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

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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

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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 muscurinic 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

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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)

Lilly-SAT2-1
No abstract received

Lilly-SAT2-2
LITHIUM AND ANTIEPILEPTICS IN THE TREATMENT OF BIPOLAR DISORDER

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

https://doi.org/10.1016/S0924-9338(99)80315-0 Published online by Cambridge University Press

secondary to toxicity it was banned by the US FDA in 1949. In the same year in Australia John Cade published an open, small scale study which employed Lithium in the acute treatment of mania. Following this the use of Lithium spread to the UK, continental Europe (particularly Denmark where it was pioneered by Schou) and the USA. Lithium is currently used in a number of conditions. For Bipolar disorder these include acute mania and long-term prophylaxis. There has been a vigorous debate recently about the evidence supporting the use of Lithium and it is clear that whilst there is evidence to support its continuing use it is not an ideal drug. Problems include limited efficacy and side-effects including rebound mania upon sudden discontinuation. Because of these phenomena it has been suggested that prolonged treatment may be necessary to gain a new advantage from Lithium treatment. One advantage that Lithium may have over other mood-stabilisers is that it is associated with a lower suicide rate; although the pharmacological mechanism of action of Lithium is unknown it has effects on brain 5-HT function which have been suggested to be responsible for this property. However, recent work from this laboratory has shown that acute depletion of plasma tryptophan in Bipolar patients stable on long-term Lithium prophylaxis does not cause any change in suicidality ratings suggesting that Lithium's beneficial effects on suicide are not mediated via 5-HT.

Use of anticonvulsants in bipolar disorder is relatively recent and the best evidence to date is for Carbamezepine and Valproate. There have been some open studies suggesting beneficial effects from Gabapentin and Lamotrigine and full trials are underway.

Lilly-SAT2-3

OLANZAPINE VERSUS PLACEBO IN THE TREATMENT OF ACUTE MANIA

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A double-blind, placebo-controlled study was conducted. Patients were randomized to either olanzapine (5–20 mg/day) or placebo during a three-week period. Patients were required to be hospitalized for a minimum of one week. The primary assessment tool was the Young-Mania Rating Scale (Y-MRS), and a minimum score of 20 was required for randomization. Efficacy was measured from baseline to end point in the Y-MRS. In addition, patients were dichotomized into responders and nonresponders, where responder was defined as a 50% or greater decrease in the Y-MRS from baseline to last measurement in acute treatment.

Results: 69 patients were randomized to placebo and 70 patients were randomized to olanzapine. Olanzapine was statistically significantly superior to placebo in mean reductions of Y-MRS total (−10.3 vs −4.9, P = .09), PANSS total (−11.1 vs −3.1, P = .019), and PANSS positive scores (−4.7 vs −2.0, P = .040) from baseline to end point. In addition, there was a statistically significantly greater number of responders on olanzapine than placebo (48.6% vs 24.2%, P = .004).

Lilly-SAT2-4

THE PLACE OF ANTIPSYCHOTICS IN THE THERAPY OF BIPOLAR DISORDER

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In various parts of Europe, antipsychotics are used as first line antimanics for the majority of patients. In recent U.S. treatments guidelines for mania, lithium and antiepileptics are recommended as first line treatments, whereas antipsychotics are considered only as adjunctive agents.

Results from randomized controlled trials indicate, that typical anti-psychotics are powerful antimanics, in particular beneficial for severe agitation. As a major advantage in the treatment of these often poorly cooperating patients, no blood monitoring is required, and some typical antipsychotics can even be administered parenterally. However, the high frequency of neurological side effects from these agents may increase the risk of non-compliance, not only in the present episode but also en subsequent episodes. Moreover, due to the lack of prophylactic efficacy and due to their potential depressogenic effects, typical antipsychotics cannot be characterized as mood stabilizers. A recent placebo-controlled trial has shown that olanzapine is effective in mania with or without psychotic features. Results from uncontrolled studies also indicate that risperidone has antimanic potentials. Finally, clozapine seems efficacious in treatment resistant mania. It is beyond any doubt that the use of these atypical antipsychotics before the use of typical agents will minimize the development of neurological side effects and thereby improve compliance. However, there is still no evidence for any prophylactic efficacy of the atypical antipsychotics.

It is well-known that an antipsychotic added to an antidepressant may improve outcome in the treatment of psychotic depression, but no such data on bipolar psychotic depression are available.

In conclusion, antipsychotics are beneficial for some clinical presentations of mania. Unless parenteral administration is needed, atypical agents should be preferred before typical agents. In general, the use of antipsychotics should be prolonged into the maintenance phase only under certain circumstances.

Lilly-SAT2-5

DEPRESSION IN PSYCHOSIS AND BIPOLAR DISORDER

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The depressive symptomatology is present in several diagnostic groups, and as such it is of interest in relation to the discussion about the relevance of the existing nosological entities and consequently in relation to choice of treatment. During the previous two decades there has been a tendency in the direction of an increasing use of polypharmacy where single symptoms such as depressive mood, aggressive behaviour and anxiety are treated specifically, although they occur in the context of an otherwise well defined nosological entity for which we think we to have a specific treatment. In relation to schizophrenia we are discussing the existence of postpsychotic depression, depression related to the acute schizophrenic symptomatology and to akinesia and psychogenic depression. In affective disorder we are discussing whether there is a clinical difference between bipolar and unipolar depression with regard to symptomatology, course and epidemiology and whether the depressive state under these two conditions should be treated differently. Moreover the problems occurring in treating mixed states of mania and depression are in focus. The challenge in the future is to develop treatment modalities, which have a positive effect on all elements of a disorder - including depressive symptoms - in a specific diagnostic group, or, if this is not possible, to develop treatment programs based on polypharmacy. Finally it maybe relevant to reevaluate whether the existing diagnostic classification is meaningful in relation to choice of treatment.