

The German model project for heroin assisted treatment of opioid dependent patients – a multi-centre, randomised, controlled trial

Summary of study reports of the first and second study phase

The German model project for heroin assisted treatment of opioid dependent patients was operated and financed jointly by the Federal Ministry of Health (BMG), the federal states of Niedersachsen, Nordrhein-Westfalen and Hessen and the cities of Hamburg, Hanover, Frankfurt, Cologne, Bonn, Karlsruhe and Munich.

In March 2002, study treatment started. The recruitment of patients went on till the end of 2003. 1,015 patients in seven cities were included in the study; about twice as many had been screened.

The main objective of the heroin trial was to investigate whether, in a structured treatment setting, the prescribing of intravenous diamorphin to heroin addicts, who had not responded sufficiently to methadone treatment or were not reached by the therapeutic system, would have greater effects in terms of health stabilisation and decrease of illicit drug use than methadone treatment. Secondary objectives were issues such as abandoning the drug scene context, improved social situation, decline of delinquency, change of quality of life and issues regarding treatment dropouts and follow-up treatment. Concomitant special studies are concerned more in-depth with the development of delinquency, health economic effects, utilisation and specific effects of psychosocial treatment, cognitive and motor functioning and care related issues.

The study was designed as a 4x2 stratified, randomised, multi-centre study. Two sample strata, the target groups “methadone treatment failures, MTF” (heroin addicts, who had not sufficiently benefited from methadone treatment) and “not reached, NR” (heroin addicts, who were not effectively reached by the drug treatment system) were each randomised to four groups. These four groups differ in terms of medical treatment (experimental group: heroin group vs. control group: methadone) and psychosocial treatment (psychoeducation/drug counselling vs. case management/motivational interviewing). As a result, there were eight groups with a study treatment of 12 months within the first study phase. At the end of this period, patients could continue with study phase two, also over 12 months.

The analyses focused on *two primary outcome measures*:

A) Improvement of health – a response exists if physical or mental health improved by at least 20% between baseline and 12-month examination.

B) Decrease of illicit drug use – a response exists if the use of street heroin markedly declined (no more than 2 positive urines out of 5 at month 12) and cocaine use did not increase (measured by hair analyses).

The study was considered successful if *both* primary outcome measures show a significant superiority of heroin treatment compared to methadone treatment. The primary analysis was carried out as an ITT-analysis of all randomised patients. Dropouts were coded asymmetrically according to the conservative worst-case strategy: Patients from the heroin group without valid data were considered as non-responders, patients from the methadone group as responders. The first study phase was terminated for all study patients at the end of 2004.

The central result of the German model project indicates a significant superiority of heroin treatment over methadone treatment for both primary outcome measures. Heroin treatment achieved significantly higher response rates with respect to the state of health (heroin: 80.0%, methadone: 74.0%, $p=0.023$) as well as the decrease of illicit drug use (heroin: 69.1%, methadone: 55.2%, $p<0.001$). Evidence of the higher efficacy of heroin treatment compared to methadone maintenance treatment has thus been provided in terms of the study protocol. Heroin treatment is also clearly superior to methadone treatment in patients who fulfil both primary outcome measures (heroin: 57.3%, methadone: 44.8%, $p<0.001$). A significant influence of the factors target group (MTF vs. NR) and kind of psychosocial treatment (psychoeducation vs. case management) cannot be detected in the statistical analyses.

The retention rate of heroin treatment is 67% after 12 months and slightly lower than the rates of the Dutch and Swiss studies. Only 39% of the patients of the methadone group concluded study treatment ($p<0.001$). However, it must be considered that 39% of the dropouts of heroin treatment and 44% of the dropouts of methadone treatment were in maintenance treatment outside of the study or in some other addiction treatment at month 12.

The average daily heroin dose is 442 mg for the whole period of the first study phase (365 days). The mean daily dose of additional methadone prescribed to heroin patients is about 8 mg, relating to all the days of heroin dispensing. Methadone patients were treated with an average daily dose of 99 mg.

The study design was successfully implemented according to the specifications of the study protocol. A sufficient number of patients were recruited both for the target group of methadone treatment failures (MTF) and the so-called not reached (NR). The study participants must be counted among the most severely dependent patients because of the great number of physical and mental impairments they suffer from and their heavy, mainly intravenous heroin and cocaine use. One result, however, is that both groups hardly differ with respect to their health and social position at baseline. The only difference consists in a higher degree of intravenous heroin use and a more instable housing situation among the NR. Accordingly, no differences of treatment effects can be detected between the target groups. Heroin treatment is equally effective in methadone non-responders and in opiate addicts not reached by the drug care system.

The setting of psychosocial treatment has no relevant influence on treatment success. Although retention in the methadone group is slightly higher for case management than for psychoeducation (whereas no differences between psychoeducation and case management in the heroin group), the superiority of heroin treatment over methadone treatment for both kinds of psychosocial treatment points to the overall result confirming that the psychosocial setting has no influence on the outcome.

To conclude, it should be noted that heroin treatment involves a somewhat higher safety risk than methadone treatment. This is mainly due to the intravenous mode of administration. Rather frequently occurring respiratory depression and cerebral convulsions are not unexpected and can easily be medically controlled. During the first study phase, the overall mortality rate was 1.2% and rather low considering patients' poor state of health. No death occurred in causal relationship to the study medication. Considering the much higher risk of intravenous application of street heroin, the safety risk of medically controlled heroin application must be assessed as low.

Patients, who had completed study treatment of phase one, started the second study phase, also over a period of 12 months. Patients of the experimental group were able to continue heroin treatment, patients of the control group had the opportunity to occupy vacated heroin treatment places. (Subsequent to the second study phase, heroin assisted treatment could be continued in a follow-up phase of individual treatment.)

A total of 434 patients started the second study phase, 344 continued heroin assisted treatment (79.3%) and 90 patients switched from methadone treatment (20.7%). According to the study design of the second phase, the 434 patients were distributed to four groups of about equal size: stratum MTF, heroin treatment with psychoeducation (27.2%); MTF, heroin treatment with case management (23.5%); NR, heroin treatment with psychoeducation (23.0%); NR, heroin treatment with case management (26.3%).

As expected, patients of the second study phase have a higher retention rate in the second year of treatment. Four fifths of them regularly concluded the study treatment of the second phase. Related to all the 515 patients ever randomised to the heroin group, 55% are still in treatment after 24 months. The retention rate is 10% higher among MTF patients than among NR patients.

A comparison between switchers from methadone to heroin after the first study phase with patients, who received heroin for the entire 2-year period, shows that the switchers succeed in catching up with the 2-year heroin patients in the second year of treatment (under heroin medication). In contrast to the results after 12 months, no significant differences can be detected between the 2-year heroin patients and the methadone-heroin switchers with respect to the outcome criteria health improvement and reduction of illicit drug use after 24 months. The analysis of the “switcher group” thus provides independent scientific-methodological evidence of the superiority of heroin treatment over methadone treatment. *Both groups achieved more, statistically significant improvements or stabilisation of the existing changes during the second year of treatment.* Risk behaviour related to intravenous drug use (sharing of needles and injection equipment) is completely dropped.

The second study phase focuses on the effects of the 2-year heroin treatment. The average daily dose of diacetylmorphine is 452 mg during the entire 2-year period. Additionally, 7 mg of methadone were prescribed on average, relating to all the days of heroin dispensing. The heroin dose continuously decreased during the 24 months, while the average dose of methadone slightly increased. Not only the health situation of heroin patients stabilises or improves during the second study phase but also their social situation continues to take a positive course. Their housing situation stabilises, social contacts slightly increase and leisure occupations develop positively. But the problem of loneliness stays with many heroin patients. Two thirds have no steady partner and one tenth no reliable friends. This indicates that the process of social integration outside the drug context is a slow one.

The professional situation develops in a remarkable extent. Against the background of a difficult labour market situation, the increase of patients in regular work by 11%, attaining 27% after 2 years of heroin treatment, is a considerable success. Among the patients assessed as “capable of work”, the proportion of wage earners even increases from 25% to 43%. This demonstrates that heroin treatment in connection with psychosocial treatment has a direct and indirect (through health improvement and restoration of fitness for work) positive effect on the working situation.

The two types of psychosocial treatment – psychoeducation and drug counselling; case management and motivational interviewing – are intensively utilised by the heroin patients in the second year. Treatment satisfaction is slightly higher in patients who received case management. As already mentioned, during the first study phase, no differences in the primary outcome criteria were found between the types of psychosocial treatment, but after 24 months, the situation is different. Treatment success (according to the primary outcome measures) is greater in patients, who received individual drug counselling and participated in psychoeducative groups. This result is independent of centre effects and raises questions regarding the optimisation of psychosocial treatment offers.

With respect to the safety of medication, (severe) adverse events generally declined during the second study phase. Switching from methadone to heroin hardly involves new complications for the patient. The reason could be effects of habituation both in patients and in treatment personnel (concerning the handling of patients and of medication) as well as selection effects, since patients prone to complications are more likely to have dropped out earlier. The mortality rate of the second study phase is 0.9%, no death was found to have a causal relationship with the study medication.

The German model project for heroin-assisted treatment of opioid dependent patients has so far been the largest randomised control group study investigating the effects of heroin treatment. The results of the second study phase confirm and substantiate the findings of the comparative study of the first phase in an impressive way. Heroin-assisted treatment proves to be decidedly successful in the treatment of the most severely dependent heroin users. With the introduction of heroin-assisted treatment as an approved treatment option, the “selection mechanism” related to study conditions will no longer exist and examinations will be less elaborate so that acceptance of this type of treatment is likely to increase even more. The inclusion criteria and quality standards of heroin-assisted treatment proved to be effective and should be maintained in regular treatment – until more recent findings suggest modifications. Meanwhile, several studies found scientific evidence of the positive effects of heroin treatment; therefore, the necessary health policy steps towards creating the legal pre-conditions for the implementation should be initiated without delay. Delays lead to a vague situation – especially for patients and professionals of the treatment units – so that it becomes difficult to carry on treatment and support in an ethically responsible way. In accordance with the assessments and requirements of numerous internal and international experts and the representatives of doctors, treatment institutions and addiction associations, *the evaluation of the positive results of both study phases of the German heroin project leads to the explicit recommendation to include this type of treatment into the treatment catalogue for heroin-dependent patients.*

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Appendix

Aim of the German Heroin Study

To examine if with medical prescription of pharmacologically clean *heroin* (diacetylmorphin) in a *structured and controlled treatment setting* for specific groups of heroin addicts, improvement of health and reduction of illicit drug use can be achieved.

Target groups (strata)

- Methadone treatment failures (MTF)
 - Opiate addicts presently in methadone-maintenance treatment, who have not profited sufficiently from treatment
- Untreated / not reached (NR)
 - Heroin addicts, who have dropped out of treatment services and are presently not in treatment, but in need of treatment due to their state of health or present life situation



Inclusion criteria

- At least 23 years old
- Opiate dependency for at least 5 years
- Present intravenous heroin use
- Poor physical health (OTI-Score ≥ 13) or poor mental health (GSI T-Score ≥ 60)
- NR: Not in treatment for last 6 months
- MTF: negative course of methadone maintenance treatment

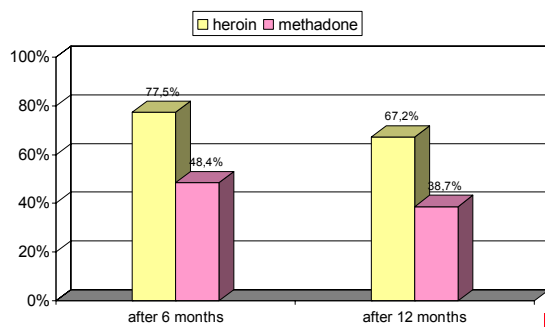


Study Treatment

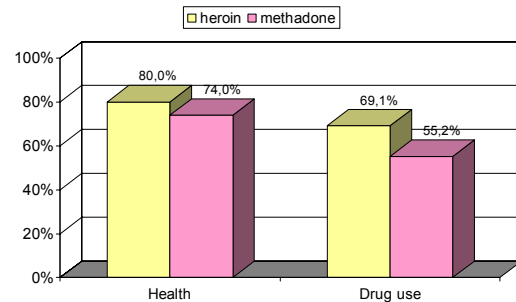
- *Heroin*: daily dispensing (up to 3x), maximum daily dose 1,000 mg, maximum single dose 400 mg, possibility for methadone intake at night (max. 60 mg)
- *Methadone*: daily dispensing, take-home regulation, no dose limit
- Individual dosage \rightarrow stable steady state dose
- Case-Management: structured, person-centred, intervening concept; with integrated element: Motivational Interviewing (CM/MI)
- Drug counselling and psychoeducation (PE/DC): counselling upon demand and psychoeducation according to manualised group setting



Retention Rate, first Year



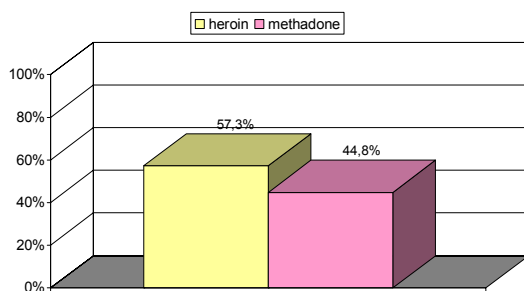
Primary Analysis (ITT) – Response Rates (Worst case analysis, N=1,015)



Statistics: Health: OR = 1.41 * (1.05-1.89), Drug use: OR = 1.85 *** (1.43-2.40)



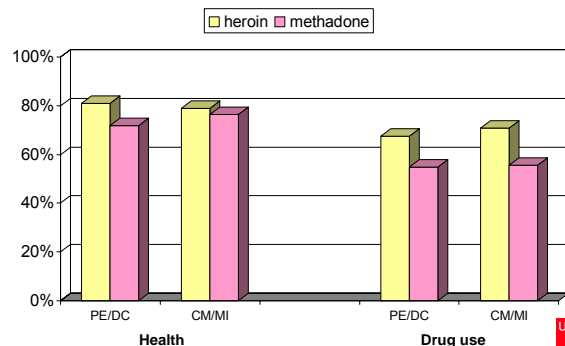
ITT-Analysis – Response in both Primary Outcome Measures



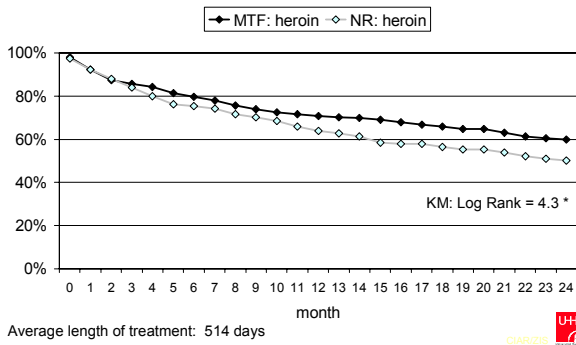
Statistics: OR = 1,67 *** (95%-CI: 1,30-2,14)



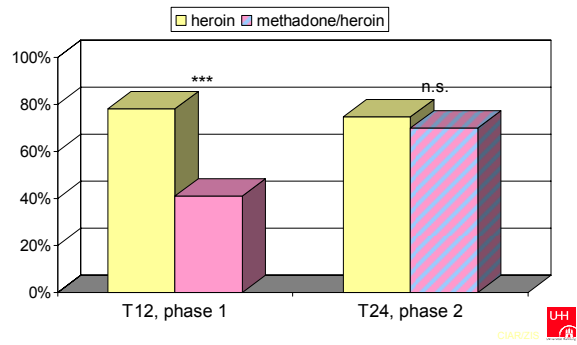
Primary analysis ITT according to psychosocial intervention



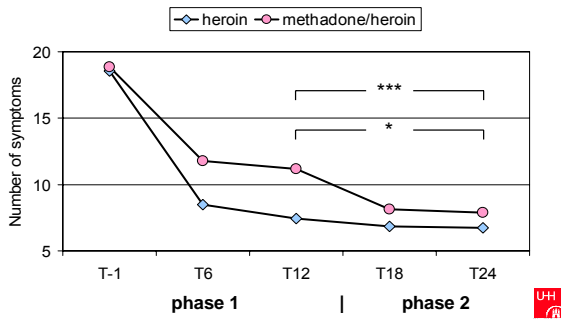
24-Months Treatment Retention (Heroin group, N=515)



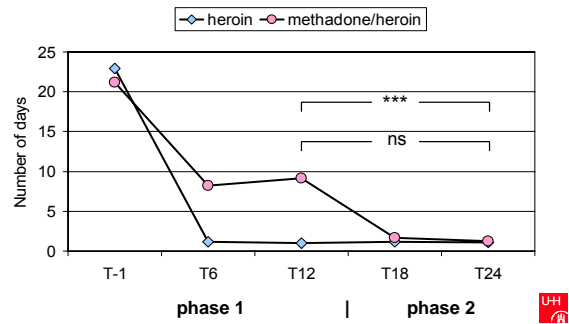
Primary Analysis (P2-Sample, N=434) – Response in *both* POM



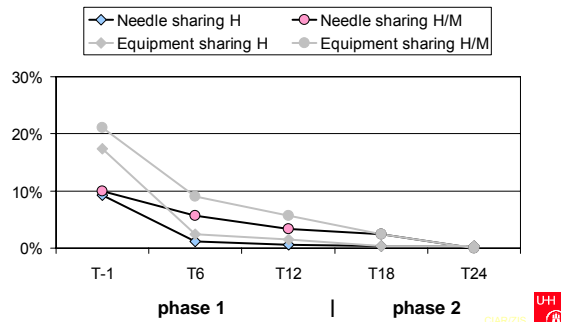
Physical Symptoms (OTI Health Scale) (P2-Sample, N=434)



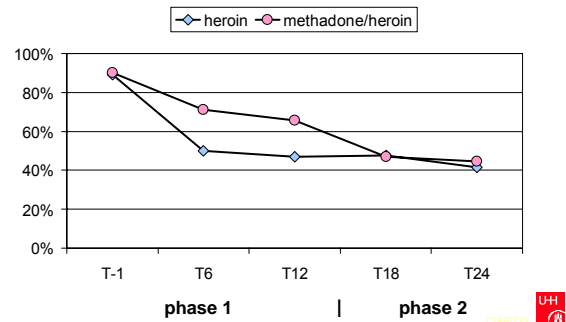
Use of Street Heroin past 30 Days (P2-Sample)



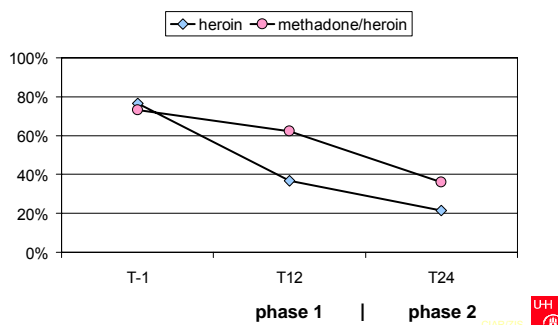
Risk Behaviour last 6 Months (P2-Sample)



Contacts to the Open Drug Scene (P2-Sample)



Delinquency, 12-Mo-Prevalence (Total Number of Offences, P2-Sample)



Response Rates (both Primary Outcome Measures) at T₁₂ and T₂₄ by kind of PST

