García-Amador. *Hospital Clinic Institut Clínic Neurociemcies, Barcelona, Spain*

Objective: Neuroleptic drugs can prolong cardiac depolarization and repolarization phases, often causing reversible and mild abnormalities. The prolongation of the QT is far less frequent but clinically more relevant. To assess changes in the length of the QT interval, the ECG records of psychotic patients before and after a 6-month treatment with clozapine were compared.

Methods: An experienced cardiologist assessed the ECG records of 40 patients. The Bazett formula was used in order to calculate the correction of the QT interval.

Results: Unespecific abnormalities in the T wave were the most frequent finding. The analysis of the QTcB interval revealed a mean prolongation of 14.37 msec in the assessments carried out after six months of treatment with clozapine. Such difference was statistically significant, though the mean value of the QTcB (409.70 msec) is still in the normal interval.

Conclusion: ECG changes caused by clozapine do often appear at the beginning of the treatment. While ECG abnormalities show a dose-dependent association that is statistically significant, prolongation of the QTcB does not. Thus, clozapine appears to be a safe drug in terms of cardiovascular risks. However, prospective data on this issue are scarce and ECG monitoring continues to be advisable.

P-02-12

Haematic follow-up of patients treated with clozapine

A. Pons, A. Romero, X. Carné, G. Massana. *Hospital Clinic Institut Clínic Neurociemcies, Barcelona, Spain*

Objective: The incidence of agranulocytosis in patients treated with clozapine has markedly decreased thanks to follow-up programs. In this study the main aim was to assess the risk of neutropenia and agranulocytosis in patients followed up and monitored in our Clozapine Clinic.

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Methods: The course of the differential leucocytic count was analyzed in our sample of 215 psychotic patients treated with clozapine during a minimum of 18 weeks and a maximum of 24 months.

Results: No cases of agranulocytosis were identified, though three cases of neutropenia appeared during the study period. On the contrary, 23 cases of neutrophilia were observed.

Conclusion: The well-proved efficacy of clozapine is inconsistent with its rather limited use. One of the main reasons for this is probably the claimed risk of agranulocitosis. While such risk is higher during the first 6 months of treatment, from there on, the ratio risk/benefit becomes reversed. Haematic dyscrasias induced by clozapine in our ethnical and geographic setting are scarce, suggesting the involvement of genetic factors in its etiology. A less restrictive follow-up program seems advisable bearing in mind that other drugs with similar risks are not bound by such a strict control.

P-02-13

Bifeprunox: A unique, atypical antipsychotic

A. McCreary. *Solvay Pharmaceuticals Researc Biological Lead Optimization U, Weesp, Netherlands*

Objective: The effect of bifeprunox was evaluated in a number of preclinical models which have been useful in predicting antipsychotic action in man: conditioned avoidance response, antagonism of amphetamine and phencyclidine-induced hyperactivity. Haloperidol, clozapine, risperidone, olanzapine and aripiprazole were used as reference agents.

Methods: Bifeprunox was shown to have potent antipsychotic like effects in a therapeutic model sensitive to all antipsychotic agents (suppression of conditioned avoidance behavior in rats, MED of 0.25 mg/kg sc). Administration of phencyclidine [PCP, a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors] results in a psychotomimetic state that has been suggested to be a valid pharmacological model of schizophrenia. In rats and mice, PCP administration leads to hyperactivity and stereotypy, as well as cognitive deficits. Bifeprunox inhibited the PCP-induced hyperactivity in mice (ED50=0.00096 mg/kg sc), while inhibition of baseline activity was seen only at much higher doses (ED50=0.083 mg/kg sc). The high potency and degree of selectivity compared to base-line activity, of bifeprunox against PCP-induced hyperactivity, is unique compared to known antipsychotic drugs.

Results: Bifeprunox more potently antagonized overt behavior stimulated by d-amphetamine (ED50=0.005 mg/kg and 0.02 mg/kg sc versus low dose (0.5 mg/kg) and high dose (2.0 mg/kg) amphetamine, respectively) as compared to the doses needed for affecting baseline activity (ED50=0.036 mg/kg sc) in rats. The selectivity, between inhibition of amphetamine (0.5 mg/kg)-induced hyperactivity and baseline activity, was highest for aripiprazole, followed by bifeprunox and risperidone.

Conclusion: These data indicate that bifeprunox has antipsychotic like activity in a wide range of animal models.

P-02-14

Binding characteristics of bifeprunox to dopamine and serotonin receptors

A. McCreary. *Solvay Pharmaceuticals Researc Biological Lead Optimization U, Weesp, Netherlands*

Objective: Bifeprunox was investigated in a number of in vitro test systems for its receptor binding profile, and interaction with the dopamine D2 receptor. Bifeprunox has high affinity for hD2, hD3 and hD4 receptors and a partial agonist effect at serotonin 5-HT1A receptors, but virtually no affinity for 5-HT2A and 5-HT2C, noradrenergic 1 and 2, muscarinic and histaminergic receptors.

Methods: In a functional assay (adenylate cyclase activity in CHO cells expressing hD2L receptors), bifeprunox showed incomplete antagonism of the effects of the dopamine agonist quinpirole, and weak agonist properties. Bifeprunox inhibited D2 receptor-sensitive adenylate cyclase activity in rat striatal slices. In the same preparation, measuring the inhibitory effect on K+-induced release of [3H]-dopamine, bifeprunox acted as a potent antagonist at presynaptic D2 receptors. Of all reference antipsychotic drugs tested (haloperidol, clozapine, risperidone, olanzapine and aripiprazole), only aripiprazole showed a comparable partial agonist profile in vitro.

Results: These functional assays support the dopamine D2 partial agonistic properties of bifeprunox and aripiprazole in vitro. Partial agonist-like effects were induced when endogenous dopamine tonus was low, e.g. adenylate cyclase activity assays in CHO cells and in striatal slices. However, when the endogenous dopamine level was high, the partial agonists acted as functional antagonists.

Conclusion: These findings confer a unique antipsychotic profile: in brain regions (n. accumbens) where dopaminergic neurotransmission is believed to be increased in schizophrenia, the partial agonists act as functional antagonists, thus moderating dopaminergic activity. In contrast, in prefrontal cortex, where the dopaminergic system is believed to be hypoactive, the partial agonists restore dopaminergic neurotransmission.

P-02-15

Behavioral and neurochemical effects of bifeprunox

A. McCreary. *Solvay Pharmaceuticals Researc Biological Lead Optimization U, Weesp, Netherlands*

Objective: Bifeprunox has been compared to four reference dopaminergic drugs in a number of in vivo models predictive of modulation of dopamine-mediated behavior.

Methods: In rats, with unilateral 6-OHDA lesion of the dopaminergic input into the striatum, quinpirole and preclamol caused contralateral turning behavior resulting from stimulation of lesion-induced, supersensitive, postsynaptic D2 receptors. Bifeprunox caused comparable behavior, however the effect of aripiprazole was minimal and failed to reach the criterion of 50% established for apomorphine.

Results: In microdialysis studies in the nucleus accumbens of the freely moving rat, bifeprunox dose-dependently decreased extracellular dopamine and serotonin levels to 80% of control levels. This is believed to be a consequence of presynaptic D2 receptor and 5-HT1A receptor activation, respectively. The D2 receptor partial agonist preclamol, and the full dopamine agonist quinpirole, decreased extracellular dopamine levels, while aripiprazole was without effect on dopamine and 5-HT levels. The D2 receptor antagonist haloperidol acted differently, increasing dopamine levels without affecting 5-HT levels. In addition to dopamine agonistic behaviors, bifeprunox acted as a dopamine partial agonist in vivo, inhibiting dopamine agonist mediated behavior. The dopamine partial agonist aripiprazole and the

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antagonist haloperidol showed a comparable effect, while the partial agonist preclamol inhibited amphetamine-induced locomotor activity, but not apomorphine-induced climbing behavior.

Conclusion: In conclusion, bifeprunox shows a profile, consistent in many ways with that of existing antipsychotic agents, an ability to antagonize behaviors caused by dopamine agonists, but unlike dopamine antagonists, also able to stimulate dopaminergic receptors in situations where the dopaminergic tone is low, or dopamine receptors have become supersensitive.

Sunday, April 3, 2005

P-04. Poster Session: Psychotic disorders I

Chairperson(s): Anita Riecher-Rössler (Basel, Switzerland), Eva Meisenzahl (München, Germany)
18.00 - 19.30, Gasteig - Foyers

P-04-01

Chromosome 3q29: Possible Schizophrenia Susceptibility Region

A. Schosser, K. Fuchs, F. Leisch, U. Bailer, S. Kasper, W. Sieghart, K. Hornik, H. N. Aschauer. *Univ.hospital for Psychiatry Dep. of General Psychiatry, Vienna, Austria*

Objective: We recently published a follow-up linkage study (Schosser et al. 2004) within the chromosome 3q29 region in both schizophrenia and bipolar affective disorder families (highest NPL [non parametric lod] score Zall=1.93296, highest p-value=0.032166) after conducting a genome scan (Bailer et al. 2002), resulting in evidence for linkage of both disorders to this region (highest NPL score Zall=3.74, highest p-value=0.0003). Within the follow-up linkage analysis we also conducted subset analyses of the schizophrenia families separately, including the marker of highest linkage of our prior genome scan, resulting in evidence for linkage of schizophrenia to chromosome 3q29 (highest p-value=0.009155).

Methods: Using the same family sample of schizophrenia patients (n=33), we now genotyped five additional markers, spanning 2.6 cM (centiMorgan) within the region of highest linkage of our recently published follow-up linkage analysis, thus narrowing down our newly identified candidate region. Linkage analysis was performed using the GENEHUNTER program version 2.1_r3 beta.

Results: The most significant p value observed within this study was 0.031433 with both SNP marker rs1357289 and SNP marker rs3747672.

Conclusion: Within this additional fine-mapping of chromosome 3q29, we again found evidence for linkage of schizophrenia to this chromosomal region. The results of this study are in accordance with our previous linkage findings of schizophrenia to chromosome 3q29.

P-04-02

Identification of schizophrenia genes in an animal model for psychosis

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Objective: The psychotomimetic effects of noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists such as PCP and ketamine in healthy humans and their ability to exacerbate several psychotic symptoms in schizophrenic patients have promoted a view of schizophrenia as being related to an altered glutamatergic neurotransmission. Attempts to mimic these effects in rats have lead to the recognition of parallels between schizophrenia and molecular, cellular, functional and behavioral abnormalities in animals chronically treated with NMDA receptor antagonist MK801 in a low dosage.

Methods: We performed microarray analyses comparing the expression of 28.000 genes between MK801 treated rats and saline treated controls in order to identify candidate genes contributing to schizophrenia. We found several genes to be differentially expressed in hippocampus. Our findings demonstrate that a functional genomics approach can be applied in the identification of new and unexpected candidate genes for psychosis-related traits as well as confirm published data.

Results: We found several genes to be differentially expressed in hippocampus.

Conclusion: Our findings demonstrate that a functional genomics approach can be applied in the identification of new and unexpected candidate genes for psychosis-related traits as well as confirm published data.

P-04-03

Looking for susceptibility genes in schizophrenia

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There is evidence for a strong genetic component in the aetiology of schizophrenia, as demonstrated by family, twin and adoption studies. Several putative schizophrenia genes have been described recently. Some replication studies confirmed the association evidence, some did not. We examined whether genetic variations (SNPs) in six genes (COMT, PPP3CC, NRG1, AKT1, GRIA4, DAAO, g72) are associated with schizophrenia in a German population consisting of 366 patients and 367 healthy controls. The SNPs under investigation have been previously reported to be associated with schizophrenia in other samples. Single marker and haplotype analyses did not reveal an association with schizophrenia in our sample. Our findings do not support our initial hypothesis that the SNPs under investigation are associated with enhanced schizophrenia susceptibility in our sample of German origin

P-04-04

Psychotic disorders and genetic syndromes

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Objective: In clinical practice, psychiatric examination does not include a detailed assessment of physical anomalies, neither a careful evaluation of the neurodevelopmental trajectory and the family load with intellectual disabilities. Although there is substantial evidence for a genetic aetiology of schizophrenia and for a higher prevalence of subnormal IQ in this disease, patients with a psychosis are as a rule not screened for chromosomal or monogenic disorders. It was demonstrated recently, however, that cytogenetic abnormalities have a prevalence up to 30% in a population with schizophrenia.

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