S45.02

Dysfunction of the neuroendocrine system: Implications for the treatment of schizophrenia

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There is large evidence that stress plays a crucial role in the pathophysiology and course of many psychiatric disorders. The stress-vulnerability model has been widely accepted for many years. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been previously reported in schizophrenia. Patients in the acute phase of the disease seem to have an activated HPA axis (Holsboer-Trachsler et al. 1997) compared to patients who are clinically stable. Results from studies on ACTH regulation are inconsistent. abnormal dexamethasone suppression test (DST) results have been shown in normal aging, depression and schizophrenia. DST non-suppression was associated with cognitive impairment, ventricular enlargement and poorer prognosis (for review: Yeap and Thakore, 2005). Long-term hippocampal exposure to excessive levels of glucocorticoids can induce cognitive dysfunctions due to reduced neuronal volume of this limbic structure. the pharmacological reduction of glucocorticoid excess may help to improve cognitive functioning in schizophrenia.

S45.03

Therapeutic Drug Monitoring and its implications on acute and long-term treatment with neuroleptics

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Therapeutic Drug Monitoring (TDM) is a useful tool to survey individual patients for the correct prescription and dosing of neuroleptic drugs. Confounders for causal drug effect relations are both patient-related and drug-related. An example of a patient-related confounders is problems with compliance to prescribed medication that can be objectively identified or ruled out by TDM in cases of non-response or partial but insufficient clinical response. This problem may arise both in the acute phase of treatment as well as during long-term treatment. Examples of combined patient-related and drug-related confounders are the very individual pharmacokinetic (PK) handling of the drug once the patent has ingested a neuroleptic compound. All such drugs undergo significant metabolism in the body, which is subjected to major inter-individual variability to a large extent due to existence of polymorphic genetic expressions among enzymes responsible for drug detoxification processes in the liver. Moreover, each separate neuroleptic compound, whether its is a classical or an atypical agent, has different affinities for these drug catabolic enzymes. The entire picture of PK-variability existing for antipsychotic drugs is therefore in healthy young male volunteers about one order of magnitude. In real life, i.e. in the everyday naturalistic clinical setting where for example also polypharmacy is a common feature, this variation in the PK between individuals increase 10-fold to be about two orders in magnitude.

This presentation focus TDM-studies where PK-variability and drug PK-effect relations for traditional as well as atypical antipsychotic agents are scrutinized.

S45.04

Pharmacogenetics in first-episode patients with schizophrenia

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Uncertainties in individual response to specific antipsychotics are a major limitation in improving treatment. Pharmacogenetics offers the opportunity to help the clinical decision process by allocating individuum-specific odds for response versus non-response. Pharmacogenetics in schizophrenia has up to now produced only a very limited number of valid results. A main reason might be the heterogeneity of samples under study and lack by standardization of treatment (e.g. mixture of first onset and chronic patients).

The German Competence Network of Schizophrenia has completed a long-term treatment protocol in first-episode patients with schizophrenia (double-blind randomized study with risperidone versus haloperidol). We explored the predictive power of disease-associated variants in disposition genes and modifier genes for schizophrenia. We detected predictive markers in the genes for dysbindin, neuregulin 1 and COMT. These variants were also associated with neuropsychological correlates of schizophrenia.

Thus we can be confident that time has come to improve the tools for prediction of response to antipsychotics.

S46. Symposium: THE 5-HT — ADRENERGIC INTERACTION IN THE PATHOPHYSIOLOGY AND TREATMENT OF DEPRESSIVE DISORDERS

S46

Contemporary approaches for an optimal treatment of major depression

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The pharmacotherapeutic approach to the treatment of major depression consists in giving an optimal dose of an antidepressant medication for a sufficient time. Using this conventional strategy in standard medication trials, approximately half the patients present a response, defined as a 50% improvement, but only about 30-40% generally achieves remission. This is a poor treatment outcome and these numbers have been questioned the patient population tested may be different from those in regular ambulatory conditions. The STAR*D project addressed the latter concern by treating patients all comers, including patients with physical and psychiatric co-morbidities, first with a SSRI and then with switch and combination approaches. Not covered in STAR*D was the strategy of adding an atypical antipsychotic in SSRI-resistant patients. Finally, a novel strategy consists in using two antidepressant medications from treatment initiation.

Wednesday, 21 March 2007
CS08. LONG TERM TREATMENT IN PSYCHIATRY

CS08.01

Long-term treatment of schizophrenic patients

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All the available evidence from randomised controlled studies indicates that antipsychotic medications substantially reduce the risk of relapse in the stable phase of illness. The lowest dose should be chosen at which preferably no side effects occur, the risk of relapse seems to be optimally reduced and, if symptoms are still present, suppression of these is optimised. Side effects have to be assessed and, if necessary, pharmacotherapy has to be adjusted. Despite several methodological design issues, second-generation antipsychotics have proven similar or superior efficacy in preventing relapse and suppression (or even improvement) of symptoms compared to FGAs (available studies of the specific agents supply evidence for periods of up to 2 years). Due to the decreased risk of EPS, especially tardive dyskinesia, and, as observed in most studies, the superior efficacy in improving negative, cognitive and depressive symptoms together with at least comparable (for some agents, e.g., risperidone, olanzapine, superior) efficacy in relapse prevention, second-generation antipsychotics should be preferred in long-term treatment. Given all the known problems in compliance and discontinuation, which were underlined by the CATIE study, depot preparations should be considered for optimum effectiveness in preventing relapse. Randomised, control-group studies to determine the advantages of depot preparations of atypical neuroleptics compared to depots of typical neuroleptics are still lacking. The target strategy in long-term treatment of schizophrenia should be a combination of long-term antipsychotic treatment and psycho- and sociotherapeutic procedures, so that the relapse rate is further reduced and the course of disease can be further improved.

CS08.02

Long-term treatment of unipolar depression

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There is a need for long-term treatment of unipolar depression. With the older medication, tricyclic antidepressants, acute treatment was possible, but unfortunately, the patients did not take the long-term medication, specifically in the correct dosage. With the introduction of modern antidepressants, this dilemma has been partly solved, as the patients are more willing to take their medication. However, compliance studies indicate that this is only the case for a very low percentage. The European Health Regulatory authorities (EMEA) demand for every antidepressant introduced into the market to demonstrate efficacy for at least 6 months. These requirements are not necessary for the American counterpart, the Food and Drug Administration (FDA). Therefore, all the modern medications demonstrate this efficacy, a few of them even for a longer period. The question arises if this benefit can also be achieved for children and adolescents as well as for the elderly. Just a few studies suggest this also for the younger and older population. Side effects as well as the failure of understanding the nature of unipolar depression limit the necessary long-term usage of antidepressants. Education programmes, which indicate that depression is a disease like hypertension, asthma or diabetes, help the patients understand the disease and the triggers, which might accompany the long-term outcome.

During the lecture the unmet needs for treatment of unipolar depression as well as modern outcome studies of recently introduced medication will be presented.

CS08.03

Long-term treatment of bipolar depression

E. Vieta, J.M. Goikolea. *Clinical Institute of Neuroscience, Bipolar Disorders Program Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain*

Bipolar depression, and particularly its long-term treatment, represents a challenge nowadays. Although mania and hypomania are the distinctive mood disturbances in bipolar disorder, it is becoming increasingly apparent that depression is the predominant mood alteration in bipolar disorder, and the main cause of dysfunction and mortality for patients. However, despite the clear clinical and public health implications of these facts, research has traditionally neglected bipolar depression, and clinicians continue to encounter many difficulties in the management of patients. Lithium and anticonvulsants, with the exception of lamotrigine, appear to be more effective in mania than in depression. Antidepressants, particularly tricyclics and dual acting compounds, may induce mania, especially when used in the absence of an antimanic drug. The evidence on this safety concern is less compelling as far as SSRIs are concerned. Changes in dopaminergic activity have been implicated in the pathogenesis of bipolar depression and now two apparently opposite strategies are being used to improve depressive symptoms in bipolar patients: adjunctive dopamine agonists, such as pramipexole, or dopamine antagonists, such as atypical antipsychotics. Three recent placebo-controlled studies support the use of olanzapine, and particularly quetiapine, in the treatment of bipolar depressed patients. Electroconvulsive therapy remains as an option in treatment-resistant patients. Cognitive-behavioral therapy and psychoeducation seem much better for the prevention of relapse than for the treatment of acute episodes. Further studies are ongoing to test novel strategies for the long-term treatment of bipolar depression.

CS08.04

Long term treatment of anxiety disorders

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Anxiety disorders, including panic disorder (PD), generalized anxiety disorder, and social anxiety disorder (SAD), generally have a chronic course.

Based on clinical experience, experts recommend that effective treatment be continued for at least 12 months. Only in the recent years, randomized long-term and relapse prevention studies with a duration of 24-52 weeks have been conducted to establish sustained efficacy of drug treatment, triggered by the requirements of the regulatory authorities. Now, an expanding body of evidence from controlled trials demonstrates the long-term efficacy and tolerability of the serotonin selective reuptake inhibitors (SSRIs) such as escitalopram, fluvoxamine, paroxetine, or sertraline, the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine, the calcium channel modulator pregabalin, the reversible inhibitor of MAO-A moclobemide and other drugs for the long-treatment of anxiety disorders.

All these studies confirm the necessity of continuous treatment over at least several months, as differences to placebo were still observable after treatment over half a year. Generally, the drugs were tolerated well during maintenance therapy. In the long-term treatment of anxiety disorders the same doses are usually prescribed as in the acute treatment phase.

There is also evidence for the effectiveness of cognitive-behavioral therapy (CBT). CBT and drug treatment can be combined, and at least for panic disorder, synergistic effects have been observed.

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