Scale (AIMS). 12 patients had never received antipsychotic medication and none had dyskinesia. Dyskinesia was found in 10–45% of patients who had received medication.

308 elderly individuals in Madras, India, were also examined for dyskinesia, using the AIMS. Dyskinesia was found in 15% of normal subjects (N = 101, mean age 63 years), 15% of first degree blood relatives of younger schizophrenic patients (N = 103, mean age 63 years), 38% of never medicated patients (N = 21, mean age 65 years) and 41% of medicated patients (N = 83, mean age 57 years).

We conclude that dyskinesia in elderly schizophrenic patients is an integral part of the illness and not associated with antipsychotic medication.

Results from a one-year follow-up of the 21 never treated patients will also be presented.

COMPARATIVE STUDIES OF ABNORMAL INVOLUNTARY MOVEMENTS IN NEVER-TREATED VS TREATED POPULATIONS WITH SCHIZOPHRENIA

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There is an important question to answer: is tardive dyskinesia due to neuroleptics only, or does schizophrenia itself represent a risk factor for these abnormal movements? A number of studies have been conducted in Casablanca to answer this question, some of them in collaboration with the Department of Psychiatry of Portland, Oregon, USA.

Some preliminary results of a ongoing study can be presented:

Methods and patients: 61 never medicated schizophrenics (G1), 45 treated schizophrenics (G2), and 25 normal controls (G3) were included, matched for sex, age and duration of illness. The mean age for the 3 groups was G1: 29.8 ± 6.5 years; G2: 28.9 ± 5.7 years; G3: 28.6 ± 3.7 years.

The mean duration of illness for G1 was 6 ± 5.0 years; G2: 5.3 ± 3.9 years.

The clinical assessment used the Abnormal Involuntary Movement Scale (AIMS), Each examination was videotaped and assessed in two ways: open and blind.

Results: The mean global score of AIMS for the open assessment was for G1: 3.5 ± 2.7, for G2: 3.2 ± 3.5 and for G3: 0.4 ± 0.7.

For G1, there was a positive correlation with age. The abnormal movements observed were firstly in the limbs, followed by the orofacial area, and by the trunk.

THE LONGITUDINAL ASSOCIATION OF COGNITIVE DYSFUNCTION WITH TARDIVE DYSKINESIA IN SCHIZOPHRENIA

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Though the subject of much controversy in a historical context, there is an increasing body of contemporary evidence that in schizophrenia the contribution of spontaneous, disease-related involuntary movements to tardive dyskinesia appears to have been underestimated. We have been studying correlates of such movement disorder among features of the illness in neuroleptic-treated populations. In younger outpatients, we found those with orofacial dyskinesia to evidence an increased ratio of minor physical anomalies of the head to those of the periphery, indicating an association with a relative predominance of early craniofacial dysgenesis, and greater neuropsychological impairment on frontal lobe testing; severity of movement disorder was associated both with this anomalies distribution index and with extent of neuropsychological impairment. In older inpatients followed longitudinally over 10 years, those with persistent orofacial dyskinesia showed poorer function in more basic cognitive domains than did those consistently without such movement disorder, though in neither group did that function change over the decade; the only patients to show significant deterioration in these cognitive domains were those evidencing the *de novo* emergence of orofacial dyskinesia, and this deterioration occurred only over the time-frame in which their dyskinesia developed. Orofacial dyskinesia emerging during long-term neuroleptic treatment in schizophrenia appears intimately related to features of the illness for which that treatment was prescribed; it would seem to reflect, at least in part, the neuroleptic-induced precipitation or enhancement of motor patterns intrinsic to the disease process.

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S17. Special aspects in the treatment of opioid addicts

Chairmen: M Gastpar, P Baumann

NEW ASPECTS IN THE PHARMACOKINETICS AND METABOLISM OF METHADONE

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Methadone (MTD) is a racemic drug, but (R)-MTD accounts for nearly all opioid effects of the racemate. However, most countries have introduced racemic MTD for maintenance treatment of opioid addicts. Plasma level monitoring of MTD has been introduced, but an optimal concentration range cannot be agreed upon, as almost all studies did not measure the plasma levels of the enantiomers. In situations of comorbidity, such as depression, comedications may be necessary, but little is known of their interactions with the stereoselective metabolism of methadone and their clinical consequences. We have conducted several studies on the metabolism of MTD in patients:

A. In Germany, until recently, only (R)-MTD has been used. For economic reasons, the racemic form is presently being introduced into this country. In a collaborative study, 22 patients under (R)-MTD treatment were switched to a double dose of (R,S)-MTD. Under racemic treatment, the (R)/(S)-ratios ranged from 0.63 to 2.40, and there was a significant decrease ($p < 0.005$) in the mean serum concentration/dose ratios of the active (R)-enantiomer before and after the change was measured (3.97 vs 3.33). This suggests self-induction of MTD metabolism, as already observed during maintenance therapy with racemic methadone. As a consequence, this may necessitate, in some patients, a dose adjustment.

B. 6 and 7 addicts treated with racemic MTD were comedicated with fluvoxamine and fluoxetine, respectively. Fluvoxamine (50–250 mg/day) addition resulted in a significant increase in the plasma concentrations of both enantiomers, while only those of (R)-MTD were increased by fluoxetine (20 mg/day). These results suggest that CYP2D6 (inhibited potently by fluoxetine) preferentially metabolizes (R)-MTD, and CYP1A2 (inhibited by fluvoxamine) contributes to the metabolism of both MTD enantiomers.

In conclusion, plasma level monitoring of the enantiomers of MTD is recommended when MTD treatment has to be adapted in patients. The knowledge of the enzymatic mechanisms which are implicated in the stereoselective biotransformation of MTD helps to select appropriate comedications in MTD-treated patients, if needed.

ULTRA-RAPID OPIATE DETOXIFICATION: A CLINICAL INVESTIGATION

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Although largely discussed in public media, there are few scientific reports about the ultra rapid detoxification procedure during which the opiate addict is given a benzodiazepine-induced general anaesthetic while an opiate antagonist is administered. These scarce reports are generally enthusiastic about this method whereas many experienced clinicians are rather reluctant to develop upon it. Clearly more clinical studies are needed.

We report an open study with twenty patients treated using a procedure of direct transition to naltrexone (50 mg) twenty to thirty minutes after the oral administration of midazolam (90 to 120 mg), clonidine (0.300 mg), ondansetron (8 to 16 mg) and an anti-diarrhoea medication. Seventeen patients were on methadone maintenance (among them 4 regularly using heroin) and three patients were heroin dependent. The indications were detoxifications before admission in a therapeutic community (n = 4), a long lasting stay abroad (n = 4) or transition to a naltrexone out-patient treatment (n = 12). The procedure appears to be safe: no serious problems occurred. Patients were able to sleep most if not all of the first 5–8 hours, although they could not be considered anaesthetized. Clonidine and other comedications were prescribed for the rest of the first day and the next few days, but most of the patients were able to leave the hospital 36 hours after their admission. The procedure however was not well tolerated: almost all the patients had diarrhoea and/or vomitting. A six month follow-up has shown a high rate of relapse (80%) as usual after any detoxification and a rather high variability among the patients self-evaluated satisfaction.

After these first twenty patients, we modified the method and introduced a transition to a mixed agonist-antagonist (buprenorphine) one a week before transition to naltrexone, resulting in a better clinical tolerance to the detoxification, particularly for vomitting and diarrhoea. The future of the method probably relies on this two step transition: full agonist/mixed agonist-antagonist/full antagonist. This method could than find a place among the different detoxification methods although the indications will probably remain limited.

BUPRENORPHINE IN THE TREATMENT OF OPIATE ADDICTION

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Buprenorphine is a semi-synthetic opioid with agonist/antagonist properties. Since 1980, its pharmacological properties have led some to suggest that it could be used in the treatment of heroin addicts (Mello and Mendelson, Science. 1980; 207: 657–659).

In 1985, we published the first study of maintenance treatment of opiate-dependent subjects with buprenorphine (Drug Alcohol Depend 1985; 16: 257–262). Of 34 patients followed over a period of 2–17 months, 5 (15%) finished treatment after a progressive decrease in the dose of buprenorphine (starting around 2 mg/day). Their treatment lasted 2 months in one case and 7–8 months in the 4 others. Urine samples collected 3–12 months later were free of opiates; 26 (76%) patients were still in treatment; 3 (9%) patients abandoned treatment after 4–8 months.

More than 90% of the patients who undertook the treatment with buprenorphine for more than 2 weeks followed it. However, almost 50% of the addicts to which treatment was proposed abandoned it after less than 2 weeks. This high percentage of dropouts at the beginning might be due to the fact that the initial dosage of buprenorphine was too low for those patients.

In fact, recent studies have shown that 2 mg of buprenorphine were inferior to 35 mg of methadone in reducing illicit opioid use (Kosten and al., J. Nerv. Ment. Dis. 1993; 181: 358–364) and that 8 mg/day of buprenorphine were as effective as 60 mg/day of methadone (Johnson et al., JAMA 1992; 267: 2750–2755). As 50 mg of methadone is now widely accepted as the lowest effective dose, it appears that buprenorphine effective dose should be higher than 2 mg/day.

Under this condition, buprenorphine may be an interesting alternative to methadone treatment, especially since regulations make the availability of methadone treatment inferior to the demand in many countries. One advantage of buprenorphine treatment may be that the possibility of lethal overdose is remote owning to the opiate antagonist properties of buprenorphine (Cowan and Lewis, Buprenorphine, Wiley-Liss, 1995: 247).

MORTALITY IN THE METHADONE-MAINTENANCE-PROGRAM/NORDRHEIN WESTFALIA, GERMANY

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In a retrospective analysis all cases of death among patients of the Methadone-Maintenance-Program in Nordrhein Westfalia are reviewed and evaluated. Patients who died after exclusion from substitution are analysed with special attentiveness.

In a 6 years observation period, 27 patients out of the total number of 244 died by different reasons. The cumulated death risk related to the real number of a defined cohort was about 15% after 6 years. Half of them died by drug related reasons.

It is shown, that patients excluded from substitution by different reasons show a highly increased risk of drug related mortality in the near future.

So the cumulated probability after a 6 years observation period to stay alive (it means not to die by drug related causes) for patients remaining in substitution (n = 184) is about 98%, whereas in the excluded population (n = 60) the correspondent value is only about 77%.

This finding indicates a protective effect of this methadone-program on the drug related mortality. Aspects of psychiatric comorbidity and possible consequences for treatment settings are discussed.

S18. Ethnic diversity and mental health in Europe

Chairmen: J van Os, D Brugha

PROVIDING MENTAL HEALTH CARE FOR IMMIGRANTS

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International migration is increasingly affecting industrialised coun-

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