interested in participating, but no more than every other of these centers expected the respective ethics committee to provide an approval for such a study. However, even among this diminished number of centers it is believed that about 800 depressive patients could be screened for a two-armed, phase II study and about 1200 for a three-armed phase III study within one year. The rous centers which were unsure about the ethics committee's opinion to be expected might involve a large potential for contributing additional patients.

Wednesday, April 6, 2005

S-66. Symposium: Bipolar disorder – Differential diagnosis as basis for differential treatment

Chairperson(s): Andreas Marneros (Halle, Germany), Giulio Perugi (Pisa, Italy)
08.30 - 10.00, Gasteig - Carl-Orff Hall

S-66-01

The mixed state phenomenon

A. Marneros. *Martin-Luther University Halle Psychiatry and Psychotherapy, Halle, Germany*

Objective: The pharmacological revolution in psychiatry also contributed to more extensive research in the so-called mixed states, although they are well known in the last 200 years. But nevertheless clinical, paraclinical and therapeutical aspects are not yet very well known, especially for schizoaffective mixed states.

Methods: To answer the above question we carried out the Halle Bipolarity Longitudinal Study (HABILOS), investigating 276 bipolar patients presenting 2133 episodes. We investigated the above population longitudinally (approximately 15 years after the beginning of the illness, 5 years prospectively), using international standardized instruments.

Results: Schizoaffective mixed states occur as frequent as pure affective mixed states. They present the most severe type of bipolar disorders. It seems that affective and schizoaffective mixed states are "intercurrent", representing a minority of the episodes but having a poor prognosis.

Conclusion: Schizoaffective mixed states are equally represented as affective mixed states. They present the most severe type of bipolar disorders. Both pure affective and schizoaffective mixed states represent a minority in relation to the other types of episodes during the longitudinal course, but they have a very strong negative prognostic validity.

S-66-02

Recognition and treatment implications of comorbidity in bipolar children and adolescents

G. Perugi. *Universita degli Studi di Pisa, Pisa, Italy*

Objective: Even if bipolar disorder (BD) is a well established clinical picture, studies of juvenile BD are more recent vintage. Reasons for such understudy include the developmentally different presentation of the early-onset form, as well as the high rate of co-morbidity, namely with attention deficit hyperactivity disorder (ADHD), multiple anxiety disorders, and conduct disorder. Other comorbidities have also been observed, including obsessive-compulsive disorder, drug and alcohol abuse, as well as eating and impulse control disorders.Diagnosis of associated disorders in juvenile BD is crucial, because comorbid conditions may mask or modify clinical picture and affect prognosis and treatment response.

Methods: Predictors of treatment non-response in early onset BD are not well defined. We explored this issue in a study, conducted in the last 3 years, in 40 referred bipolar children and adolescents with manic or mixed episodes, after controlling for age, age at onset of BD, gender and severity of the index episode.

Results: Non-responders had more frequently co-morbid conduct disorder and/or ADHD. Furthermore, they were globally more severe at baseline and required more frequent addition of antipsychotic medications than treatment-responder patients. Gender, age, age at onset of the bipolar disorder, index episode (manic versus mixed), pharmacological hypomania and comorbidity with anxiety disorders did not differentiate responder and non-responders.

Conclusion: Different mechanisms can be involved in treatment-resistance of bipolar subjects with co-morbid externalizing disorders. The identification of a subtype of BD children and adolescents linked to externalizing disorders and higher severity should improve the outcome of these subjects, using timely and effective combination of pharmacological and psychosocial interventions.

S-66-03

Soft bipolarity: The mask of anxiety, panic and obsessions-compulsions

E.-G. Hantouche. *Pitie-Salpetriere Hospital, De Mood Center, Adult Psychiatry, Paris, France*

The anxiety-bipolar connection still largely under-recognized. However in practice, resistant, complex or severe anxious patients not infrequently may suffer from hidden soft bipolarity. In a collaborative study with the French Aftoc, we find in a total sample of 628 OCD patients: 30% hypomanics and 50% cyclothymic (Hantouche et al, JAD 2003). There are many important facets, which should be considered in the anxious-bipolar comorbidity: 1) instability and complexity of clinical picture; 2) negative impact of anxiety on severity and impairment in bipolarity; 3) suicide risk; 4) recurrence of depression; 5) substance abuse; 6) high rate of diagnostic errors; 7) less favorable response to drug therapy; 8) psychiatric admissions. These phenomena could look like "refractory anxiety". Soft bipolarity should be the primary target for treatment. The lesson would be to avoid the unnecessary complications, and protect the patient by mood-stabilizers, possibly even before exposure to antidepressant. Clinicians would be able to suspect early "Bipolar Anxiety" when changing diagnosis with doctors or over time; presence of delusions and/or hallucinations; periods of rapid biphasic shifts; family history of bipolarity. Also we can use the rule of "3 or more", such as "3 Depressive Episodes"; "3 Doctors", "3 Marriages", "3 Antidepressants", "3 Anxiety Disorders". Reactivity to treatment is important: failure of treatment; medication start very good then benefits disappeared; induced hypomania or aggressive behaviors; efficacy of anti-psychotics; attempts to respond the patient's needs (symptoms that are really bipolar swings) by adding medications that are just "patches" for the holes.

S-66-04

Clinical and psychosocial factors predicting response to prophylactic lithium

W. Greil, N. Kleindienst. *Ludwig-Maximilians-Universität, München, Germany*

Objective: Recent randomized clinical trials have shown that lithium continues to be an excellent treatment option in the prevention of manic-depressive episodes. Given the burden and risks related to a long-term treatment with lithium and given the increasing number of alternative mood-stabilizing treatments it would, however, be highly desirable to individually predict response to prophylactic lithium.

Methods: A systematic review was carried out in order to integrate the available evidence on response prediction to prophylactic lithium based on clinical and psychosocial factors. On the basis of the variables identified as potential predictors in this systematic review, an easily applicable prognostic instrument was developed. Finally, validity of this "Lithium Response Scale" (LRS) was evaluated in an independent sample of n=86 bipolar patients prospectively followed up for 2.5 years.

Results: The systematic review identified 21 variables as potentially predictive for response to prophylactic lithium. Based on these potential predictors hospitalization under lithium was correctly predicted in 75% of the patients (AUC=0.72, p<0.001; f=0.35, p=0.008).

Conclusion: These findings suggest that it is possible to predict effectiveness of prophylactic lithium to a clinically significant extent. The instrument used for prediction - the LRS - is open for further improvement - e.g., by integrating biologic and genetic variables in order to enhance its predictive power.

S-66-05

Treatments for different presentations of bipolar disorder

J. Cookson. *Royal London Hospital, St. Cle, London, United Kingdom*

Objective: Treatments for Different Presentations of Bipolar Disorder The manic presentation responds to antipsychotics, lithium, valproate or carbamazepine; bipolar depression responds to old and newer antidepressants, and to treatments including lithium, lamotrigine and the atypical antipsychotics quetiapine and olanzapine. Special treatment is needed for mixed states, psychotic mania or depression, rapid-cycling, co-morbidity with substance misuse and co-morbidity with other diagnoses such as anxiety states. Even large clinical trials are often insufficiently "powered" to demonstrate efficacy in sub-groups of manic or depressed patients. However efficacy has been demonstrated for mixed manic states with certain atypical antipsychotics. Some evidence suggests differential efficacy of valproate over lithium in mixed mania. Classical antipsychotics are more effective in reducing psychotic mania than quetiapine or olanzapine. Psychotic mania is equally responsive to valproate and to antipsychotics. Non-psychotic mania responds better to an atypical antipsychotic than to a classical antipsychotic or to valproate. Studies of prophylactic treatment support a difference in response of predominantly manic bipolar conditions (BP-I and MDI patterns) from those that present mainly with depression (BP-II). The former respond to lithium and to certain antipsychotics, and the subsequent depressive phases may also be reduced by lamotrigine. Lithium is less effective in preventing depression but combined treatment with selective serotonin reuptake inhibitors (SSRIs) plus lithium or an atypical antipsychotic may be effective. Quetiapine improves anxiety that is co-morbid with bipolar depression. Large observational studies indicate different patterns of response in co-morbid substance misuse. Rapid-cycling BP-I may respond to an antipsychotic; rapid-cycling BP-II sometimes benefits from lamotrigine.

Wednesday, April 6, 2005

S-67. Symposium: Influence of neurobiological factors on the course of depressive disorders

Chairperson(s): Matthias Rothermundt (Münster, Germany), Detlef E. Dietrich (Hannover, Germany) 08.30 - 10.00, Gasteig - Black Box

S-67-01

The influence of neuronal restructuring on the course of depressive disorders

M. Rothermundt, G. Ponath, G. Hetzel, D. E. Dietrich, V. Arolt. *University of Muenster Dept. Psychiatry, Münster, Germany*

Objective: Recent evidence suggests that neurodegenerative mechanisms may be involved in the pathophysiology of major depression. Structural and functional changes might be caused by alterations of dendrites and synapses. The astroglial protein S100B regulates the balance between proliferation and differentiation in neurons and glial cells affecting protective and apoptotic mechanisms. Two earlier studies reported increased S100B CSF and serum levels in acutely depressed patients.

Results: In study 1 the mean S100B serum concentration (immunofluorimetric sandwich assay) was significantly increased in depressed patients compared to healthy controls. The relative response rate to antidepressant therapy after 4 weeks correlated positively with S100B levels. In a regression analysis, only S100B concentrations and HAMD total score predicted the therapeutic response. In study 2 patients with increased S100B concentrations in the acute state showed a normalization of the initially extended P2- and P3-latencies in remission. In patients with unchanged S100B levels, however, the increased latencies remained elevated even in a remitted state. In study 3 patients with recurrent major depression were investigated in the state of clinical remission. Those patients with increased S100B concentrations in a remitted state demonstrated normalized N2- and P3-amplitudes while patients with lower S100B levels displayed pathologically decreased N2- and P3-amplitudes.

Conclusion: These findings suggest that alterations in dendrites and synapses might be involved in the pathogenesis of depression. S100B may be a parameter indicating neuronal restructuring.

S-67-02

The HPA system in depression: Indicator of vulnerability and treatment response