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

E. Salinas. *Director, Clinical Science CRD Europe, Wyeth-Lederle CRD, 80 Ave du President Wilson, 92031 Paris la Defense Cedex, France*

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

A.S. Hale. *Department of Psychiatry, University of Sheffield, Northern General Hospital, S57AU U.K.*

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?

B.E. Leonard, C. Faherty. *Department of Pharmacology, University College, Galway, Ireland*

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

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appears to involve the direct stimulation of 5HT1A receptors; these characteristic motor effects are enhanced by blockade of 5HT2A receptors. An equivalent motor syndrome has been reported in man following the co-administration of SSRI's with MAOI's. However, while there is no evidence to show that clinically SSRI's alone cause such profound motor effects, there is evidence that fluoxetine exacerbates extra pyramidal reactions that are initiated by chronic neuroleptic use due to idiopathic Parkinsonism. Dystonic reactions have also been reported to occur in a minority of patients treated with this SSRI, while experimental studies in non-human primates have shown that SSRI's can produce an oral dyskinesia and exacerbate haloperidol induced dystonia. The question arises whether the movement disorders, produced by some SSRI's is a class effect arising as a consequence of an inhibition of dopaminergic function in the basal ganglia or a unique property of specific SSRI's due to their action on sigma receptors. In the rat, a high density of sigma-2 receptors is found in the red nucleus, and cerebellum, a regions concerned with the control of head and upper limb movements. Both fluoxetine and fluvoxamine cause moderate dystonia and torticollis following acute injection into the red nucleus, whereas sertraline and citalopram increased spontaneous chewing and grooming behaviour without causing dystonia. The results of the experimental and clinical studies suggest that an increase in 5HT in motor regions of the brain can cause a disruption in aspects of motor behaviour probably directly by reducing dopaminergic function in the basal ganglia or by stimulating sigma 2 receptors in the rubro-cerebellar pathway.

SEROTONIN AND THE EXTRAPYRAMIDAL SYSTEM — A NEUROLOGICAL PERSPECTIVE

R.J. Meara. *University Dept of Geriatric Medicine, Glan Clwyd DGH, Rhyl, North Wales*

Neurological disease is increasingly recognised as a significant cause of psychiatric illness. Studies at this complex interface have contributed to our understanding not only of the mechanisms of the neuropsychiatry of neurological disease but also of mechanisms underlying neurological dysfunction in primary psychiatric illness. Neurological disease of sub cortical structures involving the paramedian-limbic zone of the brain appears to be particularly associated with neuropsychiatric and movement disorders. Extrapyramidal dysfunction resulting in movement disorders (Parkinson's disease, Huntington's disease, sub cortical small vessel disease) is commonly associated with neuropsychiatric disorders and, conversely, movement disorder is increasingly recognised as an integral part of psychiatric illness such as in schizophrenia and as a result of drug treatment of psychiatric disease (neuroleptic and antidepressant drugs).

Serotonin appears to be involved in a wide range of physiological and behavioural processes and represents an important neurotransmitter system in the paramedian limbic zone of the brain that appears to have important actions in the extrapyramidal system. The rapidly developing knowledge of the neuropharmacology of serotonin in the central nervous system has led to the development of a considerable number of pharmacological agents and drugs (serotonin selective reuptake inhibitors) capable of interacting with the serotonin system.

Serotonin has been implicated, at least in part, in the neuropsychiatric disorders seen in Parkinson's, Huntington's disease and in some forms of cerebrovascular disease. Depression, anxiety and dopaminomimetic psychosis in Parkinson's disease appear to be responsive to drugs active at serotonergic sites such as serotonin selective reuptake inhibitors and atypical neuroleptic drugs. Serotonin is also implicated in the wide range of psychiatric illness seen in Huntington's disease, including depression, emotional lability, impulsivity, obsessive-compulsive disorder and suicide. Emotionalism after stroke also appears to respond to serotonin reuptake inhibitors.

Detailed study of the neurological diseases involving the extrapyramidal system in terms of abnormalities of monoaminergic transmission offers exciting new therapeutic options for neurological and primary psychiatric disease.

SEROTONIN CENTRAL SYNAPTIC TRANSMISSION AND THE REGULATION OF THE EXTRAPYRAMIDAL SYSTEM: THE PSYCHIATRIC PERSPECTIVE

Howard Ring. *St. Bartholomew's and the Royal London School of Medicine London E1 2AD*

It is becoming clear that dysfunction in the extrapyramidal system, in particular the limbic striatum, is associated with the development of a wide range of psychopathology. Anatomical links between these brain regions and associated cortical and subcortical structures have been discussed in terms of parallel circuits through these sites in increasing detail over the past 10 years. However, understanding of the neurotransmitter correlates of these circuits, of their functional significance and of their modulation by other cerebral systems has lagged behind the anatomical developments.

It was established more than 25 years ago that in rats serotonin could effect extrapyramidal function and alter the release of dopamine in the striatum. However, it is only relatively recently that these neurophysiological observations have been incorporated into the investigation and management of human psychiatric states. This review will focus on several psychiatric conditions in which consideration of interactions between serotonergic and dopaminergic activities in the extrapyramidal system may shed light on the underlying pathophysiology and may suggest novel opportunities for psychopharmacological intervention. In particular, the review will aim to synthesise findings from several psychiatric states in order to suggest why the extrapyramidal system, which until relatively recently was largely of interest only to neurologists working with movement disorders, is now implicated in the development and management of a wide range of psychopathology. Data will be drawn from studies of the 'serotonin-dopamine antagonist' concept in the development of antipsychotics, from the extrapyramidal side-effects associated with antidepressant therapy, from neurochemical theories of drug dependence and from observations made in patients with idiopathic Parkinson's disease, obsessive compulsive disorder and the Gilles de la Tourette syndrome.

Zeneca Pharmaceuticals – UK

ST7. Do teams work? A multidisciplinary perspective on collaborative care

Chairman: J Leff

Abstracts not received.

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