

clear that other yet unknown loci must be involved in AD, findings of studies aiming to identify new (candidate) genes have been controversial. Putative environmental risk factors for AD are alcohol, smoking, head injury and several disorders including vascular disease and depression. Anti-inflammatory drugs and estrogen replacement therapy have been reported to have a protective effect on AD. There is some evidence for synergistic effects between environmental and genetic factors, in particular the APOE gene. The APOE genotype may modify the risk of AD associated with head trauma and several vascular factors, i.e., atherosclerosis, serum cholesterol and estrogen replacement therapy. However, studies of environmental factors have generally been small and of low validity. Large scale, long term follow-up studies, ongoing at present, may clarify the role of environmental factors in AD and their interaction with genetic factors.

### S71-2

#### GENETIC AND ENVIRONMENTAL FACTORS IN SCHIZOPHRENIA

P. McGuffin. *University of Wales, College of Medicine, Cardiff, UK*

The accumulated results of family, twin and adoption studies leave little doubt that genetic factors have a substantial role in the aetiology of schizophrenia. However, the discordance rate of just over 50% in identical twins indicates that genetic factors (at least of the straightforward mendelian type) are not sufficient to cause the disorder. It can be estimated from quantitative genetic analyses that about 20% of the variation in liability to schizophrenia is accounted for by non-genetic factors and that these are entirely non-familial, that is, they do not include environmental factors shared within families. A number of putative environmental factors have been identified such as birth injury and maternal infection but these are likely to have small effects. It is possible that "environmental" factors also include stochastic epi-genetic phenomena that cannot be detected using standard epidemiological approaches.

### S71-3

#### STATUS OF THE SEARCH FOR GENES INVOLVED IN BIPOLAR AFFECTIVE DISORDER

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The search for genes involved in bipolar affective disorder is difficult as the mode of inheritance is unknown and very likely involves different combinations of genes with major, moderate and minor effects acting in concert. The relative lack of pathophysiological knowledge makes the perhaps 30,000 genes of relevance for the function of the brain potential candidates. The search is made even more complex as there is no universally recognised biological abnormality which helps to separate affecteds from unaffecteds, to identify homogenous subgroups or to identify gene carriers.

Different methods aiming at localising the disease loci by identifying a shared chromosomal segment inherited from a common ancestor have resulted in suggestion of loci on a number of chromosomes of which at least chromosomes 4p16, 18q23 and Xq26 are very promising.

In parallel investigation of the minority of neurogenes that are presently known have lead to identification of interesting DNA sequence variation in a number of genes including the serotonin transporter gene.

Though primarily disease susceptibility genes have been sought for genes influencing several important features such as severity,

course, treatment response, side effects, abuse and personality characteristics of importance for compliance to treatment is beginning to receive attention.

When the relevant DNA sequence variation have been found it will be possible to determine the neurobiological and clinical significance of the gene. This will be hopefully allow faster diagnoses, prediction of course, severity, treatment response and side effects aided by DNA knowledge in the individual patient and the development of new and powerful forms of treatment.

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## TC72. ICD-10 advanced training seminar IV

*Chairs: A Bertelsen (DK), J van Drimmelen (WHO, CH)*

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## DEB74. Physician-assisted suicide

*Chairs: P Cosyns (B), M Kelleher (IRL)*

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## Lilly-SAT1. Zyprexa™: Redefining the management of schizophrenia

*Chair: J Gerlach (DK)*

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### Lilly-SAT1-1

#### MANAGEMENT OF FIRST-EPIISODE PATIENTS

René S. Kahn. *Department of Psychiatry, University Hospital, Utrecht, The Netherlands*

Patients with recent-onset schizophrenia – that is, patients who recently experienced their first psychosis – are a very important group, both in clinical management and from a research point of view. It appears that these patients are different in some respect from patients who have been ill for several years. In the first place, these patients show a better treatment response. Second, this patient group is exquisitely sensitive to the side effects of the typical antipsychotics. Therefore, newer medications, such as the atypical antipsychotics, may be particularly indicated in this patient group.

From the research point of view, first-episode schizophrenic patients are very important because it is during this period that most of the deterioration in functioning becomes evident. Therefore, studying these patients with regard to their course of illness, treatment interventions, and neurobiological changes may be fruitful in elucidating the pathogenesis of the disease.

Indeed, several studies have suggested that schizophrenic symptoms appear many years before the onset of first psychotic symptoms. Early intervention may therefore be indicated, although difficult to establish, since the first presenting symptoms are non-specific. Early treatment is important because treatment response is more favorable, and biological changes (such as increasing

ventricular brain ratio) may be more pronounced in patients who have delayed onset of treatment.

Finally, there is the issue of compliance. It has been repeatedly demonstrated that multiple relapses are detrimental to the course of illness. Enhancing treatment compliance, particularly in young schizophrenic patients, may be essential in determining the course of illness. Side effects are a major cause of noncompliance in schizophrenic patients. Therefore, new medications that are better tolerated than the typical antipsychotics may be important assets that the physician can use to improve the course of illness in schizophrenia.

### Lilly-SAT1-2

#### CHALLENGES IN PATIENT MANAGEMENT

David Pickar. *Experimental Therapeutics Branch, Division of Intramural Research Program, National Institute of Mental Health, NIH, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA*

The introduction of the atypical antipsychotic, clozapine, signaled a major advance in the pharmacotherapy of schizophrenia. The subsequent new generation of atypicals (e.g., olanzapine, risperidone) have gained widespread clinical application and have already made a substantial contribution to improving the outcome of patients with schizophrenia. The neuroscience/pharmacology underpinnings of these compounds have presented new opportunities for further drug development. Coupled with advances in molecular science, including pharmacogenetics, protective genes, etc., the prospects for a further refinement in drugs to treat schizophrenia are excellent.

### Lilly-SAT1-3

#### MOOD AND RELATED SYMPTOMS IN SCHIZOPHRENIA

S.A. Montgomery. *Imperial College School of Medicine at St Mary's, London, UK*

Depressive symptoms are frequently found to be part of schizophrenia. Estimates of between 25% and 60% of acute episodes of schizophrenia are associated with depression that often persists after treatment with classical antipsychotics. The depression has a profound effect on the quality of life and is an important predictor of suicide. The depression is often mistakenly confused with the negative symptoms of schizophrenia.

Olanzapine is the most thoroughly studied of the atypical antipsychotics in schizophrenia with associated depressive symptoms. It has been found to produce a significantly better response of the depressive symptoms compared with haloperidol measured on the MADRS.

Classical antipsychotics do not appear to treat the full range of symptoms in schizophrenia, as evidenced by depressive symptoms. Effective treatments like olanzapine should be preferred.

### Lilly-SAT1-4

#### COGNITIVE DEFICITS IN SCHIZOPHRENIA

Alan Breier. *Lilly Research Fellow, Lilly Research Laboratories and Professor of Psychiatry, Indiana University School of Medicine, USA*

Schizophrenia is characterized by cognitive deficits that span several domains and include dysfunction in attention, information processing, memory and executive performance. These deficits are observed in first-degree family members suggesting a heritable component. In addition, cognitive deficits pre-date the onset of

schizophrenia indicating they are core components of schizophrenia and not secondary to medication side effects, positive or negative symptoms. There is a growing body of literature suggesting that cognitive abnormalities predict occupational and social dysfunction and may be a major determinant of long-term outcome. The traditional neuroleptic drugs have proven to be relatively ineffective for these deficits and earlier information suggests the new so-called atypical antipsychotic agents have cognitive properties. One of these agents, olanzapine, selectively increases norepinephrine and dopamine in prefrontal cortex, produces early mediated disruption in information gating, and has mixed effects at the muscarinic M-4 receptor – all preclinical evidence supporting cognitive enhancing potential. Moreover, in a recently completed Canadian multi-center, double-blind, one year comparative trial of olanzapine, risperidone and haloperidol in early phase schizophrenia (Purdon, et al, 1998), olanzapine demonstrated superiority for a number of cognitive domains. The future role of atypical antipsychotics for the treatment of cognitive deficits will be discussed.

### Lilly-SAT1-5

#### QUALITY OF LIFE AND RE-INTEGRATION OF CHRONICALLY ILL PATIENTS

D.A. Revicki. *MEDTAP International, Bethesda, MD, USA*

Schizophrenia is a disabling and chronic disorder associated with severe social, occupational, and quality of life (QOL) impairments. Olanzapine (Olz), an atypical antipsychotic, has demonstrated improved clinical efficacy compared with haloperidol (Hal), but little is known on Olz's impact on QOL and other outcomes. A 6-week clinical trial, with a long-term extension, was conducted to evaluate QOL, occupational, and social outcomes. Patients with schizophrenia or other psychotic disorders were randomized to acute treatment with Olz or Hal and treatment responders entered a 46-week extension. QOL was measured using the Quality of Life Scale (QLS) and SF-36 health survey. During acute treatment, significant improvements were seen in the Olz group compared with the Hal group on QLS total scores ( $p = .005$ ) and SF-36 mental component summary scores ( $p < .001$ ). During the extension, the Olz group continued to show improvements on QLS total scores compared with Hal ( $p = .001$ ). Olz treated patients reported more useful work and employment, compared with Hal treated patients. Olz was effective in improving QOL and other outcomes necessary for re-integration into the community.

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## Lilly-SAT2. Zyprexa: New advances in the management of bipolar disorders

*Chair:* R Licht (DK)

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### Lilly-SAT2-1

No abstract received

### Lilly-SAT2-2

#### LITHIUM AND ANTIEPILEPTICS IN THE TREATMENT OF BIPOLAR DISORDER

A.H. Young. *Department of Neurosciences and Psychiatry, University of Newcastle Newcastle NE1 4LP, UK*

The element Lithium was discovered in 1817 and used to treat mood disorders in the 19th century. However, because of deaths