search to manumotor tracking or (2a) with an external support of the category shift and (2b) a task which assesses the ability to switch response categories without concurrent visuomotor search and manumotor tracking were applied to 22 remitted schizophrenics (S), 15 remitted major depressives (D) (DSM-III-R) and 25 normal controls (N).

Our former results from acute S showing deviations in visual scanning strategies associated with a TMT-B performance deficit — but unrelated to neuroleptic medication — could be replicated in remitted S, too. Moreover, results of the TMT variations reveal that the performance in TMT-A relies mainly on manumotor tracking abilities, whereas TMT-B performance is mainly determined by the ability to shift response categories, which seem to be especially impaired in schizophrenics. This points to a reduced cognitive flexibility in schizophrenics, most probably related to prefrontal lobe dysfunctions. Using the research approach outlined in the present study research on this relationship probably will be facilitated in future.

S63. The natural history of psychotropic drugs

Chairmen: M Lader, J Angst

MOCLOBEMIDE: A PARADIGM OF RESEARCH IN CLINICAL PSYCHOPHARMACOLOGY

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The pre-clinical development of moclobemide is an example of broad research combined with serendipity. Moclobemide was first hypothesized as being an anti-lipemic or antibiotic, but the screenings were negative. The search for its antidepressant qualities, based on anticholinergic tests, proved also negative and moclobemide was then suspected of being an antipsychotic before its specific and reversible MAO-A inhibition qualities were detected. After the establishment of its lack of relevant interference with tyramine pressure response, clinical trials were launched in 1977.

In a first stage, multiple, small open and double-blind studies were carried out. Two decisive large multicentre double-blind studies were later performed in Latin America and Austria. Further trials have confirmed the broad antidepressant activity of RIMAs, which is not confined to any one subtype of depression and which show good tolerability and low toxicity. Since moclobemide has been available on the market, extensive meta-analyses of a large data set provided a series of methodological results: factor structure of the HAM-D, optimal criteria of efficacy, predictors of response, onset of action for antidepressants and placebo.

THE HISTORY OF TACRINE IN THE TREATMENT OF ALZHEIMER'S DISEASE

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Since Tacrine, a cholinesterase inhibitor was first reported to enhance cognitive function in patients with Alzheimer's Disease by Summers et al in 1986, it has indeed been a controversial drug. The history of its use in this context, the numerous trials and issues raised will be covered by this presentation.

It has become the first licensed treatment for Alzheimers Disease primarily approved by the FDA in the United States, some European countries and Australia.

THE RISE AND FALL OF THE BENZODIAZEPINES

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The first of the benzodiazepine group of drugs, chlordiazepoxide, was introduced after 1960 to most countries of the world. It was followed by a large number of similar compounds which were used as anxiolytics, hypnotics, anticonvulsants, muscle relaxants and as pre-operative sedation. The major advantage of these compounds was their safety in overdose and an apparently low predisposition to inducing dependence and abuse. Although early studies suggested some dependence potential, this did not seem to materialize in practice. Because of this, early concerns about the benzodiazepines soon subsided and they became amongst the most successful drugs ever introduced. Inevitably, their usage increased and their indications widened into non-medical conditions such as worry and misery. The number of chronic users escalated and concerns began to be expressed about the extent and usage — the *"Benzodiazepine Bonanza"* and the *"Opium of the Masses"*. It was even suggested that these tranquilisers were prescribed by male doctors to help disadvantaged females acclimatize to their social and economic problems.

A series of studies showed that dependence could occur at normal dose ie without escalation. It became apparent that a substantial proportion of long-term users encountered clinical problems on attempting to withdraw. A concerted campaign was conducted by many doctors and by the media in order to warn users of the potential dangers. At the same time it became increasingly aware that the benzodiazepines were major drugs of abuse being taken either adjunctively to other drugs of abuse or as the primary agent. The mode of administration could be orally by sniffing, but increasingly by intravenous injection. The last resulted in extensive vascular trauma. Finally, it became clear that these drugs produced toxic effects, especially in the elderly.

Regulatory authorities throughout the world brought inwarnings about the benzodiazepines and attempted to limit their use both as tranquilisers and as hypnotics. The benzodiazepines were scheduled as potential drugs of abuse and this is becoming more rigorous.

CLOZAPINE — THE FALL AND RISE OF AN ANTIPSYCHOTIC

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Clozapine is an atypical neuroleptic drug, not only because of its clinical profile, but also due to a peculiar history. It was investigated in Central Europe, the first open trial with 19 chronic schizophrenic patients did not show neuroleptic efficacy, a second one with pain patients was also unsuccessful. The company was close to "bury" the drug, when, in 1962, Gross and Langner found impressive improvements in 54% of chronic schizophrenic patients treated with 400 mg/day. Technical difficulties in the synthesis of clozapine resulted in the delay of further clinical trials, but more important was the surprising finding that clozapine had no extrapyramidal effects, despite antipsychotic efficacy. At that time, there was a "psychopharmacological dogma" that motor effects were necessary for a "real"

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