S49. New evaluations in ageing and dementia

Chairmen: M Philpot, S Kanowski

BEHAVIOURAL ASSESSMENT OF MEMORY IN NORMAL OLD AGE

J.M. Cockburn. *Department of Psychology, University of Reading, Reading, RG6 6AL, UK*

Experimental and anecdotal evidence indicates that both memory capacity and memory processes change with age. However, results from some experimental studies may be confounded by use of inappropriate test material in settings unfamiliar to older adults. In these circumstances, decrements found may not necessarily map onto changes in ability in everyday life.

Recent developments in neuropsychology have demonstrated the role of ecologically valid tests in delineating behaviour relevant to real-life experiences. This paper reports findings from a study of performance on the Rivermead Behavioural Memory Test by 119 people aged 70–94 years. It explores dissociations in subtest performance and identifies correlates that may indicate why some aspects of memory fail faster than others. Comparison will be made with other studies of response to self-report questionnaires and results from a test of everyday memory designed specifically to predict memory impairment associated with old age.

A LONGITUDINAL STUDY OF BEHAVIOUR IN DEMENTIA

R. McShane, T. Hope.. *Section of Old Age Psychiatry, Warneford Hospital, Oxford, OX3 7JX, UK*

The behavioural complications of dementia present major challenges for carers and often contribute to the need for institutional care. There has been little research into the natural history of such 'non-cognitive' problems or into their neuropathological correlates, in contrast to the wealth of information on cognitive decline. This is partly because appropriate instruments have only been recently applied in longitudinal studies.

The Present Behavioural Examination is a detailed, semi-structured interview which was administered longitudinally by trained interviewers to the carers of 98 subjects with dementia. The PBE assesses behaviour in eight domains: physical and mental health, walking, eating, diurnal rhythm, aggression, sexual behaviour, incontinence and other individual behavioural abnormalities. Most items are rated on a seven point scale corresponding to the number of days on which the behaviour is present in the month prior to the interview. Carers and subjects were interviewed at four monthly intervals until death over a period of up to 7 years.

The results of two studies, which use PBE data in different ways, are used to illustrate how measurement of behaviour can be applied to clinical and clinicopathological research. The first study uses longitudinal data to define syndromes of behaviours which appear to cluster together. The second shows how cortical Lewy body pathology is related to psychosis.

S50. Evidence-based psychiatry and the Cochrane collaboration

Chairmen: I Chalmers, S Wessely

EVIDENCE BASED PSYCHIATRY AND THE COCHRANE COLLABORATION

Clive Adams. *Co-ordinating Editor, The Cochrane Schizophrenia Group, University Dept. of Psychiatry, Warneford Hospital, Oxford, UK*

The Cochrane Collaboration is a global organisation producing, maintaining and disseminating systematic reviews of every aspect of health care. This organisation started in 1992 and now has active Centres in Denmark, France, Italy, the Netherlands and the UK. In addition, there are Centres outside Europe — in Australia, Canada, South Africa and the USA. Each of these Centres fosters the work of problem-based groups such as the Cochrane Schizophrenia Group and the Cochrane Depression and Neurosis Group. The Cochrane Schizophrenia Group is based in Oxford, and has already collected and coded 2500 randomised control trials relevant to the care of those with schizophrenia. Reviewers, in Europe and further afield, are not only helping the primary data collection (the identification of relevant trials) but are also producing and maintaining the reviews. These reviews are, in turn, published in electronic form in the Cochrane Library (BMJ Publications). The Cochrane Library will be demonstrated.

META-ANALYSIS USING INDIVIDUAL PATIENT DATA

P. Bech. *Psychiatric Research Unit, Frederiksborg General Hospital, DK-3400 Hillerød*

Meta-analyses based solely on data extracted from published articles have limitation, especially in psychopharmacology where published data are spread to many different journals with very different policies in showing results. There is now a Cochrane Working Group on meta-analysis using individual patient data [1].

In psychopharmacology the most optimal approach to using individual patient data is to use the drug companies' data base of controlled clinical trials for the drug under evaluation. This approach has been used when evaluating serotonin-specific reuptake inhibitors (e.g. citalopram and fluoxetine) and when evaluating selective neuroleptics (e.g. risperidone).

The practical methodology of such meta-analyses wil be presented.

[1] Stewart LA, Clache MJ (1995) Statistics in Medicine, 14: 2057–2079.

SYSTEMATIC REVIEWS — THEORY AND PRACTICE. SSRI'S AND TRICYCLICS FOR THE TREATMENT OF DEPRESSION

R. Churchill, M. Hotopf, R. Hardy, G. Lewis, C. Normand. *Section of Epidemiology and General Practice, Department of Psychiatry, Institute of Psychiatry, De Crespigny Park, London*

Systematic reviews and meta-analysis have been used to summarise information from disparate intervention studies, mainly randomised controlled trials (RCTs). Although often used interchangeably, systematic reviews and meta-analyses have different aims and objectives. Meta-analysis is a quantitative synthesis of results from pooled trials which is capable of increasing statistical power and thereby

improving understanding of relative benefits of interventions. Whilst the results of meta-analyses may be readily accessible, they are limited by the quality of the original RCTs. Systematic reviews involve the identification and qualitative assessment of all trials. We argue that systematic reviews may provide information of greater value, both to researchers and clinicians, since they illustrate the limitations of trials and ultimately of meta-analysis. 105 RCTs and four meta-analyses have failed to provide a clear answer to the question of whether selective serotonin reuptake inhibitors (SSRIs) or tricyclic/heterocyclic antidepressants should be used as first line treatment for depression in primary care settings. We will present a systematic review which examines the quality of trials and meta-analysis presenting some quantitative findings. The key findings of the systematic review are that the majority of trials are small, fail to conduct intention to treat analyses, are based in secondary care where only a minority of patients are treated, use observer rated assessments of depressive symptoms which are open to observer bias, and fail to give economic evaluations. We performed a meta-analysis using drop outs from treatment and found that overall the SSRIs had a modest advantage over tricyclics and heterocyclics (Risk Ratio 0.90; (95% CI: 0.86–0.97)). We formulated the *a priori* hypothesis that this effect would be strongest when older tricyclics were used as the comparison group, due to their more prominent side effects. We found that the SSRIs maintained their advantage when compared with the older tricyclics, amitriptyline and imipramine (RR 0.88; 95% CI: 0.82–0.95). When compared with newer tricyclics or heterocyclics no significant advantage for the SSRIs could be found (RR = 0.92; (95% CI: 0.82–1.04) for new tricyclics, and RR 1.02; (95% CI: 0.83–1.25) for heterocyclics). We suggest that the poor quality of many trials and these still equivocal results, based on drop out not clinical recovery, indicate a need for a large RCT based in primary care, and using a newer tricyclic as the comparison drug.

S51. Novel antidepressants

Chairmen: H Freeman, B Leonard

CHANGES IN 5-HT RECEPTOR SENSITIVITY DURING TREATMENT WITH SSRIs: IMPLICATIONS FOR MODE OF ACTION

P.J. Cowen. *University Department of Psychiatry, Littlemore Hospital, Oxford, OX4 4XN, UK*

The acute pharmacological effect of selective serotonin re-uptake inhibitors (SSRIs) is essentially confined to the blockade of serotonin (5-HT) re-uptake. SSRIs are effective antidepressants and block 5-HT re-uptake a few hours after a single administration. Their antidepressant effect, however, takes several days to become apparent.

Recent animal experimental investigations have suggested that adaptive changes in 5-HT receptors may play an important role in mediating the antidepressant effects of SSRIs and, perhaps, account for the delay in onset of therapeutic effect. One popular theory suggests that acute administration of SSRIs does not increase overall 5-HT neurotransmission because activation of somatodendritic 5-HT_{1A} autoreceptors attenuates the firing of 5-HT neurones. With continued treatment, however, there is an evolving desensitisation of 5-HT_{1A} autoreceptors which permits a sustained increase in 5-HT neurotransmission. In addition, continued treatment with SSRIs may desensitise the 5-$HT_{1B/1D}$ nerve terminal autoreceptor, again facilitating 5-HT release.

Neuroendocrine studies in our laboratory with the selective 5-HT_{1A} agonist, gepirone, and the 5-HT_{1D} agonist, sumatriptan, suggest that SSRIs do indeed desensitise 5-HT_{1A} receptors, but 5-HT_{1D} receptors were unaffected. These findings are of interest in view of reports that co-administration of SSRIs with the 5-HT_{1A} receptor antagonist, pindolol, can speed the onset of antidepressant effect. Drugs that produce acute increases in 5-HT neurotransmission may therefore have an earlier onset of action than conventional antidepressant compounds.

TOLERABILITY AND SAFETY OF NOVEL ANTIDEPRESSANTS

H. Freeman. *21 Montagu Square, London, W1H 1RE, UK*

As a group, the novel antidepressants (such as selective serotonin reuptake inhibitors, venlafaxine, nefazodone and mirtazapine) compared to older tricyclics show substantially lower incidences of adverse events in general, and improved safety due to a reduction of anticholinergic side effects. This finding is consistent with the fact that novel antidepressants are developed to be more selective in their mechanism of action. In the case of the SSRIs, the pharmacological action is exerted almost exclusively via the serotonergic (5-HT) system. However, their non-specific actions at receptor level, through stimulation of all 5-HT receptors, give rise to a variety of typical side effects, namely gastrointestinal side effects such as nausea and vomiting, headache, insomnia, restlessness and symptoms of sexual dysfunction. Venlafaxine inhibits reuptake of both noradrenaline (NA) and 5-HT, but because of a lack of receptor-specific actions its side effect profile still shows similarities with both the TCAs and SSRIs. Nefazodone, in addition to inhibiting 5-HT reuptake, specifically blocks 5-HT_2 receptors. This profile results in substantial reduction of 5-HT_2-mediated side effects, namely nervousness, insomnia, diarrhoea and sexual dysfunction. Mirtazapine combines enhancement of both NA and 5-HT neurotransmission by blocking α_2 adrenoceptors with specific blockade of 5-HT_2 and 5-HT_3 receptors. As a result, the incidences of anti-adrenergic and serotonergic side effects are comparable to placebo. Transient initial somnolence can be related to its antihistaminergic properties. In conclusion, the selective receptor actions of new antidepressants result in a substantial improvement in their overall tolerability and safety. The data suggest that the receptor-specific antidepressants which will become available throughout Europe during the years to come show a significantly better tolerability profile which may improve compliance and decrease the burden of pharmacological therapy without influencing efficacy.

NEW TRENDS IN THE PHARMACOLOGICAL TREATMENT OF DEPRESSION

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

The need to develop new antidepressants has been motivated by the frequency and potential severity of the adverse effects of the tricyclic and monoamine oxidase inhibitor antidepressants. This search for new classes of antidepressants has led to the development of selective inhibitors of noradrenaline or serotonin (5-hydroxytryptamine; 5-HT) reuptake, reversible inhibitors of monoamine oxidase, and noradrenergic and specific serotonergic antidepressants. More recently, novel antidepressants such as mirtazapine, which modulate both noradrenergic and different populations of 5-HT receptors, have been developed. However, while such novel antidepressants have different pharmacological profiles, there is no evidence that their therapeutic