nity setting. Medication management poses a particular challenge with the new antipsychotic medications, as all are available only in oral formulation. This raises issues of compliance and the ability to adhere to long-term maintenance pharmacotherapy.

Attention should also be given to individual's subjective experience of the illness and recovery. What questions and concerns does this person have? Issues of fear, apprehension, anxiety, excitement, and loneliness have been documented. How treatment professionals respond to these issues may have strong impact on the course of the individual's recovery. Engagement of the family and/or other caregivers is another important non-pharmacological intervention. As family members are still the primary care provider for adults with schizophrenia, their knowledge, availability, and involvement are crucial areas for assessment.

Outcome measurements must be interwoven with the actual healthcare delivery. Multidimensional measurements which address issues of psychopathology, social adjustment, role functioning, quality of life, violence/suicidality, family burden, patient satisfaction, and hope are examples of assessment areas.

Videotape of case examples will be presented to better illustrate effective non-pharmacological strategies when working with adults with schizophrenia.

IMPACT OF OLANZAPINE ON QUALITY OF LIFE IN SCHIZOPHRENIA

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There is greater recognition that alleviation of the psychopathology of schizophrenia and other psychotic disorders only addresses part of the problems experienced by these patients, and that comprehensive evaluations of new antipsychotic drugs require both clinical and quality of life outcome assessments. Olanzapine (Olz), a thienobenzodiazepine, is a putative new "atypical" antipsychotic agent that has been shown to be effective and well-tolerated in the treatment of schizophrenia. In a double-blind clinical trial conducted in 174 academic and community centers in 17 countries, 1,996 patients with schizophrenia, schizophreniform disorder or schizoaffective disorder were randomized to either Olz (5–20) mg/day; n = 1,336) or haloperidol (Hal) (5–20 mg/day; n = 660). BPRS total scores, PANSS positive and negative scores, CGI severity scores, and Quality of Life Scale (QLS) total and subscale scores were measured at baseline, after 6 weeks of treatment, and over a treatment period of 52 weeks for patients who responded to 6 weeks of acute therapy. All patients with a baseline and at least one postbaseline QLS assessment (Olz: 636; Hal: 257 patients) were included in the quality of life analyses. During the acute treatment phase, mean improvements in BPRS total, PANSS negative, CGI severity, and QLS total scores were statistically significantly greater in the Olz group compared to the Hal group. The greater improvements in quality of life scores were maintained over the 52-week treatment period and appeared to be due to a more pronounced impact of olanzapine on intrapsychic foundations, a measure of patient sense of purpose, motivation and emotional interaction.

In conclusion olanzapine was effective and superior to haloperidol in improving quality of life in patients with schizophrenia and related psychotic disorders.

BIOLOGICAL AND SOCIAL PREDICTIONS OF OUTCOME IN PSYCHOSIS

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A series of 166 psychotic patients was extensively investigated and followed up for 4 years. Among schizophrenic patients, males had an earlier onset of psychosis than females, but this difference disappeared when patients who had suffered obstetric complications were removed. Ventricular volume did not differ among female schizophrenics with or without a family history, but non-familial male schizophrenics had greater ventricular volume than familial cases; this was not explained by obstetric complications.

Male patients had a poor outcome while patients who had suffered adverse life events had a good outcome. Early insidious onset, low IQ, and childhood problems were bad prognostic indicators as was increased Sylvian fissure and third ventricular volume.

Wyeth-Ayerst International

ST3. The evolving role of venlafaxine: a dual action antidepressant

Chairman: C de Montigny

THE SYNERGISTIC BENEFITS OF SEROTONIN AND NORADRENALINE REUPTAKE INHIBITION

J. Craig Nelson. *Professor of Psychiatry, Department of Psychiatry, Yale University School of Medicine, 20 York Street, New Haven, Connecticut 06505*

The recent success of the SSRIs has underscored the importance of serotonin in the pathophysiology of depression. Yet, norepinepherine and serotonin both appear to play important roles in mediating antidepressant response. Tryptophan depletion studies have demonstrated that serotonergic antidepressants are dependent on serotonin for their efficacy, but that blocking serotonin synthesis has little effect on the efficacy of noradrenergic antidepressants, such as desipramine. Alternatively, administration of alpha-methyl-paratyrosine, a drug inhibiting catecholamine synthesis, causes relapse in patients successfully treated with desipramine, but not serotonergic antidepressants. The findings suggest both neurotransmitters provide alternative pathways mediating antidepressant response. Preclinical work suggests the combination of drugs acting on both systems may enhance neuropharmacologic changes. Based on these preclinical findings, we conducted a preliminary study comparing the combination of desipramine and fluoxetine to desipramine alone in a group of severely depressed inpatients. The combination was more rapidly effective, with differences noted after one and two weeks. At the end of four weeks, more patients had responded to the combination. While this was an open study, the data suggested the combination of a serotonergic and noradrenergic drug enhanced efficacy. Recent drug development has focused on the possible benefits of drugs with combined action. Venlafaxine, a new SNRI antidepressant, has both serotonergic and noradrenergic effects. Clinical studies suggest it is more effective than selective drugs in severely ill patients.

EXPANDING APPLICATIONS FOR VENLAFAXINE, A DUAL ACTION ANTIDEPRESSANT IN CLINICAL MEDICINE

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In addition to their use in depression, there is growing interest among researchers and clinicians in a variety of new indications for antidepressants. Future clinical trials of venlafaxine, a new

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serotonin-norepinephrine reuptake inhibitor, will examine venlafaxine's usefulness in a broad range of depressed patients and characterize features that distinguish venlafaxine from other antidepressants. Double-blind, parallel-group studies are planned to compare venlafaxine with other antidepressants including fluoxetine, paroxetine, sertraline, citalopram, and moclobemide. A series of studies is in progress to provide clinical confirmation for in vitro findings which suggest that venlafaxine has a low potential for producing drug interactions, because it does not significantly inhibit any of the major cytochrome P450 enzymes. Specific studies are in progress or planned to further elucidate venlafaxine's mechanism of action and onset of action. A once daily formulation of venlafaxine is under development to provide additional simplicity of dosage administration. Although depression will continue to be the major focus for venlafaxine clinical investigations, there is growing interest among researchers and clinicians in a variety of other clinical applications for antidepressants. Possible new applications include generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social phobia, neuropathic pain syndromes, premenstrual dysphoric disorder, obesity, Alzheimer's disease, and attention deficit disorder.

A CLINICAL PERSPECTIVE ON THE THERAPEUTIC ROLE OF VENLAFAXINE, A SNRI, IN DEPRESSION

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Venlafaxine, a new serotonin-norepinephrine reuptake inhibitor (SNRI), has been evaluated over a range of doses in phase II and III clinical trials involving over 3,000 patients with major depressive disorder. Data from comparative studies with fluoxetine indicate that venlafaxine at the usual dose of 75 mg/day is comparable in efficacy and tolerability to selective serotonin reuptake inhibitors (SSRIs) in most patients with major depressive disorders. Among those patients who remained at the low dose level, ie, venlafaxine 75 mg/day or fluoxetine 20 mg/day, no significant differences in response were observed on the HAM-D total or factor scores or on the MADRS total. In contrast to many SSRIs, results from double-blind, randomized trials with venlafaxine provide evidence of a dose-response effect. This positive dose-response effect results in an improved clinical response with higher doses of venlafaxine in contrast to a relatively flat dose-response with SSRIs. In two randomized, comparative trials, venlafaxine at doses of $\geq$ 150 mg/day was superior to fluoxetine. Additional randomized, comparative trials of venlafaxine versus imipramine or fluvoxamine support the superior efficacy of higher venlafaxine doses. Thus, venlafaxine offers the potential for effectiveness comparable to SSRIs at its usual 75 mg/day dose with the option of improving the response with dosage escalation.

Janssen-Cilag/Organon Laboratories

ST4. New perspectives in the treatment of schizophrenia

Chairmen: E Johnstone, R Borison

Abstracts not received.

Smithkline, Beecham

ST5. Panic and depression: not all SSRI's are the same

Chairmen: J Ballanger, J Mendlewicz

Abstracts not received.

Pfizer Limited

ST6. The role of 5HT central synaptic transmission in the regulation of the extra pyramidal system

Chairman: T Dinan

DOPAMINE AND THE USE OF SSRIs FOR CONDITIONS OTHER THAN DEPRESSION

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Serotonin reuptake inhibitors (SSRIs) have been used as adjunctive agents in open and recently double blind studies of the treatment of patients with schizophrenia, showing improvements in negative symptoms over 6 months. Extrapyramidal symptoms (EPS) were not exacerbated. Serotonergic blockade is one mechanism advocated for the apparent efficacy of many atypical neuroleptics in the treatment of negative schizophrenic symptoms and also for the low rate of EPS. SSRIs undoubtedly cause EPS in some patients, perhaps linked to the modification both of dopamine and acetylcholine release. Recent PET studies show that SSRIs differ in their effects on striatal dopamine concentration and receptor binding. Both serotonin and dopamine have been implicated in the pathophysiology of OCD and use of combined neuroleptic and SSRI treatment has also been described in cases refractory to an SSRI alone with disorders related to OCD, such as Tourette's syndrome and tricotillomania. It has also been suggested that the anorectic effects of SSRIs are mediated by dopaminergic mechanisms. The dopamine reuptake blocker bupropion has been used to treat sexual dysfunction secondary fluoxetine, implicating dopamine in these side effects. Animal studies suggest a dopaminergic mechanisms for anhedonia, a core feature of major depression. Dopamine receptor blockade has been shown to reverse improvement seen with a range of antidepressants, including drugs selective for serotonin or noradrenaline, in animal models. This must be reconciled with the adjunctive effect of dopamine blockers added to antidepressants, including SSRIs, in psychotic depression.

SSRI'S AND MOVEMENT DISORDERS: IS SEROTONIN THE CULPRIT?

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Experimentally it has been shown that 5HT agonists or 5HT releasing agents in rodents produce the serotonin motor syndrome which

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