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"

https://doi.org/10.1016/0924-9338(96)88645-7 Published online by Cambridge University Press

neuroleptic. The manufacturer was hesitant to introduce the drug, because it lacked an adverse effect!

In 1972, clozapine was introduced in Austria, Switzerland and Germany and, within the next 5 years, in another 30 countries; more than 100,000 patients were treated. 13 double-blind investigations supported Hippius and Stille who, in 1971, confronted the prejudice about the connection between antipsychotic activity and motor effects.

In 1974, psychiatrists in Finland observed 16 cases of agranulocytosis amongst patients being treated with clozapine, eight patients died. Sandoz, the manufacturer of clozapine by that time, wanted to withdraw the product. Fortunately, however, in some countries clozapine remained on the market, where it was available for restricted use, though only with strict supervision of patients, involving regular monitoring of the white blood cells.

Between 1979 and 1988, studies in Scandinavian and German-speaking countries indicated that, under hematological control, the risk of agranulocytosis was tolerable in comparison to the marked benefit in those schizophrenic patients who do not improve under typical neuroleptics or suffer from severe motor symptoms. The study by Kane et al. (1988) confirmed the European experience and led to the introduction of clozapine in the US and UK. Clozapine, still the only "real" atypical neuroleptic on the market, is formally indicated only in therapy-resistant schizophrenia, but many psychiatrists use it successfully in a variety of psychotic patients such as depression, mania or Parkinson's disease.

S64. Eating disorders: needs must

Chairman: J Treasure

SOME ATTEMPTS TO GENERATE OUTCOME MEASURES IN THE TREATMENT OF ANOREXIA NERVOSA

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Relatively little has been written about treatment outcome in anorexia nervosa in terms other than weight gain, eating behaviour and menstrual status. This is even though it has recently been suggested that mortality may vary as much as three or fourfold between different treatments in UK. Meaningful outcome studies must not only reflect patients' own opinions and be comparable with other psychiatric and non-psychiatric conditions, but must be comprehensible to "Purchasers" as well as to various Clinical Health professionals. Our initial pilot study used the SF36 scale in ten new anorexic in-patients and its face validity looked promising. Patients appear to feel that they had made real gains as judged by the "Mental Health" social function, "vitality" physical role, "emotional role" sub tests. We next attempted to assess the possibilities of anthropometric studies (using "bodystat") and psychometric tests (the stroop which is said to be a strong indicator of unconscious eating pathology) and the BITE and EAT 26 (perhaps of conscious eating attitudes).

We are now engaged in a multi-centre Anglo American outcome study (CPC info and PHG info) using the DSM4 Global assessment function with a simultaneous detailed nursing assessment questionnaire and a patient questionnaire. The paper is intended to simply act as a stimulus to discussion and future research.

WEIGHT ASPECTS IN ANOREXIA NERVOSA

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Underweight is a core feature in anorexia nervosa (AN). The recent scientific breakthroughs regarding body weight regulation — among these the cloning of the genes coding for leptin and its receptor — will have a major impact on biologically orientated research of eating disorders. As a first step it is necessary to clinically address weight aspects in AN. For an individual patient these include assessment of

1.) premorbid body weight

2.) the course of the disorder including the minimal weight achieved and

3.) subsequent weight regain.

At the family level lifetime weight histories of family members need to be evaluated. Psychopathological features should be co-assessed in order to detect possible joint regulatory mechanisms. At the biochemical level leptin serum concentrations can be measured in addition to other hormones. Finally, research at the molecular level encompasses both association and linkage studies using genes involved in body weight regulation as candidate genes.

RISK FACTORS FOR EATING DISORDERS: DIFFERENCES IN INCIDENCE RATES IN RELATION TO URBANIZATION AND CULTURE

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Objective: The purpose of this study was to examine the incidence and prevalence of anorexia nervosa (AN) and bulimia nervosa (BN) and to evaluate the impact of differences in age, sex, urbanization and culture.

Method: Four data sources were used: a) a Dutch nationwide network of primary care physicians (1985–1989 records); b) the Dutch psychiatric admissions register (1983–1992 records); c) the Curaçao Psychiatric Case Register (1987–1989 records); and d) the medical records of the Curaçao General Hospital (1987–1989 records). Main outcome measures were one-year period prevalence rates, crude annual incidence rates, and age-adjusted rate ratios.

Results: The point-prevalence among young (15–34-year-old) females was 0.28% for AN and 1% for BN. The crude annual incidence rate of detected cases in Dutch primary care per 100,000 person-years was 8.1 for AN and 11.5 for BN (Am J Psychiatry 1995; 152:1272–1278). For both AN and BN, incidence rates were higher for females than for males, with the highest risk for AN in the group of 15- to 19-year-old females (79.6 per 100,000 women-years), and for BN in the group of 20- to 24-year-old females (82.1 per 100,000 women-years). The incidence of BN was lowest in rural areas, intermediate in urbanized areas, and highest in large cities; no rural-urban differences for AN were found. In line with expectations based on the sociocultural theory for the causation of eating disorders, on Curaçao (Netherlands' Antilles) no patients were registered with BN. However, contrary to expectations, registered cases of AN showed that inhabitants of Curaçao were at risk for AN. For Antillians living in the Netherlands, both AN and BN were found at rates comparable to those for the Dutch.

Conclusions: The incidence rates of eating disorders are higher than previously reported. Young females are at increased risk. Urbanization seems to be a risk factor for BN but not for AN. BN is culture-bound, restricted to western countries, while AN is not.

https://doi.org/10.1016/0924-9338(96)88645-7 Published online by Cambridge University Press