a rational use of TDM with genotyping / phenotyping strategies could improve pharmacotherapy, will be presented.

S-03-03

Therapeutic drug monitoring of risperidone in relation to MDR1 genotype and hormone levels

M. Riedel. *Psychiatric Hospital, LMU Muni, Munich, Germany*

S-03-04

Therapeutic drug monitoring of quetiapine and its major metabolites quetiapine-sulfoxide and 7-hydroxy-quetiapine

M. J. Schwarz, *Psychiatric Hospital, LMU Muni, Munich, Germany*

I. Spellmann, A. Müller-Arends, S. Dehning, R. Musil, M. Opgen-Rhein, J. Zach, H.-d. Li, N. Müller, H.-J. Möller, M. Riedel.

Quetiapine is one the most frequently prescribed new atypical antipsychotic drugs. After oral administration, it is rapidly absorbed and extensively metabolised, resulting in relatively low serum concentrations of the parent drug. For years, quetiapine was believed to be mainly (if not exclusively) metabolised by the cytochrome P450 enzyme 3A4. Recent in vitro data, however, show that Cyp2D6 is also an important component of quetiapine metabolism. We were interested in the relationship between different metabolites and the parent drug in serum, the daily dose, and the clinical effect of quetiapine therapy in schizophrenic patients. Forty patients were included into a six-week monotherapy study with variable dose of quetiapine. Response to treatment was monitored by weekly assessment of the PANSS. We established a HPLC method for the simultaneous determination of quetiapine and seven of its metabolites including quetiapine-sulfoxide and 7-OH-quetiapine after solid phase extraction. Serum levels of quetiapine showed a strong correlation with quetiapine-sulfoxide, but not with the daily dose. 7-OH-quetiapine moderately correlated with the daily dose, while an unspecified metabolite, which we called 'metabolite 6', strongly correlated with the daily dose. No relationship between either quetiapine or one of its metabolites with therapy response was found. To confirm these data, we investigated 100 schizophrenic in-patients, who underwent quetiapine treatment (mostly in combination with other antipsychotics) with repeated therapeutic drug monitoring during a one-year period. Again, we found a strong correlation between metabolite 6 and daily dose, but not between quetiapine and daily dose. Moreover, there was again no relationship between quetiapine or metabolite 6 levels and therapy response as indicated by the clinical global impression scale. Since metabolite 6 appeared very early during the first week of quetiapine administration, we propose that it is a direct quetiapine metabolite. We propose that this metabolite may be produced by CYP2D6, but in vitro studies will have to confirm this hypothesis.

Tuesday, April 5, 2005

S-20. Symposium: Evolutionary psychiatry

Chairperson(s): Pierre Schulz (Chêne-Bourg, Switzerland), Thierry Steimer (Genf, Switzerland)
16.15 - 17.45, Holiday Inn - Room 8

S-20-01

What is evolutionary psychiatry?

T. Steimer. *Clinical Psychopharmacology, Genf, Switzerland*

The clinical approach to psychiatric disorders has been mainly phenomenological and empirical. Progress in the understanding of the biological substrates underlying some pathologies (e.g. the neuroendocrine stress system in depression) has led to more theoretical considerations regarding the etiology and physiopathology of mental illness. Animal models of psychiatric disorders, on the other hand, have shown a role for adaptive vs maladaptive responses to environmental and social challenges, and the importance of genetic vs environmental influences during ontogenesis. These findings have been incorporated into the current "biopsychosocial model". Recently, evolutionary psychiatry has emerged as a new theoretical framework, based on concepts derived from evolutionary theories, also including ethology and sociobiology. It is an attempt to reconsider psychopathology within the context of phylogenesis and alternative adaptative strategies: behaviours have been selected – or retained - for their adaptive value. Although this new way of considering psychiatric diseases is interesting and potentially fruitful, it has to be assessed critically. First, the "evolutionary explanation" may not apply to all kinds of psychiatric diseases, or their individual manifestations. Some of them are more likely the result of dysfunctions which, being of limited prevalence, can be tolerated as part of natural variation. Second, evolutionary theories themselves are open to criticism and, in particular, the "adaptationist" view must be considered with some caution, because adaptation may not be a driving force of evolution. In this Introduction, we will try to give a balanced account of the evolutionary approach to psychiatric syndromes and consider some of its further developments.

S-20-02

A. Langaney. *Dpt. of Anthropology and Ecolo, Geneva, Switzerland*

S-20-03

Therapeutic implications of Darwinian psychiatry

A. Troisi. *Dpt. of Neurosciences, Univers, Roma, Italy*

Darwinian psychiatry applies the concepts and methods of evolutionary biology to the study of mental disorders. As a new approach to the explanation for the origin of psychopathology, Darwinian psychiatry has attracted much interest among clinical and research psychiatrists. However, its utility in terms of treatment strategies and therapeutic interventions has been repeatedly questioned. The aim of this presentation is to demonstrate that, contrary to this common prejudice, Darwinian psychiatry has relevant therapeutic implications and can contribute to improve treatment strategies in psychotherapy and psychopharmacology. Unlike the biomedical model of mental disorders, Darwinian psychiatry distinguishes between dysfunctional and adaptive symptoms. Dysfunctional symptoms reflect neurobiological damage and their therapeutic elimination (if possible) does not entail any risk for the patient. By contrast, adaptive symptoms are evolved responses that serve the function of limiting or offsetting the adverse consequences of maladaptive circumstances. Symptoms of anxiety and depression may act as alarm signals and may favor the implementation of alternative behavior strategies. The use of drugs or psychological therapies to eliminate these

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symptoms may diminish suffering but worsen the global condition of the patient, as in the case of antipyretics in infectious diseases. Another important point emerging from a Darwinian approach to psychiatric therapy is that functional outcome is more important than symptom evaluation. In line with an evolutionary perspective, recent research has shown that functional impairment is a core aspect of different psychiatric disorders and that its occurrence is largely independent from symptom severity.

S-20-04

The human nature of animals

J. Koolhaas. *Dpt. of Animal Physiology, Uni, Haren, Netherlands*

In scientific research, animals are generally used as a model to obtain fundamental insight into human functioning. It is generally accepted that there is a considerable similarity between animals and human beings in physiological processes. However, with respect to behavior and psychology, this correspondence is far less self evident. Although the overt expression of behavior knows large species specific differences, all vertebrates share a number of fundamental mechanisms underlying behavior. A phylogenetically ancient capacity involves the way individuals deal with environmental challenges. Different coping styles can be distinguished and it will be argued that individual differentiation in coping style is fundamental to a wide variety of animal species. Studies on feral populations of rodents, fish and birds show that the differentiation in coping style has an important function not only in the social organization, but also in the evolutionary ecology of the species. Animals with a different coping style differ also in the neurobiological and neuroendocrine mechanisms underlying behavior. These include serotonergic and vasopressinergic neurotransmission and HPA axis reactivity. Some evidence will be presented that these physiological differences may explain the individual vulnerability to stress related disease. At first glance, the physiological and behavioral characteristics of coping styles are similar to human personality or temperament characteristics. However, the question if, and to what level the individual differentiation in coping style reflects the biological basis of human personality or temperament requires an experimental approach that requires a joint search for the human nature in animals as well as the animal nature in humans.

Sunday, April 3, 2005

S-14. Symposium: Polypharmacy in psychiatry

Chairperson(s): Siegfried Kasper (Wien, Austria), Eduard Vieta (Barcelona, Spain)
16.15 - 17.45, Gasteig - Black Box

S-14-01

Polypharmacy in schizophrenia

S. Kasper, A. Konstantinidis. *Medizinische Universität Allgem. Psychiatrie, Wien, Austria*

Although there is a lack of data indicating the efficacy of polypharmacy in schizophrenia there seems to be a widespread belief, not only in Europe, that the combination of antipsychotics/ neuroleptics enhances the efficacy of antipsychotic treatment. This approach, the polypharmacy approach, is specifically undertaken in the group of treatment-refractory schizophrenia. Before the introduction of the group of atypical antipsychotics the combination of high-potency neuroleptics (e.g., haloperidol) with low-potency neuroleptics (e.g., levomepromazine) was quite common practice. Sedation was the target for low-potency neuroleptics and antipsychotic efficacy for the high-potency neuroleptics. However, there seems to have been a shift in recent years for the combination of an atypical antipsychotic (e.g., clozapine) with a high-potency neuroleptic (e.g. haloperidol), although the available data base does not clearly indicate the effectiveness of this approach. For clozapine and risperidone, a few case reports and case series are available to support this type of combination treatment, which is argued to be based on pharmacodynamic considerations with the different striatal D2 receptor occupancy rates of these compounds. The combination of two atypical antipsychotics is not so much performed in Europe but seems to be the practise in Canada. Specifically the financial limitations do not favor this approach, given also the lack of available data. Controlled studies of polypharmacy, including brain imaging and molecular psychiatric parameters, need to be conducted to find out the therapeutic potential of polypharmacy approaches in schizophrenia.

S-14-02

Polypharmacy in bipolar disorder

E. Vieta. *University of Barcelona Hospital Clinic, Barcelona, Spain*

Objective: To address the main benefits and inconvenients of polypharmacy in the treatment of bipolar illness.

Methods: A systematic literature search was carried out. Controlled and naturalistic reports were extensively scrutinized.

Results: Bipolar disorder is difficult to treat. Only about one third of bipolar patients respond to monotherapy. For this reason, combination therapy is increasingly the rule rather than the exception. The advantage of polypharmacy, particularly when drugs with different mechanisms of action are combined, is enhanced efficacy. This is, however, not the same as enhanced effectiveness, as side effect burden and interactions may result in higher attrition rates and poor compliance. However, for a substantial proportion of patients, the skilful combination of anticonvulsants with atypical antypsychotics (in mania), antidepressants (in bipolar depression) and lithium (in prophylaxis) seems most promising. In coming years, high standard randomized controlled trials should address the specific efficacy and tolerability of certain combinations. Meanwhile, clinicians who are faced with the treatment of this disabling condition, have started to use these combinations in order to achieve better outcome for their bipolar patients.

Conclusion: While monotherapy would be the ideal therapy, the reality is pushing clinicians to combine two, three or more drugs, together with psychoeducative approaches, for many, if not most, of their patients.

S-14-03

Combinations of antidepressants with other psychotropic drugs: Evidence from naturalistic studies and randomised controlled trials

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

Objective: Antidepressants are often combined with other psychotropic drugs in primary and secondary mental health care settings. In some instances, combination treatment may be supported by the results of meta-analysis and randomised

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