INTERNATIONAL ANXIETY DISORDERS CONFERENCE

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ORAL PRESENTATION ABSTRACTS

Treatment of Generalised Anxiety Disorder

Christer Allgulander
Karolinska Institutet, Stockholm, Sweden

The neurobiology of anxiety and mood disorders appears to be shared, and patients with primary anxiety disorders are at increased risk of developing secondary depressive episodes. Frequently, these disorders are found within the same family, indicating a shared diathesis. One study found an increased frequency of the short/short allele genotype for 5-HTTLPR (You et al 2005). According to twin studies, vulnerable women may develop either generalized anxiety or depression depending on environmental circumstances (Middeldorp et al 2005).

Venlafaxine, paroxetine, sertraline, and escitalopram have been shown to be effective in the acute and maintenance therapy of GAD (Baldwin & Polkinghorn 2005). In controlled studies the response rate is about 70 per cent, and maintenance treatment enables remission in a majority of the cases. There are no known irreversible adverse effects, yet sexual effects and discontinuation symptoms are to be expected. In some children and adolescents, caution must be paid to increased irritability and suicidal ideation with some of these medications.

Pregabalin is a novel anxiolytic with a novel mechanism of action for which regulatory approval is pending for GAD treatment.

The increased utilization of serotonergic medications has been parallelled with reductions in suicide rate in several countries. In Sweden the number of suicides decreased with an unprecedented 31 per cent in the last decade. Six per cent of primary care patients are on maintenance treatment with SSRIs or SNRIs, as anxiety and depressive disorders are the most common in primary care second to musculoskeletal conditions.

Emerging research shows benefit of treatment in GAD patients with concurrent stroke, myocardial infarction, and diabetes in whom the risk of subsequent somatic complications is reduced, and the likelihood of successful rehabilitation is increased. Alcohol dependence can probably be prevented and treated by identifying subjects with comorbid GAD who self-medicate with alcohol.

Studies show that it is cost-effective to empower nurses to take charge of caring for subjects that doctors have targeted for treatment of anxiety and depression. Treatment adherence can be further enhanced by teaching the patient elementary coping skills by means of individual or group counselling.

The internet provides access to support groups, to educational websites, and to online cognitive skills training. Yet, a minority of subjects with GAD in the community receive any kind of treatment, probably due to stigma and to concerns over drug dependence.

Evidence-based Guidelines for Anxiety Disorders - Can they Improve Clinical Outcomes?

David Baldwin
Division of Clinical Neurosciences, University of Southampton, UK

Although many anxiolytic drugs and psychotherapies are available for the treatment of anxiety disorders, the overall care of patients with these typically persistent and impairing disorders is usually far from optimal. One strategy to improve clinical outcomes would be to prescribe drugs and deliver psychological treatments according to evidence-based guidelines, with or without supplementary algorithms, designed to help practitioners and patients make appropriate decisions in specific clinical circumstances. Two prominent recent evidence-based guidelines for the treatment of anxiety disorders of high quality are those produced by the British Association for Psychopharmacology and the World Federation of Societies of Biological Psychiatry.

Randomised controlled trials of the treatment of depressed patients in primary care show that clinical outcomes can be improved, with greater symptom reduction and improved social function: when examined, the costs of individual care may be increased, but overall cost-effectiveness is greater. In the treatment of depressed patients, the interventions that result in improved outcomes share certain characteristics: namely 'case management' and some involvement of specialist mental health services. Case management includes a number of activities, such as assuming responsibility for patient follow-up, assessing whether depressive symptoms are resolving, monitoring adherence to treatment, and taking action when patients depart from guideline-based treatment.

There have been few randomised controlled trials of the effects of implementing treatment guidelines for anxiety disorders within routine clinical practice, and those which have been published reveal disappointing results. A recent comparison of the effects of treatment guidelines, cognitive-behaviour therapy and self-help techniques in Dutch patients with panic disorder or generalised anxiety disorder found no significant differences in clinical outcomes at 12 weeks or

after 9 months. A comparison of local treatment guidelines with computerised patient-specific treatment recommendations in UK primary care patients with 'common mental disorders' (with principally mild anxiety and depressive symptoms) found no significant differences in outcomes at 6 months. Neither of these studies involved case management.

Outcomes will not necessarily be improved by the arrival of evidence-based treatment guidelines or by more effective or better tolerated treatments; the whole process of care for patients needs to be enhanced, which requires considerable change in the organisation and function of health care teams. Theoretical treatment advances can only improve clinical outcomes if used rationally, in collaboration with the patient.

What are the Best Ways of Defining Remission in Anxiety Disorders?

Borwin Bandelow

Department of Psychiatry and Psychotherapy, University of Göttingen, Germany

Symptomatic remission is a goal for treatment in anxiety disorders, but the threshold for determining remission is uncertain. Treatment outcome is measured by using disease-specific scales that include a number of items, each of which covers separate aspects of the disorder. For anxiety disorders, standard scales exist that are applied routinely in clinical trials. These scales include the Hamilton Anxiety Scale (HAMA; for generalized anxiety disorder and the Liebowitz Social Anxiety Scale (LSAS) for social anxiety disorder (SAD), and the Panic and Agoraphobia Scale (P&A) for panic disorder. ''Response'' is commonly defined as a _ 50 % reduction on these standard scales. However, this definition is arbitrary, and cut-off points should rather be founded on empirical data than on a thumb rule. The definition of ''remission'' on standard scale scores varies from study to study and is also very subjective. Analysis of all available studies of the treatment of panic disorder, generalized anxiety disorder, and social anxiety disorder with the same treatment provides an opportunity to determine these thresholds by comparing the Clinical Global Impression Scale (CGI) and standard rating scales.

Is there Evidence that Combined Pharmacotherapy and Psychotherapy are Better than Single Modalities?

Donald W. Black

University of Iowa, United States of America

Anxiety disorders are among the most prevalent psychiatric conditions world wide, and are responsible for considerable morbidity and functional impairment. Patients with these conditions make extensive use of mental health resources, but are also frequent utilizers of primary care and emergency medical services. While it is common practice to recommend combined treatment to patients (i.e., psychotherapy plus pharmacotherapy), some have argued that this is not been shown effective in practice and is an inefficient use of limited mental health resources. This presentation will examine relating to integrative therapy for the major DSM-IV anxiety disorders. In summary, the literature suggests that, with some exceptions, combined treatment has no clear benefit over monotherapy. The best case for combined treatment has been made with obsessive-compulsive disorder, wherein the two treatments (behavior therapy and selective serotonin reuptake inhibitors) may boost response rates. In the case of panic disorder, there is evidence that cognitive therapy and pharmacotherapy may actually interfere with each other. In this era of shrinking health care resources, additional studies are needed to investigate the utility of combined treatments for the anxiety disorders.

Body Dysmorphic Disorder and Obessive-Compulsive Disorder: The Same, but Different?

David Castle

Mental Health Research Institute & University of Melbourne, Australia

Some degree of concern with appearance is normal. However, for some people, the concern becomes extreme and causes subjective distress and impairment in social and other life roles. In such extreme cases, individuals are considered to have body dysmorphic disorder (BDD). Whilst BDD is a recognized clinical entity, a number of issues remain contentious. One such issue is the disorder's relationship to other psychiatric disorders, notably OCD. This talk will take a broad approach to the nosology, clinical characteristics, and treatments for BDD, and relate these to OCD and other members of the putative OC spectrum of disorders.

Resilience: Phenomenology and Psychobiology.

Kathryn M. Connor

Department of Psychiatry, Duke University Medical Centre, Durham, USA

Resilience embodies the personal qualities that enable one to thrive in the face of adversity. As such, resilience may be viewed as a measure of stress coping ability and could be an important target of treatment in anxiety, depression and stress reactions. In this presentation, characteristics of resilience will be examined and approaches to assessment and measurement will be reviewed. As a multidimensional construct, the various factors that influence resilience will be discussed, including neurobiologic, genetic, and environmental determinants, as well as the role of temperament and aging. While reduced resilience is observed in anxiety and depression, resilience is modifiable and can be strengthened by pharmacologic and non-pharmacologic interventions. Data supporting these observations will be presented. Lastly, implications of these findings for the individual and the community will be explored.

What is the Role of DBS in Anxiety Disorders?

Damiaan Denys
Department of Psychiatry, University of Utrecht, the Netherlands

Obsessive compulsive disorder (OCD) is a frequent and chronic psychiatric disorder. Up to 7.1% of OCD patients remain refractory and run a chronic deteriorating course despite adequate treatment. Severely incapacitated patients may be indicated for treatment with psychosurgery. Recently, deep brain stimulation (DBS) has been successfully employed for the treatment of OCD. In the following presentation, the indication and value of deep brain stimulation for OCD will be discussed. Inclusion, exclusion criteria and general requirements for treatment of deep brain in OCD will be reviewed. Preliminary results from a placebo controlled study will be presented and will be interpreted at the background of current paradigms in OCD.

Do we still need Placebo-Controlled Trials for Obsessive Compulsive Disorder?

Naomi A. Fineberg[1], Hawley C[1,2] and Gale T[2].
[1] *Post-Graduate Medical School, University of Hertfordshire, College Lane, Hatfield, UK*
[2] *Dept. of Psychology, University of Hertfordshire, Hatfield, UK*

For years the randomised controlled trial (RCT) has been considered the keystone for evaluation of the quality, safety and efficacy of a new treatment (EMEA council directive 751318/ EEC). In the absence of effective treatments, the placebo controlled design, which uses a neutral agent against which to compare the purportedly active treatment, was the obvious strategy. However with the accumulation of evidence supporting efficacy for a range of established treatments and growing concern over the ethics of using placebos in illnesses where effective treatments are known to exist, attitudes towards trial design have been changing. Placebo-controlled studies expose recipients to ineffective treatment, which might have adverse consequences for them. Many ethical committees have therefore become reluctant to sanction the use of placebos in trials designed to test the efficacy of new treatments, preferring as an alternative trials that use an active treatment for comparison.

In response to this concern, the scientific community is objectively re-evaluating the rationale for the use of placebos across a range of medical and psychological disorders. In this paper we review ethical, methodological, legislative and pragmatic arguments for and against the ongoing use of placebo in trials designed to evaluate new treatments for obsessive compulsive disorder, as a touchstone for further expert discussion and debate.

Cognitive Aspects of Obsessive-Compulsive Disorder

Jun Soo Kwon
Department of Psychiatry, Seoul National University Hospital, Seoul, Korea

Obsessive-compulsive disorder (OCD) is characterized by obsessions and compulsions severe enough to interfere with a person's ability to function on a daily basis. Recently, a growing body of evidence, derived from neuropsychological studies suggests that the cognitive dysfunction underlie the symptoms of OCD. Further, whether the cognitive dysfunction in OCD could be improved with treatment is not well known. We investigated the neuropsychological functions at baseline, 4-month and 1-year period of treatment in patients with OCD. We used neuropsychological tests, including Rey-Osterrieth Complex Figure Tests (RCFT), Trail Making Test (TMT), Controlled Oral Word Association Test (COWA) and Wisconsin Card Sorting Test (WCST). OCD patients continued to show significant impairments in the cognitive measures compared with the normal controls over a 4-month and 1-year follow-up treatment, even though the cognitive function was improved with treatment compared to baseline.

Next, we applied the cognitive training program focusing on the improvement of organizational strategies to enhance the cognitive function over 5 weeks in OCD patients. To improve the visual organizational strategies, we revised the block design, which is a sub-test of K-WAIS, and used it as a training tool. To improve the ability to approach their everyday problems with an organizational method and solve them strategically, the training for organizational strategies in relation to everyday life was administered through the training for problem-solving strategies. Cognitive training of OCD patients not only improved their memory function, but also alleviated their symptoms. Therefore, cognitive training, focusing on the improvement of organizational strategies, could be an effective treatment modality for patients with OCD. In the future, the computerized training program should be developed for the patients with limited clinical resources.

Are Normal and Pathological OCD on a Continuum?

Donatella Marazziti
Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, Italy

The controversy between categories and dimensions in psychiatric nosology is far from being resolved.

If with no doubt, the recognition of discrete diagnostic entities has become very sophisticated and standardized in the DSM systematization, the lack of precise casualty models according to the medical model of the illness, represents the weakest point of categorical approach. In classifying psychopathology, however, phenomena rarely fit into clear-cut and homogenous categories, but rather fall on a continuum: for this reason, a dimensional approach that underlines the relationships between signs and symptoms appears more flexible and suitable for the recognition of atypical patients.

The categorical and dimensional approach are not necessarily exclusive and the emergence of the so-called concept of obsessive-compulsive disorder (OCD)-related or OCD spectrum disorders (OCSDs) represents an intriguing

and serious attempt to overcome this duality. The observations that obsessive-compulsive symptoms, despite being the core features of the disorder, did not appear to be limited to it, led to consider diagnostic categories along a spectrum that grouped together different disorders, on the basis of shared characteristics which could be identified not only clinically, but also in terms of family history, age at onset, comorbidity, pathophysiology and pharmacological response.

The various disorders can be grouped together also according to a dimensional approach. Those dimensions which have so far been proposed are the following: estimation of risk, or risk-aversive (compulsive) /risk-seeking (impulsive), cognitive (obsessional) /motoric (ritualistic), and another one ranging from the obsessive certainty through overvalued ideas to delusional certainty (uncertainty/ certainty dimension).

However, the dimensional approach may be broader at the point of including even normal conditions, such as falling in love and jealousy, for which may be applied the same considerations and neurobiological hypotheses.

Following this thought line, OCD and related disorder may be considered the ''dark'' side of normal behaviours, which possess an intrinsic value of adaptation, all located along the same dimensions yet to be identified.

Highlights in Obsessive-Compulsive Disorder Research: "What is the Optimal Way to Sub-divide Obsessive Compulsive Disorders?"

Euripedes C. Miguel

Institute of Psychiatry, School of Medicine, University of São Paulo, Brazil

The clinical presentation of the obsessive-compulsive disorder (OCD) is remarkably diverse; symptoms vary not only across patients but also over time. This diversity suggests that OCD is a heterogeneous disorder, what may have important impact on psychopathological, longitudinal, genetic and treatment research.

To better understand OCD possible heterogeneity, more homogeneous phenotypic descriptions are necessary to delimitate clinically specific subgroups of patients. But not only the phenotypic descriptions can be used to subdivide OCD, other forms to delimitate OCD subgroups of patients include the search for endophenotes (extend phenotypes) based on neurophysiological, immunological, genetic, neuropsychological or neuroanatomic (neuroimaging) paradigms.

The success of an optimal subdivision of OCD may help in the investigation of the etiological mechanisms of OCD as well as its vulnerability genes what may lead to the development of new pharmacological and psychotherapeutic treatment modalities (those are currently partially effective for only 60 to 80% of the patients).

Therefore, the goal of this presentation will be to discuss some available strategies that deal with OCD heterogeneity. Those include: identifying phenotypic categories which represent more homogeneous and mutually exclusive subtypes of OCD; understanding the dimensionality of the OC symptoms as quantitative traits, and broadening the diagnostic boundaries of OCD to include other etiologically related conditions. The relevance and limitations of each approach are also discussed. Probably the most effective way to identify the heritable components of OCD includes an association of both categorical and dimensional characteristics of OC symptoms. Other aim of this talk is to provide arguments for the determination of the role of epigenetic risk and protective factors in OCD in the expression of OCD presentation. Finally, the impact of these findings for new therapeutic strategies and future studies will be discussed.

How Do we Understand the Neurobiology of Comorbidity across Anxiety Disorders?

David Nutt

Psychopharmacology Unit, University of Bristol, U.K.

Anxiety disorders are common and share many features – yet each has a distinct phenomenology that allows the unique diagnosis – so any theory of neurobiology has to accommodate these seeming opposites. For some time we have been working on the conceptualisation that there is a circuit of anxiety that is common to each of these disorders and which encompasses core features such as the physiological changes [tachycardia, increase in respiration , sweating, etc] plus the sense of fear that leads to escape and avoidance behaviour. It seems likely these symptoms are mediated by a limbic and brain stem circuit that will include the amygdala, hypothalamus, amine nuclei e.g. raphe and locus coeruleus and their spinal projections. On top of this each disorder must have discrete regional brain involvement that provides the unique symptoms such as worry in GAD, speak block and blushing in Social Anxiety Disorder, panic attacks in panic disorder etc. Imaging studies have begun to give us some insights into these other regions and undoubtedly this is a field that will grow rapidly in the near future.

The other important question is why do the same drugs most notably the SSRIs work in all the anxiety disorders as well as in depression? We have examined this issue using the technique of tryptophan depletion to rapidly reduce the availability of 5HT in the brain in various patient groups. We found that in both panic and Social anxiety disorder tryptophan depletion resulted in a partial relapse in patients remitted on SSRIs – just as in depression. Ongoing studies are examining this in SSRI treated GAD patients and also after successful treatment of panic disorder with CBT. These findings so far are similar to those in SSRI treated depression and contrast with one study in OCD where relapse did not follow tryptophan depletion. We suggest that in anxiety and depression SSRIs might serve to improve lowered affective state in many disorders and that this action is dependent on ongoing elevations in 5HT function.

Transcranial Magnetic Stimulation in the Study of Anxiety

Stefano Pallanti, I Pampaloni

University of Florence, Italy & Mount Sinai School of Medicine.

Transcranial magnetic stimulation (TMS) has been a well-established diagnostic tool in neurological practice for many years. It has been shown to be a safe and well tolerated method. Lately this technique has also found its way to psychiatry for the treatment of mood disorders, and only very few studies have explored anxiety disorders.

The first disorder to be investigated has been obsessive-compulsive disorder (OCD) where lowered motor evoked potential (MEP) threshold to transcranial magnetic stimulation (TMS) and decreased intracortical inhibition in OCD has been reported (Greemberg et al., 2000) compared to normal control. According to Wasserman EM (2001) decreased intracortical inhibition related more to trait anxiety and depression, than to OCD symptoms itself.

On this background, we hypothesized that in subjects with social anxiety disorder (SAD) may have an altered cortical excitability, also given previous imaging results showing changes in cortical activity in SAD. During this talk preliminary results data of a first study about cortical excitability in SAD subjects will be discussed. We recruited n=10 Social Anxiety Disorder (according to DSM IV diagnosis) subjects and n=11 Healthy Controls. We have utilized Transcranial Magnetic Stimulation (Paired and single pulse) on Primary Motor Cortex (M1) in order to study neuronal excitability and cortical inhibitory mechanisms. These has been achieved by examining EMG recording Motor Evoked Potentials (MEP). We measured MEP, Motor threshold, Cortical Silent Period (CSP), paired pulse inhibition both in patients and healthy controls. CSP is reduced (p=.055) in Social Anxiety subjects. The other variables are not significantly different between two groups. CSP represent an index of cortical inhibition. Social Anxiety subjects show a reduction of CSP, that is a reduction of inhibition, and therefore an increased cortical excitability.

These reports might highlight the modelling of anxiety as well as could support and monitor different therapeutic approaches.

Is Pharmacological Prophylaxis of PTSD a Good Idea?

Soraya Seedat
MRC Unit on Anxiety Disorders, Department of Psychiatry, University of Stellenbosch, South Africa

While, on the one hand, it is likely that some early traumatic responses, such as intrusive memories and flashbacks, may facilitate the processing of trauma, on the other hand failing to intervene in recently traumatised individuals may increase the risk of development of posttraumatic stress disorder (PTSD). Secondary prevention involves intervening in the aftermath of a traumatic event to hinder the development of PTSD. One model of pathogenesis implicates stress hormones (epinephrine, norepinephrine, cortisol, adrenocorticotropin [ACTH]) in the overconsolidation of emotionally distressing memories. This suggests that pharmacological disruption of neuronal mechanisms underlying fear conditioning and reconsolidation could prevent progression to PTSD in vulnerable individuals. To date, there have been very few empirically-driven studies on effective pharmacological interventions in the immediate aftermath of severe trauma. Propranolol, when given as a 2-3 week course within 2-20 hours following a traumatic event, has been shown in two preliminary controlled studies of trauma survivors presenting to emergency rooms, to be effective in reducing subsequent PTSD.

This review will highlight potential pharmacological preventive approaches (including the anti-adrenergic agents, selective serotonin re-uptake inhibitors or serotonin-norepinephrine reuptake inhibitors, benzodiazepines, cortisol, anti-kindling agents [e.g., phenytoin], cortocotrophin releasing factor receptor antagonists), rationale for their use, and ethical considerations in this setting.

How Important is Suicide across the Anxiety Disorders?

Cornelis van Heeringen, Myriam Vervaet, Kurt Audenaert
Unit for Suicide Research, University of Gent, Belgium

Major reviews indicate that all psychiatric disorders, including anxiety disorders, are associated with an increased risk of suicide, and can be regarded as a necessary but insufficient cause of suicidal behaviour. Cross-sectional and longitudinal studies in clinical and community samples have indeed indicated such an increased risk in patients suffering from panic disorder, social phobia, obsessive-compulsive disorder and post-traumatic stress disorder. However, the findings have been questioned, and alternative interpretations such as selection biases and comorbidity of depression, substance abuse and/or borderline personality disorder have been put forward. Recent meta-analyses of data from large sample drug studies, for which comorbidity and suicidality were exclusion criteria, have confirmed the increased risk of suicide regardless of the type of anxiety disorder. However, a recent analysis of NCS data showed an increased risk of suicidal ideation and suicide attempts in PTSD, but not in the other anxiety disorders, while controlling for comorbid mood and substance abuse disorders. Other studies have shown the presence of anxiety to further increase the risk of suicide among patients suffering from psychiatric disorders such as bipolar disorder or cyclothymia. An increased risk of suicidal behaviour in association with anxiety disorders is possibly the consequence of a shared, whether or not serotonergically mediated, temperamental background, i.e. increased harm avoidance. It can be concluded that suicide ís important across the anxiety disorders, but that further study is clearly needed, focusing e.g. on the genetics of behavioural dimensions (such as compulsivity versus impulsivity) or cognitive endophenotypes.

Anxiety Disorders During Pregnancy and Post-partum

Bavinasha Vythilingum
MRC Unit on Anxiety Disorders, Department of Psychiatry, University of Stellenbosch, South Africa

Anxiety disorders in pregnancy and the pueperium are often underecognised, yet may be more common than mood disorders in this period. They carry morbidity for both mother and infant and are a significant risk factor for the development of postnatal mood disorders. Researchers have begun to characterise the phenomenology of anxiety disorders during this period. Furthermore, new findings in the neurobiology of pregnancy and the puerperium provide interesting insights into the pathogenesis of anxiety disorders in this time, and may help identify women at risk. In addition, the possibility of novel treatment modalities exists.

The Role of Dopamine in Anxiety Disorders - Focussing on Obsessive Compulsive Disorder

Herman G.M. Westenberg
Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, UMC Utrecht, The Netherlands

In recent years, the role of serotonin in the psychopharmacology and neurobiology of anxiety disorders has received a great deal of attention, not least because selective serotonin reuptake inhibitors are efficacious in virtually all anxiety disorders. The role of other monoamine systems, including dopamine, has been largely neglected. There is now growing evidence that dopamine systems in the brain may be implicated in anxiety. Evidence on the role of dopamine is derived from studies using animal models of anxiety disorders and from clinical studies using neurochemical, pharmacological, and neuroimaging strategies. One of the most common paradigms used to study the biological underpinnings of anxiety, is fear conditioning. There is growing evidence that dopamine plays a pivotal role in the formation, expression, retrieval and extinction of fear. Alterations in the dopamine transmission in the amygdala, medial prefontal cortex and nucleus accumbens, three main projection sites of the mesolimbic dopamine system, have been associated with different aspects of conditioned fear. Existing evidence indicates that both D_1 and D_2 receptors are required for associative processes. In the nucleus accumbens and related areas, dopamine plays a role in associative ('habit') learning and error-processing, functions that are impaired in OCD. Dopamine also codes for the hedonic aspects of reward and it has been proposed that dopamine neurons may signal the 'certainty' that ongoing events will happen. Clinical and preclinical evidence also suggests that dopaminergic neurotransmission in the prefrontal cortex is critically involved decision making. Uncertainty and indecisiveness are the hallmarks of OCD and neuroimaging studies have implicated these brain regions in the pathophysiology of this condition. Recent neuroimaging studies have confirmed the role of dopamine in OCD. It is the aim of this contribution to review the role of dopaminergic pathways in the neurobiology of anxiety disorders with emphasis on Obsessive Compulsive Disorder (OCD).

Are There Good Animal Models of PTSD?

Joseph Zohar
Department of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, Israel

Considerable heterogeneity exists in the response of human subjects exposed to extreme traumatizing events. Posttraumatic stress disorder (PTSD) is diagnosed in 20–30% of those exposed. Clinical studies of this population employ stringent inclusion/exclusion criteria, yet animal studies have routinely included the entire exposed population as the study population.

We examined the effect of grouping stressed rats according to the magnitude of their response on the statistical analysis of behavioral models. Exposure to a predator stimulus (smell of a cat) was used as the stress paradigm. Response magnitude was assessed in two consecutive behavioral tests measuring anxiety- and stress related behaviors and was used to divide the animals into groups. The two extremes were studied, that is, those clearly "maladapted" and those clearly "well-adapted," using arbitrarily selected severity-measures, the "cut-off behavioral criteria" (CBC). Data for the partially affected middle group were discarded for reasons of clarity. The hypothalamic-pituitary-adrenal axis and heart rate variability were analyzed for the entire exposed population and then reexamined according to the CBCs. When the CBCs were applied, we found PTSD-like symptoms in only 22.0% of exposed rats. Compared to controls and to well-adapted exposed rats, the behaviorally maladapted rats displayed disordered physiological measures. These differences surfaced only when data were analyzed according to the CBCs. Animals respond to stress heterogeneously, resembling humans. Overlooking heterogeneity in responses obscures the results of biobehavioral data analysis. We submit that animals exposed to trauma should be divided into groups according to the magnitude of their response and be studied accordingly.

Utilizing this model, we also studied the effect of early life adversities, high cortisolemia, the potential preventive effect of early administration of SSRI and administration of anisomycin and its effect on PTSD. Results will be presented and discussed, emphasizing the potential theoretical implications of utilizing this animal model of PTSD.

POSTER PRESENTATION ABSTRACTS

Comparative Efficacy of Long-Term Treatment with Escitalopram and Paroxetine in Severe Major Depression

Boulenger JP[1], Huusom AKT[2], Florea I[2], Bækdal T[2], Sarchiapone M[3]

[1]University Department of Adult Psychiatry, CHU de Montpellier and INSERM E361, France

[2]H.Lundbeck A/S, Copenhagen, Denmark

[3]Institute of Psychiatry and Clinical Psychology, Catholic University of Sacred Heart of Rome, 00186 Rome, Italy

Objective: Escitalopram and paroxetine show efficacy in the treatment of patients with social anxiety disorder and generalised anxiety disorder. This randomised, double blind, fixed-dose study evaluated the efficacy of escitalopram and paroxetine in the long-term treatment of patients with severe major depressive disorder (MDD). **Methods:** Patients with DSM-IV-defined MDD and baseline MADRS ≥30, with or without comorbid anxiety, were randomised in a 1:1 ratio to 24 weeks of double-blind treatment with fixed doses of either escitalopram (20 mg) or paroxetine (40 mg). The primary analysis of efficacy was an analysis of covariance (ANCOVA) of change from baseline to Week 24 in MADRS total score (LOCF). **Results:** At endpoint (24 weeks), the mean change from baseline in total MADRS score was –25.2 for patients treated with escitalopram (n=228) and –23.1 for patients with paroxetine (n=223), a difference of 2.1 points ($p<0.05$). The difference on the MADRS (LOCF) was significantly in favour of escitalopram from Week 8 onwards. The proportion of responders (≥50% decrease in MADRS) after 24 weeks was 82% (escitalopram) and 77% (paroxetine). The corresponding values for remission (MADRS ≤12) were 75% (escitalopram) and 67% (paroxetine) ($p<0.05$). The results on the primary efficacy scale were confirmed by significantly greater difference in favour of escitalopram on the HAMA, HAMD, CGI-S, and CGI-I scales. For very severely depressed patients (baseline MADRS ≥35), there was a difference of 3.5 points in favour of escitalopram ($p<0.05$). The overall withdrawal rate for patients treated with escitalopram (19%) was significantly lower than with paroxetine (32%) ($p<0.01$). The withdrawal rate due to adverse events (AEs) was significantly lower for escitalopram (8%) compared to paroxetine (16%) ($p<0.05$). There were no significant differences in the incidences of AEs. **Conclusion:** Escitalopram was significantly more effective than paroxetine in the treatment of patients with severe MDD.

Development of a Psychopharmacology Algorithm for PTSD: The International Psychopharmacology Algorithm Project (IPAP)

Connor K

*Department of Psychiatry and Behavioral Sciences, Duke University, USA, for the PTSD IPAP Group**

Objectives: Posttraumatic stress disorder (PTSD) is a chronic and disabling disorder, which presents a major global public health challenge. While various treatment guidelines exist, they are either out of date or fail to inform how treatment may be sequenced or adapted to the individual. Such guidelines also do not take into account factors such as comorbidity, culture, and medical concerns. **Methods:** To address these needs, and acknowledging the recent growth of information, we convened a group of international experts in PTSD and psychopharmacology to develop an evidence- and consensus-based set of web-based treatment algorithms. Using published literature and consensus, the PTSD IPAP Group* engaged in dialogue via electronic communication and teleconferences to affirm levels of evidence and treatment strategies to achieve these goals. Results: Our recommendations were posted on the IPAP website in the summer of 2005. The algorithm is organized in the following manner: introduction; general treatment guidelines; issues to consider at each stage (e.g., suicidality); flow diagram and related discussion at each decision point; and other relevant attachments (e.g., definition of levels of evidence, bibliography). Translations into a number of other languages are underway, including Mandarin Chinese, Japanese, Spanish, Thai, and Indonesian. **Conclusions:** The consensus recommendation is to initiate treatment with a serotonergic antidepressant. Depending on the level of response, and the nature of residual symptoms, subsequent treatments may need to be focused on controlling sleep/nightmares, comorbid psychosis, comorbid mood, anxiety, or substance use disorders, or persistent core PTSD symptoms. Among the subsequent options would be atypical antipsychotics, mood stabilizers, anticonvulsants, alpha1 adrenergic antagonists, and other antidepressants. The benefit of evidence-based psychotherapy is also addressed throughout the algorithm.

**The PTSD IPAP Group. Chair: Jonathan Davidson; Co-Chairs: Ken Jobson, Dan Stein, Kathryn Connor; Faculty: Marcio Bernik, Matthew Friedman, Yoshiharu Kim, Yves Lecrubier, Hong Ma, Frank Njenga, Joseph Zohar; Consultants: Dean Hartley, David Osser, David Penniman, Oakley Ray*

Higher Serotonin Transporter Occupancy after Multiple Dose Application of Escitalopram Compared to Citalopram: A [I123]ADAM SPECT Study in Healthy Subjects

N Klein[1], J Sacher[1], T Geiss-Granadia[1], T Attarbaschi[1], N Mossaheb[1], R Lanzenberger[1], C Pötzi[3], C Spindelegger[1], A Holik[1], S Asenbaum[2], R Dudczak[3], J Tauscher[1], S Kasper[1]

[1]Department of General Psychiatry, Medical University of Vienna, Austria

[2]Department of Clinical Neurology, Medical University of Vienna, Austria

[3]Department of Nuclear Medicine, Medical University of Vienna, Austria

Objectives: Previous studies have investigated the occupancy of the serotonin reuptake transporter (SERT) after clinical doses of citalopram and other SSRIs using the PET ligand [11C]DASB. Citalopram is a racemic mixture of the therapeutically active S-enantiomer and the R-enantiomer. In the present study, the occupancy of SERT after multiple doses of escitalopram and citalopram was compared using the radioligand [123I]ADAM and single photon emission computer tomography (SPECT). **Methods:** Healthy subjects received escitalopram 10mg/day (n=6) or citalopram 20mg/

day (n=9) for a total of 10 days. SERT occupancy level was determined from midbrain SERT binding potential, which was measured with [123I]ADAM using SPECT at three different occasions: at baseline (no medication) and 6h and 54h after last drug dose. Blood samples for pharmacokinetic analysis were analysed using a stereo-selective assay. **Results:** 6h after last dose (Day 10), the mean SERT occupancy in midbrain was 81.5±5.4% (mean ± SD) for escitalopram (10mg/day) and 64.0±12.7% for citalopram (20mg/day) ($p<0.01$). 54h after last dose, the mean SERT occupancy was 63.3±12.1% for 10mg escitalopram and 49.8±10.9% for 20mg citalopram ($p<0.05$). The serum concentrations of the S-enantiomer were very similar after both escitalopram and citalopram, whereas the concentration of the R-enantiomer was approximately twice that of the S-enantiomer. The elimination half-life of the S-enantiomer in serum was approximately 30h, while the mean half-lives estimated from the two time points for occupancies was approximately 130h; thus occupancy levels declined more slowly than serum concentrations. **Conclusion:** The significantly higher occupancy of SERT after multiple doses of escitalopram compared to citalopram indicates a more complete inhibition of SERT by escitalopram. Since the concentration of the S-enantiomer was essentially the same, the lower occupancy seen with citalopram is surprising and cannot be explained by a competitive interaction of the R-enantiomer at the primary site of the SERT.

Qualitative Changes in Symptomatology with Treatment in Generalised Anxiety Disorder and Major Depression

Lecrubier Y[1], Weiller E[2], Andersen H[2]
[1]*INSERM, Hospital la Salpétrière, Paris, France*
[2]*H. Lundbeck A/S, Copenhagen, Denmark.*

Objectives: The aim was to investigate the symptomatic profile as measured by HAMA, MADRS, and HAD, in patients with either GAD or MDD, or both, before and after treatment, in order to answer two questions: 1) Are these symptomatic profiles initially different? ; 2) Do the symptomatic profiles change with treatment? **Methods:** Data were analysed from all randomised double-blind clinical studies with escitalopram that measured symptoms using HAMA, or MADRS, or HAD: 6 in GAD (n=2008), 13 in MDD (n=2481) and 1 open study in MDD with comorbid anxiety (n=774). In order to assess the profile independently of severity, the symptomatic profile analysed the contribution of each item of the HAMA, MADRS, and HAD to the total score at baseline and after treatment with escitalopram. **Results:** Most HAMA symptoms contribute almost equally to the total baseline score in GAD patients. In MDD patients, depressed mood and psychic anxiety (anxious mood, tension, insomnia, and concentration) account for most of the HAMA total score. Three symptoms contribute to two-thirds of the MADRS total score in GAD patients (tension, sleep, and concentration), whereas almost all MADRS items contribute equally to the total score in MDD. The symptomatic profile reported by GAD and MDD patients using the HAD is consistent with those based on HAMA and MADRS. After treatment with escitalopram, the overall severity of anxiety and depressive symptoms significantly decreased in GAD and MDD patients. Interestingly, no qualitative change was observed after treatment and the symptomatic profiles remain stable in both conditions. **Conclusion:** Anxiety symptoms are very common and ''qualitatively ''similar to those of GAD in MDD whereas ''core'' depressive symptoms are rare in GAD patients. After treatment with escitalopram, the symptomatic profile is remarkably stable in patients with GAD or MDD, indicating that treatment is most probably effective on a common dimension.