P04.04

Olanzapine cotherapy in prevention of recurrence in bipolar disorder

M. Tohen[1]*, K.N.R. Chengappa[2], T. Suppes[3], R.W. Baker[1], R.C. Risser[1], A.R. Evans[1], J.R. Calaberse[4]. [1]*Lilly Research Laboratories;* [2]*Western Psychiatric Institute & Clinic, University of Pittsburgh Medical Center;* [3]*Department of Psychiatry, University of Texas Southwestern Medical Center;* [4]*Department of Psychiatry, Case Western Reserve, USA*

This study examines whether olanzapine cotherapy with lithium or valproate reduces symptomatic recurrence compared to lithium or valproate monotherapy in patients suffering from bipolar disorder. Patients in syndromic remission of bipolar disorder after 6 weeks of acute therapy with olanzapine plus lithium (0.6–1.2 mEq/L) or valproate (50–125 microg/mL) were randomized to receive olanzapine (5–20 mg/day) or placebo with continued cotherapy for 18 months of double-blind therapy. Among patients who were in symptomatic remission of mania and depression, time to recurrence to either pole significantly favored the olanzapine cotherapy group (cotherapy, 124 days; monotherapy, 15 days, p=.023). Recurrence into mania following remission of mania was also significantly longer for olanzapine cotherapy-treated patients (n=46, 362 days) compared to monotherapy-treated patients (n=48, 63 days, p=.005). Time to recurrence into depression was not significantly different between cotherapy (n=30) and monotherapy (n=38) groups, but was numerically favorable for the cotherapy group (155 vs 27 days, respectively; p=.071). The results indicate that the combination of olanzapine plus lithium or valproate effectively prolongs time in remission in comparison to lithium or valproate monotherapy.

P04.05

Olanzapine versus divalproex sodium for bipolar mania: a 47-week study

M. Tohen[1]*, R.W. Baker[1], L. Altshuler[2], C.A. Zarate[3], T. Suppes[4], T.A. Ketter[5], R.C. Risser[1], E. Brown[1], M.F. Luther[1], J.A. Gilmore, L. Schuh. [1]*Lilly Research Laboratories;* [2]*UCLA Neuropsychiatric Institute and Hospital;* [3]*National Institute of Mental Health;* [4]*University of Texas Southwestern Medical Center;* [5]*Stanford University, USA*

Objective: Compare olanzapine and divalproex for longer-term efficacy and safety in mania.

Method: This 47-week, randomized, double-blind study compared olanzapine (5–20 mg/day) to divalproex sodium (500–2500 mg/day) for bipolar I disorder (N=251). Young-Mania Rating Scale (Y-MRS) >=20 was required for inclusion, with <12 for "remission."

Results: Olanzapine-treated patients had better mean Y-MRS improvement (p<0.01) and shorter time to mania remission (p=0.047). After 3 weeks, mania remission rate was significantly higher for olanzapine (47.2%) than divalproex (34.1%) (p=0.039); among remitters, mania relapse rates did not differ statistically between treatments during the 44-week continuation: olanzapine (40.7%), divalproex (50.0%) (p=0.418). Median time to relapse was 270 and 74 days for olanzapine- and divalproex-treated patients, respectively (p=0.392). Treatment-emergent adverse events and laboratory abnormalities for olanzapine (p<.05) were somnolence, dry mouth, increased appetite, weight gain, akathisia, and liver function test (increased ALT), and for divalproex (p<.05) were nausea, nervousness, manic reaction, rectal disorder, and decreased platelets. Mean weight increase (LOCF) was olanzapine 3.4 kg vs. divalproex 1.7 kg (p=.045).

Conclusions: Compared to divalproex-, olanzapine-treated patients had significantly greater mania improvement and faster time to remission.

P04.06

Case report of 5 bipolar disorder patients (Rapid Cycling) followed for 3 years, treated with lamotrigine

S.A. Asghar. *Department of Acute Psychiatry, Ullevål University Hospital, Oslo, Norway*

Introduction: There are a number of categories of Bipolar Disorder (BPD), one of which is Rapid or Ultra Rapid Short Cycling. Patients with a severe form of Rapid Short Cycling Disorder responded well to lamotrigine in combination with neuroleptics when followed up over a shorter period of time. The purpose of this study was to investigate the effect of the drug regimen in 5 cases that have been followed up since 1998.

Methods: Rapid Cycling patients are those who have two or more affective episodes per year. Five Rapid Cycling BPD patients aged 50–70 years have been followed since 1998 for varying periods of time. Diagnosis was made in accordance with the DSM IV criteria. When treatment was initiated all these patients were experiencing a major depressive or manic episode. The patients had previously been treated with mood stabilizers, neuroleptics and anti-depressive agents without good response. The following rating scales were used to monitor the patients and register improvement: HAMILTON-D; Mania Rating Scale (MRS) from SAD; Clinical Global Improvement (CGI); Clinical Global Severity (CGS) and Global Assessment Function (GAF) measuring Scale.

Conclusions: In this study lamotrigine showed promising efficacy in limiting depression and manic episodes in the patients with Rapid Cycling Bipolar Disorder. However, a multi center, randomized, double blind trial is warranted in order to examine the efficacy of the drug.

P04.07

The bipolar spectrum disorders: implications for new drug development

J. Kogeorgos*. *Psychiatric Department, Konstantopoulio General Hospital "Aghia Olga", Athens, Greece*

The integral character of the bipolar spectrum disorders is undoubted, testified by such powerful common denominators as genetics and natural history. This fact raises several important questions. For example, could the non-specific sedative or "anti-psychotic" effect of an antischizophrenia drug, make it an antimania agent, in the absence of a specific mood stabilizing action? The question is all the more important given the inherent tendency of manic states to be followed by major depressive episodes and vice versa, with or without intervening periods of enthymia, tendency facilitated or prompted by the effect of the "anti-psychotic" drugs. A related question concerns the legitimacy of extending findings on drug efficacy in type I, to type II bipolar disorder, a subtype characterized by it's own, very particular features, notably higher commorbidity, chronicity and impairment, multiple episodes especially of depression and more frequent hospitalization.

The implications for future drug development would seem obvious. An antimania drug should be one with specific and good effect on acute manic symptoms, combined with long-term mood-stabilizing, prophylactic and relapse-preventive action. Despite the formidable difficulties inherent in organizing and conducting proper drug trials in patients with bipolar disorders, a suitable overall design should include: a) Short-term (4-week), 2-or 3-arm

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acute therapy studies b) Maintenance (3-month) controlled studies, with proper stratification of stabilized patients and c) Long-term (12-month) manic/depressive episode-preventive studies. Lithium, carbamazepine, sodium Valproate are examples of drugs that could serve as suitable active comparators and standard validated rating scales for the assessment of clinical states are also available. Examples of decision trees for manic or depressed index cases are possible and these are out-lined.

P04.08

Obstetric complications as risk factors for bipolar disorder

B. Kirk Øgendahl*, R.W. Licht, P.B. Mortensen. *National Centre for Register-Based Research, University of Aarhus, Denmark*

Objective: To study whether obstetric complications increase the risk of developing bipolar disorder.

Method: The Danish Psychiatric Central Register contains data on all psychiatric hospitalizations in Denmark since 1969. The Danish Medical Birth Register covers all births in Denmark since 1973. The registers were linked using the CPR-number. In the study we have identified 161 persons born between 1973–1983 being diagnosed with bipolar disorder (after the ICD-10 classification F30 or F31 or the ICD-8 classification 296.19 or 296.39) before 1999. To each of the cases we have matched 50 controls. The controls are born the same year as the case, and are alive on the day the case has been diagnosed. All the cases and controls have an identifiable mother. The controls have no psychiatric diagnosis.

Results: The data will be present on the possible role of low birth weight and gestational age and other obstetric factors as risk factors for bipolar disorder. It will be adjusted for family history for mental disorders as well as social variables.

Conclusion: In case of a correlation between obstetric complications as risk factors for bipolar disorder it can be used as prevention.

P05. Brain imaging – structural

P05.01

A diffusion tensor and metabolite spectroscopic imaging study of white matter connectivity in schizophrenia

J.K. Burns[1]*, M. Bastin[1], S. Lawrie[2], I. Marshall[1], T. McGillivrary[2], H. Whalley[3], D. Job[1], E. Johnstone[1]. [1]*University of Edinburgh, Department of Psychiatry, Scotland;* [2]*University of Edinburgh, Department of Medical Physics, Scotland;* [3]*Welcome Trust Clinical Research Fellow, University of Edinburgh, Scotland, UK*

Background: Structural and functional imaging of the brain has demonstrated abnormalities of both grey and white matter. Functional studies (fMRI and PET) suggest aberrant fronto-temporal connectivity, but further evidence is required. Diffusion Tensor Imaging (DTI) measures diffusion anisotropy, an indicator of the structural integrity of neuronal tracts. MR Spectroscopy studies (MRS) have found reduced N-acetyl aspartate (NAA) concentrations in frontal and temporal regions, indicating reduced neuronal density or viability. We used both techniques in an attempt to identify the structural correlates of impaired functional connectivity in schizophrenia.

Methods: Thirty patients with DSM-IV schizophrenia were compared with thirty healthy controls. DTI, MRS and sMRI were performed on all subjects. A symptom scale (PANSS) and IQ score (NART) was recorded. Data analysis included both whole brain voxel by voxel analysis using Statistical Parametric Mapping (SPM), and a region of interest approach.

Results: Data from previous smaller studies show reduced diffusion anisotropy and reduced NAA concentrations in schizophrenia. We expect to replicate these findings in our larger study and specifically localise abnormalities to fronto-temporal white matter tracts.

Conclusions: DTI and MRS have the capacity to identify the structural correlates of impaired functional connectivity in schizophrenia.

P05.02

Magnetic resonance tomography (MRT) of brain of serial sexual sadists

O.A. Bukhanovskaya[1]*, A.O. Bukhanovsky[2]. [1]*Scientific Center for Cure and Rehabilitation, Rostov-on-Don;* [2]*Department of Psychiatry, Rostov State Medical University, Russia*

Objectives: a study of the state of the terminal brain and its deep parts, as well as the skull in serial sexual sadists (SSS) with a revelation of a possible dysgenetic origin.

Methods: clinical and pathopsychological, magnetic resonance tomography.

Summary of the results obtained: The principal group included 22 SSS, the control group consisted of 28 males between 18 and 66. All were heterosexual, did not show any signs of paraphilia or sexual aggression and were in general law-abiding. In each case (100%) the following pathological MRT symptoms were revealed: dilation of subarachnoid fissures of frontal, frontal-temporal and frontal-temporal-parietal parts; dilation and flatting of contours of grooves and disordered differentiation between the grey and white substances of the frontal and frontal-temporal parts; dilation of the lateral ventricles and a significant asymmetry due to large right against left; dilation or narrowed fissure-like third ventrile; transparent partition pathology (left displacement up to 7 mm and cysts diameter up to 9 mm; dysgenetic of the callous body; congenital skull dysraphy.

Conclusions: the revealed and described cerebral deviations, changing a number of neurodynamic and psychological characteristics, create a cerebral predisposition to SSS, significantly raising the risk of serial sexual crime appearance.

P05.03

Progression of hippocampal atrophy is associated with clinical deterioration in Alzheimer's disease

P. Schönknecht[1]*, J. Pantel[1], M. Essig[2], M. Amann[2], L. Schad[2], J. Schröder[1]. [1]*Department of Psychiatry, University of Heidelberg;* [2]*German Cancer Research Center, Heidelberg, Germany*

Introduction: Using quantitative magnetic resonance imaging (MRI), recent studies found atrophic changes of the medial temporal lobe structures already in early stages of Alzheimer's disease (AD). These changes were cross-sectionally correlated with the severity of dementia which led to the hypothesis that progressive medial temporal lobe atrophy might be used as a marker of disease progression.

Method: We investigated the progression rate of hippocampal atrophy with respect to rate of clinical deterioration in 13 AD patients and 8 healthy controls using volumetric MRI.

Results: Already at baseline, the AD patients showed significantly smaller hippocampal volumes than controls. While AD – in comparison to healthy ageing – was characterized by a rapid decline of hippocampal volumes (-8.1%/year) only a moderate decrease of

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