The German project of heroin assisted treatment of opiate dependent patients

– Short description of the study design –

The German project of heroin assisted treatment of opiate dependent patients addresses drug addicts who were not successfully treated by the existing addiction therapies or whose course of methadone maintenance treatment was not satisfactory; these patients will receive injectable heroin as medication on a trial basis; a parallel control group will receive the substitution drug methadone. Both groups will be in medical care on a regular basis and receive additional psychosocial treatment.

The therapy study, which will evaluate the efficacy of heroin assisted treatment, is carried out as a clinically controlled comparison study according to the guidelines of "Good Clinical Practice" (GCP) and the regulations of the drugs act (Arzneimittelgesetz, AMG) and the narcotics act (Betäubungsmittelgesetz, BtMG). The treatment extends over a period of 24 months. The design is conceived to assess the therapeutic value and efficacy of heroin treatment in defined target groups in comparison to the established alternative treatment, i.e. methadone maintenance treatment. The study will be conducted in an integrated treatment setting, i.e. a combined treatment consisting of pharmaco/medical intervention and additional psychosocial treatment.

The study design is the result of a thorough analysis of previous knowledge and research on opiate assisted treatment, of the requirements set down in the invitation for proposals of the German Ministry of Health, the critical comments by experts concerning the submitted proposal and the additional comments of the participating centres resulting from many discussions. The adopted interdisciplinary approach fulfils the requirements of the invitation for proposals with regard to a clinical pharmacological trial (in a stricter sense) *and* additional issues of treatment and care research.

In simplified terms, the treatment study has the following three basic tasks:

- a clinical pharmacological trial to test the efficacy of heroin assisted treatment in comparison with methadone treatment,
- an examination of potential indication criteria for heroin assisted treatment (which groups of heroin dependent patients profit most?) and
- an investigation of feasibility and efficacy of the various medical and psychosocial treatment elements.

Background information

The reasons for heroin assisted treatment are the limitations of the existing treatment system. Part of the opiate dependants are reached only insufficiently – they do not enter treatment, they are not maintained in treatment, treatment success is too low. Heroin assisted treatment is considered as „ultima ratio", i.e. as complementary to the existing addiction help system (abstinence therapy, maintenance treatment).

Based on various estimation procedures, it is realistic to assume that at least 120,000 persons use heroin on a regular basis in Germany. Following the expansion of methadone maintenance treatment in the second part of the 1990ies, about 40,000 patients are treated with (levo-)methadone. Added to these are about 4,000 drug dependants who are treated with dihydrocodeine or buprenorphine. Thus, according to a conservative estimate of prevalence rates, 35%-40% of German heroin dependants are in maintenance treatment. About 900 drug dependent patients are in outpatient rehabilitative treatment and almost 10,000 clients in inpatient withdrawal treatment.

Various German evaluation studies on methadone maintenance treatment showed – in accordance with international experiences – that methadone maintenance treatment is effective in the treatment of heroin dependency. These studies also show that 10%-20% of patients profit only to a low degree from the maintenance treatment.

The risks of untreated opiate dependency are, as a rule, extremely high both on the individual and social level. Especially older addicts who are not adequately treated have an increased mortality risk and are likely to suffer from chronic illness such as hepatitis, HIV/AIDS, other infections and psychiatric disorders. Most often, their life situation is additionally characterised by strong social marginalisation and a high degree of delinquency. Their potential infections are a health risk to their

social environment. Due to delinquency and the treatment of concomitant illnesses, opiate dependency incurs considerable costs for society. The (regional) burden caused by open drug scenes, particularly in big cities, is a problem that society tolerates less and less.

Based on a (rather conservative) estimate of 35,000 patients in methadone treatment and at least 35,000 persons currently not in treatment, the number of potential patients for heroin assisted treatment in Germany would be at least 3,500 to 7,000 among the patients in maintenance treatment (corresponding to 10%-20%) and additionally about 10,000 (corresponding to 30%) opiate dependent persons not in treatment – thus a total of 13,500 to 17,000 persons.

Heroin assisted treatment is justified, if the target effects can be reached better than with other, established therapies. The evaluation of these issues is the subject of the German project of heroin assisted treatment: the treatment results are compared with those of a parallel control group of persons in methadone maintenance treatment.

Objective

The study's objective is to assess whether the medical prescription of pharmacologically pure heroin in a structured and controlled treatment setting is more successful in certain groups of heroin addicts in reaching the goals that are normally associated with standard addiction therapies: harm reduction, integration into the help system, reduction of illicit drug use and the related problems, health, mental and social improvement, controlling and overcoming dependency.

The focus of interest concerns three main topics:

- A pharmacological comparison will examine the efficacy of i.v. heroin as compared to oral methadone for both target groups in identical treatment settings.
- By a systematic variation of standardised psychosocial support – case management with integrated motivating interviews vs. drug counselling with psychoeducation – treatment effects will be evaluated in terms of specific settings. This procedure clearly increases the significance of the efficacy analysis of heroin prescribing and represents an important part of the required added value of this treatment. Furthermore, these results have relevant implications for the health care system in general.
- Sub-studies with a focus on patients and health care will investigate the effects of medical heroin prescribing, especially with regard to a decrease of delinquency, the possibilities to integrate heroin treatment into the existing addiction network and an overall cost-benefit analysis.

Target groups

The treatment focuses on the target group of heroin dependants, who need treatment but could *not be reached with therapeutic success* by the existing addiction support system (in short: NE for "nicht erreicht", not reached) or could *not sufficiently profit by the existing methadone maintenance treatment* (in short: MS for "Methadon-Substituierte"). The need of treatment results from the length of the drug career and severe forms of physical, mental and social destitution.

Following are the main inclusion criteria:
- Minimum age 23 years,
- Opiate dependency for at least 5 years,
- Current main diagnosis of opiate dependency according to ICD-10 criteria,
- Current daily and predominantly intravenous heroin use or continuing heroin use in maintenance treatment,
- Symptoms of physical illness indicating a poor state of health *or* current mental symptoms or impairments,
- No participation in an addiction treatment programme (mainly maintenance, outpatient or inpatient treatment) at least for the last 6 months, but documented previous experience with addiction treatment programmes *or* negative course of maintenance treatment according to the guidelines of the German Medical Council and
- Residence or registration in the city or region that conducts the heroin treatment since at least 12 months.

Hypotheses

The aim of heroin treatment is the reduction of individual and social risks, of consequences and costs related to non-treatment or insufficient treatment of opiate dependency.

The central hypothesis is as follows: Heroin assisted treatment is a therapeutically significant addition to the current addiction network in the treatment of specific target groups of heroin dependent persons. Heroin assisted treatment leads to greater positive effects than oral methadone maintenance with respect to

- the improvement of health,
- reduction of illicit drug use,
- decrease of criminal behaviour,
- increase of accessibility and retainment in treatment,
- detachment from a social drug context,
- social stabilisation in the sense of new drug-free contacts, improved ability to work, financial security, stabilisation of housing situation and
- enrolment in subsequent treatment.

Further *hypotheses* are:

- A tendency of superior efficacy of heroin treatment as compared to methadone treatment can be proven in both target groups (MS and NE).
- The effects of heroin treatment are similar in various psychosocial settings (case management with integrated motivating interviews vs. drug counselling with psychoeducation). Depending on the target group of heroin treatment and the phase and intensity of the addiction career, differences with regard to adequate psychosocial procedures can exist within the treatment groups.
- Heroin assisted treatment can be implemented to the same extend as oral methadone treatment; it can be integrated into the existing addiction network with the acceptance of the public, the environment and those affected.
- Heroin treatment is cost effective (prevention of social costs through health stabilisation and crime reduction; benefit through rehabilitation).

Test groups

Half of the experimental *treatment* in *both* target groups consists of

- i.v. heroin (experimental group)

and half of

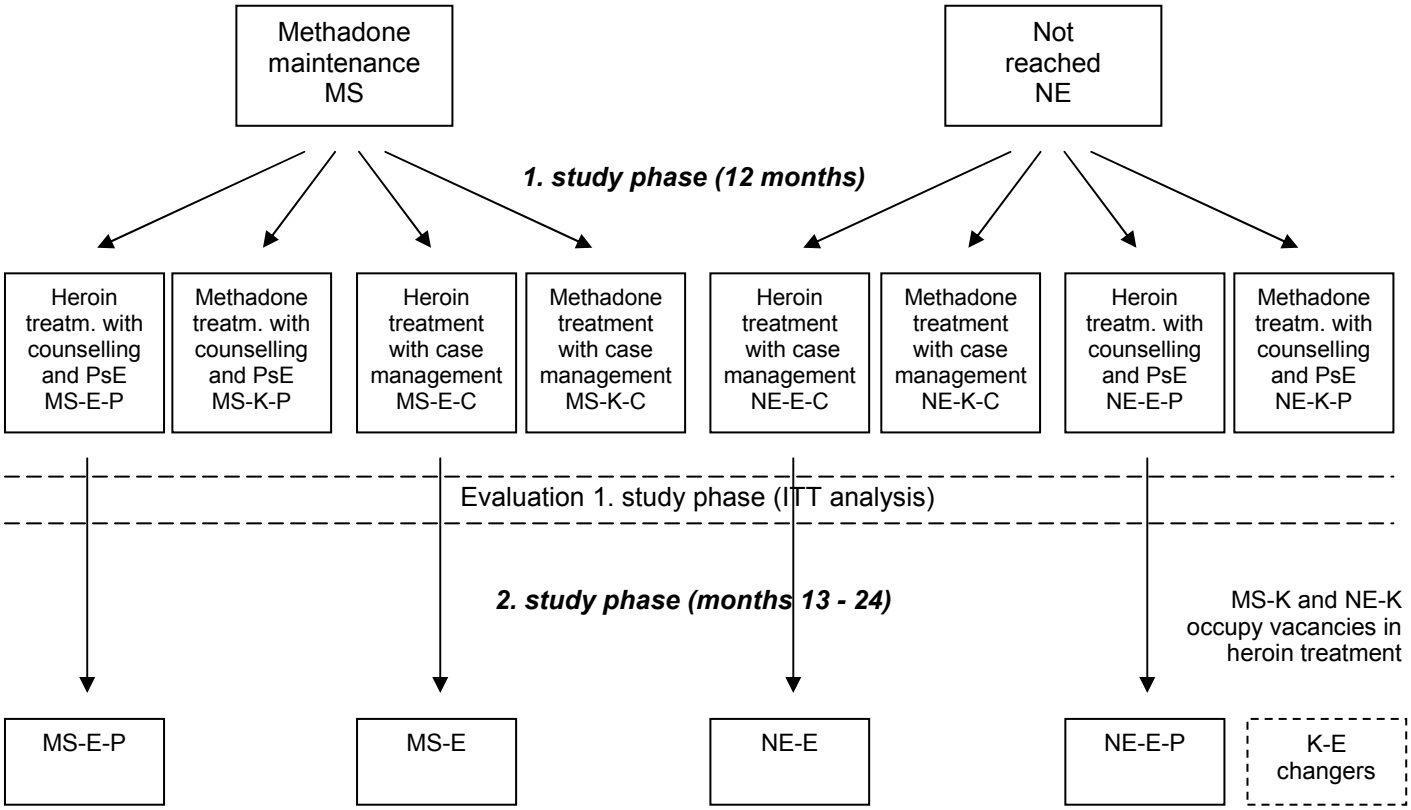
- oral methadone (control group).

In addition, *two different types of psychosocial care* are applied to opiate addicts:

- Case management as a structured, follow-up concept of care using the method of motivational interviewing,
- Drug counselling with psychoeducation and the optional use of local drug counselling and an additional psychoeducation programme with 12 sessions over a period of 3 months in a therapeutic group setting with subsequent refresher meetings.

The 4 x 2 stratified study is a multi-centre, randomised and controlled study: All treatments (experimental and control treatment) are carried out in a controlled and standardised setting (equipment, administration of medication, medical treatment, psychosocial care).

Test groups in phase 1 and 2 of the study:



Abbreviations:
E = experimental group, ITT = Intention-to-Treat, K = control group, MS = methadone maintenance, NE = not reached, PsE = psychoeducation

Medical treatment

Medical treatment is based on regular contacts with the treating doctor in order to coordinate the course of treatment and to react as soon as possible to possible complications. Detailed physical examinations and blood counts take place at the start of treatment and after 1, 3, 6 and 12 months. The course of treatment will also be controlled by weekly urine analyses.

Patients of the experimental groups (heroin) and the control groups (methadone) are treated in *outpatient settings* with interdisciplinary treatment teams. Patients of the control group who have been in methadone maintenance treatment might be required to leave their former doctor and change to an institution that participates in the clinical trial.

Heroin is administered up to three times a day during the opening hours of the institutions, in the morning, at noon and in the evening. In accordance with the Swiss and Dutch Studies, the maximum daily dose of i.v. heroin within the study is 1,000 mg, the single maximum dose 400 mg. From the start, i.e. *from the second day at the earliest*, an additional medication of methadone at night is available.

Oral methadone is administered to the control group once a day. It is taken on the premises under observation as a drinkable, not injectable single dose (normally mixed with fruit juice). There is no fixed maximum daily dose; according to experience, dosages between 40 and 160 md/d of methadone (in individual cases up to 250 mg/d) must be expected.

Psychosocial co-treatment

In contrast to the medical care of opiate addicts, no standards exist for the psychosocial co-treatment, neither for procedures nor for intensity. In order to evaluate the psychosocial part of treatment, two procedures, differing in their conceptions, will be implemented and compared in the course of the project. Both procedures – case management with integrated motivating interviews and

psychoeducation in addition to drug counselling – will be standardised and manualised as far as possible.

Concerning case management, it is possible to tie on to the experiences of the German model project with this intervention strategy. The German model project showed that drug addicts with chronical multiple impairments that were previously not reached by the addiction network, could be accessed and maintained in care. This is also true for drug addicts, who have no longer used drug services for a long time. Motivating interviewing is a counselling concept meant to stimulate the willingness to change; it has been tested with persons with a problematic drug use during the last few years. In this concept, motivation is not understood as an unchanging state, but is subject to many variations and ambivalences. It is the task of the counsellor to support and reinforce the existing motivation to change.

Positive experiences with the treatment of chronic illness, especially psychoses and chronic physical diseases, show that psychoeducation is a procedure that is easily standardised and is an effective addition to the existing variety of treatment programmes. Practical experiences in Switzerland and the United States in connection with methadone maintenance treatment confirm this expectation. Beside working on deficits and risks, psychoeducation offers the opportunity to establish resource orientation and resource activation as an integral part of the programmes. The integration of existing intervention strategies would thus be made possible (e.g. self help concepts and help offers of local counselling services).

Course and duration of the study

The duration of the clinical pharmacological trial is 24 months. It has to be expected that the organisation of the entire study will cover about 36 months.

The project starts with the application phase where appointments for the indication examination will be issued (after positive screening results). This is followed by a transitional phase leading to the randomised assignment and the start of treatment. The examinations and screening for the inclusion criteria extend over a period of about 6 to 9 months.

The study is divided into *two phases*: In the first 12 months, a stratified 4 x 2 randomised control group study will be conducted in order to examine the effects of heroin treatment as compared to methadone treatment under similar setting conditions (study phase 1). In the subsequent phase 2, a follow-up study will be conducted over 12 months in order to investigate the long-term effects (stabilisation and ties to the addiction help system) and the questions addressed in the invitation for tenders such as integration into the regional addiction network or the regular conclusion of the heroin treatment or entering further treatment. All patients of the experimental group (heroin) will be accepted in phase 2 of the study. Except for a randomly selected group of the control patients, who will be offered the vacant heroin treatment places after 12 months of treatment, patients of the control group (methadone) will leave the study and further treatment will be provided by legal health care.

Moreover, special studies addressing criminological, health care (health economy, implementation, cooperation), cognitive-motor and neuropsychological issues will be integrated within the 24-months total study period.

The clinical trial will be concluded after 24 months. Further treatment of the patients is assured in each case. According to currently valid procedure, heroin cannot be issued to them any more after the study conclusion, but, on request, they will receive another opioid such as methadone. If, however, at the end of phase 1, an evaluation of the main target criteria proves that heroin treatment is significantly superior to the control treatment with methadone, patients who successfully participated in the heroin treatment and who wish to do so may, after the 24 months, continue heroin treatment under certain conditions in a subsequent study. This treatment will be based on a separate study protocol regulating inclusion criteria and implementation requirements.

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