Biological Psychiatry Congress 2007

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STATE OF THE HEART: THE TREATMENT OF DEPRESSION IN PATIENTS WITH CORONARY ARTERY DISEASE

Baker, Brian (Department of Psychiatry, University of Toronto, Canada)

Background: Depressive symptoms and major depressive disorder (MDD) occur ≥ 3 times as common in coronary artery disease (CAD) patients as in the general community, which confers an adjusted relative risk of 2 to 4 for mortality. There are emerging data on how to manage depressed CAD patients with MDD.

Method: The two previous clinical trials (SADHART and ENRICHD) confirm (*i*) failure of cognitive-behavior therapy to affect survival, (*ii*) improvement with placebo and usual care, (*iii*) clinical effect of sertraline, particularly in those with recurrent MDD, (*iv*) cardiac safety of sertraline. This presentation will highlight the findings of the recently concluded CREATE (Canadian cardiac evaluation of antidepressant and psychotherapy efficacy) study.

Results: In a 2-by-2 factorial trial 284 patients with stable CAD were assigned to interpersonal psychotherapy (IPT) or clinical management (CM) and citalopram or placebo for 12 weeks. Citalopram reduced depressive symptoms more than placebo at 6 weeks (p=.01) and at 12 weeks (HAM-D-Hamilton Depression difference 3.3 points, p=.005). Citalopram was efficacious for 43% with recurrent depression compared to those experiencing MDD for the first time. However, there was no additional benefit of adding IPT to CM (HAM-D difference -2.3 points; p=.06), favoring CM over IPT in lowering depressive symptoms. IPT improved depression compared to CM for those subjects with high levels of functional performance. There were 12 cardiovascular and 23 other serious adverse events classified by independent committee and no electrocardiogram effects of the active drug were noted.

Conclusion: Citalopram can be considered as a first line treatment of MDD in CAD patients. So far, besides CM, it has not been shown if any form of psychotherapy is indicated for such patients.

RATIONALE FOR USING TWO ANTIDEPRESSANT MEDICATIONS FOR TREATMENT INITIATION IN DEPRESSION

Pierre Blier (Professor, Department of Psychiatry and Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; Director, Mood Disorders Research Unit, University of Ottawa Institute of Mental Health Research, Royal Ottawa Mental Health Centre, Ottawa; Membre Conseil Médecin, Centre Hospitalier Pierre Janet, Hull, Québec, Canada; Adjunct Professor, Department of Psychiatry, McGill University, Montréal, Québec, Canada; Courtesy Clinical Professor, Department of Psychiatry, McKnight Brain Institute, University of Florida, Gainesville, Fla, USA)

Several illnesses are treated with two medications from the beginning. In the case of major depression, the standard practice is to sequentially try one medication at a time, each attempt requiring a minimum of 6 to 8 weeks. Given that the remission rate with any single drug is around 30-40%, the standard of care is not very efficient. Studies carried out at Columbia University in New York City indicate that following three consecutive trials of medications with a different mechanism of action, it is possible to get about 65% of patients in remission. This sequential treatment, however, requires several months and it is known that about 50% of patients stop their antidepressants in the first three months of treatment. Therefore, consecutive monotherapies is not an efficient approach. Since depression has a major negative impact on the life of the patients and families, generally makes any concomitant medical illnesses worse, and is associated with a significant suicide rate, attempts to hasten response and remission appear fully justified.

Results from a prior double-blind study from our group had shown that using two medications from treatment initiation produced a more robust antidepressant effect than either medications used alone. Optimized regimens of paroxetine and mirtazapine only produced a 25% remission rate, whereas their combination doubled this remission rate in six weeks. After an additional two weeks whereby the non-responders received the combination, a 62% remission was achieved. A second study recently completed, produced similar results. The remission rate obtained with a combination of Remeron (mirtazapine) with either Prozac (fluoxetine), Effexor (venlafaxine), or Wellbutrin (bupropion) was in the 50-60% range after 6 weeks of treatment when compared to Prozac alone which produced only a 25% remission rate. The number of patients stopping their treatment because of side effects was essentially the same in all groups indicating that medication combinations were well tolerated. In patients who remitted on a combination, the discontinuation of one medication after 6 weeks produced a relapse in 40% of the cases, suggesting that in some patients the combination was responsible for the remission.

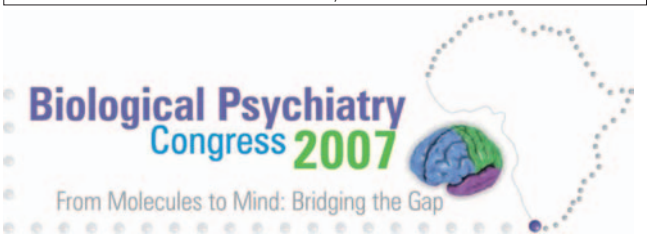
These results indicate that using two medications from treatment initiation is safe and effective. Furthermore, it markedly improves success in the first six weeks. This approach is in fact more acceptable than using a first line medication like a serotonin reuptake inhibitor plus a benzodiazepine. In conclusion, patients should not have to fail various trials with a single agent before using two medications at once, a procedure which is now limited to highly treatment-resistant patients.

INTERACTION BETWEEN NEUROTRANSMITTERS: THE KEY TO THE ANTIDEPRESSANT RESPONSE

Pierre Blier (Professor, Department of Psychiatry and Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; Director, Mood Disorders Research Unit, University of Ottawa Institute of Mental Health Research, Royal Ottawa Mental Health Centre, Ottawa; Membre Conseil Médecin, Centre Hospitalier Pierre Janet, Hull, Québec, Canada; Adjunct Professor, Department of Psychiatry, McGill University, Montréal, Québec, Canada; Courtesy Clinical Professor, Department of Psychiatry, McKnight Brain Institute, University of Florida, Gainesville, Fla, USA)

The neurobiological bases for the delayed increase in serotonin (5-HT) and/or norepinephrine (NE) transmission by various types of antidepressant drugs is now fairly well understood. Depletion studies of 5-HT and/or HE in depressed patients have revealed that such enhancements underlie in large part the manifestation of the antidepressant response. Selective 5-HT reuptake inhibitors (SSRIs) exert a delayed action on 5-HT transmission because the inhibitory 5-HT_{1A} autoreceptors on the cell body of 5-HT neurons need to get desensitized before allowing these neurons to regain their normal firing rate in the presence of sustained reuptake inhibition. In contract, SSRIs gradually attenuate NE neuronal firing as a result of an increased inhibitory 5-HT tone. NE reuptake inhibitors increase transmission by desensitizing inhibitory α_2-adrenoceptors on the cell bodies and terminals of NE neurons. Mirtazapine enhances NE release by blocking inhibitory α_2-adrenoceptors

Selected abstracts (received by *SAJP* by 9 February 2007)



on the terminals of NE neurons. Such an increased release of NE also leads to increased 5-HT neuron firing through excitary α_1-adrenoceptors on 5-HT neurons. This upregulation of firing requires, however, the same delay as for SSRIs because 5-HT_{1A} autoreceptors become desensitized after 21 days of mirtazapine administration. Since mirtazapine does not block 5-HT reuptake, it is postulated that this desensitization occurs through an interaction with the α_1-adrenoceptors. Finally, bupropion rapidly enhances NE release resulting in a suppression of firing of NE neurons. They gradually regain their normal firing rate over two weeks of administration. In contrast, bupropion leads to a rapid and sustained increase in the firing rate of 5-HT neurons. This occurs because of desensitization of 5-HT_{1A} autoreceptors after only two days.

The dopamine system is widely accepted to play a major role in depression and/or the antidepressant response. While the reciprocal interactions between 5-HT, NE and dopamine neurons have been studied to some extent, the effects of antidepressant treatments on dopamine neuronal firing has not been examined thoroughly. Through lesion studies in laboratory animals, we have put into evidence a robust excitatory action of dopamine neurons on 5-HT neuronal firing and a more modest inhibitory effect on NE neuronal firing. The SSRI escitalopram produces a marked and sustained decrease of dopamine neuronal firing.

These studies clearly highlight that by targeting specifically a neuronal system, there can be compensatory effects in one or the two other main monoaminergic systems. Controlled studies by several groups, including in our Unit, have shown that by combining complimentary mechanisms of antidepressants on these systems, it is possible to markedly enhance remission rates in depressed patients.

MECHANISMS REGULATING ONSET OF ACTION OF ANTI-DEPRESSANTS: NOVELPERSPECTIVES FROM PRE-CLINICAL BEHAVIOUR AND NEURORECEPTOR STUDIES

Brink, Christiaan (Associate Professor in Pharmacology, Potchefstroom Campus, North-West University), Harvey, Brian

Background: While current antidepressants are clinically effective, therapy is still plagued with troublesome side-effects, treatment resistance and delayed onset of action. Strategies to address the latter include the modulation of the neurotransmission of multiple neurotransmitters (e.g. serotonin, *l*-norepinephrine and *l*-dopamine) and action at various receptor sites (e.g. $5HT_{1/2}$ and, $\alpha_{1/2}$-adrenergic auto- and heteroreceptors). The neurodegenerative hypothesis of depression opened new avenues for investigating antidepressant strategies, including the role of the glutamate/nitric oxide (NO)/cGMP pathway.

Methods: Cultured human neuroblastoma cells were treated with vehicle, fluoxetine, mirtazapine, yohimbine, idazoxan, sildenafil, atropine or various combinations thereof and drug properties at α_2-adrenergic receptors (α_2-ARs) and muscarinic acetylcholine receptors (mAChRs) determined. Rats were treated for 3, 7 or 11 days with these drugs and immobility measured in the forced swim test (FST) and cortical β-AR density determined.

Results: Radioligand binding studies confirmed the α_2-AR binding properties of ligands, while mirtazapine acted as a neutral antagonist or inverse agonist. Rat studies su antagonism is not critical in this regard. Sildenafil enhanced mAChR signalling capacity in neuroblastoma cells. In rats, sildenafil alone did not exert any antidepressant-like effects in the FST or changes in β-AR density, while the responses to sildenafil + atropine was comparable to fluoxetine, warranting further investigation into potential early onset of action.

Conclusion: The data do not support an important role for α_2-AR antagonism in the early onset of action of mirtazapine in rats. Also, the data suggest that sildenafil may possess antidepressant-like activity (possibly via a ggested an earlier onset of action by mirtazapine, but that α_2-AR cGMP-related mechanism), unmasked by an anticholinergic agent.

TRAUMA RECOVERY

Campbell, Herbert (Psychiatrist for the US Embassy, Pretoria)

Trauma has become an every day word in the past ten years. The word in medical terms and especially in psychiatric terms has a more defined meaning. In this presentation after the word is clearly defined the process and stages of recovery are then described. In the past medical literature has emphasized the pathological events post-trauma. Here the recovery process will be seen as a normal and healthy progression. The presentation is in a form so any level of health care provider can use it for their own purposes and practice. Emphasis is given to the distinction of victim and survivor. The timeline of recovery is well described including the occurrences of anniversaries of the event. Cross-cultural components are important factors of how the recovery varies with different people but overall the recovery process is the same for all people. The main variable is if the trauma is recurring such as during a war versus a one time event.

If time allows the presentation includes how to help children through their recovery, the impact on media, how the grief response is intertwined in the recovery process, and trauma to the superlative: terror and those who inflict terror and how to best personally counteract terrorism.

At the end of the presentation the listener should be able to:

- Define trauma
- Understand the steps of trauma recovery
- Differentiate victim from survivor and the impacts those terms have on recovery.

PHARMACOLOGICAL TREATMENT STRATEGIES FOR BIPOLAR DISORDER

Colin, Franco (Private practice, Pretoria, and Department of Psychiatry, University of Pretoria)

Bipolar disorder remains one of the most challenging conditions in modern psychiatry to manage adequately. In this review I shall attempt to address some of the complicating conditions of this disorder, namely severe co-morbid anxiety, severe aggittation, mixed states and rapid cycling. I shall examine some of the latest evidence in the etiology of this disorder, i.e. mitochondrial dysfunction.

MULTIPLE PROTEIN CHANGES FOLLOWING TRAUMA EARLY IN LIFE

Daniels WMU (Head, Division of Medical,Physiology, Stellenbosch University), Uys JDK, Faure JJ, Marais L, Fairbairn L, Stein DJ

Trauma early in life frequently leads to psychopathology at a later stage. These may include depression and anxiety disorders. We have subjected a rat model to a traumatic event, exposed the animal to reminders thereof, and subsequently assessed changes in a number of proteins by means of ELISA's and proteomic techniques.

Rats were subjected to time-dependent sensitization (TDS) on postnatal day 28 and swim re-stress on postnatal days 35 and 60. The hippocampi of some rats were dissected and neurotrophins (BDNF, NGF and NT-3) determined by ELISA. The hippocampi of other rats were used for protein arrays.

Our data showed that TDS and repeated stress lead to significant decreases in BDNF (dorsal hippocampus) and NT-3 (dorsal and ventral hippocampus) concentrations. There were significant increases in the levels of a number of proteins that included MAP-ib, cytokeratin, S-100B, Histone 3, phosphor-serine-FAK, syntaxin, cdc2, calcineurin, caspases 9, 10, 12, c-Myc and $p57^{Kip2}$. The levels of other proteins (eg. cdc25, cdk6, ARNO, p16, c-Abl, neurofilament, phospho-Pyk2) were all significantly decreased.

These results clearly reflect the complexity of the impact of trauma and stress on the cellular level and its subsequent effect on behaviour.

DEEP BRAIN STIMULATION

Denys, Damiaan (Professor and Chair, Department of Psychiatry, University of Amsterdam, 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.

SEROTONIN-DOPAMINE INTERACTIONS IN OBSESSIVE-COMPULSIVE DISORDER

Denys, Damiaan (Professor and Chair, Department of Psychiatry, University of Amsterdam, The Netherlands)

Obsessive Compulsive Disorder (OCD) is a psychiatric condition characterized by recurring obsessions and compulsions that significantly interfere with patient's daily functioning. Over the past two decades, efforts to elucidate the neurobiology of OCD have centered largely on the role of serotonin (5-HT). Direct evidence that serotonergic perturbations are implicated in the pathophysiology of OCD is still sparse, but some recent studies suggest that it might play a role. There is now also growing evidence from both preclinical and clinical studies that the dopamine system may be involved in the pathogenesis of OCD1. The role of dopamine is intriguing in view of its role in decision-making – compulsive individuals are habitually indecisive – and because the basal ganglia, which are heavily endowed with dopaminergic fibres, are an important substrate for OCD symptoms. In this presentation, the preclinical and clinical evidence supporting the role for serotonin and dopamine in the pathophysiology of OCD will be reviewed.

THE HYPOCRETIN/OREXIN NEUROPEPTIDES IN SLEEP AND PSYCHIATRIC DISORDERS

Ebrahim, I (NHS-appointed Consultant Neuropsychiatrist in Sleep Disorders, based at the Sleep Disorders Centre, St Thomas' Hospital, London)

The discovery of the Orexin/Hypocretin neuropeptides has revolutionised the way we view Narcolepsy and related neurochemical mechanisms in the limbic system and brainstem. Narcolepsy is now considered a neuropeptide dystransmission disorder and new agents being developed are being modelled on this concept. We present here the latest findings from research into the Orexins/Hypocretins including an update on our study of CSF Hypocretin in patients with Excessive Daytime Sleepiness (EDS) and discuss its potential role in psychiatric disorders.

The dense hypocretin projections to the noradrenergic LC system, the serotonin (dorsal raphe), dopaminergic (ventral tegmentum and nucleus accumbens), the cholinergic brainstem and, the GABA/Glutamate areas of the brain suggest a possible role in psychiatric and neuropsychiatric disorders. [2,50] The hypocretin system may be important in affective disorders such as major depression and bipolar affective disorder. The monoamine hypothesis (biogenic amine hypothesis) of depression suggests that dysfunctional or deficient neurotransmission of noradrenaline (NA) and/or serotonin (5-HT) underlies the symptoms of depression. More recently, emphasis has shifted to the possible roles of neuropeptides in the aetiology and treatment of depression. The possibility that the hypocretin system may be involved in depression is suggested on neuroanatomical and pharmacological grounds. The only substance known to innervate all the relevant areas of the brain implicated in the neurobiology of depression is hypocretin and the excitatory innervation of the LC and dorsal raphe region, the stimulation of dopamine and acetylcholine and the pro-histaminergic actions all point toward an antidepressant effect. These speculative therapeutic possibilities remain to be clarified by appropriate studies.

CLINICAL, PHYSIOLOGICAL AND BIOLOGICAL ASSESSMENT OF SLEEP – HOW TO

Ebrahim, I (NHS-appointed Consultant Neuropsychiatrist in Sleep Disorders, based at the Sleep Disorders Centre, St Thomas' Hospital, London); Ammen, Emsley, O; Kander, V

This 3 hour symposium will focus on educating the non-sleep specialist on the basics of sleep medicine, outlining the discipline of sleep medicine, an introduction to the clinical assessment of patients with sleep disorders, halping in the recognition of sleep disorders and assisting in identifying action points in the patient pathway for referal to a sleep specialist. It will cover the following topics:

1. Introduction and Overview of Sleep Disorders
2. Clinical Assessment of patients with Sleep Complaints - including an introduction to commonly used screening questionnaires
3. Overview of Investigation of Sleep Disorders
4. Neurological Sleep Disorders
5. The Sleep Medicine - Psychiatry Interface.

SCHIZOPHRENIA: A PROGRESSIVE ENCEPHALOPATHY

Emsley, Robin (Professor and Chair, Department of Psychiatry, Stellenbosch University)

Schizophrenia forms a significant part of the global health burden, being placed among the world's top ten causes of disability-adjusted life-years. The illness affects almost 1% of the population at some point in their life. Characterised by psychosis, apathy, social withdrawal and cognitive impairment, it imposes a disproportionate burden on patients and their families, health care systems and society. This is because of its early onset, devastating effects, and usually lifelong course. The overall outcome in schizophrenia is poor, and typically the course of the illness is characterised by frequent relapses, re-hospitalisations, prominent impairment in social and occupational functioning, and suicidality.

Compelling evidence suggests that schizophrenia is a neurodevelopmental disorder, caused by a complex interaction of multiple susceptibility genes with small effect interacting with various environmental factors. The development of the brain is affected, leading to anomalies that express themselves only once cerebral maturity has been attained. But a major difficulty with the neurodevelopmental model is the delayed onset of the psychotic phase of the illness.

Whereas it was previously thought that the cerebral changes observed in schizophrenia were present at the onset of the illness, and remained static over time, it is now recognized that these changes are progressive. Recent evidence indicates that the progressive course of schizophrenia is associated with ongoing neurodegenerative processes. It has been suggested that the ongoing deterioration operates during the active psychotic phase of the illness. In other words, the presence of positive symptoms is indicative of an ongoing morbid process. In particular, the first few years are when most of the deterioration occurs, and perhaps also in the prodromal phase. Therefore, early identification and effective treatment are critical to ensuring optimal outcome. Treating patients to remission and preventing relapse may dramatically alter the outcome of the illness.

REACTIVE NITROGEN AND OXYGEN INTERMEDIATES AND OXIDATIVE STRESS IN NEUROLEPTIC-INDUCED TARDIVE DYSKINESIA: IMPLICATIONS FOR PREVENTION AND TREATMENT

Harvey, Brian (Research Programme Leader, Drug Research and Development Focus Area, Unit for Drug Research and Development, School of Pharmacy (Pharmacology), North-West University (Potchefstroom Campus), and Co-Director (pre-clinical research), MRC Unit on Anxiety and Stress Disorders)

The dopamine supersensitivity hypothesis remains an important construct in explaining the aetiology of neuroleptic induced tardive dyskinesia (TD). Despite advances in the treatment of schizophrenia and the lower tendency of new generation agents to evoke motor dysfunction, TD remains a clinical concern (3). Long-term neuroleptic

administration alters dopaminergic turnover, which has been proposed to lead to increased formation of reactive oxygen species (ROS) and the induction of oxidative stress. The striatum, a critical brain region involved in regulating movement, is highly susceptible to oxidative stress. Clinical and pre-clinical studies in TD have demonstrated increased free radicals and decreased superoxide dismutase in the disorder (5) as well as increased synthesis of ROS by haloperidol (2), while lipid peroxidation has been found to be significantly higher in patients treated with older antipsychotics compared to newer atypical agents (1).Antioxidants have possible therapeutic value in treating TD (4). However, under certain conditions of redox status, antioxidants may act as pro-oxidants. We have investigated the biological and pharmacological role of nitric oxide, superoxide and antioxidant treatment in an animal model of TD, looking specifically at important factors associated with the development of TD, including withdrawal of the neuroleptic, advancing age, status of cellular markers of oxidative stress and reversal of the bio-behavioural manifestations of TD with an atypical neuroleptic. This paper will present animal and human data supporting the role of oxidative stress in TD, and will attempt to suggest new avenues of treatment, possible drawbacks and also discuss its prevention.

References:

Kropp *et al* (2005). *J Neuropsychiatry Clin Neurosci* 17: 227, Parikh *et al* (2003). *J Psychiat Res* 37: 43, Tarsy *et al* (2002). *CNS Drugs* 16: 23, Zhang *et al* (2004). *J Clin Psychopharmacol* 24:83, Zhang *et al* (2004). *Schizophrenia Res* 62: 245

MAINTENANCE PRESCRIBING FOR OPIOID DEPENDENCE WITHIN SOUTH AFRICAN SETTING

Hitzeroth, V (Psychiatrist specialising in substance misuse practice, UK)

Background: Maintenance prescribing for opioid dependence has been with us since the 1960's. Initially, this service has been limited to the USA, but has subsequently spread to numerous other countries. Maintenance prescribing probably remains the most studied of all interventions within the addictions field. Yet, it continues to attract controversy and criticism.

Method: This presentation will set the scene for maintenance prescribing within the South African setting. It will review the addiction literature with specific reference to the following:

The historical origins of maintenance prescribing
The aims and purpose of maintenance prescribing
The place of maintenance prescribing within a comprehensive addiction service
The use of different medications for maintenance prescribing
How maintenance prescribing works, as well as different models and mechanisms of maintenance prescribing
Maintenance prescribing as a harm reduction strategy
The efficacy of maintenance prescribing
Characteristics of a good maintenance prescribing program
The risks of maintenance prescribing
Criticism of maintenance prescribing

Results: Maintenance prescribing for opioid dependence can be an effective and safe intervention. Numerous reports and studies continue to show that maintenance prescribing, when implemented in a safe and structured manner, remains a useful tool for specialist clinicians working within the addiction field.

Conclusion: Maintenance prescribing for opioid dependence within the South African setting remains in its infancy. Any comprehensive addiction service should be able to offer maintenance prescribing as one component of its armamentarium. In order to provide good care for this client group we have to be able to provide such a service to those select few who require it. Yet, being in a position where our services are still being developed, it is imperative that we do not lose the overview, do not make mistakes that others have made before us and are aware of the numerous hurdles and risks associated with this intervention. Acquiring this knowledge will ensure that we are able to provide a safe and effective service for a difficult-to-treat client group.

ANTIDEPRESSANTS AND SUICIDALITY IN CHILDREN AND ADOLESCENTS

Hawkridge SM (Principal Specialist for Child and Adolescent Psychiatric Services, Western Cape)

Background: Following the introduction of specific serotonin reuptake inhibitors (SSRIs), their use in children and adolescents suffering from a variety of disorders became extremely common, despite the fact that few SSRIs are approved by statutory bodies for use in this age group. While evidence of efficacy was often lacking, the apparent safety of the drug seemed to balance the "risk-benefit" equation. The discovery of unpublished trial data suggesting that there are serious risks attached to the use of SSRIs specifically in child/adolescent depression has necessitated deeper analysis of the evidence and a review of clinical practice.

Methods: An online search of the English language literature was conducted and expert opinion concerning the interpretation of adverse effects of SSRIs in young patients as well as implications for clinical practice was extracted.

Results: The meaning of "suicidality" is complex and ill-defined. There is an overall increased risk of suicidal ideation and behaviour (but not suicide) from 2% to 4% in children and adolescents receiving SSRIs in randomised controlled trials for both mood and anxiety disorders. Currently the only SSRI with sufficient evidence of efficacy in child and adolescent depression to balance this risk is fluoxetine. Both the FDA and the NICE recommend increased use of psychosocial interventions and cautious use of fluoxetine in juvenile depression, and the use of other SSRIs only by suitably qualified clinicians in selected circumstances. A recent "drug alert" issued by the NADEMC in South Africa declared all SSRIs except fluoxetine "contraindicated" in patients younger than 18 years. Little consideration has been given to the treatment of children and adolescents with anxiety disorders, where evidence of SSRI efficacy is stronger.

Conclusions: This paper critically examines the official recommendations and attempts to formulate clinical guidelines that are both practical and safe for mental health practitioners in resource-scarce countries.

CORTICOSTEROIDS AND AFFECTIVE DISORDERS

Colin Ingram (Professor of Psychobiology, Director, Institute of Neuroscience, and Head, School of Neurology, Neurobiology and Psychiatry, Newcastle University, UK)

Over the last few years we have been conducting experiments to look at the role of the HPA axis in the aetiology of depression, in particular the role of the diurnal rhythm of corticosteroids. We have examined how changes in the rhythm can affect 5-HT transmission and have recently been working on the effects of GR antagonists as possible therapeutic factors. This is what I would prefer to talk on.

Early life stress and psychopathology: There is a growing literature about the relationship between early life stress and the onset of affective disorders and anxiety in adulthood. I have worked on the long-term consequences of early life stress both for the HPA axis and for 5HT transmission, and we have recently been looking at how this may also affect neurogenesis.

Oxytocin and anxiolytic activity: For a number of years I have had an interest in the effects of oxytocin within the limbic system and have shown that this may have a role in controlling anxiety states and stress responses. This work has recently gained interest in the pharmaceutical sector with the development of small molecular oxytocin agonists and with the results of studies in which oxytocin has been administered to humans via an intranasal route.

TESTING TIMES: NEW PARADIGMS FOR HIV TESTING IN PATIENTS WITH SEVERE MENTAL ILLNESS

Joska, J (Senior lecturer and specialist, Groote Schuur Hospital and University of Cape Town Department of Psychiatry and Mental Health), Kaliski, S

Background: The high prevalence of AIDS in South Africa poses enormous challenges. Currently, testing for HIV is subject to ethical rules that probably ensure that many high-risk individuals' HIV status can never be known. There is no policy

in the Western Cape with regard to HIV testing in patients admitted to psychiatric hospitals with severe mental illness. Clinicians rely on clinical indications for HIV testing. Undiagnosed HIV infection in people with severe mental illness carries many adverse consequences.

Methods: This problem is explored through three methodologies: First, by performing a systematic literature review to establish the prevalence of HIV infection in in-patient populations with severe mental illness; second by reviewing the literature to ascertain current practice for testing for HIV in this population; and third, by presenting findings of a local survey of psychiatrists of their experience and attitudes towards HIV infection in in-patients with severe mental illness.

Results: The prevalence of HIV infection in psychiatric in-patients ranged from 0-23.8%. With the adult HIV seroprevalence in South Africa in 2003 being 18.8%, similar or higher seroprevalences may be expected in local psychiatric populations. Recent published literature has suggested that HIV testing has moved beyond the constraints of protecting individual rights to consent. State psychiatrists in the Western Cape do not test routinely for HIV, but are divided on whether such testing should be mandatory. The main barriers to such testing are ethical constraints and the limited access to anti-retroviral treatment.

Conclusions: Due to the probability of a high prevalence of HIV infection in patients with severe mental illness, and the potential risks to the patient and the community, a policy for testing should be debated and put into place. This may include instances, such as in forensic settings, when HIV testing can be conducted without a patient's consent.

OPTIONS FOR TREATMENT-RESISTANT DEPRESSION: LESSONS FROM STAR*D AN INTERACTIVE SESSION

Joubert, A (Divisional Director: Psychiatry and Neurology and Co-director, Lundbeck Institute, Copenhagen, Denmark)

There are several decisions regarding Treatment-Resistant Depression (TRD) that do not have a sufficient evidence base. Therefore we rely on expert opinions and common sense. Also, some of the emerging evidence is changing previous guidelines. The Star*D data answer a few of these questions, but raise even more.

The session will start by proposing a definition of TRD and follow with a review of the current literature regarding the available treatment options for TRD. A comprehensive synopsis of the Star*D data will be presented, highlighting the outcomes, but also the pitfalls, in the data.

International treatment guidelines and evidence regarding the options available will be reviewed hoping to answer some of the following questions:

- **When does antidepressant effect start?**
  How long after starting an antidepressant can 'response' be evaluated?
  When should the dose be increased?
  When is switching medication recommended?
- **What is the first decision in the case of non-response and partial response?**
  Most will first optimise the dose of the antidepressant. Is this correct?
  Increase dose, switch, augment, combine? When to choose which option?
- **The role of the new generation antipsychotics in TRD**
  The CANMAT guidelines suggest the use of the new generation antipsychotics only as an augmentation with the second-line antidepressant used. With the considerable new data, are we seeing this guideline change so that new generation antipsychotics will be recommended with the first-line antidepressant – along with lithium and T_3?
- **Augmentation**
  When should we use augmentation, and which options have the best evidence?
  Which new options are being studied? There have been several new studies published since February 2006 showing promise for 'newer' strategies in the future.
- **Switching antidepressants**
  When switching from the first antidepressant to the second antidepressant, due to non-response, should the class of antidepressant be switched? There are conflicting data.
- **Combination treatment with antidepressants**
  Combinations of antidepressants are often used in patients who need specific symptom alleviation and are not 'treatment resistant'.
  In TRD, many psychiatrists use combinations of antidepressants (SSRI + SNRI; SSRI + mirt, SNRI + mirt *et al.*) There are few data to support these practices. What are the principles involved in combining antidepressants, and do they work?

STAR*D

The Star*D study data has been published over the past few months presenting a wealth of data, despite some obvious (and some less obvious) methodological limitations. The study and a comprehensive summary of the data will be presented.

AN UPDATE ON THE NEUROBIOLOGY OF VIOLENCE

Kaliski, S

Violent behaviour results from complex interactions of a myriad of psychosocial, neurobiological, static and dynamic risk factors, that probably number more than 200. The neurobiological substrate for aggression is inherent, and obviously is of evolutionary importance. This means that differentiating between normal and pathological aggression is often achieved by resorting to socially and culturally determined norms. There are some individuals who display extreme habitual violence, usually in response to minor, or no provocations. Current research has concentrated on 4 important risk factors, namely anger control, impulsivity, substance abuse and psychopathy. This talk will attempt to correlate and compare the proposed neuropsychiatric mechanisms for each, and suggest how these interact with psychosocial variables.

MENTAL HEALTH OF AFRICAN SCHOOLCHILDREN: EPDEMIOLOGICAL, CLINICAL AND NEUROPSYCHOLOGICAL STUDIES FROM THE DEMOCRATIC REPUBLIC OF CONGO

Kashala-Abotnes, E, Elgen, I, Sommerfelt, K, Tylleskar, T

Background: Mental health disorders frequently occur in school children but little attention has been paid to this topic in Africa. A project on mental health among school children aged 7 to 9 years old was carried out in the DR Congo. It aimed at exploring mental health problems among school children in an African urban setting and performing further investigations on those likely to have mental problems, with a focus on children with attention deficit and hyperactivity disorder symptoms (ADHD).

Methods: Epidemiological, clinical and neuropsychological studies were conducted on 1187 school children aged 7 to 9 years. The Strength and Difficulties Questionnaire (SDQ) addressed to the teachers was first used as a screening tool to pilot its use in this urban setting and to explore mental health problems. Teachers were also asked to give information about children's school performance.

Using the 90th percentile cut-offs, 15% of the studied children had an abnormal score on the hyperactivity-inattention scale of the SDQ (SDQ-HI), and thus considered as likely to have hyperactivity-inattention symptoms. Children with abnormal scores and a randomly selected control group were assessed with the Disruptive Behaviour Disorder rating scale (DBD). The DBD was used to assess whether or not the hyperactivity-inattention symptoms corresponded to the symptoms of ADHD as defined according to the DSM-IV. All children underwent a clinical and a neuropsychological testing. Their parents were also interviewed regarding the socio-demographic background and the child medical history in order to identify possible associated risk factors.

Results: Mental health problems do exist among school children in Kinshasa. ADHD symptoms were common with an estimated prevalence of 6%. Conduct problems were the most common co-existing symptoms. Poor school performance and family health problems were the most common risks factors associated with mental health problems. The neuropsychological evaluation revealed that children

with ADHD symptoms had overall good cognitive functioning but exhibited motor skills impairments.

THE LAMINAR ARRANGEMENT OF THE CEREBRAL CORTEX AND SYNAPTIC DENSITY QUANTIFICATION

Kellaway, L (Senior Lecturer in Physiology and Neuroscience, Department of Human Biology, University of Cape Town)

The cerebral cortex is traditionally recognized as a six layered structure. How the six-layered architecture contributes to the mechanism of sensory perception, the cognitive process and ultimately consciousness is both an exciting quest and major research frontier in Neuroscience. A number of techniques and approaches are being used to probe and explore the laminar circuitry of cortex with a view to understanding the relationships between neuronal function and the anatomical rules of cortical composition.

It is now a generally accepted principle that the laminar position in which the cell bodies of cortical neurons are located, is an important determinant of the cell's morphology, its laminar circuitry and its functional role. Clearly, theoretical analyses of the types of computations that the cerebral cortex perform and how these might be implemented in specific cortical circuits is of great assistance with the task of interpreting this complex structure. However, these models are only as good as the detail that inform them. To illustrate this point, the parvocellular stream of visual information processing based upon detailed information of feedforward, feedback, horizontal connections and synaptic distribution have provided the basis of a detailed neuronal model for this sensory processing stream (Raizada & Grossberg , 2003) In sharp contrast very little information on the detailed connectivity and function of cells in Layer 1 of cerebral cortex exists. One possible reason for this is that cells are very sparsely distributed in this layer, contributing to its reputation, as described by Hubel (1982) as the 'Crowning mystery' of cerebral cortex. It is however recognised that Layer I is a major target of intra-cortical feedback and sub-cortical input, yet there are many details of Layer 1 that are still unknown and a detailed model of its role has yet to be formulated. One method of assessing inter-neuronal connectivity within a specific lamina is by accurate quantification of neurons and synaptic density by unbiased stereology. The disector methodology and some preliminary data on synaptic density in cat Layer 1 visual cortex will be presented.

The stereological study of Layer 1 is in collaboration with Professors Kevan Martin and Rodney Douglas at the Institute of Neuroinformatics, University of Zurich/ETHZ, Zurich, Switzerland.

BRIEF INTERVENTIONS – BRIDGING THE GAP BETWEEN THE PREVENTION AND THE TREATMENT OF DRUG-RELATED PROBLEMS

Kramer, L (currently manages a psychiatric practice in Cape Town and works as a GP with an interest in mental health and substance misuse)

Background: In both theory and in practice many of the methods used to prevent drug-related problems are directed at populations and thus intervene on an aggregate level. However, there is another approach to prevention known as 'Brief Interventions', which targets the individual. Brief Interventions are short, inexpensive interventions delivered opportunistically to drug users by clinicians in the normal course of their duties. Not only do Brief Interventions have overt benefits for the individuals receiving them, but they can also make important contributions to the public health of the community in which they are delivered.

Method: The presentation will investigate the origins of Brief Interventions and explain the interest in Brief Interventions within the smoking and alcohol fields. It will critically analyze the research evidence bearing on the efficacy and cost-effectiveness of Brief Interventions in various settings.

Results: The listener will be introduced to the aims of Brief Interventions, a description of the forms they take in practice, as well as the components of effective Brief Interventions. The presentation will aim to show that Brief Interventions are effective/cost-effective and can benefit both individuals and communities. Finally, the presentation will describe the barriers to the successful implementation of Brief Interventions in practice and how these may be overcome.

Conclusions: The listener would have been introduced to an important tool used to reduce the harms associated with substance use. Brief Interventions can be used to prevent the progression of problem use of substances, by assisting users to reduce to a safer or less harmful level of use, or even abstain altogether. Brief Interventions are relevant to, and can easily be applied in everyday practice and can thus contribute to the reduction of substance-related problems in the community where you live.

ANTIDEPRESSANT AUGMENTATION STRATEGIES

Lerer, Bernard (Professor of Psychiatry and Director of the Biological Psychiatry Laboratory at the Hadassah-Hebrew University Medical Center, Jerusalem, Israel)

Major depressive disorder (MDD) is the fourth largest contributor to the global burden of disease and by 2020 is anticipated to rise to second place after ischemic heart disease. Up to a half of patients with MDD are not diagnosed as such and do not receive treatment. Among those that are treated, the effectiveness of the therapy they receive is limited. Less than two thirds respond to their first treatment and less than 40% achieve remission (complete resolution of their illness). The definition of treatment resistant depression (TRD) varies among clinicians; the most widely accepted criterion is failure to respond to at least two adequate treatment trials with agents that differ in their mechanism of action. More detailed classifications stage TRD from I-V according to the number and type of unsuccessful treatments the patient has received. There is growing recognition of the need to develop more effective treatments for MDD. Greater emphasis is being given to remission as the primary outcome objective with the recognition that patients who have responded to treatment but are not remitted still have troubling symptoms, difficulty functioning, a poorer quality of life and a higher likelihood of relapse. In managing a patient with TRD, the treatment approach is dependent on the stage of resistance. From the perspective of evidence based medicine relatively few of the options available are at the A (supported by multiple randomized controlled trials [RCTs]) or B (limited RCT support) levels: a) *Switch* to another antidepressant of the same or different (functional) class or to ECT. b) *Combine* two antidepressants with different functional mechanisms. c) *Augment* with an agent that potentiates the action of the antidepressant the patient is receiving. Augmentation with lithium is well supported by RCTs although these focused on tricyclic antidepressants (TCAs) and not SSRIs. A second strongly supported approach (RCTs and meta-analysis) is augmentation with the thyroid hormone, triidothyronine (T3). Paradoxically, these two strategies are not widely used. Augmentation with T3 is supported by a growing body of preclinical evidence and by two recent RCTs, a placebo-controlled trial from our laboratory (Cooper-Kazaz *et al.*, in press) and a comparator study with lithium from the STAR*D project. Popular augmenters such as buspirone and atypical antipsychotics are less well supported although the recent STAR*D findings with buspirone improved its evidence base. Other augmenting strategies are at the C or D level in terms of their evidence base (supported by extensive or limited open studies and substantial or minimal expert endorsement). These include augmentation with the 5-HT1A partial agonist, pindolol; psychostimulants such as methylphenidate and amphetamine; the anti-narcoleptic drug, modafinil, for SSRI non-responders with fatigue and hypersomnolence; direct dopamine agonists such as pramipexole; omega 3 fatty acids; lamotrigine; estrogen; dehydroepiandrosterone (DHEA) and testosterone (in older men). Each of these interventions is based on a reasonable theoretical conceptualization and preclinical studies in some cases, but the clinical evidence is limited. Given the urgent need to develop agents that will improve outcome in TRD future research directions should be considered. From the pharmacological perspective these include drugs on the dopamine 'track' such as dopamine receptor agonists and combined uptake blockers, the endocrine track including corticotrophin releasing hormone (CRH) antagonists, glucocorticoid receptor blockers and cortisol synthesis inhibitors and drugs on the NMDA track such as glycine site agonists and glycine uptake inhibitors. Novel brain stimulation techniques are an exciting area of development with emphasis on transcranical magnetic stimulation (TMS),

vagus nerve stimulation (VNS), and deep brain stimulation (DBS). Augmentation of antidepressant effects with the currently available brain stimulation techniques, ECT and TMS, warrants further study at the basic and clinical levels

GENOME SCAN AND ASSOCIATION STUDIES LOCALIZE A NOVEL SCHIZOPHRENIA SUSCEPTIBILITY GENE TO CHROMOSOME 6q23

Lerer, Bernard (Professor of Psychiatry and Director of the Biological Psychiatry Laboratory at the Hadassah-Hebrew University Medical Center, Jerusalem, Israel); Amman-Zalcentein, Daniela; Kanyas, Kyra; Avidan, Nili; Ebstein, Richard; Hamdan, Adnan; Lancet, Doron

Schizophrenia, a severe neuropsychiatric disorder, is believed to involve multiple genetic factors. A significant body of evidence supports a pivotal role for abnormalities of brain development in this disorder. Linkage signals for schizophrenia and bipolar disorder map to human chromosome 6q. A genome scan in an inbred Arab-Israel, localized a schizophrenia susceptibility locus to chromosome 6q23. To obtain a finer localization, we genotyped 180 single nucleotide polymorphisms (SNPs) in the same sample. These were mostly within a ~7 Mb region around the strong linkage peak at 136.2 Mb that we had previously mapped. The most significant genetic association with schizophrenia for single SNPs and haplotypes (after Bonferroni correction for multiple testing) was within a 500 Kb genomic region of high linkage disequilibrium (LD), in the 95% linkage confidence interval of 3.9 Mb (134.3 Mb -138.2 Mb). In a different, outbred family sample of Arab origin, under-transmitted haplotypes incorporating the same SNPs were significantly associated with schizophrenia. The implicated genomic region harbors the *Abelson Helper Integration Site 1* (*AHI1*) gene, which showed the strongest association signal, and an adjacent, as yet uncharacterized, primate specific gene, *C6orf217*. Mutations in human *AHI1* underlie the severe, autosomal recessive brain disorder, Joubert Syndrome which is characterized by brain malformation and mental retardation. Previous comparative genomic analysis has suggested accelerated evolution of *AHI1* in the human lineage. Thus, *AHI1* appears to be a highly relevant candidate gene for schizophrenia. A role for the adjacent, primate-specific gene, *C6orf217*, remains to be elucidated.

CLINICAL FEATURES OF METHAMPHETAMINE PSYCHOSIS

Lewis, Ian

Background: Abuse of the illicit drug methamphetamine ("Tik") has resulted in a massive increase in methamphetamine psychosis (MAP) in the Western Cape. MAP is exceedingly difficult to distinguish clinically from psychosis due to other causes. The aim of this study was to establish whether patients with confirmed MAP have characteristic symptoms, clinical course and response to medication different from those with other forms of psychosis.

Methods: The records of patients admitted to the Groote Schuur Hospital Psychiatry Emergency Unit (PEU), with first presentation psychosis, during a 30 month period from April 2004, were reviewed. Those with MAP and MA abuse (confirmed on urine and/or history from the patient or relatives), were compared with a matched control group with psychosis better accounted for by a cause other than MA.

Results: Patients with MAP had a more severe behavioural disturbance, characterised by insomnia, paranoia, restlessness, aggression and sexual disinhibition. They were prescribed higher doses of benzodiazepines, were more likely to develop extrapyramidal side-effects on conventional antipsychotics, and were more likely to be commenced on Clozapine.

Conclusions: This study confirms that behavioural symptoms associated with MA psychosis are severe; that haloperidol, in contrast to the current recommended treatment guidelines was poorly tolerated and relatively ineffective, Many of the MAP patients only showed signs of clinical improvement after they had been commenced on Clozapine.

THE A,B,C OF CONDUCTING CLINICAL TRIALS IN PSYCHIATRY

Maud, C; Potocnik, F; Seedat, S

This 3 hour, hands-on workshop is suitable for anyone who has a serious interest in conducting, designing and leading clinical trials. It is widely acknowledged that well-controlled, well-conducted, double-blind randomized placebo-controlled studies remain the best way to establish the efficacy of psychotropic agents. This workshop will address the nuts and bolts of being a clinical investigator by guiding attendees through the theoretical and practical issues they will face, and will provide an understanding of: (*i*) the steps to clinical trial success, (*ii*) compliance and standard operating procedures, (*iii*) clinical outcome measures and endpoints (e.g. commonly used psychiatric rating scales), (*iv*) design of investigator initiated protocols, (*v*) issues regarding patient recruitment and selection, and (*vi*) ethical aspects conducting clinical trial research (e.g. familiarity with applicable regulations, special aspects of particular patient populations).

THE MANAGEMENT OF PSYCHIATRIC CONDITIONS IN PATIENTS WITH ADDICTIVE DISORDERS

McCarthey, Greg (Honorary Lecturer, Department of Psychiatry, University of Cape Town), Weich, Lize

A brief outline of the neurobiology of addiction will be presented, along with the latest neuro-pathological findings (inc functional imaging) of methamphetamine ('Tik') addicts and their management. A lecture on the management of psychiatric conditions in patients with co-morbid addictive disorders will follow. Particular attention will be given to Schizophrenia; Mood Disorders – especially Bipolar Mood Disorder; Anxiety Disorders – especially PTSD, OCD and Social Anxiety Disorder; Eating Disorders and 'Cluster B' Personality Disorders, especially Borderline Personality Disorder. The lecture links the drug of choice to the psychiatric condition and offers practical guidelines as to the psycho-pharmacological management of co-morbidity in this psychiatric sub-population. A panel discussion with audience participation will make up the last third of the seminar.

AN OVERVIEW OF SUICIDES IN THE TRANSKEI REGION OF SOUTH AFRICA

Meel, B (Faculty of Medicine, University of Transkei)

Transkei is the least developed of the former black homelands in South Africa and has a population of about 4 million. People in this area are poor and depend mainly on the income from migratory workers to the gold mines. Suicide is a complex problem, with no definitive causative agent identified yet. There are numerous factors such as unemployment, marital problems, financial constraints, and loss of dignity or pride associated with suicide. Suicide among teenagers and young adults is now emerging as an important mental health issue. Suicidal behavior in the population is under-researched, and therefore under-reported. Ongoing and continuing research is required, especially within this community for a better understanding of their circumstances.

The suicidal temperament including hopelessness and interpersonal difficulties render an individual vulnerable for suicidal behavior. The hopelessness and low self-esteem are important indicators of future suicidal behavior. Suicide is preventable provided preventive strategies are strong enough to change the behavior. HIV/AIDS is a life threatening illness and is contributory in causation of self-harm. Implementation of a 'life-saving-program' in the community is urgently required.

STUDY OF MATH PROCESSING IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER

Ernesta M Meintjes (Research Chair in Brain Imaging, MRC/UCT Medical Imaging Research Unit), Sandra W Jacobson, Joseph L Jacobson, J Christopher Gatenby, Christopher D Molteno, Christopher Warton, Christopher J Cannistraci, Stanislas Dehaene, & John C Gore

Background: Number processing is one aspect of cognitive function most consistently linked to FASD. Studies using structural MRI reported disproportionately reduced volumes and other abnormalities in parietal lobe, basal ganglia, cerebellum, and corpus callosum (Mattson *et al.*, 1992,1994; Archibald *et al.*, 2001). The only previous fMRI study in children with FASD reported reductions in superior parietal and frontal activity in a spatial working memory task (Malisza *et al.*, 2005). In fMRI studies in adults Dehaene and colleagues identified three parietal areas that play a critical role in number processing: the horizontal intraparietal sulcus

(HIPS) is activated bilaterally when numerical quantities are manipulated; the left angular gyrus for number processing in verbal form; and the posterior superior parietal lobule (PSPL) supports attentional orientation in the manipulation of quantities (Dehaene *et al.*, 2003). We report the first fMRI data of number processing in children with FASD.

Methods: We examined 15 right-handed children (8-11 years old) with FASD and 17 non-exposed, age-and gender-matched controls from Cape Town, South Africa. Two self-paced paradigms were administered: Proximity Judgment (PJ, which of two numbers is closer to a third) and Exact Addition (EA). Control tasks involved letter matching. FMRI analyses were performed using Brain Voyager QX. Preprocessing included motion correction, correction for different slice acquisition times, linear trend removal, spatial smoothing using a Gaussian filter, and high frequency temporal filtering. Each subject's data were normalized to Talairach space. Group analyses were performed with a fixed effect analysis of variance using the general linear model with predictors based on known experimental blocks convolved by the standard hemodynamic function as well as the six motion correction parameters as variates of no interest. We computed statistical parametric maps of the between group differences in activation for each task, corrected for the effect of the control task (Controls [task – control task] – FAS/PFAS [task – control task]). The voxelwise threshold was set to $q < 0.03$ (corrected for multiple comparisons using the False Discovery Rate method). Minimum cluster-size was set to 200 adjacent voxels.

Results: Although children with FASD performed significantly more poorly on behavioral tests of PJ and EA, both groups performed equally well on simplified scanner versions of these tasks (group means 83-89%, all p's > 0.20). In both tasks control children show greater activation of the right anterior HIPS and bilaterally of the posterior HIPS spilling over into the PSPL. In EA control children also show increased bilateral activation of the head of the caudate nucleus. During PJ children with FASD show increased activation of the left angular gyrus, anterior cingulate, and an area of cortex adjacent to the anterior cingulate.

Conclusion: In both tasks children with FASD show reduced activation of two parietal areas identified by Dehaene as central to number processing. Our results suggest that children with FASD recruit other areas, notably the angular gyrus and anterior cingulate region, to a larger degree to compensate for impairment in HIPS and PSPL function to successfully complete the PJ task.

THE BIOLOGY OF DEPRESSION

Moosa MYH (Principal Specialist, Mental Health Sub-directorate, Gauteng Department of Health)

The lifetime prevalence of depression is about 15%. Only 30% of depressed patients will come to the attention of medical services due to under-recognition, masking of symptoms and associated stigma. The mean age of onset is 40 years with about 50% of patients developing it between the ages of 20 and 50 years. The prevalence in females is twice as high as males and there is no difference between racial groups or socio economic groups. Aetiological factors include genetic, psychological and biological factors. The biological basis of depression and evidence for and against each hypothesis will be discussed under the following:

a) Monoamine hypothesis
b) Neurotransmitter receptor dysfunction
c) Neuroendocrine dysfunction
d) Alteration of Sleep neurophysiology
e) Immunological dysfunction

The aetiology cannot be attributed to a single entity but rather it is interplay between the various factors. Biological and psychological factors can affect gene expression and likewise biological and genetic factors can affect the psychological response to stressors. This makes it possible to have a multi dimensional approach to the management of this disorder.

AMPLICHIP CYP450 GENOTYPE PROFILING FOR IMPROVING TREATMENT OUTCOMES IN PSYCHIATRIC PATIENTS

Pepper, Michael (Director, NetCare Institute of Cellular and Molecular Medicine (ICMM), based at Unitas Hospital, Lyttelton, Pretoria, Extraordinary Professor in the Department of Immunology, Faculty of Health Sciences, University of Pretoria, and Professeur Associé in the Department of Genetic Medicine and Development, Faculty of Medicine, University of Geneva, Switzerland)

Pharmacogenetics is a field that aims to utilize genotype to predict variations in drug efficacy and toxicity to assist in determining drug choice and schedule. Two principal factors have motivated work in this field: adverse drug reactions (ADRs) and the lack of efficacy of certain drugs at conventional doses. The fate of a drug once it has been ingested is dictated by the principles of pharmacokinetics, characterized by four phases: absorption, distribution, metabolism and elimination. Much of current pharmacogenetics has to do with metabolism. Poor metabolizers are at risk of toxicity at standard drug doses. In ultrarapid metabolizers, therapeutic levels may not be achieved. With regard to pro-drugs, which need to be metabolized to be active, the opposite occurs. Metabolism is also determined by drug interactions and environmental factors (notably diet). These factors may result in enzyme inhibition or induction. In order for genotype to accurately reflect phenotype, it is important that there is minimal interference with enzyme synthesis and activity. Cytochrome P450 (CYP450) is one of the key enzyme families involved in drug metabolism. There are more than 50 CYP genes in human genome. The AmpliChip CYP450 technology combines Roche PCR amplification with Affymetrix oligonucleotide microarray instrumentation. Two genes are included on the chip: CYP2D6 and CYP2C19. Both are highly polymorphic, and together are involved in the metabolism of ±30% of existing drugs, including antipsychotics and antidepressants. The chip has been designed to provide the broadest allelic coverage for all ethnic groups. The current therapeutic approach often relies on trial and error. However, there are important interindividual differences in response to drugs, both with respect to efficacy and toxicity. The individual differences in therapeutic and adverse effects of psychotropic drugs are determined to a large degree by genetic factors. The predictive capacity of the CYP450 AmpliChip will be discussed in relation to the clinical response to antipsychotic and antidepressant drugs. Genotyping, especially for drug metabolizing enzymes like CYP450, should enable rational and cost-effective prescribing in psychopharmacotherapy in the future.

GET TO KNOW YOUR GENES, OR SHOULD WE? ETHICAL DILEMMAS IN GENETIC SCREENING AND THERAPY

Pienaar, Willem

The human genome was unravelled in record time, thanks to contemporary scientific and technological excellence. Germ-cell therapy currently poses huge ethical dilemmas, as future generations are being affected by this form of therapy. Somatic-cell therapy is a reality, but with some unexpected results. Many scientific and ethical dilemmas are emerging in the field of genetics research and therapy. Do we want to know what the future holds for us? Can we today decide for the generations of tomorrow? Should we tamper with our genetic diversity? What should we do with the personal knowledge or information of our genetic make-up – job applications, insurance, decisions to procreate? Should we slow down research in the field or should we carefully bridge the gap between research and intervention in the form of gene-therapy? This presentation will focus on the ethical dilemmas in respect of the above questions.

ZINC AND VITAMINS A AND D IN ULCERATIVE COLITIS

Felix C V Potocnik

Aims: Ulcerative colitis is a systemic disease of which inflammation of the bowel is the primary manifestation. The study aimed to evaluate whether zinc in combination with vitamins A&D would: (1) alleviate both physical and psychiatric symptoms; (2) elevate plasma zinc levels; (3) show cost benefits.

Method: In a single-blind pilot study, 20 ulcerative colitis patients had their psychiatric symptoms rated at 3-monthly intervals on the Hamilton Depression Rating Scale (Ham-D) and Sheehan Disability Scale (SDS). Their standard daily treatment regimen was substituted with:

a) 10 patients: 15mg zinc plus 4750 IU vit A and 400 IU vit D3 in cod-liver oil;
b) 10 patients: 15mg zinc plus 5000 IU vit A and 40 IU vit D3 as dry powder.

Ethics do not allow for a placebo group. Relapses were treated with standard therapy. Each visit included: monitoring of blood zinc, copper, vitamins A&D; stool chart diaries, endoscopy, and bowel biopsies (blinded investigator). Patient's treatment charts underwent cost-analysis for the year prior to the study and the year of the study.

Results: Both the Ham-D and SDS demonstrated a significant improvement in depressive symptoms and quality of life, in keeping with positive changes in laboratory and other clinical parameters. This included symptomatic improvement of polyarthralgia (in all 4 patients), and resolution of pyoderma gangrenosum (in the one patient with this lesion). The cost-analysis of the patient's treatment charts for the year prior to this study amounted to R147 746.49, and R32 291.58 for the year under study (ie an approximately 80% cost reduction or 21,86% of former costs).

Conclusions: Results indicate that treatment with zinc and vitamins A&D: (a) is an effective treatment modality for this illness and that the degree of psychiatric morbidity is underestimated; (b) raises plasma zinc levels; (c) shows cost benefits.

PHARMACOTHERAPIES FOR ALZHEIMER'S DISEASE, STATE OF THE ART

Felix C V Potocnik

There is a spectrum of overlap between cognitive (memory), psychological (psychoses, mood) and behavioural symptoms. The latter two, referred to as behavioural and psychological symptoms of dementia (BPSD), will arise at some time during the course of the illness necessitating medication, if not placement.

Antidepressants work well up to a MMSE of approximately 22/30, especially if augmented with a neuroleptic agent. First onset 'bipolars' usually herald an early dementia, and mood-stabilizers by and large do not play a significant role.

Cognitive enhancers influence the whole spectrum of cognition and BPSD, showing improvement in activities of daily living (ADL) or overall functioning. There are three acetylcholinesterase inhibitors (AChEIs) and one NMDA-receptor antagonist available on their own or in combination with the latter, that are effective at different stages of the illness and target specific areas of the BPSD (such as apathy, irritability and restlessness). In general one initiates treatment with a cognitive enhancer and then mops up residual symptoms with other agents.

Neuroleptics play an important role in all stages of the disease. While the possible emergence of a metabolic syndrome may be of less concern than a 'soft' delirium or extrapyramidal side-effects; the psycho-education of the caregiver regarding the effects of the medication is more complex owing to a very narrow therapeutic window.

Furthermore, there are recommended pharmacotherapeutics for use in 'difficult areas' such as acute sedation, insomnia using non-benzodiazepine hypnotics, sexual disinhibition and possibly vocalization. Guidelines regarding pharmacotherapeutics and the issue of falls have been established and the route of administration broadened. Current novel pharmacotherapeutics involve the use of vitamin E and possibly in the near future the B-group vitamins, omega-3 and statins.

HYPNOTIC ADDICTION

Rataemane, S (Head, Department of Psychiatry, University of Limpopo (Medunsa Campus), Pretoria)

Sedative hypnotic drugs are used to reduce tension and anxiety and to induce calm (sedative effect) or to induce sleep (hypnotic effect). They exert a quieting and calming effect at low doses and sleep-inducing effect in larger doses. These drugs depress the central nervous system and have a selective ability to achieve their effects without affecting mood or reducing sensitivity to pain. They are relatively safe and with overdose, rarely result in death. However, used chronically, they can be addicting. These agents are often taken in combination with other drugs by patients with addiction disorders. Today benzodiazepines have replaced barbiturates as the mostcommonly abused sedative-hypnotic drugs. Side effects, abuse risk and alternatives will be discussed.

PEARLS IN CLINICAL NEUROSCIENCE: A SERIES OF REVIEW ARTICLES

Dan J Stein (Professor and Chair, Department of Psychiatry, University of Cape Town, and Director, MRC Unit on Anxiety Disorders, Stellenbosch University)

Conceptual and empirical research in psychiatry is increasingly able to synthesize findings from basic and clinical studies; this translational work provides a foundation for approaching psychiatry as a clinical neuroscience. In addition, there is a growing ability to combine findings from neurocircuitry (imaging) and molecular (genetics, proteomics) clinical studies, and from evidence-based pharmacotherapeutic and psychotherapeutic studies; this provides a framework for conceptualizing psychiatric disorders in terms of an integrated cognitive-affective neuroscience. Finally, there is ongoing interest in bringing together work on both proximal (psychobiological) mechanisms and distal (evolutionary) mechanisms underlying psychopathology, further strengthening the power of our explanations. "Pearls in Clinical Neuroscience" is a regular teaching column in "CNS Spectrums" (www.cnsspectrums.com), which attempts to provide theoretically integrated and practically useful approaches to diverse psychiatric disorders and phenomena. This lecture presents a number of recent columns, on topics such as empathy, phobias, and exercise.

FROM MOLECULES TO MIND AND DISORDERS: WHERE IS THE GAP TO BE BRIDGED?

Szabo, Christopher (Professor and Head of Clinical Psychiatry, Division of Psychiatry, University of the Witwatersrand, Johannesburg, and Chief Specialist and Head, Department of Psychiatry, Johannesburg Hospital)

Eating disorders are traditionally viewed as conditions not easily treated, with varying success when they are. The dominant approach to treatment generally involves cognitive-behaviour therapy. Successful pharmacological intervention, as a primary modality, remains an elusive goal. Within the context of molecules and the mind, it appears that we do not really know which molecules are aberrant. As for the mind, it is not clear that there is a concise understanding of the concept. In addition, given our relative lack of fundamental knowledge related to the aetiology of eating disorders it might appear premature to seek to bridge a potential gap between molecules and the mind. However, one might argue that in exploring this issue a way forward becomes clearer.

MENDING THE MYELIN IN MULTIPLE SCLEROSIS – A PARADIGM SHIFT

Susan J van Rensburg (Department of Pathology, NHLS, Tygerberg Hospital, W Cape), Dinie Hon, Peter Haug, Rajiv Erasmus, Liezl Bloem and Monique Zaahl

Introduction: Multiple sclerosis (MS) has come to be regarded as a disease of progressive neurodegeneration, inevitably resulting in paralysis and death. However, it has been known for a long time that disease outcome correlates with lifestyle, and specifically with saturated fat intake (Swank, 1950). The latter research led to a diet that had a very good outcome, but was difficult to follow, because saturated fat intake had to be limited to less than 20 g per day. Further intervention studies also had positive effects on disease outcomes. The aims of the present research are to find the biochemical and genetic basis of MS, using the dietary information in the literature as a starting point.

Patients and methods: 43 patients were diagnosed with MS according to the criteria of McDonald (2001). Blood was analysed for iron, folic acid and homocysteine concentrations. Mutation analysis of several genes involved in iron and vitamin metabolism were performed using polymerase chain reaction (PCR), heteroduplex single strand conformational polymorphism (HEX-SSCP) detection and semi-automated DNA sequencing techniques.

Results: Serum iron concentration correlated with age at diagnosis (p = 0.008). More than half of the patients had low iron parameters. Polymorphisms in several iron metabolism genes (*HFE*, *SLC40A1*, *CYBRD1*, *HAMP* and *HJV*) were found in MS patients. In the folic acid metabolic pathway, at least one mutation in the MTHFR gene was identified in all the MS patients (100%), compared to 45% in controls. Patients responded well to nutritional supplementation, which included folic acid, vitamin B_{12} and iron in patients with iron deficiency (30% improvement in neurological symptoms over 6 months, according to the Kurtzke EDSS neurological test).

Conclusion: Our research results indicate that the aetiology of MS is related to genetic and environmental factors, implicating a role for the MTHFR gene (the folate-vitamin B_{12} metabolic pathway) in the MS, and also confirm that disease outcome can be improved by nutritional intervention.

GENETIC ASSOCIATION ANALYSIS OF VARIANTS IN CYTOCHROME P450 AND OTHER CANDIDATE GENES AND THE SUSCEPTIBILITY TO ABNORMAL INVOLUNTARY MOVEMENTS IN XHOSA SCHIZOPHRENIA PATIENTS

Warnich, L (Professor and Chair, Department of Genetics, Stellenbosch University); Hitzeroth, A; Truter, E; Botes, W; Koen, L; Niehaus, D

The identification of a pharmacogenetic basis for dissimilar drug responses may have significant clinical implications in the treatment of schizophrenia, allowing individualised prescription of antipsychotic drugs and eventual elimination of undesirable side effects. While no obvious explanations exist for the development of abnormal involuntary movements (AIM), including tardive dyskinesia TD, several hypotheses have been proposed to explain TD development. Based on these and on the finding that TD has a genetic basis, several genetic variants have been investigated in the development of this disorder in various populations. This study focused on genetic variants in the *CYP1A2*, *CYP17α-Hydroxylase*, *MnSOD* and *DRD3* genes, and the development and severity of AIM, as well as TD, in a Xhosa schizophrenia population. Variants in the *CYP1A2* and *DRD3* genes did not demonstrate a significant association with AIM or TD. The *CYP17α-Hydroxylase* variant showed a significant difference in genotype (p=0.036) and in allele frequency (p=0.031) between patients with and without TD. No association between *MnSOD* Ala-9Val and the development and severity of schizophrenia was found. However, a relationship between genotype and AIM or TD development was observed (p=0.008 and p=0.011). Furthermore, an association between TD severity (though not AIM), in terms of AIMS score, and Ala-9Val genotype was found (p=0.037). The preliminary results warrant additional investigation to elucidate the role of these variants in the development of AIM and TD, but contribute to the future development of methods to predict drug response in local populations.

THE THREE PHASES OF EVE; AN ANALYSIS OF THE INFLUENCE OF HORMONAL FACTORS ON WOMEN'S MENTAL HEALTH AT MENARCHE/MENSES, PREGNANCY, MENOPAUSE

White, D (Associate Professor, Department of Psychiatry, UCT, and Head of Clinical Services, Lentegeur Psychiatric Hospital)

We live in an era where the importance of women's health has been emphasized. Women's mental health is benefiting from studies that seek to understand the sex differences in onset, presentation, course and treatment of mental illness.

The presentation focuses on evidence from recent research of the influence of hormones of the reproductive endocrine system, in particular oestrogen, on disturbances in mood, behaviour and cognition associated with the key hormonal events in the life-cycle of women.