A variety of specific putative environmental factors for the multiple occurrence of psychiatric disorders in families have been explored. However, methodological limitations prohibit conclusive results on the specific nature of the predisposing environmental risk factors.

The available tools for the identification of causal and/or susceptibility genes are more stringent. Previous claims of predisposing genes for both disorders did not pass the test of replication. Very recently, multiple susceptibility genes for schizophrenia as well as for bipolar disorder were found in a replicable fashion. Current evidence emerging from genetic association and linkage studies in schizophrenia and bipolar disorder will be reviewed.

NEW PERSPECTIVES ON THE CLINICAL EPIDEMIOLOGY OF SCHIZOPHRENIA

B. Nowotny, H. Häfner. *Central Institute of Mental Health, PO Box 12 21 20, D-68072 Mannheim, Germany*

In this paper clinical epidemiology is used as an approach to explain the onset, development and course of schizophrenia. The period before first admission becomes especially important because the analysis of onset and development of symptomatology allows for the following:

1. To discriminate precipitating events from social consequences of the illness and to compare the social biography of the future patients with the biography of an age and sex matched control group from the general population. The ABC schizophrenia study, an investigation of the early course of a large epidemiologically defined first episode sample, has shown that already in the prodromal phase the illness causes age and sex specific effects on success in fullfilling social roles.

2. Cognitive deficits prior to onset of the illness or developmental disorders in childhood have been observed and have supported the hypothesis, that schizophrenia is in part caused by an early developmental disorder of the brain.

3. The gender difference in age at onset, tested on different investigational levels in the ABC study, and the second peak in rates of women around menopause have been explained by means of the oestrogen hypothesis of schizophrenia on the epidemiological level. This hypothesis has also been supported in animal studies, neurochemical analyses and controlled clinical studies.

A further hypothesis of sub-types of schizophrenia is for example a narrowly defined S+ schizophrenia based on neurodevelopmental disorders occurring mostly among young men and a benign form of the disorder usually a spectrum diagnosis occurring mostly in women usually several years older than their counterparts. The effort to determine empirical sub-types based on symptomatology in the early course, illness behaviour, further course and other factors within the ABC schizophrenia study yielded not very stable sub-types without any differences in gender distribution.

We can conclude, that symptomatology and the course, of schizophrenia are partly determined by age at onset, gender and developmental factors.

S79. Substitute prescribing and substance dependence

Chairmen: M Farrell, B Ritson

BUPRENORPHINE IN THE TREATMENT OF OPIATE ADDICTION. EUROPEAN STATUS

Marc Auriacombe. *Université de Bordeaux II, Faculté de Médecine Victor Pachon, Centre Carreire, 121 rue de la Béchade, 33076 Bordeaux, France*

This presentation will review the clinical and pharmacological basis for the rational use of buprenorphine for the treatment of opioid dependence. The first clinical report on the use of buprenorphine will be presented as well as a comprehensive review of the clinical data currently available from treatment centre based treatment settings. Long-term outcome results of buprenorphine treatment from office-based practice setting will be discussed, and the specifics of buprenorphine treatment in France will be presented as well as results from ongoing evaluation research.

DELIVERY OF METHADONE MAINTENANCE IN THE EUROPEAN UNION

Michael Farrell, Jan Neeleman, Michael Gossop, Paul Griffiths, Emily Finch, John Strang. *National Addiction Centre, 4 Windsor Walk, London SE58AF*

Objective: To provide an overview of the current level of provision of methadone maintenance in eleven European Union countries.

Method: National Data and key informant data was aggregated to provide a national overview and 2–3 clinics were visited to describe operational procedure in each country with such services.

Results: There is no consistency in definition of mode of delivery of methadone treatment in different countries and there is no consistent definition of the terms "detoxification" or "maintenance" across countries. The range of provision of methadone maintenance ranges from 10 per 100,000 to 100 per 100,000. There are three dimensions of treatment, the type of drugs and formulation of drugs delivered, the mode of administration and the associated types of psycho-social treatment delivered. The styles of delivery in different countries will be reviewed.

Conclusions: There has been a considerable growth in methadone treatment. There is major variation in mode of delivery and style of treatment.

METHADONE MAINTENANCE OR WITHDRAWAL: HOW REALISTIC IS IT TO CONDUCT A CONTROLLED TRIAL?

E.J.L. Finch, J. Strang, L. Hankinson, M. Gossop, M. Farrell, C. Taylor. *National Addiction Centre, Institute of Psychiatry, DeCrespigny Park, London SE5 8AF, UK*

Objectives: A controlled trial was conducted to compare an on site daily dispensing methadone maintenance programme (MMC) with a community detoxification programme (CDT) for opiate users. The study aimed to demonstrate differential treatment effects over time on treatment retention, illicit drug and alcohol intake, HIV risk behaviour, criminal behaviour and physical and psychological health.

Methods: Injecting opiate users presenting consecutively for treatment who had a previous episode of treatment were randomly assigned to community drug team treatment which consisted of

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a methadone prescription dispensed from a community pharmacy, regular counselling appointments with a community nurse and a treatment objective of detoxification or a place in a methadone maintenance programme where they attended daily to take their methadone on the premises and had stable maintenance as the treatment goal. Subjects who refused to accept their allocated treatment were offered the other condition. They were assessed at intake and again 1, 2, 3, 6, and 12 months after entering treatment.

Results: 119 subjects entered the trial, 75 went to CDT treatment, 47 randomised 28 chosen, and 44 to MMC treatment 33 randomised and 11 chosen. The CDT group stayed in treatment for a mean of 5.76 months, the MMC group for 8.69 months. 91% of the whole sample were contacted for follow up at 12 months. Data on the conduct of the study will be presented, alongside preliminary outcome data and analysis.

Conclusions: Randomising subjects to different treatment modalities presents special problems in the addictions field. Monitoring the process of treatment may also prove difficult. However the follow up of subjects when they have left treatment in order to obtain good quality data is feasible.

COMMONALITIES IN METHADONE SUBSTITUTION THERAPY PROGRAMMES IN EUROPE: A CASE FOR A UNIFIED POLICY?

A.H. Ghodse, C. Clancy, A. Oyefeso. *European Collaborating Centres in Addiction Studies (ECCAS), Department of Psychiatry of Addictive Behaviour, St. George's Hospital Medical School, London SW17 0RE, United Kingdom*

A muticentre survey of treatment practices related to Methadone Substitution Therapy was conducted in a cluster of eleven MST programmes in nine European countries (eight EU countries plus Switzerland) during the summer of 1995. The following practice variables were investigated: type of MST; eligibility criteria for admission; treatment contract; pre-treatment orientation of patients; informed consent; dosing policy; length of treatment; and policies on discharge and readmission. The detailed analysis of data revealed the following common practices across programmes: established links with hospital services and family doctors; prescription of methadone only by licensed medical practitioners; programmes are directed primarily by psychiatrists; specialist training in addiction not a prerequisite for employment; multidisciplinary personnel, with nurses in the majority; self referral is the predominate pattern; established interagency collaboration; treatment is predominantly Methadone Maintenance Treatment (MMT); mandatory patient identity common; verification of physical dependence by urinalysis; oral preparation for methadone; and on-site dispensing.

The findings of this survey suggest the possibility of a Europe-wide policy on Methadone Substitution Therapy and the implementation of Article 129 of the Maastricht Treaty as it affects a European health policy on drug dependence, is discussed.

THE ROLE PHARMACOKINETICS AND PSYCHOPATHOLOGY IN THE PREDICTION OF CRAVING AMONG OPIATE ADDICTS IN METHADONE MAINTENANCE THERAPY

W. van den Brink, J.W. de Vos. *Amsterdam Institute for Addiction Research, Jacob Obrechtstraat 92, 1071 KR Amsterdam, The Netherlands*

Objective: The aim of the study is to determine the role of pharmacokinetics and psychopathology in the prediction of craving among opiate addicts in methadone maintenance therapy (MMT).

Methods: A consecutive series of 20 long-term opiate addicts currently enrolled in MMT was recruited from a closed ward. During the study period of four days, craving was assessed 10 times per day using the experience sample methodology. On the first day, psychopathology was measured with the 28 item General Health Questionnaire (GHQ-28) and the 90 item Symptom Check List (SCL-90). During the second day 8–9 plasma samples were drawn and plasma methadone concentrations were determined using a newly developed high pressure liquid chromatography (HPLC) procedure.

Results: A significant positive relationship was observed between oral methadone dose and craving ($r = 0.55$). No significant relations were found between craving and pharmacokinetic parameters (plasma methadone through level, methadone half-life) or existing psychopathology. Two specific craving patterns were identified: a very high peak around 9 a.m. (methadone dispensing time clinic) and a slightly smaller peak around noon (methadone dispensing time in outpatient MMT).

Conclusions: The results suggest that factors other than pharmacokinetics and (axis I) psychopathology are responsible for craving in MMT clients. It is hypothesized that anticipatory conditioned responses or circadian rithms are responsible for the observed fluctuations in craving. Consequences of these findings and their interpretation for the clinical management of MMT clients are discussed.

S80. The history of physical treatments in psychiatry

Chairmen: P Pichot, D Healy

A HISTORICAL NOTE ON THE DEVELOPMENT OF ZIMELIDINE, THE FIRST SELECTIVE SEROTONIN REUPTAKE INHIBITOR

A. Carlsson. *Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg, Sweden*

In the early 1960s the development by Hillarp and his colleagues of a histochemical method for the visualisation of monoamines at the cellular level led to the demonstration of monoamines in specific neuronal systems in the brain and opened up possibilities for a precise localisation of different synaptic events in the monoaminergic systems. Together with members of the Hillarp school we were thus able to demonstrate the occurrence of a transmitter reuptake mechanism located to the cell-membrane of serotonergic neurons and to show that imipramine is capable of blocking not only the reuptake of noradrenaline, until then assumed to constitute the major mode of action of the tricyclic antidepressants, but also the reuptake of serotonin [1]. Our subsequent work revealed that the relative power of blocking noradrenaline and serotonin reuptake differed among the tricyclics. For example, the tertiary amines were more potent blockers of serotonin relative to noradrenaline than the secondary amines, and clomipramine was found to be an especially strong blocker of serotonin reuptake. We thereafter discovered a number of antihistamines with relative strong action on serotonin reuptake. Dr. Hans Corrodi and I started a synthetic programme based on one of these antihistamines, i.e. brompheniramine, in order to develop a selective serotonin reuptake inhibitor (SSRI). It turned out that a couple of modifications of the brompheniramine molecule sufficed to arrive at a highly selective serotonin reuptake inhibitor, i.e. zime-

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