**Conclusion:** TSD in patients with depression leads to an activation of the RAAS in the recovery night.

## S-53-03

HPA system and neurosteroid regulation in relation to sleep deprivation in major depression

C. Schüle, T. Baghai, P. Zwanzger, D. Eser, C. Nothdurfter, R. Rupprecht. *University of Munich LMU, Clin, Munich, Germany*

**Objective:** In the present investigation, the hypothalamic-pituitary-adrenocortical (HPA) axis activity (study 1) and concentrations of neuroactive steroids (study 2) were measured in depressed patients treated with partial sleep deprivation (PSD).

**Methods:** 39 (study 1) and 29 (study 2) drug-free patients suffering from major depression (DSM-IV criteria) were treated with PSD. PSD response was defined as a reduction of at least 30% according to the 6-item version of the Hamilton-Depression Scale (6-HAMD). HPA axis activity was measured using the dexamethasone/CRH test (study 1). In study 2, plasma samples were taken the day before and after PSD and after one night of recovery sleep at 8:00 AM for quantifying neuroactive steroids (combined gas chromatography/mass spectrometry analysis).

**Results:** In study 1, patients with postdexamethasone cortisol levels < 15 ng/ml (before CRH administration) showed a significantly greater 6-HAMD score reduction after PSD than patients did with postdexamethasone cortisol > 15 ng/ml. Moreover, a significant negative correlation between postdexamethasone cortisol and 6-HAMD score reduction was demonstrated. In study 2, there was no influence of PSD on the concentrations of neuroactive steroids neither in PSD responders nor in non-responders. However, non-responders showed significantly higher concentrations of 3alpha,5alpha-tetrahydroprogesterone (3alpha,5alpha-THP), 3alpha,5beta-tetrahydroprogesterone (3alpha,5beta-THP), and dehydroepiandrosterone (DHEA) before or after PSD compared to responders.

**Conclusion:** Apparently, HPA axis activity and the concentrations of certain neuroactive steroids are associated with response to PSD. However, in contrast to antidepressant drugs which correct the dysequilibrium of neuroactive steroids in major depression within several weeks, PSD does not affect the concentrations of neuroactive steroids neither in responders nor in non-responders.

## S-53-04

The role of brain monoamines in the antidepressant response to sleep deprivation

F. Benedetti, B. Barbini, A. Bernasconi, M. Cigala Fulgosi, C. Colombo, S. Dallaspezia, A. Pontiggia, E. Smeraldi. *Università Vita-Salute San Raf, Milano, Italy*

Combined treatment of bipolar depression with lithium salts, antidepressant drugs, and chronobiological inteventions such as single or repeated total sleep deprivation (TSD), sleep phase advance (SPA), and morning light therapy (LT), allowed to reach response rates of 60-70% and could successfully prevent relapse, thus providing clinical psychiatrists with new instruments to achieve rapid and sustained antidepressant response in bipolar depressed patients. The synergist combination of chronotherapeutic treatments and drug enhancing the activity of brain monoamines suggested common mechanisms of action. In the last years data from genetic research allowed to partially explain the mechanism of action of chronobiological treatments. The influence of a functional polymorphism in the transcriptional control region upstream of the coding sequence of the 5-hydroxytryptamine transporter (5-HTTLPR) on response to TSD was found to be similar to that observed on response to serotonergic drug treatments. Patients treated with TSD followed by light treatment showed the same influence of 5-HTTLPR. Finally, preliminary recent observations suggested that variants of genes pertaining to the molecular clock (CLOCK and GSK3-) influence core features of the illness such as age at onset and recurrence of illness, and response to TSD and lithium salts.

## S-53-05

Therapeutic efficacy of sleep deprivation and other sleep-wake-manipulations in major depression

D. Riemann. *Universitätskrankenhaus Klinic für Psychiatrie, Freiburg, Germany*

**Objective:** It has been demonstrated convincingly, that a night of total sleep deprivation leads to an immediate and swift amelioration of mood in approximately two thirds of patients with a major depression who are subjected to the procedure. Unfortunately, the effect of sleep deprivation is short lived and usually after the next night of sleep the majority of patients relapse into depressed mood. Insofar, total sleep deprivation has always been seen as an adjunct therapy, in order to shorten the time lag between initiation of antidepressant pharmaco- or psychotherapy and the onset of action of these kind of therapies.

**Methods:** Own studies focused on the question, whether it is possible to prolong the short lived effect of sleep deprivation by other sleep-wake-manipulations. In our strategy, after sleep deprivation patients were subjected to a phase advance of sleep time. Initially, patients were allowed to sleep from 17.00 to 24.00 hours and then bedtime was graduately shift back to the normal phase on one hour per day until the normal phase position was reached.

**Results:** In several studies it was shown that with this procedure approximately two thirds of patients who respond to sleep deprivation can be stabilized in their mood state as experienced directly after sleep deprivation. This was shown in medicated and unmedicated patients and also in a controlled design where one half of the patients was subjected to phase advance and the other half to phase delay. In the most recent study we were also able to replicate our results with a shortened period of only 3 days of sleep phase advance after sleep deprivation.

**Conclusion:** It has also been shown for sleep deprivation and partial sleep deprivation, combined sleep deprivation and light therapy and combined regimes of sleep deprivation and medication that it is possible to sustain the positive effect of sleep deprivation at least in subsamples of depressed patients.

**Tuesday, April 5, 2005**

# S-58. Symposium: Placebo-controlled studies for the research of new antidepressant drugs: Necessary, ethical and feasible?

*Chairperson(s):* David Baldwin (Southhampton, United Kingdom), Siegfried Kasper (Wien, Austria)
16.15 - 17.45, Gasteig - Philharmonie

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## S-58-01

Placebo controlled studies to establish efficacy and safety of antidepressants: Regulatory requirements for the development of antidepressive drugs

K. Broich, A. Koch. *Bundesinstitut für Arzneimittel, Bonn, Germany*

**Objective:** Controlled, randomized, double-blind parallel-group clinical trials are needed to establish efficacy and safety of new antidepressants. Usually this is done by clinical trials including placebo control. These placebo controlled trials have been critizized as being unethical in clinical situations where effective and acceptable treatment options are available. It has been argued that studies with potential new antidepressants should employ only a comparator-controlled design, whereby new drugs have to be non-inferior or superior to existing treatment. However, sole acceptance of „superior" compounds will hinder the development of more efficacious and better tolerated drugs. Moreover, acceptance of non-inferiority designs in psychopharmacology will be associated with the risk to approve ineffective compounds. In general both active-controlled designs require the inclusion of larger patient populations. Therefore from a regulatory point of view placebo-controlled studies of new antidepressants are still justified and necessary, both ethically and scientifically. However, it has to be secured that patients are not harmed by the act of forgoing established treatment options and did provide fully informed consent. The methodological and ethical rationales for the requirement of placebo-controlled trials with antidepressants are reviewed.

## S-58-02

Placebo-controlled studies in depression: Necessary, ethical and feasible

D. Baldwin. *Royal South Hampshire Hospital, Southhampton, United Kingdom*

**Objective:** Placebo-controlled trials are used widely in the development of new pharmacological treatments. They have sometimes been challenged as being unethical, in clinical situations where patients can receive an existing effective and acceptable treatment.

**Methods:** It has been argued that studies of potential antidepressants should employ only a comparator-controlled design, whereby new compounds have to be found at least as efficacious as existing treatments. By contrast, others have argued that sole use of comparator-controlled trials is itself unethical, as more patients will be exposed to potentially unhelpful treatments.

**Results:** This presentation reviews the rationale for conducting placebo-controlled treatment studies in depressed patients, examines the underlying ethical issues, and describes the provisions that should be applied when investigating the efficacy and tolerability of potentially valuable new antidepressant treatments.

**Conclusion:** A European Expert Forum on Placebo-Controlled Studies in Depression (Baldwin et al., 2003) has concluded that placebo-Controlled studies of new antidepressants are justified, both scientifically and ethically. Restrictions on placebo-controlled investigations will hinder the arrival of more efficacious and better tolerated antidepressants. Reference Baldwin DS, Broich K, Fritze J, Kasper S, Westenberg H, Möller H-J, on behalf of the European Expert Forum on Placebo-Controlled Studies in Depression. Placebo-controlled studies in depression: necessary, ethical and feasible. European Archives of Psychiatry and Clinical Neuroscience 2003; 253: 22-28.

## S-58-03

Placebo-controlled studies in depression from the patient's point of view: Efficacy and safety

S. Kasper, R. Frey. *Medizinische Universität Allgem. Psychiatrie, Wien, Austria*

**Objective:** Placebo response can be attributed to non-specific measurements as well as in connection to spontaneuos outcome. In large pools of placebo-controlled trials, it has been demonstrated that there is a negative correlation between mean baseline Hamilton Score and change scores in depression ratings which indicate that higher severity of depression is associated with a lower placebo rate. Epidemiological data indicated that the placebo response cannot be attributed to factors such as gender, age, smoking or personality variables (obsessive vs. histrionic). The placebo effect appears to be a contextual-situational phenomenon which is more likely than an enduring personality trait and the specific physician-patient relationship can be discussed within the most important factors of placebo-nocebo response. Therefore, it seems to be necessary to standardize the patient-doctor relationship and there is also the necessity to measure expectations prior to the start of treatment. Placebo can also be viewed as a symbolic value since placebo-treated patients receive all the „healer's" commitment, enthusiasm and positive reward. There are several myths associated with placebo treatment, e.g. there should be a reduced recovery from placebo treatment which has not been demonstrated, at least in the last ten years and furthermore, there seems a myth of attempted of completed suicide rates which also cannot be demonstrated in randomized controlled trials. For placebo-controlled studies, from a patient's perspective, it's necessary for researchers to include safeguards, standardized exit criteria, informed consent etc. to avoid a detrimental outcome.

## S-58-04

The feasibility of placebo-controlled studies in depression in Europe: A survey by GlaxoSmithKline

D. Angersbach. *GlaxoSmithKline GmbH & Co. KG Medizinische Abteilung, München, Germany*

Despite the availability of rous effective antidepressants, psychiatrists agree that in everyday clinical practice there is a large need of still more potent substances. From a scientific point of view, placebo-controlled, double-blind studies are inevitable in having new drugs approved for marketing and they are actually a regulatory requirement. In a "Note of Clarification" on the Declaration of Helsinki, the World Medical Association (WMA) clarified that on certain conditions, which also apply to antidepressants, placebo-controlled studies are admissible from an ethical point of view, even if effective drugs are available. In order to explore the feasibility of such studies in Europe, a survey was conducted in more than 900 psychiatric centers (psychiatrists established in private practices, smaller hospitals and university hospitals) in 21 European countries to examine their interest and potential for participating in such studies with predefined study designs. Just over half of the 331 centers answering the survey were

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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.

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