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Models of Medication

Supported Treatment for Opioid Addicts

Report

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Workshop

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1. Preface

For decades, progress in the field of drug treatment and drug research has been rather limited. Although the efficacy of interventions such as methadone maintenance treatment or certain residential approaches could be proved, the range and availability of drug treatment remains low in general. The AIDS epidemic and an increasing number of hepatitis C infections among intravenous drug users showed a need for greater differentiation and additional treatment approaches. Especially in the early nineties, a few important trends established themselves, due to increased research activities on drug treatment in the United States and in Europe:

- Differentiation of treatment opportunities

The integration of drug addicts into the treatment system and their retention in treatment require the development of a broad range of special facilities. Drug addicts are not just one group of patients but they are a very diverse group with different needs and a high level of somatic and psychiatric comorbidity. In the nineties, several important development steps adapted treatment approaches to the different client needs. The WHO - ADAT () project was a key contribution in this field.

- New pharmacotherapies

Although methadone maintenance is successful and well evaluated, it has its limitations. Therefore, different European experiences led to the development of new treatment approaches like buprenorphine, morphine, heroin assisted treatment, which have proved their effectiveness in clinical trials or in normal treatment settings.

- Integration of psychotherapy and pharmacotherapy

Big integrated treatment trials such as the study “match” or the “cocaine psychotherapy study”, carried out in the US, were able to show the effectiveness of

psychosocial interventions and the potential of combined and integrated treatment approaches. In some areas of drug treatment, psychosocial interventions proved to be particularly effective.

During the past years, the cooperation between the different international research groups has been an important motor for progress in this field. In the coming years, exchange of experience and international networking will become increasingly important. This conference, organised by the WHO, is an important step in this direction.

M. Krausz

2. Opening session of the Workshop

The WHO Workshop “Models of Medication Supported Treatment of Opioid Addicts” in Velen was organised with the aim of updating on international trends in this important area of research. The workshop was inaugurated by Dr. Schröder, State Secretary at the Federal Ministry of Health, and Mrs. Prüfer-Storcks, State Secretary at the Ministry of Health of Nordrhein-Westfalen. Both State Secretaries emphasised the political importance of new initiatives in the field of drug treatment. Dr. Nikogosian, Head of the Department of Noncommunicable Diseases and Mental Health of the WHO Regional Office for Europe, presented the WHO strategy in her capacity as official host of the conference.

Dr. Schröder stated that heroin assisted treatment in Germany is still hotly debated in the general population. New treatment concepts are essential, since only every second drug addict is currently reached by the German addiction help system. This is particularly true for long-term addicts. Moreover, policy and health care planning have to take into account the great risk of developing social problems, the risks of infectious diseases such as HIV, increased delinquency and increased mortality following drug overdoses. These requirements are met in Germany by a wide range of integrative treatment settings; however, it is equally important to have an adequate legal basis for fighting drug abuse and drug dependence. Heroin assisted treatment is not a part of drug fighting policy, but a valuable addition to the existing treatment approaches with a focus on survival. It is considered to be the very last choice for people suffering from severe drug addiction. Therefore, the introduction of the German heroin trial should not be seen as a replacement for existing therapies but as a chance for severe opiate addicts to improve their situation.

Mrs. Prüfer-Storcks, State Secretary at the Ministry of Health of Nordrhein-Westfalen, stated that international exchange of experiences and cooperation in drug treatment and research are of major importance in a growing European Community. Results from

former and current maintenance programmes show that there exists no ideal addiction treatment but different useful concepts including abstinence orientated treatment and supplementary supportive treatments with focuses on survival and social reintegration. Maintenance treatment became an established treatment method and is part of health care insurance and medical rehabilitation. Mrs. Prüfer-Storcks described heroin assisted treatment as a supplementary treatment for opiate addicts who did not profit from the current system. Therefore, the primary aim of the German model project of heroin assisted treatment is to reach severe opiate addicts, to stop the vicious circle of losing social relations, of physical decline and delinquency and to provide survival support. Though maintenance treatment is medically proved and accepted, it is still controversially discussed by the general public. Some critics consider heroin assisted treatment as a national capitulation to the drug problem. However, it is the task of politics and research people to develop solutions for “hopeless” cases. This workshop is an important step in the development of perspectives to help severely opiate addicted people, who have the right to receive attention and treatment for their disease; this might include new and controversial treatment approaches.

Dr. Nikogosian, Head of the Department of Noncommunicable Diseases and Mental Health of the WHO Regional Office for Europe, expressed a strong concern about the dynamic of drug abuse and drug related problems. The current negative trend in many countries with respect to the development of drug abuse and dependence is a big challenge. Drug use and drug-related mortality and disease are increasing, while the age of first drug use and the average age of the drug using population are decreasing. Therefore, the development of a policy and strategies that are able to reduce drug demand is an important issue for the World Health Organisation and its Regional Office for Europe. Current treatment systems are not able to satisfy the needs and the increased treatment demands in most countries. The WHO Regional Office recognises the multifactor genesis and nature of drug problems and the necessity of a systemic and multidimensional approach. The WHO supports the development of harm reduction approaches and is interested in the development of new drug programmes, such as the programmes in Switzerland, The Netherlands, UK, Germany and other countries.

3. Heroin-assisted treatment of opioid addicts (Session 1)

Chair: K. Mann, Mannheim, Germany

3.1 Summary

Professor Rehm, director of the Zürich Institute of Addiction Research (ISF) from Switzerland, presented an update on the results of the Swiss trial, with a special focus on the long-term effects of the treatment. He stated that research needs a broad view on all components of the health care system. He described heroin assisted treatment as a valuable supplement to the existing treatment options for the group of chronically addicted patients who could not profit from other treatments. This conclusion was based on the high retention rate of 70% of clients remaining in treatment after one year. Non-compliance occurred in the early phase of heroin treatment. Moreover, the treatment showed positive effects with respect to health and social outcomes and illicit drug use, and the improvement persisted during the observation period. A longer stay in treatment was related to a higher chance of starting abstinence-oriented treatment. No differentiation was possible so far between the pharmacological effect of heroin and the additional effects of setting and psychosocial interventions.

The second speaker, Professor van den Brink, director of the Amsterdam Institute of Addiction Research (AIAR), reported the results of the Dutch clinical trial, which had just been concluded. It had an excellent retention rate with 12-month outcome data available for 94% of the randomised patients. In terms of symptomatic recovery and sustained response, e.g. reduction of criminal activities, improvement of subjective mental state and of medical problems, treatment with heroin and methadone was significantly more effective than treatment with methadone alone. This was true for the trial with inhalable heroin as well as the trial with injectable heroin. Discontinuation of the co-prescribed heroin resulted in a rapid deterioration in the vast majority (83%) of the treatment completers who responded to the co-prescribed heroin. Professor van den Brink concluded that a supervised co-prescription of heroin is feasible, more effective

and just as safe as methadone alone in reducing the many physical, mental and social problems of chronic, treatment resistant heroin dependent patients. Long-term maintenance with heroin might be necessary for some patients, but, nevertheless, heroin should be the last pharmacological choice and not a first line of treatment. In this context, heroin treatment has a small part in the treatment system as a harm-reduction possibility.

Professor Krausz, director of the Hamburg Centre of Interdisciplinary Addiction Research, presented the concept and current state of the German heroin trial. The German project is planned for 3 years. Heroin assisted treatment is targeted at heroin addicts who are in need of treatment and have failed to respond to or to get in contact with the existing treatment system. The heroin trial is an integrated treatment study, testing also two different standardised psychosocial procedures: Case Management /Motivational Interviewing and psychoeducation/drug counselling. Beyond the clinical drug related examinations, special studies will investigate aspects related to criminology, care system (health economy, implementation, cooperation), cognitive-motor and neuropsychological questioning as well as the internal evaluation of psychosocial care. The first client was included in Bonn, at the beginning of March. The other centres (Karlsruhe, Köln, Hannover, Frankfurt, München and Hamburg) will follow in the next few months.

Professor Casas, head of the Department of Psychiatry of the University Hospital Vall d'Hebron in Barcelona, presented the concept and rationale of the oral heroin trial in Barcelona, one of two trials planned in Spain. Although methadone has shown considerable success among heroin addicts, there remains a subgroup of users who consistently relapse while in methadone maintenance programmes. The objective of the study is the investigation of the efficacy of oral diacetylmorphine hydrochloride, morphine sulphate, and methadone hydrochloride in the maintenance treatment of heroin dependent patients who have relapsed in maintenance programmes. The primary variables of the study are treatment retention and consumption of non-prescribed opioids. The study is a 6-month phase III clinical trial, designed as a controlled, double-blind, parallel study of 4 randomised experimental groups, comparing 3 opiate substances in 4 groups.

The last speaker, Professor Fischer from Canada, presented an overview on developments in different countries, with special emphasis on the North American situation.

One major purpose of the workshop was the discussion of different methodological approaches in the treatment of opiate addiction, as heroin abuse is still increasing. The experts debated how many years it would take for heroin prescription to become an accepted treatment, not only under study conditions. A second area of special interest was treatment retention and the issue of long-term or even life-long substituted patients. Heroin might have a well-defined place in the treatment system, and future research should focus on the evaluation of treatment systems. Treating drug addicts means not only treating people who use heroin, but also people with a high degree of comorbidity of psychiatric and physical diseases. This aspect deserves intensive research activities. The variations of legal and health care conditions in different countries require the implementation of different trials.

The main conclusions of the first session were:

- Heroin assisted treatment is a second line of treatment for severe and chronically opiate dependent individuals; it should not be an alternative, but an addition to current treatment options. For the further diversification of the treatment system, the development and evaluation of additional substances for maintenance treatment are necessary.
- Heroin treatment is able to improve social, medical and mental conditions of heroin addicted clients, and the prescription of heroin is a safe and practicable alternative to methadone maintenance under special conditions. Long-term maintenance treatment with heroin might be necessary in some cases, because of the high risk that these clients will return to illicit substance use with all the negative consequences for the individual as well as for public health and safety. Consumers' habits and the change of habits over time need to be investigated, e.g. the change from injecting heroin to smoking heroin.

3.2 Abstracts of the first Session

J. Rehm: Evaluation of the Swiss trial (Zurich, Switzerland)

Background: Heroin-assisted substitution treatment for severely opioid-dependent drug users has been available in Switzerland since 1994 as one part of a differentiated treatment system for drug addicts including abstinence-oriented treatment and methadone maintenance treatment (MMT). The latter treatment (MMT) comprises more than 80% of all treatment in Switzerland.

Methods design: Cohort studies of treatment entries for specific intervals of entry; standardized monitoring of all patients in heroin-assisted treatment

Setting: 21 community outpatient treatment centres in different parts of Switzerland having offered heroin-assisted treatment in the interval since 1994

Patients: 1969 patients who entered heroin-assisted treatment until December 2000; subsample of all 366 patients who entered heroin-assisted treatment between January 1, 1994, and March 31, 1995 for the 6-year follow-up; subsample of 237 patients who entered in the same time frame and who stayed in the programme for at least 18 months for 18 month follow-up

Intervention: Heroin-assisted substitution treatment with other treatment components like medical care and psychosocial interventions including assistance in finding adequate housing, financial consulting etc.

Findings: Retention rate was high with more than 70% remaining in treatment after one year. Treatment showed positive effects with respect to health and social outcomes and illegal drug consumption. Longer stay in treatment was also related to higher chance of starting abstinence-oriented treatment. Positive results on all dimensions persisted at a 6-year follow-up, even for discharged persons.

Interpretation: Heroin-assisted substitution treatment may be a meaningful supplement to existing treatment options for the group of chronically addicted patients who have failed other treatments. It should be embedded into a differentiated treatment system where other alternatives are present. At this point, because of the methods used, we cannot differentiate between the pharmacological effect of heroin and the additional effects of setting and psychosocial interventions, which were rather optimal in the Swiss heroin prescription study.

W. van den Brink: Results of the Dutch trial (Amsterdam, The Netherlands)

Beneficial effect of heroin in heroin addicts

Background. Heroin dependence is a chronic, often treatment resistant disorder, with serious public health implications. Supervised medical prescription of heroin has been proposed to improve the physical and mental health and social condition of those heroin dependent patients not sufficiently benefiting from methadone maintenance treatment.(1) In the Netherlands approximately 85% of the heroin addicts is inhaling heroin base ('chasing the dragon'), and only 15% is injecting heroin hydrochloride. Inhaling heroin is a relatively efficient route of administration.(2) In the current study both routes of administration are investigated (3).

Methods. Two open label randomized controlled trials – one with inhalable heroin (n=375) and one with injectable heroin (n=174) - were conducted, comparing a six month and a 12 month treatment of heroin (max. 1000 mg per day) plus methadone (max. 150 mg per day) with methadone alone (max. 150 mg per day), keeping the psychosocial treatment offer constant. Heroin was offered seven days per week and three times per day, whereas methadone was dispensed 2-7 times per week for daily use. The main outcome criterion was a dichotomous, multi-domain response index, including validated indicators of physical health, mental status, and social functioning. Additional outcome parameters included, full symptomatic recovery and sustained response.

Results. Adherence was excellent with 12-month outcome data available for 94% of the randomized patients. Using an intention-to-treat analysis, twelve-month treatment with heroin plus methadone was significantly more effective than treatment with methadone alone in the trial with inhalable heroin (response rate 47.9% versus 25.2%; difference 22.7%; OR=2.77; p=0.0002) as well as in the trial with injectable heroin (response rate 56.6% versus 31.6%; difference 25.0%; OR=2.99; p=0.0008). Similar effects were observed full symptomatic recovery (injectable heroin OR=3.27; inhalable heroin OR=3.50) and sustained response (injectable heroin OR=2.94; inhalable heroin OR=4.74) as effect parameters. Discontinuation of the co-prescribed heroin resulted in a rapid deterioration in the vast majority (83%) of the treatment completers who

responded to the co-prescribed heroin. The incidence of serious adverse events was similar in the treatment conditions.

Conclusions. Supervised co-prescription of heroin is feasible, more effective and just as safe as methadone alone in reducing the many physical, mental and social problems of chronic, treatment-resistant heroin dependent patients.

M. Krausz (Hamburg, Germany): Concept and status quo of the German trial

Background: Heroin is presently not a prescriptionable substance. In order to be able to use heroin for the treatment of opiate addicts, heroin has to be reclassified in the German narcotic law. In an effort to make this possible, the German government proposed a 3 year model project in which the use of heroin for treatment of opiate addicts is to be investigated. Design: One part of this study is – as a prerequisite for a possible permission for injectable heroin as prescription drug in Germany – a clinical trial, following the guidelines of Good Clinical Practice (GCP). The study is designed as a RCT with 8 treatment conditions. Heroin assisted treatment is targeted at heroin addicts that are in need of treatment and have not been able to make use of any therapeutic gain from the existing addiction treatment networks or those that failed to respond to existing treatments. Heroin assisted treatment should thus be understood as a controlled substitution with pure heroin in a structured treatment setting. It is an integrated treatment study also testing 2 different psychosocial conditions, Case Management and Psychoeducation. Beyond the clinical examination of the drug special studies concerning criminology, care system (health economy, implementation, co-operation), cognitive-motor and neuropsychological questioning as well as for the internal evaluation of psychosocial care will be examined, that are integrated in the 24-month study. The study is divided into 2 phases. The first client was recruited in Bonn, at the beginning of March. In the next few months the other centres (Karlsruhe, Köln, Hannover, Frankfurt, München and Hamburg) will follow.

M. Casas: Concept and Conditions of the Oral Heroin Trial in Barcelona (Catalunya. Spain)

Casas, M.¹; Bosch, R.¹; Valero, S.¹; Pérez de los Cobos, JC.²; del Rio, M.³; Trujols, J.²; Colom, J.⁴

¹ Servicio de Psiquiatría. Hospital Universitari Vall d'Hebron. Barcelona. Spain.

² Unidad de Conductas Adictivas del Servicio de Psiquiatría. Hospital Sta. Creu i St. Pau. Barcelona. Spain.

³ Unidad de Drogodependencias del Servicio de Psiquiatría. Hospital Mutua de Terrassa. Barcelona. Spain.

⁴ Direcció General dels Programes de Drogodependències i SIDA. Departament de Sanitat i Seguretat Social. Generalitat de Catalunya. Barcelona. Spain.

Catalan Oral Heroin Project

Comparative study of the efficacy of oral administration of diacetylmorphine hydrochloride, morphine sulfate, and methadone hydrochloride in maintenance treatment of heroin dependent patients who have relapsed in methadone maintenance programs

Background: Although methadone has showed considerable success amongst heroin addicts, there remains a subgroup of users who consistently relapse while in methadone maintenance programs. These failures are in part related to overly slow inductions, erratic metabolization, excessive drug interactions, and circadian rhythm interference. Furthermore, there are substantial pharmacodynamic and pharmacokinetic differences between the action mechanisms of heroin and methadone. It is also hypothesized that many users of opiates are in fact self-medicating, and hence the differences between methadone and heroin may effect relapse. Oral heroin has been suggested as a possible alternative to methadone, and has been tried in Britain, Switzerland and Germany.

Design: The objective of this study is to examine the efficacy of oral diacetylmorphine hydrochloride, morphine sulphate, and methadone hydrochloride in maintenance treatment of heroin dependent patients who have relapsed in maintenance programs. Oral heroin is particularly useful because it is fast acting (takes effect in 30 minutes), results in minimal euphoria, is comfortable for users, and is the usual route of most

medicines. Furthermore, oral administration allows for a double-blind trial, as the heroin is administered in the same way as is the methadone. Finally, the oral route also can facilitate the process of heroin being accepted as a medicine. The pathology to be studied is active opiate dependence (according to DSM-IV-TR criteria) smoked or injected amongst patients who have relapsed in at least two correctly indicated and implemented methadone maintenance programs that lasted at least one month, and in which the dose was equal to or more than 60 mg oral methadone per day

Methodology. The primary variables of the study are treatment retention and consumption of non-prescribed opioids. The study includes a series of secondary objectives concerned with the establishment and comparison of daily and equivalence doses of the three substances. Further objectives include comparison the use of non-opiate psychoactive substances over the course of the study, and to comparison of the presence of other risk behaviours during the study. It is a Phase III clinical trial, and the design is controlled, double-blind, parallel study of 4 randomised experimental groups, which compares 3 opiate substances in 4 groups (single dose oral methadone plus placebo, double dose oral methadone, 12 hour controlled release oral diacetylmorphine, and 2 hour controlled release oral morphine). The study will last 6 months, of which the first 14 days will be an in-patient induction phase, followed by 166 days of outpatient care of 2 daily doses. A total of 180 patients will participate in the study, in 3 centres, with 15 patients assigned to each treatment group in each centre. Individuals who are pregnant or breast-feeding will be excluded from the study, as will be those with any grave physical condition, those with serum transaminase concentrations 5 times higher than normal, those with a current diagnosis (according to DSM-IV-TR criteria) of an affective disorder, active alcohol, sedative and/or hypnotic dependence, schizophrenia, or other psychotic disorder. In addition, individuals who have recently taken methadone or been in a methadone program in the last month will not be allowed to participate. Knowledge of a situation that could impede the individual's participation in the study (e.g. serving a prison sentence) or participation in another research project will exclude the individual from the study. Finally, individuals will be excluded who are currently in treatment, or who may initiate treatment during the course of the study with any medication that could modify the effectiveness of heroin.

4. Developments in medication-assisted withdrawal and pharmacotherapy (Session 2)

Chair: M. Krausz, Hamburg, Germany

4.1. Summary and overview

Professor Wolfgramm from the Psychiatric Department at the University of Tübingen (Germany) presented results from animal experiments on the extinction of addiction memory. He hypothesised that underlying long-lasting changes of signal transduction in the brain of an addicted individual may be caused by either neuroadaptation or formation of an addiction memory. In a rat model of opiate taking and development of opiate addiction, the consequences of the two hypotheses were tested. The results showed that free choice is required for the development of addiction. Neuroadaptive regulation cannot account alone for the chronicity of addiction, supporting the idea of an addiction memory. Professor Wolfgramm described that currently, the most discussed hypothesis is that addiction memory might be related to sensitisation. Periods with a pronounced increase of daily opioid intake have been interpreted as a temporally limited “sensitive period” with a highly increased neural plasticity. During this period, limitation or cessation of drug supply combined with a strong urge for the drug leads to the formation of an addiction memory. The process resembles the phenomenon of “imprinting”. Provided that addiction memory is formed during a sensitive period, it might be possible to delete or overwrite it during another sensitive period that is induced by means of a therapeutic intervention. To test this hypothesis, a four-arm experiment was performed with opioid addicted rats which were either treated with corticoids or with placebo. The re-imprinting treatment was successful on the pre-clinical level and might be regarded as first approach towards a causal addiction therapy. It was discussed whether a “point of no return” might be specific for opioids.

Dr. Dedner, Psychiatric Department at the University of Tübingen, presented further results on the extinction of addiction memory. A clinical pilot study was the first attempt to transfer the new treatment model to human opiate addicts. The results showed that the new treatment approach appeared to be feasible for drug-dependent patients as no fundamentally new side effects have been observed. Since the dropout rate was very low, the compliance of the patients was regarded as good. The preliminary relapse rates indicated a potential effectiveness of the new treatment approach.

Professor Spanagel, head of the Department of Clinical Pharmacology at the Central Institute of Mental Health in Mannheim, Germany, presented an overview on new pharmacotherapies. He reported that opioids completely substitute each other in terms of subjective treatment response, and different pharmacological treatment approaches were presented. He concluded that it is difficult, at present, to identify new brain systems, which might play a specific role in relapse, and he also pointed out the importance of stress hormones in opiate dependency.

Professor Tretter, head of the Addiction Department in Munich-Haar, Germany, introduced data on withdrawal under anaesthesia. He reported that antagonist induced withdrawal by naltrexone can be practised under anaesthesia for clients usually undergoing stepwise reduction of methadone. The detoxification lasted about 1 week. Afterwards, naltrexone was administered for 6 months. It was concluded that rapid detoxification is able to reduce the length of a hospital stay and that the withdrawal symptoms could be tolerated by most patients. The rate of patients taking no hard drugs within 6 months after discharge was shown to be comparable to rates of patients discharged from drugfree programmes.

In summary, it was concluded during the discussion that the biological models need further investigation and development, especially regarding the so-called “point of no return” in addiction. An intensive cooperation between basic and clinical research should ensure this clinical progress.

4.2. Abstracts of the second session

J. Wolfgramm: Extinction of addiction memory (I) (Tübingen, Germany)

Jochen Wolffgramm¹, Franz Thimm² and Andrea Heyne²

¹ Section of Addiction Research, Universitätsklinikum Tübingen

² Medimod Research Institute, Reutlingen, Germany

Like other dependence disorders, opiate addiction is a chronic, relapsing psychiatric disease. The underlying long-lasting changes of signal transduction in the brain of an addict may be caused by two different processes: neuroadaptation in neurons and glial cells or formation of an addiction memory. The first alternative is primarily based on the continuous or intermittent presence of a drug at or in the cell, it may further be mediated by secondary changes in the balance of neurotransmission. Some of these adaptations may endure long periods of abstinence (protracted signs of withdrawal). For instance, the maximum stimulation of the cAMP-producing enzyme adenylyl cyclase is persistently reduced after long-term consumption of opioids by rats even after several weeks or months of abstinence. The second alternative (addiction memory) suggests a real learning process involving nets of neurons instead of local neuronal adaptation. An association between stimuli from the environment (especially cues), the motivation to take the drug, operant components, an anticipation of the expected drug effects and, at last, these psychotropic effects should lead to the formation of a nearly undeletable, persisting memory.

In a rat model of opiate taking and development of opiate addiction, the consequences of the two hypotheses could be tested. Rats received the μ -agonistic opioid etonitazene in their home cages by means of the drinking fluid(s) for a period of 30 weeks (subsequent experiments: 40 weeks and more), then the drug was withdrawn for a period of some months. Three experimental groups were compared: (a) free choice between water and three differently concentrated solutions of the opioid, (b) forced administration of a low concentrated opioid solution as sole drinking fluid, and (c) water as sole drinking fluid.

In a retest after long-term abstinence, the rats of all groups had the choice between water and the three opioid solutions. The purpose of this retest was to search for

abstinence-enduring effects of former opioid experiences. Apart from chronicity (persistently high risk of relapse), addictive behaviour is characterized by loss of control. This means that the addict is no longer capable to consider attractive behavioural alternatives and accepts adverse circumstances and consequences of drug taking. In our animal experiments, we can test loss of control by means of an adulteration of the drug solutions (but not water) with quinine hydrochloride. Rats avoid the bitter-tasting quinine containing solutions, but an addicted subject is expected to accept the adverse taste in order to take the addictive drug. The second part of the retest therefore consisted of a choice between unadulterated water and adulterated opioid solutions.

Rats out of the water control group (c) made their first experiences with an opioid in the retest. During the first few days, they tested the psychoactive drug, then they markedly reduced their opioid consumption. Under adulteration conditions they took only neglectable doses of the opioid. In the retest situation, the rats of the free choice group (a) could be divided clearly into two separate subgroups: part of the animals behaved like water controls, they did not prefer the opioid and avoided it during adulteration. The other subjects, however, revealed a high preference for the opioid. When the drug solutions were adulterated, they did not reduce their intake and consumed doses that were 10-15 times as high compared to controls and the non-preferring rats of the free-choice group. These rats matched the criteria of addictive behaviour, they were considered as addicted. Once an addiction had been established, we never observed a recovery of control over drug intake, the development toward loss of control seemed irreversible.

Rats of the forced group had experienced pharmacologically similar chronic opioid administration as those of the free-choice group, but their associations between motivation, drug anticipation and drug effects was expected to be different. Very similar to the free choice group, these “forced” rats developed a physical dependence on opioids. During the first days of opioid cessation, they showed typical signs of withdrawal, e.g. an increased sensitivity to slightly painful stimuli. Forced opioid administration did, however, not lead to an addiction. Not a single rat out of the forced group developed loss of control. In the retest, especially in the adulteration period, all these rats behaved like drug-naïve controls. The conclusion, that free choice is a

prerequisite for the development of an addiction is supported by the observation that in human patients therapeutic pain treatment with opioid drugs by use of a “forced” schedule of administration does not lead to opioid addiction.

These results show that neuroadaptive regulation cannot account alone for the chronicity of addiction, they support the idea of an addiction memory. At which time and by which kinds of mechanisms is an addiction memory established? At present, the most discussed hypothesis is that addiction memory might be related to sensitisation. Any repeated experiences with the drug lead to sensitized responses that may also be associated with stimuli from the environment. Sensitisation has turned out to be enduring, similar to an addiction memory. On the other hand, there are some important differences. Sensitisation takes place after non-voluntary administration of opioids that does not lead to addiction, and sensitization is rapidly accomplished after a couple of administrations whereas the development of addiction needs much longer time.

Our rat model of the development of opioid addiction enabled us to compare retrospectively the drug consumption parameters of later addicted and later non-addicted animals. We found no differences between these animals during the period of first opioid experiences and no differences between them during the long-term period of controlled opioid consumption (20-30 weeks). During this time, the rats take moderate doses according to their social situation, stressors and e.g. the taste of the solutions. At any time they are able to reduce or cease drug intake when it is coupled with adverse circumstances or when attractive alternatives are available. Obviously, this controlled consumption was not altered in those animals that later became addicted.

From one week to another, the later addicts then stepped to a transition phase, they consumed several times as much opioid as before. Later non-addicts maintained their moderate level of intake. This abrupt change is not related to sensitization (which has been accomplished a long time ago) but rather meets the concept of a “point of no return”. When during this transition period the opioid is withdrawn, the respective animals form an addiction memory and persistently lose their control over opioid intake. When, however, drug supply continues, the transition period of increased consumption spontaneously ends after 6-8 weeks. The animals return to controlled consumption, but after another couple of weeks a new transition period may begin.

Such periods with a pronounced increase of daily opioid intake can be interpreted as a temporally limited “sensitive period” with a highly increased neural plasticity. During this period, limitation or cessation of drug supply combined with a strong urge for the drug leads to the formation of an addiction memory. The process resembles the phenomenon of “imprinting”. Like other forms of imprinting (filial or sexual imprinting), formation of memory only takes place during a temporally limited sensitive period and is related to very simple stimuli, the memory contents are nearly undeletable and have compulsive consequences for the behaviour of the imprinted subject.

Provided that addiction memory is formed during a sensitive period, it might be possible to delete or overwrite it during another sensitive period that is induced by means of a therapeutic intervention. For this purpose we should first find a way to induce a sensitive period of high neural plasticity and then apply appropriate stimuli to disconnect the associations that form an addiction memory. It has frequently been observed that either heavy stress or administration of glucocorticoid hormones facilitates both formation and deletion of memory contents and may thus be suitable to induce a sensitive period. A dissociation between motivation, anticipations and drug effects can be performed by a forced manner of drug administration, e.g. by offering a single drinking fluid that contains the opioid.

We performed a four-arm experiment with opioid addicted rats (N=31) which were treated over a period of 2-3-weeks with (a) Placebo, (b) corticosterone (for 2 weeks), (c) re-imprinting treatment: first week corticosterone, second week corticosterone and forced administration of the opioid, third week forced opioid without the corticoid, (d) first a 2 week pre-treatment with the NMDA antagonist ketamine, then forced treatment with the opioid for 1 week. After treatment and a subsequent period of abstinence the rats were submitted to another retest including a test on loss of control. All animals that had been treated with the re-imprinting procedure (N=8) had lost their addiction. Even in later retests, none of these rats returned to loss of control. All other rats remained addicted. Under aversive conditions they consumed 10-15 times more opioid than their “cured” conspecifics ($p < 0.001$). The re-imprinting treatment was therefore completely successful on the preclinical level, it can be regarded as an approach toward a causal addiction therapy.

G. Mundle (Hornberg, Germany): Extinction of addiction memory (II)

Background: Addictions are lifelong, chronic disorders whose fundamental characteristics are irreversible. No treatment attempt to reverse the „point of no return“ has been successful to date. An innovative approach has now been presented with the „re-imprinting“ treatment model, which targets the causes of addiction directly by influencing the „memory of addiction“. In the animal model the new treatment approach was successful in all rats treated in this way.

Methods: The clinical pilot study was the first attempt to transfer the new treatment model to human opiate addicts. The main outcome criteria were the feasibility of the new treatment method and indicators of potential effectiveness. Overall, 25 drug-dependent patients were treated under inpatient conditions; the follow-up period was 3 months. Open questions concerned the medications selected and their dosage, the duration of the individual treatment phases and, in particular, the mode of drug administration.

Results: In this first open clinical study, no major side effects under the new treatment method were observed. Also, the drop-out rate was very low. Only one patient left the 3-phase treatment period prematurely for social reasons. In the three months follow up, three patients did not have a relapse, additional three patients were opiate free after three months, despite having experienced opiate relapses during the follow-up period.

Interpretation: The new treatment approach appears to be feasible for drug-dependent patients since no fundamentally new side effects have been observed. Since the drop-out rate was very low, patient compliance was there for interpreted/viewed as being very good. Also, the preliminary relapse rates indicated a potential effectiveness of the new treatment approach.

F. Tretter (München, Germany): Withdrawal under anaesthesia

F. Tretter et al.

District Hospital Haar/Munich (FRG)

Introduction. Opiate withdrawal syndromes show a wide range of symptoms, predominantly focused on various pain disorders. At present most opiate addicts are substituted with methadone. This substance evokes long and heavy withdrawal syndromes. Thus stepwise reduction of dose is the method of choice. However, about

50 % are dropping out of inpatient withdrawal treatment. According to Loimer et al. (1989), predominantly for such clients antagonist-induced withdrawal by naltrexone can be practiced under anaesthesia. This detoxification lasts about 1 week. Afterwards 50 mg/d naltrexone is administered for 6 months.

Methods. Since 1997 we have treated about 250 patients in our clinic with a modified protocol from Loimer et al. The patients should individuals who have received prior treatment with methadone. A follow-up study was made by the IFT by Kűfner et al. (2000) in 108 patients by telephone interview according to a special questionnaire.

Results. 66,3 % patients responded. Recordings from inpatient treatment documentation showed a heavy but very short opiate withdrawal syndrome (av.: 6,3 days).

When considering replies at interview clients reported severe discomfort for up to one month (comp.fig.1). Six months after discharge about 33 % were abstinent from hard drugs. Only a few took naltrexone after discharge (50 % after one month; comp. fig.2). A high proportion of clients (37,7%) would not participate in rapid detoxification any more, about 66,7% would recommend the procedure under certain conditions.

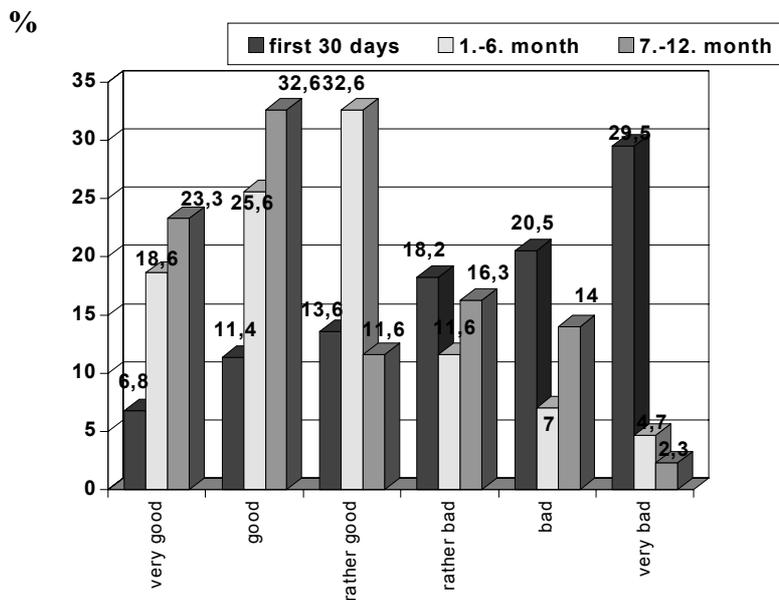


Fig. 1: General condition after the withdrawal

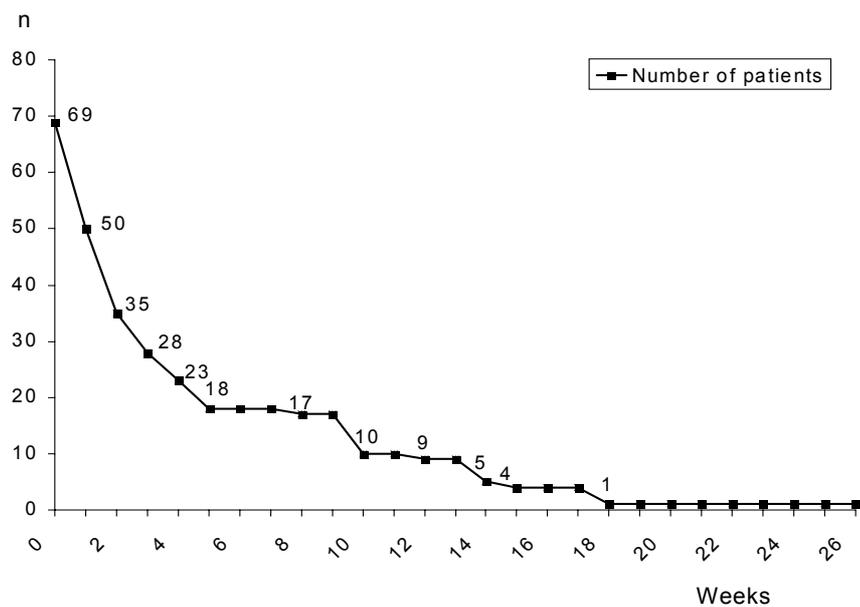


Fig. 2: Course of Naltrexone intake

Discussion. Rapid detoxification can make the hospital stay shorter. The withdrawal symptoms are heavy for about two days. Something that is tolerated by most patients.

The rate of patients taking no hard drugs within 6 months after discharge is comparable to rates of patients discharged from drug free programmes. This high rate might be due to the high selection of the patients.

The low rate of acceptance of naltrexone is due to the fact that naltrexone in Germany is not yet established as a medication for heroin addicts. This is caused by the dominance of drug free treatment philosophies.

Literature. Kűfner, H., Kűmmler, P., Beloch, E., Drobik, U., Tretter, F. (2000): Ertgebnisse zu Modellprojekt – Antagonistengestűtzter Opiatentzug. Schneider Verlag, Hohengehren

5. Differential practice of medication-assisted substitution treatment for opioid addicts (Session 3)

Chair: J. Rehm, Zurich, Switzerland

5.1. Summary and overview

Professor Buning, Director of Euro-Methwork from Amsterdam, presented an overview of the various activities, the mission and the formal structure of the network. The Euro-Methwork started in 1993 and advocated the positive results of maintenance treatment. It was able to give concrete support to the network participants when setting up a new methadone programme. Professor Buning described the co-operation between methadone clinics in various parts of Europe with the aim to ensure that travelling patients will get their medication at the place of destination.

In 2000, the European Methadone Guidelines network published a state of the art outline of best clinical practice and practical issues of methadone maintenance. A training package on methadone treatment is being planned. This manual will be translated into different European languages and will be based on a review of different training programmes and on the evaluation of an expert group. Euro-Methwork plans to facilitate 'training on site' in regional identified 'centres of excellence'.

Professor Gabriele Fischer, Director of a drug addiction outpatient clinic in Vienna, presented an overview of different well-established models of medication supporting the treatment of opioid dependence. Methadone and LAAM (leva-alpha-methyl-methadone) have been standard agents in the United States and Europe, oral slow release morphine (buprenorphine) has been successfully administered in some European countries. Several controlled clinical trials in the US and recently in Europe have reported the beneficial effects of slow release morphine. The study conducted in Vienna with cross-over design showed no differences in positive opioid results and retention but a better well-being for morphine. Buprenorphine was found to produce limited respiratory depression, long plasma half-life and long duration of action. The results

showed a low dependence liability and a lower level of reinforcement than a full agonist such as methadone or heroin. Professor Fischer concluded that buprenorphine might be considered as a first line of treatment especially for general practitioners as it offers a wide range of options including alternative day dosing in stabilised patients.

Dr. Verthein, Center for Interdisciplinary Addiction Research of the University of Hamburg, presented an overview on the introduction of medication assisted treatment of drug addiction in Germany in the 1990s. The estimated number of methadone patients was still increasing in 2001 (up to about 50,000 persons) based on the amount of dispensed methadone with an average daily dose of only 30 mg. A decrease of codeine patients (due to the German delay in introducing methadone) from about 4,000 patients to 2,000 has been observed. About 1,000 patients were treated with buprenorphine in 2000. The introduction of new substances such as buprenorphine two years ago and the recently started heroin project will lead to a broader range of therapeutic options for drug addicts.

Professor Woody from the Treatment Research Institute of the University of Pennsylvania, Philadelphia, presented an overview on the history of methadone maintenance treatment for opioid dependence in the United States. Evaluation studies over the years consistently showed that methadone maintenance is associated with cessation or substantial reduction of unprescribed opioid use and as well with improvement in other areas of adjustment. But nevertheless, many prejudices against methadone still exist in politics and in the general public. In the public discussion, the issue of addiction still seems to be dominated by moral, not by medical arguments. A number of people believe that patients suffering from addiction deserve punishment because they brought it on themselves. Moreover, the opinion prevails that all drug treatments are insufficient anyway, because a high number of relapses occur in the careers of drug addicts.

At present, 200,000 persons are in methadone maintenance treatment in the United States (15-20% of the total estimated number of opioid dependent persons). The expansion of methadone programmes to meet treatment demands seems to be impeded by a combination of political and funding issues.

Professor Sakoman, Department for Addiction, UH 'Sestre Milosrdnice' from Zagreb, presented the experiences with methadone maintenance programmes in Croatia.

Methadone had not been used in the treatment of addicts in daily practise until 1990. 3,000 heroin addicts received methadone for detoxification or for maintenance (estimation of heroin addicts: about 15,000) in 15 outpatient treatment centres. Professor Sakoman presented the existing treatment options and current problems concerning a change of the National Programme.

Professor Strang from the National Addiction Centre in London reported scientific results with respect to the rationale, extent and clinical practice of injectable methadone prescribing in the UK. The efficacy of injectable methadone in the treatment of addicts is currently a much debated issue in Britain. The practise is common and well known since the 60ies, but very little data on injectable methadone are available. Comparisons of oral methadone vs injectable methadone showed that injectable methadone is more expensive but has better clinical results: low dropout rates, good retention in treatment and better satisfaction with injectable methadone. There are only few studies on injectable methadone and no general evidence or clinical consensus so far.

Professor Auriacombe from the Addiction Research Group of the University “Victor Segalen” in Bourdeaux presented a report on buprenorphine based treatment in France. The broad dissemination of buprenorphine started in the French context in 1997. Dr. Auriacombe went into the question what buprenorphine, compared to methadone, could add to treatment in terms of effectiveness, safety and availability/accessability. The French experience showed an increased safety profile for buprenorphine. It was possible to treat more patients, and treatment was easily available using the normal treatment system. More patients had access to treatment at an earlier stage and stayed longer in treatment.

Currently France has an estimated number of 150,000–200,000 opioid users. 65,000 of them receive buprenorphine and 4,000 methadone per year. Regional data from the south-west of France with a population of 3 million showed that 96% of the prescribers are general practitioners; 84% of them had 5 patients or less. Since 1995, a significant decline of overdose mortality could be observed in France. All death cases occurred in relation with benzodiazepines and/or alcohol, none in relation with buprenorphine.

Dr. Elkashef from the National Institute on Drug Abuse (NIDA), United States of America, presented an overview on current developments of maintenance treatment and medication assisted treatment and current treatment needs. Main issues are a greater

availability of treatment options, medications for specific populations, non-opiate medication for opiate dependence, for withdrawal treatment and for treatment relapse. Heroin use is still increasing in the United States. There are presently 980,000 chronic opiate users in US, 180,000 of them are in treatment. Treatment options should be increased because the benefits of treatment outweigh the costs. A number of studies showed that buprenorphine is beneficial in the case of opiate dependence. The addition of naloxone reduces abuse potential and, if injected, will precipitate withdrawal in a moderate way. Different studies investigated the combination of buprenorphine /naloxone vs. placebo and buprenorphine alone in special populations, e.g. children, pregnant women, comorbid addicts. Special issues were investigated, e.g. neonatal abstinence syndrome. Further issues were the testing of medication (lofexidine) for prevention relapse, potential non-opiate medications.

The discussion accentuated the broad practice of and research on maintenance treatment in Europe. Buprenorphine has become an additional option but is not set to replace methadone. Rapid expansion requires the improvement of the quality of maintenance treatment in Europe. The dosing differences of maintenance substances between practical knowledge and research were highlighted. As shown in literature, American and European studies differ with respect to dosage. Further research issues will be the adequate buprenorphine dosage and the indication for maintenance treatment – which people profit from which maintenance concept.

5.2 Abstracts of the third Session

E. Buning (Amsterdam, The Netherlands): Activities of the Euronetwork Methadone

1. Introduction

In this presentation, I will outline the activities of Euro-Methwork.

First I will say something about the structure of the network, its mission and financing.

Then I will outline the various activities, which were undertaken in the past and some of the obstacles we encountered.

In the final part, I will further discuss the future of Euro-Methwork.

2. Euro-Methwork: mission, organisation and finances

Euro-Methwork is a forum of experts working in the field of substitution treatment. Since its start in 1993, it has always been a very practical and task-oriented network with a main focus on the exchange of expertise and information and the provision of tools to enable those working in the substitution treatment field to do a better job.

There is no formal membership. In the database of Euro-Methwork we have over 2000 persons who have expressed their interest in being kept informed about the network and its products. The majority of which are practical workers, policy makers and researchers who work in the substitution field in the European Region.

Over the years, Euro-Methwork has received various grants from the European Commission. Some additional financial support was received from other sources as well. The policy of Euro-Methwork is to welcome financial support on condition that it does not interfere with the independence of the network and its professional approach towards substitution treatment.

3. *Activities of Euro-Metwork*

Advocacy

Research has shown that the provision of methadone –if provided in a proper manner– has the following positive results:

- Decrease of the use of illegal substances
- Decrease of overdose
- Decrease of needle sharing and thus an important tool in the containment of the Aids epidemic
- Decrease of criminal activities
- Methadone provision is cost effective

Where and when appropriate, Euro-Metwork has advocated these positive results. Documentation has been provided to support these results. Since the positive results depend on a proper manner of carrying out substitution treatment, factors to optimize treatment have been highlighted, such as:

Proper dose of methadone, i.e. 60 mg or more per day

Maintenance works better than short term detox

Attitude of staff in terms of division of labour, respect for the patients etc.

Availability of social and psychological support for patients in a methadone programme

Support

Often, participants of the network have asked for concrete support when setting up a new methadone programme or for more specific questions related to the treatment of their patients. Euro-Metwork has made use of its network to answer these questions in an appropriate manner by creating a contact between those who have posed the question and experts who might be able to answer the question (role of brooker).

Newsletter

From the very beginning, Euro-Metwork has published a Newsletter. In these Newsletters, short articles were published about a variety of topics. A total of 19 Newsletters were published. With the increasing popularity of the Internet, it was decided that a Newsletter no longer had substantial additional value and thus the publications was stopped in 2000.

Meetings and workshops

Euro-Methwork has always tried to use the opportunity to discuss methadone related subjects during international conferences by organising parallel sessions. The advantage of this way of working is that no extra costs need to be made for travel etc. since the experts are already there.

Besides these meetings during conferences, Euro-Methwork has also organized some 'stand alone' training sessions. It turned out that it was not very cost effective to do this and therefore it was decided to no longer organise such isolated events.

Methadone Assistance Point

In the mid nineties, when more and more drug users were receiving methadone in Europe, it was apparent that there were distinguished problems concerning patients who were travelling within Europe. There was a need for co-operation between methadone clinics in various parts of Europe to ensure that patients who were travelling would be able to get their medication at their chosen destination. For this pupose, a database was setup with all methadone clinics in Europe. In this database it was clearly indicated under which circumstances a patients could temporarily receive methadone from a clinic in another part of Europe. The database was put on the Internet (www.euromethwork.org) and called the Methadone Assistance Point (MAP). It turned out to be a very fruitful tool.

European Methadone Guidelines

In 2000, Euro-Methwork published the European Methadone Guidelines in 4 languages (English, French, German and Spanish). It is a comprehensive booklet of about 60 pages with the following topics:

- State of the Art of Methadone in Europe
- The Evidence for the effectiveness of methadone
- Outline of Best Clinical Practice
- Practical issues of programme organisation
- Monitoring and Evaluation

The Guidelines were send to the participants of the network and published on the Internet. In additions, all the information from the WebPages (Newsletters, Methadone Assistance Point, Guidelines) were put on a CD-ROM and distributed to the participants

of the network as well. In 2001 and 2002 the Guidelines were translated into Russian, Slovenian, Greek, Slovak and Bosnian.

Obstacles

Although Euro-Methwork managed to create very useful tools for people working in the substitution treatment field, it is not an easy job to maintain the network. There are a number of obstacles, which I would like to discuss.

The first issue is ‘Who is doing the work?’ As we all know, people have busy agendas and this does not allow them to invest a lot of time in activities, which are not part of their day to day job. This means that most of the work is done by a relatively small group of people who are able to allocate time to the network. So, the idea of a network with many people involved is a somewhat idealistic view. Even after the job is almost done and the participants of the network are asked for feedback, it has often happened that only a few responded. On the one hand this can lead to frustrations amongst those who have done the work and on the other hand it can create an image of the ‘in-crowd’ who is in charge. Years of experience with running networks, forces me to say that there is no solution for this.

The next issue concerns differences in culture between the various European countries. The Northern countries are very task-oriented and see a long discussion about philosophical items as a waste of time: ‘Let’s not talk but do something’. In the Southern countries, people are used to take more time to discuss matters at lengths in order to form more in-depth insights into underlying problems and thus be able to formulate plans of actions which might be more appropriate on the long term. Both approaches have their pros and cons. In a network it is important to respect the different approaches, although it should be said that these differences can lead to frictions and frustrations at both sides.

A third issue concerns the sustainability of the network. Most networks, and Euro-Methwork is no exception, have to rely on external funds to carry out their activities. In the case of Euro-Methwork, the European Commission has been the main source of income. However, the European Commission has very bureaucratic procedures to obtain funds and there is always a substantial amount of time between two project fundings, which means that the network falls ‘asleep’ for periods of time when there is no income. This means that contacts are lost, good people leave to do other work and sometimes,

months have to be invested to get the network running again. Recently, the European Commission has decided to no longer finance networks. This means that this source of income has been lost for the future.

One way of solving this problem is to get money from other sources. However, National and local authorities are not very eager to invest in a European project (what is in it for us?) and the pharmaceutical industry have their own agenda, which might not coincide with the agenda of Euro-Metwork. In the past years, Euro-Metwork has managed to survive and make agreements with sponsors, which allowed Euro-Metwork to operate in complete independence. Whether this will be feasible in the future is yet to be seen.

4. *The future*

In a meeting organised by the Pompidougroup 'Development and improvement of substitution programmes, Strasbourg, 8-9 October 2001' it was reported that the provision of substitution treatment in Europe has increased fivefold (from 500 per million to 2500 per million) in the last seven years. It was concluded that this rapid increase poses a major challenge for the quality of substitution treatment and that special attention is needed in the areas of quality improvement via training, exchange of expertise, dissemination of up-to-date information and monitoring.

Based on the above, Euro-Metwork presented a proposal to the European Commission to carry out the following activities in 2002:

Training

Produce a training package. This package will contain a blueprint for the training, suggested time table, topics to cover, profile of trainers, instructions for trainers, materials, a list with internet references, a bibliography with suggested literature and an evaluation form. The package will be produced under the supervision of a group of experts and will be tested once. After taking the feedback into consideration the final package will be designed, made available in English, Spanish, French and German and distributed on a large scale

The best way to learn how to run a substitution programme is to do an 'on-site training' in a 'centre of excellence'. Euro-Metwork will facilitate in this 'training on-site'. Firstly, 'centres of excellence' will be identified. Candidate centres will be contacted and asked for co-operation. Subsequently, the centre will receive experts appointed by

Euro-Metwork. These experts will speak with the patients, the staff and look at treatment protocols, evaluation strategies and assess whether the staff in this centre is equipped to serve as trainers. Once approved, the centre will receive a ‘Quality Certificate’ and thus serve as a ‘centre of excellence’ for the region, which is qualified to receive trainees. It is anticipated that at least 10 centres of expertise have to be identified to meet training needs. Euro-Metwork will support those who wish to participate in training.

Quality improvement through the Internet

Two innovative measures, using the Internet, will be used. It concerns:

- *Substitution Treatment Helpdesk on the internet*

On the website of Euro-Metwork special pages will be developed with frequently asked questions and answers on substitution treatment. In cases where these answers are not sufficient, people can send an email and this email will be redirected to someone in the network who can answer the question. This website will be developed in close co-operation with participants of the network and making use of their specific expertise.

- *Development Virtual clinic*

On the website of Euro-Metwork (www.eurometwork.org) a ‘virtual clinic’ will be developed. The visitor ‘enters’ the virtual clinic and can choose to have an intake, to see a doctor, nurse, social worker or psychologist. Questions can be asked about the clinic, the rules and regulations, various substitute drugs and their effects and the treatment plan. Information can be obtained about the layout of the clinic and safety issues as well. Furthermore, information will be provided about the latest developments to optimise the provision of substitution treatment (chip cards for patients, automated dispensers etc. etc.). The target groups are (1) drug experts and policy makers who wish to start substitution treatment and (2) people working in substitution treatment, who are looking for new ideas or who wish to improve their services.

Involvement of decision makers

Still resistance can be found among decision-makers to invest in substitution treatment. Often they are not aware of the scientific data about the positive effects of substitution treatment and lack knowledge about the cost effectiveness of such treatment. Discussions are often based on outdated information and/or ideological and emotional ground. In order to stimulate a more rational debate, Euro-Metwork will produce an

information package for decision makers and those involved in discussions with decision makers. The material in the package will consist of summaries of the last scientific information, a paper about the pros and cons of substitution treatment, a paper on how to make a cost-effectiveness calculation for a specific region, and addresses for reference. The package will be made in close co-operation with a number of experts in the field, will be tested and made available in English, Spanish, French and German. The proposal was accepted and will be carried out in 2002 and 2003.

5. *Conclusion*

Ten years of experience with Euro-Methwork shows that a network can make a difference. Many concrete activities were undertaken and we managed to prevent Euro-Methwork from falling apart.

Whether there is a future for Euro-Methwork after 2003 is yet to be seen. The products, which will be produced in the near future, will have to prove their value. We have high expectations of the possibilities of using the Internet in reaching the goals of Euro-Methwork.

However, at one point we will have to draw the conclusion 'Mission completed'. How soon this conclusion will be drawn will depend on the developments of the heroin problem in Europe and whether there is still a need for the sort of service Euro-Methwork provides.

G. Fischer (Vienna, Austria): Buprenorphine and slow-release morphine in the treatment of opioid dependence

There is general agreement that opioid dependence is a chronic relapsing disorder. Psychopharmacological treatment interfering with opioid receptors is supporting the treatment of opioid dependence, especially maintenance therapy with substances acting as opioid receptor agonists have proved to be effective. Methadone and LAAM (Leva-alpha-methyl-methadone) have been standard agents in the US and Europe, oral-slow release morphine has been successfully administered in this indication in some European countries. In France, buprenorphine, a partial mu-agonist and kappa-antagonist has been registered for the treatment of opioid dependence since 1995 being followed by other European countries in 1999. Buprenorphine has been shown to

produce limited respiratory depression, long plasma half-life and long duration of action due to its slow dissociation from the receptor and can be administered once daily, or even on alternative days. In addition, buprenorphine has a low dependence liability, with a lower level of reinforcement than a full agonist such as methadone or heroin. It has a wide effective dose-range (8-32 mg;) and a wide safety margin, even if it is misused by the intravenous route. Evidence suggests in order to achieve a good retention in treatment, a rapid rather than `slow` induction phase is preferable.

As early as 1978, Jasinski recommended buprenorphine as an alternative to methadone for the maintenance treatment in opioid dependent patients. Several controlled clinical trials, the majority carried out in the US and some recently in Europe, have reported the beneficial effects of buprenorphine. These studies are of two main types: Comparisons of buprenorphine with methadone and dose comparison studies. Additionally, studies with the combination product buprenorphine/naloxone have been carried out. The standard out-come measures in these studies were concomittant consumption of illicit drug abuse evaluated through supervised urine toxicology as well as the retention rate over the investigational period.

In maintenance trials, Johnson et al. reported about a comparable retention rate of patients treated with buprenorphine 8 mg/day when compared to methadone 60 mg/day. Ling and colleagues found that 80 mg methadone was superior to both methadone 30 mg/day and buprenorphine 8 mg/day. Results from the Vienna group, who published the first comparison study with buprenorphine being administered as sublingual tablets, report a significantly better retention rate of methadone (mean daily dose 63 mg) when compared to buprenorphine (mean daily dose 7.5 mg). However, subjects maintained on buprenorphine who remained in the 6-months study trial had a significantly lower concomittant consumption of illicit opioids. Whereas the majority of US studies refers to results gained through buprenorphine administered in the liquid solution, the Vienna study used the sublingual tablets, which are actually registered for use. First blood level comparison studies of sublingual tablet formulation and buprenorphine in liquid refer to a 66-75% availability of the tablet compared to the liquid. Further investigations are warranted.

In order to avoid intravenous use of buprenorphine when take-home doses are provided, a combination product buprenorphine/naloxone was developed. In the US, a large multi-center study with the sublingual combination product was conducted comparing three maintenance doses (4, 8 and 16 mg).

In addition to the broad variety of research reports in buprenorphine maintenance therapy as well as to the practical experience in more than 80 000 patients who have been maintained on buprenorphine in France since registration, detoxification studies have been performed. The withdrawal syndrome when buprenorphine is applied in detoxification trials is reported as being relatively mild. Out-patient detoxification can be performed successfully in a short to intermediate time frame.

Limited experience is also available when buprenorphine is administered in a high risk group of pregnant opioid dependent women. Preliminary results about safety and efficacy indicate that buprenorphine maintenance during pregnancy yields to good retention and low concomittant consumption of illicit drugs in the women, as well as to healthy newborns and only a weak neonatal abstinence syndrome.

To complete the list of substances which are used for maintenance therapy, oral slow-release morphine (SR-morphine) has been applied for many years in European countries, e.g. 20 000 subjects have been maintained in France. SR-morphine has a high acceptance in the target population, however there is a lack of evidence based scientific study trials. A controlled study (methadone/SR-morphine maintenance) in pregnant opioid addicts over 13 weeks until delivery found no differences in the duration and intensity of the neonatal abstinence syndrome in the newborns, however a significant fewer benzodiazepine and opiate consumption in the SR-morphine maintenance group over the study period. Results of a double-blind, double-dummy, cross-over maintenance study (methadone/SR-morphine) in opioid dependent subjects over 14 weeks showed no significant differences in retention rate (85 %). Besides the individual benefits having a variety of substances available for the treatment of heroin dependence

special awareness needs to be addressed regarding diversion on the street and further scientific studies are needed to be carried out.

In conclusion, buprenorphine might be considered as a first line treatment for opioid addiction as it offers a wide range of options including alternative day dosing in stabilized patients. In the case of unsuccessful use, the transfer from buprenorphine to methadone or other mu-agonist opioids is relatively easy, in contrast it is much more difficult to transfer addicts from a high dose full agonist to buprenorphine. Further efforts should focus on improving information on the ideal population which might benefit the most from the individual available opioid maintenance medication.

U. Verthein (Hamburg, Germany): German experience with medication-assisted substitution treatment

Apart from one small methadone treatment program in 1973 in Hannover with 20 patients medication-assisted treatment of drug addiction in Germany was first introduced in the early eighties. The substance used was mainly dihydrocodeine, prescribed by GPs in private practices and usually paid by the patients themselves. In 1988 the state of Nordrhein-Westfalen launched the first official methadone program for opiate addicts. It was a state-run program that went over 5 years, accompanied by scientific research. Other states followed in the beginning of the 1990s. The development of methadone treatment took place under special political conditions. The federal system in Germany made it possible to establish methadone treatment against the opposition of the (former) German government. This resulted in different kinds of methadone therapy with different indications and treatment rules. There was also one experimental study using LAAM in 1998. In January 2000 buprenorphine was approved for substitution treatment. Today more than 40,000 opiate addicts in Germany are treated with methadone or levomethadone. In February 2002 the German model project of heroin-assisted treatment started. Results of different treatment studies were discussed.

The presentation is available: www.heroinstudie.de/who-workshop

G. Woody (Philadelphia, USA): Methadone treatment in the USA

Methadone maintenance treatment for opioid dependence was developed in the U.S., beginning with the studies of Dole and Nyswander in the 1960's. Approximately 200,000 persons are in methadone maintenance treatment in the U.S. at present. This number represents 15-20% of the total estimated number of persons with opioid dependence. Methadone maintenance has been extensively evaluated and the studies consistently show that it is associated with cessation or substantial reduction in unprescribed opioid use and in other areas of adjustment as well. In spite of the strong empirical support for methadone maintenance, it has been very heavily regulated and ambivalently accepted since its introduction. Expansion of methadone programs to meet treatment demand appears to be impeded by a combination of political and funding issues. There is much room for treatment expansion to meet patient needs. Efforts continue at many levels to overcome the resistance to more widespread use of this effective treatment, and there is reason to hope that these efforts will meet with some success. Details to illustrate these points will be presented.

The presentation is available: www.heroinstudie.de/who-workshop

L. Sakoman (Zagreb, Croatia): The experience with methadone maintenance programmes in Croatia

The first specialized treatment program for drug addicts exists in Zagreb since 1970. Heroin abuse has been followed-up in Croatia since the beginning of the eighties. The war (1991), post-war period and transition caused, within a short time, a large increase in drug supply and demand, what also caused an epidemic of heroin addiction. Except for the rare cases of HIV infected addicts, methadone was not usually used for the treatment of the addicts till 1990. Just before the war, a special Health Ministry Commission made a decision and worked out the model of methadone application as one of the necessary and acceptable possibilities of treating heroin addicts. The education of experts and the pilot program were carried out in Zagreb during 1990, and early in 1991 the heroin addicts were enabled to use also that way of treatment at the total territory of the country?. During 11 years, precious experiences were collected.

Since 1996, the methadone application is regulated as a component part of the National Strategy for illegal drug abuse control, as accepted by the Croatian Parliament.

Elementary Data:

The RH has about 4,500.000 inhabitants. The number of heroin addicts is estimated to about 15.000, and occasional consumers of that drug to about 6000. The treatment system includes about 50% of the cases. About 80% of heroin addicts used the drug intravenously. The HIV infected is represented by less than 1% of heroin addicts. HCV is positive in about 50% cases. At their first treatment, they are aged about 23 at the on average, with the average length of addiction until arrival to the first treatment/ their first contact with the help system/ first treatment, of less than three years. During 2001, methadone was used for a quick or slow detox, or for the maintenance in 3000 heroin addicts. In the program of long-term maintenance, there are 2500 of them nowadays. At any moment, about 600 addicts are in some of the therapeutic communities while 500 of them are in prisons. About 45 heroin addicts die of overdosing annually.

Treatment System

According to the National Strategy, provided by the State, through the Ministry of Health, for the basic treatment system of addicts. This has been defined in a specific Law on Drugs. The point in question is the organized network of County Centres for outpatient treatment of drug addicts. The work of the network is coordinated by the National Institute for Prevention of Drug Abuse. Psychiatric institutions must provide for the capacities of the specialized detoxification programs and inpatient treatment of addicts.

Presently, 15 outpatient Addict Treatment Centres exist in the country. They have employed interdisciplinary teams (medical practitioner, most often psychiatrist, psychologist, social worker, medical nurse). Besides the or alongside the therapeutic work, their duty is to coordinate all the activities, at their domain, connected with the drug demand reduction programs. Their most important duty, though, is to take care of the addicts and connect all the systems, discovering them and participating in their treatment. Among those systems, the most important are general practitioners, psychiatric detoxification programs and therapeutic communities.

The drug addicts are referred to the Centre by general practitioners, hospital institutions after detoxification program, the schools (if they discover drug-taking students), army, justice, police, etc. The largest number of them, however, come themselves or is brought by their families. About 80 % of all the treated addicts start, perform and complete their treatments in some of the Centres. The Centres accept addicts without a referral slip, the treatment is free of charge, and the addicted can approach also anonymously. Once the first contacts and diagnostic procedure is established, the initial form of treatment is agreed upon individually. That first contact has the purpose of initiating the addict to think about the possibilities of treatment and to certainly come again at agreed time. The treatment of this chronic, recurrent disease, often lasts for years. During this process, the addict has, with the time, more and more pronounced role of a subject. At the beginning (while his/her brains do not work properly) an important role belongs to the therapeutic team that suggests what should be at least attempted to achieve. But that, what is suggested by the therapeutic team, must be at a certain extent acceptable to the patient. Such approach is necessary if a high retention in the program is to be achieved. The most of the addicts, during the first 2 years of treatment, are suggested to at least try to feel the experience of abstinence.

Procedure with Heroin Addicts

Those patients make up about 60% of all the clients of the treatment system in Croatia at present, with more than 80 % of all the resources spent on them. No special methadone centers exist in Croatia. From the very beginning every heroin addict is open to choose from all the available options. If he/she is physically addicted, and the physician estimates that detoxification without the application of methadone will not produce any immediate result at the beginning of the treatment, the pharmaco-therapy with application of methadone will be suggested. The medical practitioner of the Centre will write a letter with suggestions, that the addict takes to his general practitioner who will start administering the prescribed daily dose of methadone immediately, under direct control, in his/her medical clinic. The addict is obliged, due to the urine control and the application of a specific supportive and behaviourally cognitive therapy to attend at the sessions in the Centre at the agreed time. At the beginning, it is once or twice a week. Allowing the team to follow-up on the progress of the patient and to test

his/her capacities of breaking the habit. When the daily doses of methadone are considerably reduced, part of the addicts are not able to endure the psychophysical disturbances and cravings, asking again for an increase of their daily doses of methadone. Some of them relapse, or take some other medication. In that case the addict is suggested to undertake hospital detoxification program. If hospital capacity is not immediately available, or he/she does not accept the treatment, then daily doses of methadone are temporarily increased, slowing down the process of reduction. The addict is advised to experience the abstinence feeling, to test his/her capacities of giving up and returning to “the normal” life. If he/she is not ready for that, or simply cannot bear it, he/she is offered two possibilities:

- to go to some therapeutic community;
- to continue methadone program on a stable dose, with regular controls in a outpatient program

Part of the addicts, if they already have resolved the abstinence crisis, could be helped in “keeping” their abstinence with the prescription of Naltrexon and participating in the psychotherapeutic process. This program takes place in an outpatient setting, for a period of at least two years. Urine is controlled regularly and the addict always receives his/her prescribed pharmacotherapy from his/her chosen general practitioner. With younger addicts, family therapy is strongly recommended. The procedure is performed with a lot of patience, love, understanding and is aimed at preserving the dignity of the patient and his/her family. The addict must feel comfortable when coming to “his/her” center. By means of the relationship established through psychotherapy, the addict is stimulated to become more and more responsible and mature behaviour. The requests put to an individual at a certain moment, must be adjusted to his/her capacities.

The therapeutic team of the Centre, in cooperation with the general practitioner, follows up the addict permanently, in order to suggest, in accordance with the condition, what would be the best to thing do. After 2 – 3 years in an outpatient program (with occasional hospital detoxifications in case of unsatisfactory minimum of abstinence), it becomes clear in which direction the long-term solution should be searched for the patient’s addiction problem. To those who do not wish to go for methadone “for life”, it becomes clear that the only thing that can help them is the long-term treatment in a

therapeutic community. The team of the Centre supports them by, preparing them to go/enter into to such a program. Many of them, however, “worked that off” to find themselves in the street, on heroin, again. Many, persisting to hang on heroin, ended in jail and after that, in the Centre, again. There are two elementary reasons due to which the therapeutic team suggests the long-term maintenance on methadone:

- When it is evident that the addiction has become a biological disease of deficiency, so that the patient, even if several months in abstinence, feels poorly and cannot control or restrain the permanent desire for heroin.
- When it is more than evident that the very poor life quality has no chance to improve because of the circumstances. The addict has no family support, no job, does not feel well medically, becomes delinquent due to addiction .

During the first several years, upon the introduction of substitution programs in the Republic of Croatia, a considerable percentage of the long-term, serious heroin addicts were, at the very beginning, enabled (if they asked that), to be maintain on methadone. Nowadays, after 11 years of methadone application, it can be concluded that most of the addicts had been at the time of their first approaching to treatment the young persons with a short addict “history”, and it is, due to that better not to hurry with long-term maintenance programs. But if a patient of age insists on it, he can be enabled to be included within a very short time, or at the very beginning, if the clinical picture of addiction is estimated to be difficult and complicated by numerous problems.

How to carry out the maintenance program

Only specialized teams of the networks of Centres for Outpatient Treatment of Addiction are authorized to include an addict into the maintenance program. The Medical practitioner of the Centre will determine a daily dose, and with the suggestions concerning the way of administration, refers the addict to his/her medical practitioner. In the letter for the general practitioner, the time is determined when the addict is to come for examination into his Centre, when, in relation to the condition found, either the same therapy is continued or a revision is made. The addicts, stabilized in the maintenance program, are usually ordered for control to the Centre three times a year. But in case that the addict or his/her general practitioner finds that something should be

changed in the program, the visit to the Centre can also be arranged at an earlier date/point in time. A direct communication between the doctor in the Centre and the general practitioners is therefore of great importance. The general practitioner, at the beginning, gives the methadone during everyday visits, directly “into the mouth” of an addict. Most of the addicts receive methadone for the weekend on Fridays. Those to be well-rehabilitated and stable, general practitioner gives methadone, after certain time, with one to three visits a week. In case of a journey outside of the residence place, the addict (or a family member, if younger patients are concerned) can get prepared and handed the therapy (the methadone pills are crushed and dry-mixed with vitamin powder). It can be done for up to 14 days in advance.

Necessary daily doses are individually adjusted to the needs of patients. Some are “satisfied” with 10 mg, while others need more than 100 mg. The average being, 65 mg per day. The rate of daily doses depends mostly on bio-psychological factors of the individual addict. Comparing the average maintenance doses in individual Centres, and also within the same Centre, reveals considerable differences between individual doctors. Suggesting that higher quality of psychotherapy and help offered to the addict by the technical team in solving his numerous life problems have a great influence on the result of treatment as well as on the rate of necessary maintenance doses. The quality of therapeutic work has an influence on the percentage of those addicted that are going to be stabilised in a drug-free program and well rehabilitated in the maintenance program. About 60 % of the addicts in the program abstain from heroin and have much more acceptable behaviour. Through the treatment, the heroin consumption of all the addicts included in the program is reduced by more than 70%. In the Republic of Croatia, there is no banishing the addicts from the maintenance program and the rate of retention in the program is about 85 %.

Table 1. Opioid patients treated at the year 2000 – outcomes at the last control in the Centre, Centre for Addiction, UH "Sestre Milosrdnice", Zagreb

Outcome of treatment	Detox. fast	Detox. slow	Main-tance	Methadon free	Totals	Inpatient	Unknown
Abstinence	41	140	265	270	716	2	13
	<i>27,15%</i>	<i>46,20%</i>	<i>57,24%</i>	<i>72,78%</i>	<i>55,59%</i>		
Improved	24	87	132	55	298	1	5
	<i>15,89%</i>	<i>28,71%</i>	<i>28,51%</i>	<i>14,82%</i>	<i>23,14%</i>		
No change	50	46	31	23	150	24	39
	<i>33,11%</i>	<i>15,18%</i>	<i>6,70%</i>	<i>6,20%</i>	<i>11,65%</i>		
Unknown	36	30	35	23	124	1	17
	<i>23,84%</i>	<i>9,90%</i>	<i>7,56%</i>	<i>6,20%</i>	<i>9,63%</i>		
Totals	151	303	463	371	1288	28	74
	<i>100,00%</i>	<i>100,00%</i>	<i>100,00%</i>	<i>100,00%</i>	<i>100,00%</i>		
Totals %	11,72%	23,52%	35,95%	28,80%	100,00%	102	
					1390		

Social Benefits of the Methadone Prescription in the Therapy of Opiate Addicts

- at least three times more addicts will be in contact with the treatment system (than would be the case if methadone was not used)
- the decision for the first treatment will be 2 – 3 years earlier, what means that at the stage when addiction is not yet so difficult and complicated by numerous consequences (inclusion into criminal activities, HCV, HRV, HIV infections...), the consequences will be much more rare, family and vocational problems less pronounced.... That would increase the chances for better final outcome of treatment, the addict will cause less damage to himself/herself, his/her family, and the Community .

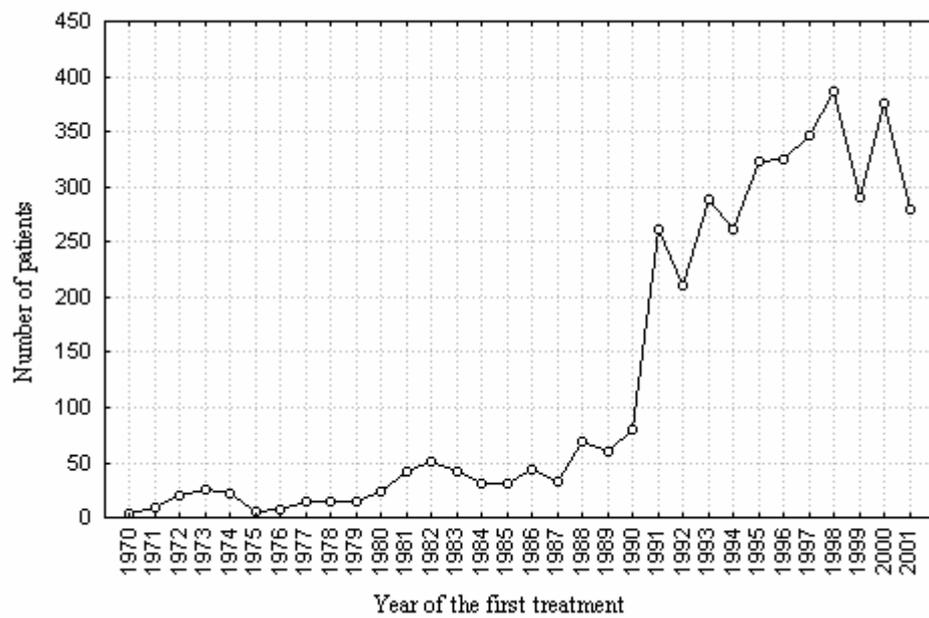


Figure 1. Opioid patients first time treated from the year 1970 to 2001 in Centre for Addiction, UH "Sestre Milosrdnice", Zagreb

Table 2. Opioid patients first time treated from the year 1970 to 2001 in Centre for Addiction, UH "Sestre Milosrdnice", Zagreb

Year	Count	Cumul. count
1970	4	4
1971	10	14
1972	20	34
1973	25	59
1974	22	81
1975	5	86
1976	8	94
1977	14	108
1978	14	122
1979	14	136
1980	23	159
1981	42	201
1982	51	252
1983	42	294
1984	31	325
1985	31	356
1986	44	400
1987	33	433
1988	69	502
1989	60	562
1990	80	642
1991	262	904
1992	211	1115
1993	289	1404
1994	262	1666
1995	323	1989
1996	324	2313
1997	346	2659
1998	387	3046
1999	290	3336
2000	375	3711
2001	280	3991
Total	3991	

In contrast to the attitudes of those pleading for drug-free programs, not accepting the application of methadone and suggesting very restrictive approach with the argumentation that in that way, the treatment just intensifies addiction and reduces the motivation of the addicted for treatment, according to the abstinence orientated programs, our experiences have not confirmed this. The results of the program initiated by my team in Mostar (BiH) support that. Prior to opening the Centre there, that, like the Centres in Croatia, uses methadone, only 4 addicts from Mostar were in the therapeutic community in Međugorje. After one-year, the treatment program included

about 100 addicts. 97% of them were hepatitis B and/or C infected, the history of addiction was on average more than 8 year. The Centre attracted from the street more than 20 addicts, motivated them, detoxified them with the use of methadone and referred them to therapeutic communities for rehabilitation.

Problems:

The last two years, when the most experienced experts in the field lost the space for decision-making concerning the National Program and within it, concerning the policy of the addict treatment, those having the decision-making positions, but not having the necessary understanding of the problem, were becoming louder and louder. The “new forces” suggested (fortunately, without success):

1. *To introduce centralization of methadone administering* (meaning the exclusion of general practitioners from the implementation of the programs) with the explanation that too much methadone “leaks” on to the illegal market.

Consequence: more restricted availability and weaker acceptability of the program. Worsened possibilities of the social rehabilitation of the addicts who must meet with a large number of other addicts every day and that negative interaction is not possible to control. Thus jeopardizing the dignity of the well-rehabilitated and employed addicts.

2. *Stricter criteria for methadone.*

Consequence: less addicts in the program and under control; they would come to treatment later, with more difficult addiction problems and more complications and damages.

3. *The limitation of daily doses.*

Consequence: more frequent heroin relapse, weaker retention within the program, larger demand after other psycho-pharmaceuticals and alcohol.

Fortunately, the common sense looks like having prevailed and the addict treatment policy is not going to change more significantly. Better methadone administering control, for the sake of reducing the leaking on to the illegal market, must not result in the larger social damage in comparison with possible benefits.

In Conclusion:

Pharmacotherapy by means of opiate agonists is an exceptionally important element of the complex and long-lasting treatment process. The methadone, itself, cannot correct the disordered behaviour of a heroin addict or solve his/her problems. Hence, the qualitative treatment program must contain several elements out of which, I would put special emphasis to:

psychotherapy (cognitive, behaviouristic, reality therapy, logotherapy, or the “specific addiction psychotherapy”)

family procedure (addiction is a family disease)

re-education to correct disordered, antisocial behaviour

education, learning about that brain disease in order to make the addict easier understand what is going on in him/her, to understand the craving after narcotic drug in order to easier build the strategy of maintaining abstinence

help in resolving many life problems (social therapy)

treatment of medical complications of the addiction (e.g. C Hepatitis)

in case of psychiatric co-morbidity, parallel treatment of both the diseases.

Whatever attempted, after several years, the therapeutic team and the addict himself/herself will be persuaded that 40 – 50% of the patients will not succeed to stabilize in the abstinence of opiates. In the conditions of the free choice, either no self-control mechanisms will be able to develop or the mechanisms and the capacities of overcoming the desire (in the large degree, biologically conditioned) will be too weak so that they will return to relapse and decline gradually. Rather the application of opiate agonists can help many to improve their quality of life and to reduce harmful consequences to their families and the Community.

The treatment of the addicts is a difficult and complex job. In order to perform that qualitatively, one needs a special education, experience but also a special team selection if one wishes to have persistent and effective professionals. The treatment of the addicts in general, and specially the treatment with the use of opiate agonists, is a specific professional but not public or political question. All the treatment programs of the addicts in the society should function as a well-connected network within which, the

technical teams should cooperate permanently in the interest of the best possible care of the addicts. All the treatment programs should be evaluated scientifically.

A. Elkashef (NIDA, USA): The development of buprenorphine for the treatment of opiate addiction in the USA

Chief, Clinical Trials Branch, DTRD, NIDA/NIH

This presentation will be a general overview of medications development for opiate addiction in the US with a focus on Buprenorphine. The current needs in the US include:

- 1- Greater availability of treatment, e.g. office based access
- 2- Medications for special population, e.g. children, pregnant women, and patients with co morbid mental illness
- 3- Non-Opiate medications for opiate dependence, e.g. NMDA antagonists
- 4- Medications to treat withdrawal, e.g. Lofexidine
- 5- Medications to treat relapse, e.g. CRF antagonists

These will be outlined and discussed further. The presentation will also discuss The Buprenorphine trials in the US, studies 999, 1008, and the phase IV office based study. The outcome of these trials and implications for Buprenorphine Development will be outlined.

6. Psychosocial interventions and their significance for treatment (Session 4)

Chair: C. Zenker, Münster, Germany

6.1. Summary and overview

Dr. Basdekis-Josza, Centre of Interdisciplinary Addiction Research, Hamburg, Germany, presented the concept of two systematic variations of psychosocial treatment in the German heroin trial. She presented psychoeducation and drug counselling as variations of standardised psychosocial support in the trial.

Dr. Basdekis-Josza first defined the concept of psychoeducation. Then she presented an overview of the structure and contents of psychoeducative group therapy. 12 sessions will be provided with a manualised and standardised procedure – one session a week for about 3 months. The programme deals with themes that are relevant to persons with a long drug career. In addition to the comparison of two pharmacological treatment conditions in the German heroin trial, the treatment efficacy will be evaluated in terms of specific psychosocial settings. This will significantly increase the strength of an efficacy investigation for heroin prescription.

Professor Vogt, Institute for Addiction Research in Frankfurt, presented the second variation of psychosocial treatment in the German heroin trial: Case Management/Motivational Interviewing (CM/MI). Case Management emphasises structure and the organisational framework, while Motivational Interviewing embraces motivational factors, and counselling techniques. He introduced the basic skills needed for social workers and the technique of Motivational Interviewing, e.g. reflective listening, development discrepancies, avoiding interpretation, supporting self-efficacy. In blending Case-Management and Motivational Interviewing, a delicate balancing of form and content, structure and style of interaction is needed. He emphasised that manualising of CM and MI will be an important step towards standardising the helping process, which will be thoroughly documented in every phase of the trial to enable a thorough analysis when the trial has ended.

Dr. Bühringer, Institute for Therapy Research (IFT-Munich, Germany) introduced the issue of the impact of payments on patients' compliance. The theoretical background for the concept is operant conditioning. Pampering the patient with specific types of reinforcements like privileges, status and praise makes it possible to destroy the addiction personality and lifestyle. Dr. Bühringer presented an overview on the concept, history and outcome of contingency management with different reinforcements in the field of substance abuse treatment compliance. He underlined the large amount of research carried out in support of the effectiveness of contingency management in different outcome variables, e.g. reduction of substance use, retention and time in treatment, health status, relapse interval. In comparison to early clinical findings, there is nearly no evidence of an implementation of contingency management into clinical

practice concerning substance abuse treatment programmes; further research is required to use concepts of payment as natural “social” reinforcements.

Professor Woody from the Treatment Research Institute of the University of Pennsylvania, Philadelphia, presented results of psychosocial treatments of cocaine dependent persons. A number of studies found an improved outcome for persons with substance use disorders, who received counselling and psychotherapy. The cocaine treatment study of the NIDA also found benefits associated with both psychotherapy and drug counselling but patients receiving drug counselling had better outcomes than those who received counselling and psychotherapy. Woody discussed possible reasons – psychiatric severity interaction or therapist effects – for the differences between cocaine and methadone studies with regard to psychotherapy.

6.2 Abstracts of the fourth Session

R. Basdekis-Josza (Hamburg, Germany): Psychoeducation in the German heroin trial

Psychoeducation and Drug Counselling - Part I of Psychosocial Treatment in the German Heroin Trial

The aim of the study is to assess whether the medical prescription of pharmacologically pure heroin in a structured and controlled treatment setting for two target groups of addicts – methadone-substituted, that are presently considered non-responders, and an untreated sample (unreached addicts), who have not been in treatment for some time – will be faster at reaching the results achieved through other standardised forms of addiction treatment.

In addition to the comparison of two pharmacological treatment conditions there will be a systematic variation of standardised psychosocial support: Case Management with integrated motivating interviewing vs. drug counselling with psychoeducation. The treatment efficacy will be evaluated in terms of specific settings. This increases the strength of an efficacy investigation for heroin prescription significantly and represents an important part of added value of the submitted study. Furthermore these results will have relevant implication for the health care system in general.

Description of drug counselling and psychoeducation

Drug counselling in the German heroin trial is not structured, the clients will use the existent drug counselling centres. There will be local differences concerning the intensity of drug counselling and the possibilities of networking. Drug counselling means rehabilitative respectively integrative support of the clients. Presupposition is a confidential and reliable relation between drug counsellor and client. A confidential and transparent procedure will be expected, with regular contacts, while frequency and intensity vary according to needs of the clients. The intervention are focussing on problems. In the typical structure of “German” drug counselling the client is seeking the drug counsellor (Komm-Struktur). The aims of drug counselling in general are the following:

- navigation/supplying in/of addiction services
- improvement of social situation
- improvement of somatic state
- reduction of substance abuse and risk-behaviour
- family counselling

Drug counselling will start with the beginning of the trial (T0). Drug counselling will be submitted to a care ratio of 1:50. There should be contact at least once a week. The drug counsellor supports the client with reference to finances, health insurance, apartment, work etc.

In addition to drug counselling there will be an offer of psychoeducative group therapy. 12 sessions with a manualised and standardised procedure will be provided. The psychoeducative group therapy will start with the third month of treatment (T3). Its intensity is based on one session a week for about 3 months. In a frame of psychoeducational behavioural therapy (according to e.g. Kieserg & Hornung, 1996), the programme deals with themes that are relevant to persons with a long drug career such as the problem of addiction, the understanding of subjective trouble concepts, relapse management and risks, dealing with comorbidity, promotion of healthy behaviour, training of social contacts and communication, problem solving strategies as well as self-help groups and the structure of regional addiction services.

Vogt (Frankfurt, Germany): Case-Management/Motivational Interviewing in the German heroin trial

Irmgard Vogt, Martina Schu, Martin Schmid, Wilfried Görger & Hans Oliva

The design of the German Heroin Trial stresses the importance of the psychosocial care as part of the treatment process. Therefore, two different approaches are tested in the trial, one of which consists of the blending of Case Management (CM) with Motivational Interviewing (MI). As can be shown, the approaches of CM and MI have some similarities and some dissimilarities but do not contradict each other in basic intentions and dimensions. Besides this, CM emphasises structure and the organisational framework, it asks for networking and cooperation with (welfare) agencies and organisation; MI embraces motivational factors, style of counselling/interaction and counselling techniques which are tailored to facilitate the exploration of motivational conflicts of clients and to support motivation to change. In blending both, a delicate balancing of form and content, structure and style of interaction is needed.

As a beginning, we tried to incorporate the positive and well confirmed techniques of both approaches into the Manual which we developed for counsellors working as Case Managers in the study with half of all clients. The manualising of CM and MI is one of many steps to standardise the helping process, which will be thoroughly documented in every phase to allow for analysing the results afterwards.

Details of the procedure and the standardising process will be discussed in more detail at the conference.

G. Bühringer (München, Germany): Impact of payments on patient compliance

Target: To give an overview on the concept, history and outcome of contingency management (CM) with monetary based reinforcers in the field of substance abuse treatment compliance. Method: CM was developed in the alcohol field. At present the emphasis is predominantly in the drug field, with a wide range of target behaviours, like adherence to appointments, medication schedules, drug free urine samples or other program rules. Outcome: There is a large body of research supporting clear effectiveness of CM in different outcome variables, e.g. reduction of substance use,

retention and time in treatment, health status, time to relapse. Problems are high costs and time for administration, training of staff, verification of target behaviours, maintenance of positive outcome after CM termination and – last but not least – an extreme low rate of dissemination into practice. Conclusions: CM should be implemented widely into clinical practice of substance abuse treatment programs, either residential, outpatient or community oriented, medication supported or abstinence oriented. Further research is needed into optimal (cost-effective) reinforcement schedules and transfer concepts of payment into natural “social” reinforcers.

G. Woody (Philadelphia, USA): Psychosocial treatments for cocaine dependents

A number of studies have evaluated the impact of counselling and psychotherapy for persons with substance use disorders during the last 20 years. These studies were done because persons with substance use disorders often have additional psychiatric disorders. Results have been that both types of psychosocial treatment improve outcome and that more treatment is generally associated with better results. Two studies in methadone programs found that additional psychotherapy improved the chances for outcome in persons with high levels of psychiatric symptoms. Cocaine treatment studies, mainly done with crack-smoking patients, have also found benefits associated with both psychotherapy and drug counselling but unlike two of the methadone studies, patients receiving drug counselling had better outcomes than those who received counselling and psychotherapy. As in the methadone studies, reductions in drug use were associated with reductions in HIV risk behaviour, mainly due to fewer sexual partners. Possible reasons for differences in the contribution of psychotherapy in the cocaine as compared to the methadone studies will be discussed.

The presentation is available: www.heroinstudie.de/who-workshop

7. Concluding remarks

Professor Rehm from Zurich, Switzerland, summarised the contents of this conference as specification of the matrix - substances, delivery (injectable or oral substances) and setting - for the treatment of drug addicts. Therefore, it is necessary to optimise the different treatment elements, especially the combination of psychosocial interventions and substance related treatment. Both treatment approaches and their combinations have to be cost-effective and meet the requirements of the clients. Modern treatments have to be cost-effective from the social and the economic point of view. However, treatment and public health are two different issues. Generalised cost-effectiveness studies are needed and a policy that follows their directives with respect to prevention, repression, treatment and harm reduction.

According to Prof. Rehm, the conference showed that a link between basic science and treatment is necessary. There had been unrealistic expectations of quick changes in the past. But it has been possible to transfer basic science models into actual treatment schedules. Though overall methodological standards improved, a multidisciplinary exchange of concepts and strategies is needed. Research must concentrate on relevant questions with a more clinically orientated focus. Instead of comparing different treatment elements, research should concentrate on how to combine the different treatment elements in the best way. Prof. Rehm emphasised the importance of frequent short focus meetings like Velen, where information on addiction research can be exchanged.

Mr. Köhler from the German Ministry of Health, Bonn, stated that, from his perspective, it is too early to answer questions about administrative consequences with respect to heroin treatment. The effectiveness of heroin treatment has once more been confirmed by research. With respect to the high number of clients in heroin treatment, regulations, development of quality standards and the improvement of the treatment with a stable financial cooperation of the health insurance system are of major importance. Mr Köhler also thanked everyone for the open discussion which was conducted in an atmosphere of mutual respect and resulted in a high standard of recommendations for future research on heroin assisted treatment; he proposed a follow-up meeting in the near future.

Dr. Lazarov, WHO Regional Office for Europe, emphasised that the conference was successful from the WHO point of view. He underlined the importance of the transfer of all discussed ideas into the clinical practice of drug treatment. The WHO is trying to organise similar workshops in other regions and supports the idea of a follow-up workshop of Velen. Finally, Dr. Lazarov thanked Prof. Rehm for the organisation of the scientific part of the conference, the Ministry of Health of Nordrhein-Westfalen and the German Health Ministry for their support and hospitality, and the DLR for the organisation of the conference.

LIST OF PARTICIPANTS

Professor Hans-Jörg Albrecht
Krimiologische Forschungsgruppe
Max-Planck-Institut für ausländische und internationales
Strafrecht
Günterstalstr. 73
79100 Freiburg
Germany
Tel.: +49 761 7081 – 201
Fax: +49 761 7081 - 316
Email: h.j.albrecht@iuscrim.mpg.de

Mrs Christina Baumeister
Behörde für Gesundheit und Umwelt
Die Drogenbeauftragte
Tesdaufstrasse 8
20148 Hamburg
Germany
Tel.: +49 40 428 48 2136
Fax: +49 40 428 48 2086
Email: Christa.Baumeister@bug.hamburg.de

Mr Rainer Blobel
Neureuter Querallee 4
76149 Karlsruhe
Germany
Tel.: +49 721 13 35 490
Fax: +49 721 13 35 490
Email: drogenhilfe@karlsruhe.de

Dr Henry Buhk
Abt. für Medizinische Psychologie
Zentrum für Suchtforschung
Martinistr. 52, Par. 69
20246 Hamburg
Germany
Tel.: +49 40 42803-6204
Fax: +49 40 42803-4940
Email: hbuhk@uke.uni-hamburg.de

Dr Ursula Christiansen
Dezernat für Gesundheit und Umwelt
Johannisstr.66-80
50668 Köln
Germany
Tel.: +49 221 221 257 61
Fax: +49 221 221 127 565
Email: Ursula.Christiansen@stadt-koeln.de

Mrs Christa Claes
Universität Hannover
Institut für Versicherungsbetriebslehre
Königsworther Platz 1
Hannover
Germany
Tel.: +49 511 762 5167
Fax.: +49 511 762 5081
Email: cc@ivbl.uni-hannover.de

Dr Christopher Dedner
Universitätsklinik f. Psychiatrie und
Psychotherapie
Osianderstrasse 24
722072 Tübingen
Germany
Tel.: +49 7071 - 2982332
Fax: +49 7071 - 29 41 41

Dr Peter Degkwitz
Zentrum für Interdisziplinäre
Suchtforschung der Uni. Hamburg (ZIS)
Klinik f. Psychiatrie und Psychotherapie
Martinistr. 52
20246 Hamburg
Germany
Tel.: +49 40 42803 - 4221
Fax:
Email: so6a023@sozialwiss.uni-hamburg.de

Mrs Ernst
Drogenreferat
Walter-Kolb-Straße 9 - 11
60594 Frankfurt/Main
Germany
Tel.: +49 69 212 30121
Fax: +49 69 212 30719
e-mail: regina.ernst@stadt-frankfurt.de

Mr Alfred Ferencz
Schulzstr. 18
45138 Essen
Germany
Tel.: +49 201 88 88 509
Fax: +49 201 88 88 510
Email: Alfred.Ferencz@essen.de

Mrs Ineke Huijsman
Central Committee Treatment
Heroin addicts
Stratenum - 5th Floor
NL3584 Utrecht-
Netherlands
Tel.: +30 25 38 802
Fax: +30 25 39 020
Email: ccbh@med.uu.nl

Dr Ruprecht Keller
Krankenhaus Merheim
- Zentrallaboratorium -
Kliniken der Stadt Köln
Ostmerheimer Strasse 200
Köln
Germany
Tel. No.: +49 221 8907-3557
Fax No.: +49 221 8907-3409
Email:

Professor Kleiber
Freie Universität Berlin
Institut für Prävention und psychosozial
Gesundheitsforschung
Habelschwerdter Allee 45
14195 Berlin
Germany
Email: Kleiber@zedat.fu-berlin.de

Dr Wilfried Köhler
Abteilung für Abhängigkeitserkrankungen
Bürgerhospital
Nebelungenallee 37-41
60318 Frankfurt-am-Main
Germany
Tel.: +49 69 15 00 880
Fax: +49 69 15 00 940
Email: mail@koehler-med.de

Dr Markus Kuntze
Psychiatrische Universitätsklinik Basel
Wilhelm-Klein-Str. 27
CH-4025 Basel
Switzerland
Tel.: +41 79 383 4713
Fax: +41 61 325 5364
Email: marcus.kuntze@pukbasel.ch

Mr Lesser
Ministerium für Frauen, Jugend, Familie
und Gesundheit des Landes NRW
Fürstenwall 25
40219 Düsseldorf
Germany

Mr Alfred Lessing
Rathaus
Sozialdezernat
30159 Hannover
Germany
Tel.: +49 511 168 46441
Fax: +49 511 168 46363
Email: alfred.lessing.dezd@hannover-stadt.de

Dr F.M. Leweke
Klinikum der Universität zu Köln
- Psychiatrie und Psychotherapie -
Joseph-Stelzmann-Str. 9
50924 Köln
Germany
Tel. No.: +49 221 478 4010
Fax No.: +49 221 478 3624
Email: m.leweke@uni-koeln.de

Dr Dirk Lichtermann
Universität Bonn
Klinik für Psychiatrie
Siegmund-Freund-Strasse 25
53105 Bonn
Germany
Tel.: +49 228 287 6082
Fax: +49 228 287 6097
Email: lichtermann@uni-bonn.de

Professor Karl Mann
Zentralinstitut für Seelische Gesundheit
J5
68159 Mannheim
Germany
Tel.: +49 621 1703 943
Fax: +49 621 1703 945
Email: Mann@as200.zi-mannheim.de

Dr Veronika Morhart-Klute
Klinikum der Universität München
Klinik und Poliklinik für Psychiatrie
und Psychotherapie
Nussbaumstrasse 7
80336 München
Germany
Tel.: +49 89 5160 5346
Fax: +49 89 5160 5552
Email: veronica.morhart-klute@psy.uni-muenchen.de

Dr Margareta Nilson
European Monitoring Centre for Drugs
and Drug Addiction - EMCDDA
Rua Cruz de Sta. Apolina 23-25
PT-1149-045 Lisboa
Portugal
Tel. : 351 21 811 3007
Fax: 351 21 813 7943
Email: Margareta.Nilson@emcdda.org

Dr Christina Poethko-Müller
Bundesinstitut für Arzneimittel und
Medizinprodukte
Friedrich-Ebert-Allee 38
Bonn
Germany
Tel.: +49 228 207 3118
Fax: +49 228 207 5489
Email: c.poetko-mueller@bfarm.de

Professor Jean Reggers
Centre hospitalier universitaire
du Sart Tilman
Department of Psychiatry
B-4000 Liège
Belgium
Tel. : +32 4 366 7960
Fax : +32 4 366 72 83

Dr Jens Reimer
Zentrum für Interdisziplinäre Suchtforschung (ZIS)
Martinistrasse 52
20246 Hamburg
Germany
Tel.: +49 40 42803 7901
Fax: +49 40 42803 8351
Email: reimer@uke.uni-hamburg.de

Dr Margret Rihs-Middel
Federal Office of Public Health
Policy and Research Section
CH-3003 Bern
Switzerland
Tel.: +41 31 322 33 00
Fax: +41 31 322 33 00
Email: margret.rihs@bag.admin.ch

Dr Jürgen Rink
Heidelberger Institut für Suchtforschung
Hardtstr. 1
69124 Heidelberg
Germany
Tel.: +49 6221 7132 21
Fax: +49 6221 7132 30
Email: FKEGesamtleitung@t-online.de

Dr Wolf Rössler
Drogenambulanz Hamburg GmbH
Kiebitzstr. 23
22089 Hamburg
Germany
Tel.: +49
Fax No.: +49 40 527 11 703
Email:

Mrs Martina Schu
FOGS Gesellschaft für Forschung und
Beratung im Gesundheits- & Sozialbereich
Prälat-Otto-Müller-Platz 2
50670 Köln
Germany
Tel.: +49 221 973 101 22
Fax: +49 221 973 101 11
Email: shu@fogs-gmbh.de

Dr Christian G. Schütz
Friedrich-Wilhelms-University Bonn
Department of Psychiatry
Sigmund-Freud-Str. 25
Bonn
Germany
Tel.: +49 228 287 9664
Fax: +49 228 287 6097
Email: christian.schuetz@ukb.uni.bonn.de

Mr Martin Schwaab
Gesundheitsamt Bonn
Engeltalstr. 6
53103 Bonn
Germany
Tel.: +49 228 77 2568
Fax: +49 228 77 3618
Email: martin.schwaab@bonn.de

Dr Juana Tomas-Rossello
Drug Abuse Treatment Adviser
Vienna International Centre
United Nations International Drug Control Programme, UNDCP
P.O. Box 500
A-1400 Vienna
Austria
Tel. No.: +43 1 26060-5284
Fax No.: +43 1 26060-5866
Email: juana.tomas@undcp.org

Dr Markus Zedler
Abt. Klinische Psychiatrie u. Psychotherapie
Medizinische Hochschule Hannover
Carl-Neuberg-Str. 1
30625 Hannover
Germany
Tel.: +49 511 532 3976
Fax: +49 511 532 2415
Email: zdler.markus@mh-hannover.de

Professor Christel Zenker
FHS Mümster
Postfach 3020
48016 Münster
Germany
Tel.: +49 421 32 10 63
Fax: +40 421 43 48 665
Email: chzenker@fh-muenster.de

Temporary Advisers

Dr Marc Auriacombe
Université Victor Segalen
Groupe d'Etude des Addictions
Laboratoire de Psychiatrie
Bordeaux
France
Tel. : +33 5 56 56 35 86
Fax: +35 5 56 56 35 15
Email: marc.auriacombe@labopsy.u-bordeaux2.fr

Dr Raphaela Basdekis-Josza
Zentrum für Interdisziplinäre Suchtforschung (ZIS)
Universitätsklinikums Hamburg-Eppendorf
Martinistrasse 52
20246 Hamburg
Germany
Tel.: +49 40 42803-4568
Fax: +49 40 42803-5121
Email: basdekis@uke.uni-hamburg.de

Dr Gerhard Bühringer
Leiter des
Instituts für Therapieforschung IFT
Parzivalstrasse 25
D-80804 München
Germany
Tel.: +49 89 36080410
Fax: +49 89 36080419
Email: buehringer@ift.isar.de

Dr Ernst Buning
Director
Euro-Methwork/Quest for Quality BV
Room No. 350
Keizersgracht 534 VI
NL-1017 EK Amsterdam
Netherlands
Tel. : +31 20 3303 449
Fax : +31 20 3303 450
Email: info@q4q.nl

Professor Miguel Casas
Professor of Psychiatry
Universidad Autnoma de Barcelona
Director of the Department of Psychiatry
Hospital Universitari Vall d'Hebron
Servicio de Psiquiatria
Pg. Vall d'Hebron 119-129
E-08035 Barcelona
Spain
Tel.: +34 93 489 42 94
Fax: +34 93 489 42 23
Email: micasas@hg.vhebron.es

Dr Ahmed Elkashef
National Institute on Drug Abuse
Clinical Medical Branch, Division of
Treatment research and Development
6001 Executive Boulevard, Room
MSC 9551 Bethesda, Maryland
United States of America
Tel.: +1 (301) 443 5055
Email: aelkashe@nida.nih.gov

Professor Benedikt Fischer
University of Toronto
Department of Public Health Sciences
MCMurrich Bldg.; 109 C
Toronto, Ontario M5S1A8
Canada
Tel.: +1 (416) 946 5792 or +1 (416) 535 8501 x4502
Fax: +1 (416) 260 4156
Email: Benedikt.Fischer@Utoronto.ca

Professor Gabriele Fischer
Director, University of Psychiatry
Drug Addiction Outpatient Clinic
Währinger-Gürtel 18-20
1090 Vienna
Austria
Tel.: +43 1 404003552
Email: Gabrielle.Fischer@ahk-wien.ac.at

Dr. Anne Karow (Rapporteur)
Zentrum für interdisziplinäre
Suchtforschung der Universität Hamburg
Matrinistr. 52,
20246 Hamburg
Germany
Tel.: +49 42803 4221
Email: karow@uke.uni-hamburg.de

Professor Michael Krausz
Universität Hamburg
Zentrum für Interdisziplinäre Suchtforschung
Martinistrasse 52
20246 Hamburg
Germany
Tel.: +49 40 4607 1550
Fax: +49 40 4607 1552
Email: krausz@uke.uni-hamburg.de

Dr Götz Mundle
Chefarzt
Klinische Betriebsgesellschaft Oberberg mbH
Oberberg 1
78132 Hornberg
Germany
Tel.: +49 07833/792230
Fax: +49 07833/792825
Email: Goetz.mundle@oberbergkliniken.de

Professor Jürgen Rehm
Addiction Research Institute
Konradstr. 32
CH-8031 Zurich
Switzerland
Tel. No.: +41 1 448 11 60
Fax No.: +41 1 273 40 64
Email: jtrehm@isf.unizh.ch

Professor Slavko Sakoman
Department for Addictions
UH 'Sestre milosrdnice'
Vinoogradska cesta 29
1000 Zagreb
Croatia
Email: d.c.o.@hi.hinet.hr

Professor Rainer Spanagel
Zentralinstitut für Seelische Gesundheit (ZI)
Abt. Psychopharmakologie
J5
68159 Mannheim
Germany
Tel.: +49 0621 – 17 03 833/836
Fax: +49 0621 – 1703 837
Email: psymail@as200.zi-mannheim.de

Professor J. Strang
National Addiction Centre
Institute of Psychiatry
King's College London
De Crespigny Park
4 Windsor Walk
London SE5 8AF
United Kingdom
Tel.: +44 20 7848 0438/0444
Fax: +44 20 7701 8454
Email: j.strang@iop.kcl.ac.uk

Dr Felix Tretter
Suchtabteilung
Bezirkskrankenhaus Haar
Postfach 1111
85540 Haar
Germany
Tel.: +49 089 4562-3708
Fax: +49 089 4562-3754
Email: Tretter@krankenhaus-haar.de

Professor W. van den Brink
Amsterdam Institute for Addiction Research
AMC
Tafelbergweg 25
1105 BC Amsterdam
Netherlands
Tel.: +31 20 566 23 38
Fax: +31 20 566 91 60
Email: w.vandenbrink@amc.uva.nl

Dr Uwe Verthein
Klinik für Psychiatrie und Psychotherapie
Zentrum für Interdisziplinäre Suchtforschung der Universität Hamburg
Martinistrasse 52
20246 Hamburg
Germany
Tel.: +49 40 877 959 or 42803-3246
Fax: +49 40 4280 3299
Email: Verthein@sozialwiss.uni-hamburg.de

Professor Irmgard Vogt
Fachhochschule Frankfurt/Main
Institut für Suchtforschung
Nibelungenplatz 1
60318 Frankfurt am Main
Germany
Tel.: +49 69 1533 2819
Fax:
Email: i.vogt@soz.uni-frankfurt.de

Professor Jochen Wolffgramm
Universitätsklinikum für Psychiatrie und Psychotherapie
Osianderstr. 22
72076 Tübingen
Germany
Tel.: +49 7071 29 86 138
Fax: +49 7071 29 53 84
Email: jochen.wolffgramm@med.uni-tuebingen.de

Professor Georg Woody
Treatment Research Institute
University of Pennsylvania/Phila. VAMC
600 Public Ledger Building
Treatment Research Institute
150 South Independence Mall (W)
Philadelphia, PA 19106
United States of America
Tel.: +1 (215) 399 0980 ext 112
Fax: +1 (215) 399 0987
Email: Woody@tresearch.com

**Representatives of the Federal Ministry of Health of Germany, Bonn
and of DLR Projektträger Gesundheitsforschung, Bonn**

Mr Martin Köhler
Arbeitsgruppenleiter
Bundesministerium für Gesundheit
DS 01
Am Propsthof 78 a
53101 Bonn
Germany
Email: martin.koehler@bmg.bund.de

Dr Anne Lücke
Deutsches Zentrum für Luft- und Raumfahrt e.V.
Südstrasse 125
53175 Bonn
Germany
Email: anne.luecke@dlr.de

Dr Ingo Ilja Michels
Geschäftsstelle der Drogenbeauftragten
Bundesministerium für Gesundheit
Mohrenstraße 62
10117 Berlin
Germany
Tel. No.: +49 030 206 40 1450
Fax No.: +49 030 206 40 4960
Email: michels@bmg.bund.de

Mrs Bianca Möller
Projektträger Gesundheitsforschung des BMG
Deutsches Zentrum für Luft- und Raumfahrt e.V. - DLR
Südstrasse 125
D-53175 Bonn
Germany
Tel. No.: +49 (0) 228 3821 221
Fax No.: +49 (0) 228 3821 257
Email: Bianca.Moeller@dlr.de

Dr Karin Post
Projektträger Gesundheitsforschung des BMG
Deutsches Zentrum für Luft- und Raumfahrt e.V. - DLR
Südstrasse 125
D-53175 Bonn
Germany
Tel. No.: +49 (0) 228 3821 261
Fax No.: +49 (0) 228 3821 257
Email: Karin.Post@dlr.de

Mrs Prüfer-Storcks
Staatssekretärin
Ministerium für Frauen, Jugend, Familie
und Gesundheit des Landes NRW
Fürstenwall 25
40219 Düsseldorf
Germany

Dr Martina Schöps-Potthoff
Bundesministerium für Gesundheit
DS03
Am Propsthof 78a
D-53121 Bonn
Germany
Tel. No.: +49 228 941 3331
Fax No.: +49 228 941 4937
Email: martina.schoeps@bmg.bund.de

Ms Michaela Schreiber
Referatsleiterin DS03
Bundesministerium für Gesundheit
Am Propsthof 78a
D-53121 Bonn
Germany
Tel. No.: +49 228 941 3330
Fax No.: +49 228 941 4937
Email: michaela.schreiber@bmg.bund.de

Dr Klaus-Theo Schröder
Staatssekretär
Bundesministerium für Gesundheit
Mohrenstraße 62
10117 Berlin

World Health Organization

Regional Office for Europe

Scherfigsvej 8, 2100 Copenhagen Ø, Denmark

Dr Haik Nikogosian
Head, Noncommunicable Diseases and Mental Health

Dr Philip Lazarov
Short-term Professional

Ms Anne-Maïlis Jepsen
Programme Assistant

Headquarters

World Health Organization, 20, avenue Appia, CH-1211 Geneva 27, Switzerland

Dr Vladimir Poznyak
Medical Officer
Management of Substance Dependence