

PART IV

FEASIBILITY OF HEROIN ON MEDICAL PRESCRIPTION

Chapter 9

Public order and controllability

9.1 Focus of the evaluation

As described in paragraph 2.10.2, undesirable events in the area of public order, controllability and public safety were defined in similar terms as those in the area of medical safety, and were likewise evaluated on their severity and causal relationship with the execution of the study. For the purpose of the present report, the observation period used for the evaluation of events in the area of public order and controllability was – similar to the evaluation of medical SAEs – limited to the first twelve months following randomization, the experimental phase of the trials. In addition, the evaluation was limited to the intention-to-treat population of the experimental treatment group of the trial on injectable heroin (76 subjects in group B), and that on the trial on inhalable heroin (236 subjects in groups B and C).

As with medical safety, the occurrence of events in the area of public order and controllability were separately evaluated during the twelve months experimental phase of the trials, and during the two months following the discontinuation of co-prescribed heroin treatment at the end of the experimental phase. The latter evaluation was limited to the patients who had received and completed the experimental treatment with co-prescribed heroin (i.e. the treatment completers in group B (trial on injectable heroin), or group B and C (trial on inhalable heroin)).

9.2 Events not attributed to individual patients

In the course of the trials, a total of 28 events could not be attributed to an individual patient, and – hence – to one of the two trials. From these, 20 events involved complaints from residents in the environment of the treatment center, whereas eight events occurred in the treatment unit. The 20 events in the surroundings of the treatment center included the use of illicit drugs in the neighborhood (five events), subjects sleeping outside or urinating in the street (three events), (attempts of) burglary (four events), subjects hanging out on the street (six events), intentional destruction of car tyres (one event), and combined illicit drug use and car burglary (one event).

The eight events in the treatment center involved six cases of small balance deficiencies on the drug (heroin) accountability forms, an absent front-door key of the treatment center, because one of the staff-members had erroneously taken the key home (one event), and disappearance of money out of a locked cabinet in the treatment center (one event).

The severity of the events, which could not be attributed to individual patients, was most often evaluated as mild (13 events). Six events were assessed as moderate, and three events as severe. For the remaining six events, the severity of the event was unknown.

9.3 Events in the trial on injectable heroin

Events during the twelve months experimental study phase

During the twelve months experimental study phase, a total of 56 events occurred among the 76 patients in the co-prescribed heroin treatment group of the trial on injectable heroin. These 56 events

involved a total of 28 patients. Hence, approximately one-third of the patients in the intention-to-treat population of group B had been involved in at least one event in the area of public order and controllability. From the 56 events, 15 events were categorized as (attempt of) smuggling heroin medication out of the treatment center, 12 events involved threat or verbal aggression, and eight events physical aggression, 10 events involved the use of illicit or otherwise prohibited drugs, and/or drug dealing, and 11 events concerned breaking other house rules.

In total, nine of the 56 events (involving six patients) in the injectable heroin trial occurred outside the center. These included, for example, a participant sleeping on the sidewalk in front of the treatment center, a participant begging for money, disturbance of the public order situation, and smoking cannabis in the direct environment of the treatment unit. One of the nine events was judged as severe, four as moderate, and four as mild.

Table 25 provides an overview of the severity of the events in the area of public order and controllability, and their causal relationship with the execution of the study. From the total of 56 events, seven events were not related to the execution of the study, six events were evaluated as possibly related, three events as probably related, and 34 events as definitely related. For the remaining six events, the relationship with the conduct of the study could not be established (see Table 25).

Table 25. Relationship between events in the area of public order and controllability and the conduct of the study during the experimental phase of the trial (injectable heroin)

<i>Relationship with study</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>	<i>Total</i>
Not related	6	1	0	7
Possibly related	4	0	2	6
Probably related	2	1	0	3
Definitely related	24	8	2	34
Not known	2	4	0	6
Total	38	14	4	56

The four events that were rated as severe, and were considered to be at least possibly related to the execution of the study involved one case of verbal aggression (definitely related to the study), one case of physical aggression (definitely related), one case of repeated breaking of the house rules (possibly related), and one attempt to smuggle heroin out of the treatment center (possibly related). Even though the amount of heroin in question was less than the patient's total daily dose, this latter event was rated as severe, because the subject became agitated when he was accused of attempting to smuggle heroin out of the treatment center.

With regard to the other attempts to smuggle heroin out of the treatment center, the severity of one other attempt was assessed as moderate. The remaining 13 attempts to smuggle heroin were rated as mild. In all cases, the attempts involved an amount of heroin smaller than the participant's total dose of that day (see paragraph 2.10.2).

Events during the two months following the discontinuation of heroin treatment

A total of 55 patients completed the 12 months treatment with co-prescribed injectable heroin. During the two months following the discontinuation of this treatment, one event in the area of public order and controllability occurred. This event involved an attempt to smuggle a small amount of heroin (smaller than the subject's daily dose) out of the treatment unit. The event was rated as mild, and was considered to be definitely related to the execution of the study. In the injectable heroin trial, no events occurred outside the treatment unit during the two months following the discontinuation of heroin treatment.

9.4 Events in the trial on inhalable heroin

Events during the twelve months experimental study phase

In the trial on co-prescribed inhalable heroin, a total of 135 events occurred among the 236 patients in the co-prescribed heroin treatment groups B and C combined. These 135 events involved a total of 81 patients (see Table 26). Hence, similar to the trial on injectable heroin, approximately one-third of the patients in the intention-to-treat population of treatment groups B and C had been involved in at least one event in the area of public order and controllability.

Table 26. Events in the area of public order and controllability during the experimental phase of the trial (inhalable heroin)

<i>Treatment group</i>	<i># Events</i>	<i># Patients with event(s)</i>
B (<i>n</i> = 117)	89	50
C (<i>n</i> = 119)	46	31
Total (<i>n</i> = 236)	135	81

From the 135 events, 35 events concerned (attempt of) smuggling heroin medication out of the treatment center, 33 events involved threat or verbal aggression, and 18 events physical aggression, 28 events involved illicit or prohibited drug use, and/or drug dealing, and 21 events concerned breaking other house rules.

In total, 19 of the 135 events (involving 17 patients) in the inhalable heroin trial occurred outside the center. These included, for example, cocaine use in the direct environment of the treatment unit, smoking illicit heroin in the tram, selling drugs outside the treatment unit, and participants arguing in front of the unit. None of the 19 events was judged as severe, nine as moderate, and 10 as mild.

With regard to the causal relationship between the event and the execution of the study, 18 of the 135 events were evaluated as not related to the study, 23 events as possibly related, seven events as probably related, and 79 events as definitely related. The relationship with the conduct of the study could not be established for eight events (see Table 27).

The 12 events that were rated as severe, and were considered to be at least possibly related to the execution of the study involved one case of illicit drug use and/or drug dealing (possibly related to the study), eight cases of verbal aggression (two possibly related, one probably related, and five definitely related), and three cases of physical aggression (all possibly related).

Table 27. Relationship between events in the area of public order and controllability and the conduct of the study during the experimental phase of the trial (inhalable heroin)

<i>Relationship with study</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>	<i>Total</i>
Not related	10	5	3	18
Possibly related	10	7	6	23
Probably related	6	0	1	7
Definitely related	59	15	5	79
Not known	7	1	0	8
Total	92	28	15	135

With regard to the (35) attempts to smuggle heroin out of the treatment center, none of the attempts was evaluated as severe. The severity of five attempts was assessed as moderate. The remaining 30 attempts to smuggle heroin were rated as mild. In all cases, the attempts involved an amount of heroin smaller than the participant's total dose of that day (see paragraph 2.10.2).

Events during the two months following the discontinuation of heroin treatment

In the trial on co-prescribed inhalable heroin, a total of 80 patients completed the 12 months treatment with co-prescribed heroin, and 82 patients completed the six months co-prescribed heroin treatment. In this group of 162 treatment completers, five events in the area of public order and controllability were registered. Three of these, each involving physical aggression, were evaluated as severe (two possibly related to the study, and one probably related). The two remaining events were assessed as mild. In the inhalable heroin trial, two of the events during the two months following the discontinuation of heroin treatment occurred outside the treatment unit.

Context of the observed events in both trials in the area of public order and controllability

Both trials combined, the observed total number of 191 public order and controllability events (of which 152 events were judged to be at least possibly related to the conduct of the study), related to 109 subjects, and 28 events which could not be attributed to individual participants in the study, occurred in a context in which approximately 140,000 heroin prescriptions were dispensed.

- In both trials combined, a total of 16 patient-related, public order and controllability events during the 12 months experimental period were considered to be severe and at least possibly related to the conduct of the study. In the two months following the discontinuation of the heroin treatment, three events were rated as severe and at least possibly related to the execution of the study.
- The observed severe and at least possibly related events should be considered in the context of approximately 140,000 heroin dispensations to more than 300 patients.
- Four reported severe public order events took place in the direct environment of the treatment unit.
- Given the nature of the severe events, the medical co-prescription of heroin did not create serious public order or controllability problems in either the treatment unit, or the neighborhood.

Chapter 10

Contact dermatitis

In the course of the study, the CCBH received indications from different treatment sites that some staff members – particularly nurses who had the task of dispensing the heroin to the patients – in the treatment units had developed contact dermatitis, possibly due to skin contact with heroin base. Preliminary "on site" explorations of the occurrence of contact dermatitis and the procedures used for the dispensing of the inhalable heroin suggested that the observed allergic skin reactions were possibly caused by small amounts of heroin base on the outside of the heroin medication capsules, which were used as pharmaceutical package for the heroin base powder during the first years of the study. Nurses in some treatment units prepared the inhalable study medication for the self-administration by the patients by opening the capsules themselves, and emptying the content of the capsule into a medication cup. During this procedure, they were likely to be into contact with small amounts of heroin base.

In the course of the year 2001, the capsules were replaced by sachets as pharmaceutical package for the heroin base in all treatment units. Parallel to the introduction of the sachets, the CCBH developed and implemented a so-called "no-touch" procedure, directed at minimizing the skin contact with the heroin base. According to this no-touch procedure, the nurse handed out the sachet in closed condition to the patient. Following the self-administration of the heroin base by the patient, all inhalation material – including the empty sachet, aluminum foil, and straw – had to be put into a little plastic bag by the patient himself, which was then sealed with a plastic strip.

In addition to the no-touch procedure, special attention was given to the ventilation equipment, used to create negative air pressure in the administration room for the inhalable heroin to prevent passive inhalation of heroin vapors by the treatment staff. In some treatment units, the ventilation equipment was adjusted.

After the introduction of the no-touch procedure and the replacement of capsules by sachets, the incidence of contact dermatitis decreased. To obtain more information about the incidence and severity of contact dermatitis among treatment staff and patients, a supplementary study is currently being conducted.

Chapter 11

The costs of medical co-prescription of heroin

Treatments are nowadays not only evaluated in terms of the balance between effectiveness and safety, but also in terms of the balance between costs and effects. An evaluation of costs and effects is also expedient for the medical co-prescription of heroin to heroin addicts. Like other new medical treatments, the co-prescription of heroin initially involves high costs, which may be compensated by cost-reductions outside the scope of the initial treatment. In addition, similar to other treatments, the costs of treatment should be evaluated in light of the physical health, mental health, and social benefits of treatment of all patients involved.

In this chapter, the results of a financial analysis of the treatment costs are presented. The focus of this first economic investigation was restricted to the direct medical costs of treatment. Possible cost-savings as a result of the medical co-prescription of heroin, and an investigation of the balance between costs and effects will be the subject of future reports.

The estimations in the analysis were based on the costs in three treatment centers. In each treatment center, interviews were held with the physician, and with the financial manager. Although the three treatment centers varied with respect to the number of patients, the estimations were based on the staff capacity required to treat the maximum number of patients.

The relationship between number of patients and costs differs for different types of costs. For example, whereas the costs of the experimental medication, heroin, are strongly related to the number of patients in a treatment center, security costs have a weak relationship with number of patients. Consequently, the costs per patient depend upon the size of the treatment center. To gain insight into the relationship between costs and size of the treatment unit, the costs were estimated separately for a treatment center with 25 patients, 50 patients and 75 patients on a daily basis. In the calculations, a distinction was made between personnel costs and material costs. The costs of overhead, charged by the organizations of which the treatment center was part of, were left out of the analysis.

Personnel costs

Table 28 provides an overview of estimations of all direct medical costs included in the analysis. The personnel costs involved the project co-ordination and administration, medical staff, security staff, and local pharmacist.

Varying between the treatment centers, either the physician or another discipline was responsible for the project co-ordination. It was estimated that the project co-ordination required 0.5 fte co-ordinator in a center with 25 patients, 0.75 fte in a unit with 50 patients, and 1.0 fte in a unit with 75 patients. As can be seen in Table 28, these full-time equivalences correspond with an estimated €25,000, €37,500, and €50,000 per treatment unit per year, respectively. Similarly, the project administration was estimated to involve 0.5 fte (€12,500), 0.75 fte (€18,750), and 1.0 fte (€25,000) administrator, respectively.

The costs, estimated for the treatment center's physician were based on an occupancy of 16 hours a week for a 25 patients unit, 24 hours a week for a 50 patients unit, and 32 hours a week for a 75 patients unit. The costs involved were estimated to amount to €22,000, €33,000, and €44,000, respectively.

Table 28. Estimated costs of medical prescription of heroin per treatment unit per year

	<i>Costs per year (in €)</i>		
	<i>25 Patients unit</i>	<i>50 Patients unit</i>	<i>75 Patients unit</i>
Personnel costs:			
<i>Project co-ordination</i>	25,000	37,500	50,000
<i>Physician</i>	22,000	33,000	44,000
<i>Nurses</i>	210,000	315,000	315,000
<i>Project administration</i>	12,500	18,750	25,000
<i>Security</i>	90,000	110,000	130,000
<i>Pharmacist</i>	5,718	5,718	5,718
Sub-total	365,218	519,968	569,718
<i>Social benefits</i>	113,217	161,190	176,612
<i>Sick-leave</i>	21,913	31,198	34,183
Sub-total	500,348	712,356	780,513
Material costs:			
<i>Depreciation rebuilding</i>	28,000	37,000	46,000
<i>Other investments</i>	6,000	7,500	9,000
<i>Rent</i>	45,000	60,000	75,000
<i>Cleaning</i>	6,000	8,000	10,000
<i>Energy, heating</i>	7,500	10,000	12,500
<i>Maintenance</i>	12,000	16,000	20,000
Sub-total	104,500	138,500	172,500
Patient-related material costs:			
<i>Heroin</i>	45,000	90,000	135,000
<i>Other medical supplies</i>	20,000	40,000	60,000
Sub-total	65,000	130,000	195,000
Total costs	669,848	980,856	1,148,013
Total costs per patient	26,794	19,617	15,307

Based on a minimum presence of two nurses during the opening hours of a treatment center, working hours from 7:30 a.m. to 8:30 p.m., and taking into account weekends, leave/holidays, and sick-leave, a minimum of seven full-time nurses is required in even a small treatment center. It was anticipated that an occupancy of two nurses during the opening hours would be sufficient for treatment centers with a maximum capacity of 40 patients a day. Above 40 patients, three instead of two nurses were anticipated to be required. In that case, the total number of full-time nurses would increase from seven to 10.5 nurses. The annual costs of the nursing staff, taking into account the presence of two nurses in the nursing staff with more responsibilities, and – hence – a higher salary, were estimated to amount to €210,000 for a 25 patients unit, and to €315,000 for both a 50 patients and 75 patients unit.

Security personnel was present at any time during the opening hours in each treatment center. As stated before, the costs of security personnel are only weakly related to the size of the treatment center. These costs were estimated to amount to €90,000, €110,000, and €130,000 for a 25, 50, and 75 patients unit, respectively.

The costs of the local pharmacist are estimated at €5,718 a year, independent from the number of patients in the treatment center.

These personnel costs were increased with 31% social benefits and 6% sick-leave. In addition, for each nurse and physician, an amount of €1,500 annually was reserved as recruitment costs.

Material costs

At each treatment location, considerable rebuilding had to take place to adapt the building to the requirements of the study. For example, the building had to accommodate a waiting room for the patients, separate heroin injection and inhalation rooms, each with specific technical requirements, staff rooms, and specially secured rooms for storage of the medication. The costs of rebuilding varied considerably across the treatment centers, and ranged from €300,000 to €1,500,000, depending on the extent to which existing infrastructure could be used. On the average, rebuilding costed €1,500 per m². A treatment unit with 25 patients is estimated to require approximately 300 m². For units with 50 and 75 patients, 400 and 500 m² are required, respectively. Based on a depreciation term of 30 years, and including interest, the costs of rebuilding per year were estimated to amount to €28,000 for a 25 patients unit, €37,000 for a 50 patients unit, and €46,000 for a 75 patients unit.

Other necessary investments included the inventory and computer hardware and software. The total costs of these investments were estimated to amount to €50,000, €60,000, and €70,000 for a 25, 50, and 75 patients unit, respectively. For these investments, an average depreciation term of 10 years was used. Based on this depreciation term, and including interest, the annual costs amounted to €6,000, €7,500, and €9,000 for the 25, 50 and 75 patients unit, respectively.

Additional costs, which are strongly related to the size of the treatment center, included the costs of rent, cleaning, energy, and maintenance. Rental costs were estimated at €150 per m² per year (i.e. €45,000 for a 25 patients unit of 300 m²). The other annual costs were estimated at €20 per m² for cleaning, €25 per m² for energy, and €40 per m² for maintenance.

Patient-related material costs

Patient-related material costs included the costs of the experimental medication, heroin, and of medical material (e.g. medical supplies, disinfectants, syringes). The costs of heroin were estimated on the basis of an average dose of 500 mg per patient per day, 100% treatment compliance (i.e. three prescriptions a day during 365 days), and included the costs of both the medication and – for heroin inhaling patients – the sachets (see paragraph 2.8.3). On the basis of these assumptions (i.e. a total of 185 grams of heroin per patient per year, and 1,100 sachets per patient per year), the total cost of heroin amounted to approximately €1,750 per patient per year for inhaling patients. For injecting patients, the same assumptions were used with regard to dose and treatment compliance. In addition, a 10% loss of heroin medication at the end of each treatment day, due to the use of multidose vials (see paragraph 2.8.3), was incorporated in the calculations. The costs of syringes and other injection material were excluded from the calculations, because these were incorporated in the category "other medical supplies" (see Table 28). Based on these assumptions (i.e. a total of 205 grams of heroin per patient per year, and 68 multidose vials (for three grams of heroin each) per patient per year), the total costs of heroin amounted to approximately €2,000 per patient per year for injecting patients. In Table 28, the reported costs are based on an average of €1,800 per patient per year, given the larger number of inhaling patients than injecting patients in all treatment units. Hence, the estimated costs of heroin per treatment center per year amounted to €45,000 for a 25 patients unit, €90,000 for a 50 patients unit, and €135,000 for a 75 patients unit.

The costs of other medical material (syringes, disinfectants, etc. for the injectors, and aluminum foil, straws, etc. for the inhalors,) were estimated to amount to €800 per patient per year, resulting in estimated annual costs of € 20,000, € 40,000, and € 60,000 for a 25, 50, and 75 patients treatment center.

In total, the personnel, material, and patient-related material costs were estimated to amount to € 669,848 for a 25 patients unit, €980,856 for a 50 patients unit, and €1,148,013 for a 75 patients unit. Hence, the costs per patient per year amounted to €26,794 in a 25 patients unit, €19,617 in a 50 patients unit, and €15,307 in a 75 patients unit.

- The costs of medical prescription of heroin are dependent on the type of treatment implementation. The costs per patient per treatment year are estimated to amount to approximately € 27,000 in a unit with a capacity of 25 patients, € 20,000 in a unit with 50 patients, and € 15,000 in a unit with 75 patients.
- In the present trials, most treatment units were able to accommodate 50-75 patients per day.

PART V

CONCLUSIONS AND RECOMMENDATIONS

Chapter 12

Conclusions

In this chapter, the main conclusions of the study are summarized and discussed. The conclusions are based on the data of the trials presented in the preceding chapters, i.e. two randomized controlled trials comparing the outcomes of a 12 months treatment, based on the medical prescription of oral methadone plus injectable or inhalable heroin with a 12 months treatment, based on the medical prescription of oral methadone alone. The aims of the study were to test the effectiveness and safety of co-prescribed heroin in a population of chronic, treatment-resistant and methadone treated heroin dependent patients, and the effects of a planned discontinuation of the medically co-prescribed heroin in this population.

Conclusion 1.

The study was conducted and analyzed successfully.

This conclusion is meant to underscore the fact that the data presented in the preceding chapters are the result of a successful recruitment process, methodologically sound study procedures and statistically robust analysis strategies.

The success of the recruitment process is illustrated by the number of patients included in the study (injecting $n=174$, divided over two study-arms; inhaling: $n=375$, divided over three study-arms), the high percentage of eligible patients randomized and included in the intention-to-treat population ($>85\%$), and the chronic, treatment-resistant heroin dependency in the study population (mean age 39 years; mean duration of heroin use 16 years; mean duration of methadone use 12 years; high levels of physical, mental and social dysfunctioning). A large percentage ($>90\%$) of the study population was involved in heavy cocaine use for many years. Cocaine in this population was either inhaled (cocaine base) or injected and only rarely snorted. Together, these results show that it was possible to recruit a sufficient number of patients from the target population.

It should be noted here, that we were not able to recruit enough patients with heroin injection as their predominant route of administration for a trial with three treatment arms. In the last decade, intravenous drug use has become infrequent (approximately 15%), and an increasing part of the drug using population has switched to inhalation of drugs.

The methodological quality of the study is illustrated by the successful randomization of patients, and the high adherence to all follow-up assessments. The randomization procedure was effectively conducted by a contract research organization, which operated independent of the treatment staff and research team. The randomization resulted in treatment groups that were similar on all baseline characteristics. Adherence amounted to 91% in the 12 months methadone alone treatment group (A), 96% in the 12 months co-prescribed heroin group (B), and 94% in the 6 months co-prescribed heroin group (C) for the main outcome assessment 12 months after randomization. Together, these achievements rule out selection bias as a potential threat to the internal validity of the findings.

However, information bias cannot be fully excluded. For reasons given in chapter 3 of this report it was not possible to have a double or single blind design. In addition, the outcome

parameters were all based on self-report. However, the research literature indicates that self-report data collected by researchers is generally truthful, reliable and valid provided that confidentiality is ensured and that no sanctions are connected to the content of the answers (e.g. Rounsaville, 1993). In the current study, data for all major outcome parameters were collected by research assistants who were independent of the treatment staff and who were extensively trained in the handling of the assessment instruments. In addition, the validation of self-report data on police charges against police records and the validation of self-reported illegal cocaine use against urinalysis data showed that the self-report data in this study corresponded rather well with the objective assessments. There was no systematic underreporting of police charges. There was, however, some systematic underreporting of cocaine use. Moreover, in the inhalable trial, underreporting of cocaine use in the experimental condition (B) was significantly higher than in the control condition (A).

In order to investigate the influence of information bias due to differential underreporting of illegal drug use on the primary outcome of the study, a supplementary analysis was performed after removal of the illegal drug use component from the primary outcome index. The results of this analysis were similar to the ones obtained with the standard primary outcome index, indicating that differential underreporting cannot account for the observed positive effects of the medically prescribed heroin. Together, these procedures, observations and supplementary analyses seem to rule out information bias as a serious threat to the internal validity of the study.

A final methodological issue pertains to the difference in treatment settings in the different treatment conditions. Methadone prescription and dispensing took place in existing treatment locations with an existing treatment staff, whereas the combined prescription of methadone and heroin took place in newly established locations with specially recruited staff members. As a consequence, it cannot be entirely ruled out that the differences in location and treatment staff are partly responsible for the differences in response between the experimental and the control condition. An important aspect in this respect is the potential difference in motivation of staff members between the different treatment locations, with higher levels of enthusiasm among the staff members in the heroin dispensing units. It is, however, to be expected that this initial difference in enthusiasm will disappear with time. In an analysis comparing the effect sizes between the first recruitment period (start 1998) and second recruitment period (start 2000) in Amsterdam and Rotterdam, no differences were found, indicating that "Honeymoon" or "Hawthorn" effects cannot account for the observed differences in response between the experimental and the control condition.

In the current study, different statistical strategies were applied in order to test the robustness of the findings. In order to account for missing data, the standard LOCF-procedure and a worst-case scenario were applied. In addition, both an intention-to-treat and a completers analysis were conducted. Different variations of the main outcome parameter were used in order to test the stability of the findings across outcome parameters. The fact that the findings of these different analyses pointed in the same direction is an indication for the validity of the outcome of the current study.

Month 12 treatment completion rates were quite high in both conditions, but somewhat higher in the control conditions (86%) than in the experimental conditions (70%). The latter percentage is identical to the percentage of month 12 treatment completion rates in the large-scale Swiss study on the medical prescription of heroin (Rehm et al., 2001).

In the present study, there were several reasons for non-completion in the experimental conditions. Some patients never entered the experimental treatment (7%). Other patients were removed from the program as a result of repeated violations of the house rules or were not able to

visit the program anymore due to incarceration (11%). Finally, some patients decided to leave the program voluntarily (12%). Many of these patients stayed in or returned to their methadone maintenance program. In the control condition, on the other hand, patients had no alternative, because methadone maintenance treatment was already their last treatment option. The difference in treatment completion rates between the experimental and the control conditions should be judged against this background.

Conclusion 2.

Supervised co-prescription of heroin to chronic, treatment-resistant heroin dependent and methadone treated patients is more effective than the continuation of methadone alone.

The main finding of the study is, that methadone plus heroin treatment was more effective than methadone alone treatment in a population of chronic, treatment-resistant heroin dependent patients treated with methadone, irrespective of route of administration, population in the analysis (intention-to-treat; treatment completers), outcome parameter 12 months after randomization (response on the multi-domain outcome index; sustained response on the multi-domain outcome index; no longer meeting inclusion thresholds for the trial), and study site. On the main outcome parameter, the effect size amounted to 25% difference in response between the experimental and control group among injectors (OR=2.99) and to 23% difference in response among inhalers (OR=2.77). In a population of chronic, treatment-resistant patients, a difference in treatment response of more than 20% is generally regarded as quite substantial. No significant differences in effect size were observed between the month 10 and month 12 outcome analyses, indicating that anticipation effects in the experimental condition during the month 12 assessment can not be held responsible for the observed effects after 12 months. The data indicate that similar positive effects were observed across the Netherlands, and that both injectors and inhalers can benefit from this treatment option.

The CCBH, therefore, concludes that a consistent treatment effect was observed in both trials at all sites, and that this effect has to be attributed to differences in treatment and/or treatment context, i.e. methadone plus heroin, dispensed in newly established treatment units by newly recruited nurses 0-21 times per week versus methadone alone, dispensed in existing treatment units by already available nurses 2-7 times per week. It is obvious that the co-prescription of heroin involved more contacts between patients and treatment staff, and a certain structure of the day related to the opening hours of the heroin-dispensing unit. These behavioral components of the experimental treatment cannot be separated from the pharmacological effects of the co-prescribed heroin. Moreover, it should be emphasized that many of the patients in the control condition obtain similar amounts of heroin from the illegal market. It is, therefore, likely that the observed effects of the co-prescription of heroin are closely associated with the behavioral changes connected with and resulting from the medical co-prescription of heroin; behavioral changes that could not be induced in this chronic, treatment-resistant population by the prescription of methadone alone. It should be noted that this effect does not seem to be the exclusive result of the initial enthusiasm of the newly recruited treatment staff because – as already mentioned – the magnitude of the treatment effects in consecutive patient cohorts did not decrease between the first and second cohort.

A remaining issue for discussion is the relatively high response rate at month 12 in the control groups (32% among injectors; 25% among inhalers), i.e. in chronic, treatment-resistant

methadone patients who continued their methadone maintenance treatment which was not effective prior to the trials. Before discussing potential reasons for these relatively high response rates in the control groups, one needs to consider the fact that response in the control groups was generally less comprehensive, with relatively few multi-domain responders. Moreover, only a small percentage of the patients in the control condition improved to such an extent that they did not meet any of the inclusion thresholds anymore at month 12 (injectors: 13%; inhalers: 9%). In addition, the percentage of sustained responders turned out to be rather low in the control condition (injectors: 18%; inhalers: 9%), indicating that stable improvements were relatively rare in the control condition.

Possible reasons for the response in the control groups are: participation in a study with frequent assessments, return to the average level of functioning in a population selected for current malfunctioning, and the choice of the response criterion. The effect of different definitions of response has been discussed already, and seems to be at least partly responsible for the observed "placebo effect". The effect of frequent assessments on response in the control condition is probably rather small given the limited intensity of these assessments (4-6 hours in a 12 months period). The selection of a population that is highly dysfunctional at study entrance might have a sizable effect on the occurrence of response in the control group. In the current study, however, the relative contribution of these different mechanisms cannot be estimated. Based on these considerations, it is concluded that the percentage of stable and comprehensive responses in the control condition was rather limited and that the study population was indeed treatment-resistant.

Conclusion 3.

Supervised co-prescription of heroin to chronic, treatment-resistant heroin dependent and methadone treated patients yields clinically relevant health benefits.

The results of both trials showed that the supervised co-prescription of heroin to chronic, treatment-resistant methadone patients lead to improvements in all health outcome domains: physical health, mental status and social functioning. The experimental treatment with methadone plus heroin did not only yield more responders than the control treatment with methadone alone, but also yielded more multi-domain responders, indicating a more comprehensive response in the experimental treatment groups. In addition, relatively high rates of multi-domain responders implies clinically relevant improvements in at least one medical outcome domain (physical health or mental status).

The clinical relevance of the findings of the current study is illustrated by the magnitude of the improvements in the different outcome domains among treatment responders in the experimental condition. As a group, these responders showed considerable improvements in physical health and mental status, with mean MAP-HSS and SCL-90 scores at the month 12 assessment, which were very similar to the mean scores in general population samples. In addition, the responders showed strong reductions in illegal activities, modest improvements in social integration, and modest reductions in cocaine use. In this context it should be noted, that considerable reductions in illegal activities were observed among the *non*-responders in the experimental condition as well, but – in contrast to the responders in the experimental group – this was not accompanied by other health benefits. Furthermore, the study showed that higher percentages of clinically relevant improvement in the experimental condition in some patients were not at the expense of higher percentages of clinically relevant deterioration in other patients.

Finally, the study showed that the percentage of patients no longer meeting any of the inclusion thresholds at month 12 in the experimental condition was significantly higher than in the control condition (injectors: 33% versus 13% (difference 20%; OR=3.3); inhalers: 27% versus 9% (difference 17%; OR=3.5). Similar results were obtained when sustained response was taken as an outcome criterion representing the stability of the obtained health improvements.

Together, these findings show that the effects of the co-prescription of heroin were not transient and restricted to improvements in the social domain or to reductions in criminality, but that the treatment effects were often quite stable and comprehensive, including clinically relevant improvements in the social as well as in the more narrowly defined health domains of physical health and mental status.

Conclusion 4.

The beneficial effects of supervised co-prescription of heroin are linked to the continuation of treatment.

Both trials showed that treatment effects of the co-prescription of heroin seemed to occur very early in the treatment process, i.e. within the first two months of treatment. At the same time, the data showed an increase in the percentage of responders and in the comprehensiveness of the effect are observed until the end of the randomized treatment phase of the study. Injectors seemed to respond somewhat quicker than inhalers. Among the injectors, the maximum effect in terms of the percentage of responders was almost reached at two months, but the quality of the response (percentage multi-domain responders; and percentage responders no longer meeting any of the inclusion thresholds) further improved during the course of the 12 months treatment. Among the inhalers, there was an increase in percentage responders over the full period of 12 months of treatment, and the relative contribution of multi-domain responders at month 12 was lower (32%) than among injectors (47%), suggesting that continued treatment in this population of inhalers could further improve the comprehensiveness of the treatment effect.

However, no significant differences were observed between an *intended* 12 months and *intended* six months treatment with methadone plus heroin among inhalers, neither in terms of response rate, nor in terms of the comprehensiveness of treatment response. This finding is consistent with observations in a randomized controlled trial among 444 drug dependent clients assigned to either three or six months treatment in a modified therapeutic community (McCusker et al., 1996). In this study, planned duration was also not associated with any of the outcome parameters, but a longer actual stay was associated with improvements in many of the outcome parameters such as mood and drug use at follow-up.

Finally, the current study showed that the majority (81-87%) of the treatment responders in the experimental condition deteriorated substantially following discontinuation of the heroin prescription. The severity of this deterioration is illustrated by the fact that the mean scores two months after discontinuation of the co-prescribed heroin had returned to the dysfunctional levels just before the start of the intervention.

Taken together, these findings suggest that the benefits of supervised co-prescription of heroin in chronic, treatment-resistant heroin dependent patients in the current study were linked to the continuation of treatment. It should be noted here that during the trials no differences between the treatment conditions in the offer of psychosocial interventions were allowed. A number of patients in the experimental condition already showed stable improvements early in the study, and

additional counseling, psychotherapy or rehabilitation activities with these patients might have been successful in preventing some of the serious deterioration after the planned discontinuation of the co-prescribed heroin. This possibility should be tested in future clinical observations or in specially designed studies.

Conclusion 5.

Supervised medical co-prescription of heroin is practicable with no excess of serious medical adverse events and with a limited number of controllable public order problems.

During the 12 months treatment period, 9.5% of the intention-to-treat population in both trials combined ($n=549$) experienced at least one SAE (58 SAEs: 47 hospital admissions, 8 life threatening events, 3 deaths). The three reported deaths resulted in a mortality rate of 5.5 per 1,000 person years (experimental conditions: 4.0 deaths per 1,000 person years; control conditions: 6.8 deaths per 1,000 person years). This rate is lower than the mortality rate of methadone maintenance patients in Amsterdam (14.2 per 1,000 person years) and also lower than the mortality rate in other populations of treated heroin addicts in Europe (ranging from Vienna, with 9.1 deaths per 1,000 person years to Barcelona, with 23.4 deaths per 1,000 person years) (Buster et al., 2002).

The incidence of SAEs was comparable in the experimental and the control conditions (12% versus 7-8%), and the difference between these conditions was not statistically significant. It should be noted that the 34 SAEs in the experimental condition occurred in the context of approximately 140,000 heroin dispensations. Moreover, only 10 SAEs (17%) were possibly related to the study medication, whereas only two SAEs (3.5%) were probably or definitely related to the study medication. None of the *fatal* SAEs was possibly, probably or definitely related to the co-prescribed heroin. As stated before, the results of the trials also show that clinically relevant improvements in the experimental condition in some patients were not at the expense of serious deterioration in other patients. A final observation relevant to the safety of the co-prescription of heroin pertains to the effects of discontinuation of the heroin treatment at the end of the experimental treatment period. Seven serious adverse events occurred after heroin discontinuation, but none of these events were related to (the discontinuation of) the co-prescribed heroin. In addition, no serious problems between patients and treatment staff were observed.

Two issues deserve some special attention here. The first issue concerns the observation of frequently occurring non-serious pulmonary problems among the study participants. It was hypothesized that the inhalation of heroin might contribute to the onset or deterioration of existing pulmonary problems. However, in a study among a mixed group of 120 injecting and inhaling heroin addicts recruited from a methadone maintenance program not related to the heroin trials, it was shown that most of these patients were very heavy tobacco smokers and that inhalation of heroin was not a strong contributor to the occurrence of objective or subjective pulmonary problems (Buster et al., 2000).

The second issue concerns the occurrence of contact dermatitis in staff members due to skin contact with small amounts of heroin base on the outside of the medication capsules. After the introduction of a so-called no-touch procedure and the replacement of capsules by sachets, the incidence of contact dermatitis decreased. In a supplementary study, the incidence and severity of contact dermatitis among treatment staff and patients is investigated with special attention for

delivery procedures (touch versus no-touch) and pharmaceutical packaging (capsules versus sachets).

Taken together, it seems justified to conclude that the supervised medical co-prescription of heroin to chronic heroin dependent methadone treated patients is possible without an excess of serious medical adverse events in participating patients and without serious health risks for the treatment staff.

The evaluation of the public order and controllability of the medical co-prescription of heroin was restricted to the intention-to-treat population in the experimental condition ($n=312$), and to the 12 months experimental treatment phase of all patients. In addition, an evaluation was performed during the first two months following the discontinuation of the co-prescribed heroin in those patients who received and completed the experimental treatment with co-prescribed heroin ($n=217$). As mentioned before, the number of adverse public order and controllability events should be considered in the context of approximately 140,000 heroin dispensations. During the first 12 months after randomization, a total of 191 events related to 109 patients were reported, indicating that approximately one in every three patients was responsible for at least one adverse public order event. The 191 events could be divided into (attempts of) smuggling ($n=50$), verbal aggression ($n=45$), physical aggression ($n=26$), (attempt of) illegal drug use or drug dealing ($n=38$), and breaking other house rules ($n=32$). Of these 191 adverse event, only 16 (8%) were rated as severe and possibly related to the study: (attempts of) smuggling ($n=1$), verbal aggression ($n=9$), physical aggression ($n=4$), (attempt of) illegal drug use or drug dealing ($n=1$), and breaking other house rules ($n=1$). In the two months following the discontinuation of medically co-prescribed heroin in 217 patients, only six adverse public order events were reported. Of these six events, three were considered to be severe and all severe events involved physical aggression.

In the course of the trials, a total of 28 adverse public order events could not be attributed to patients in one of the trials: complaints from neighborhood residents ($n=20$), small balance deficiencies on drug accountability forms ($n=6$), a missing front-door key ($n=1$), and money that disappeared from a locker ($n=1$). Only three of these 28 events were rated as severe.

In summary, these data indicate that medical prescription of heroin to chronic, treatment-resistant heroin dependent patients was not completely free of public order and controllability problems, but the data also show that most of the adverse public order events were not severe and could be solved inside the treatment unit without major problems for the treatment staff and without an increase in public nuisance for the neighborhood. It seems, therefore, justified to conclude that the supervised medical co-prescription of heroin to chronic heroin dependent patients did not create serious public order and controllability problems for the treatment staff or the neighborhood. At the same time, the data indicate that adequate levels of control and security are necessary and that these requirements should be taken into account in the planning of future treatment units.

Conclusion 6.

The costs of the medical prescription of heroin are dependent on the type of treatment implementation.

The current study shows that the costs for the medical co-prescription of heroin ranged from approximately € 15.000 per patient per treatment year in a unit with a capacity of 75 patients, through approximately € 20.000 per patient per treatment year in a unit with a capacity of 50

patients, to approximately €27.000 per patient per treatment year in a unit with a capacity of 25 patients. In our scientific investigation, most treatment units were able to accommodate between 50 and 75 patients per day. The costs for the production and distribution of the study medication (heroin base in sachets and heroin HCl in multi-dose vials) was approximately €2.000 per patient per treatment year, which is approximately 7-12% of the total treatment costs depending on the capacity of the treatment unit.

The more interesting questions, whether a medical prescription of heroin is expensive or not, and whether such a treatment provides value for money, cannot be answered yet. In order to make these judgments, detailed cost-effectiveness and thoughtful cost-benefit analyses have to be conducted. In the current study, data were collected to perform these analyses. At the time of writing this report, however, the results of these analyses were not yet available.

Chapter 13.

Recommendations

Based on the current study and the results from other studies regarding the effectiveness of the medical prescription of heroin to chronic heroin dependent patients (Uchtenhagen et al, 1997; Perneger et al., 1998; Rehm et al., 2001), the CCBH concludes that supervised medical co-prescription of heroin may constitute a useful supplement to an existing drug abuse treatment system, which should include a well-developed, state-of-the-art and accessible methadone maintenance treatment program. Based on this conclusion and the experiences during the Dutch trials, the CCBH has formulated five recommendations for the Netherlands.

Recommendation 1.

Introduce in the Netherlands supervised medical co-prescription of heroin to chronic, treatment-resistant heroin dependent and methadone treated patients as a last-resort pharmacotherapeutic option under stringent conditions.

The consistency of the results both within the Dutch trials and between the Dutch trials and the studies in Switzerland constitutes a sufficient basis for the development of a last-resort pharmacotherapeutic option of medically prescribed heroin to chronic, treatment-resistant heroin dependent and methadone treated patients. In order to secure the quality of such a treatment option, a series of actions have to be initiated.

One action will be the development of specific treatment guidelines and protocols. This important work can benefit from already existing requirements regarding a wide range of treatment and safety aspects available in the study manual of the Dutch trials (CCBH, 2000) and from the already existing treatment guidelines developed by order of the Swiss Federal Office of Public Health (Bundesamt für Gesundheit, 2000). It should be emphasized that medical co-prescription of heroin as a last-resort treatment option should consist of an integrated combination of a well developed, manualized pharmacological and a state-of-the-art psychosocial treatment offer, including counseling, psychotherapy and rehabilitation facilities. These integrated treatment programs may render even higher response rates than the interventions that were investigated in the current trials. In addition, such programs may reduce the probability of serious deterioration after discontinuation of the medical co-prescription of heroin and prevent the necessity of a long-lasting co-prescription of heroin in at least some of the chronic, treatment-resistant patients.

Another action will be the determination of the target population for medical co-prescription of heroin and the establishment of specific treatment allocation criteria. It is the view of the CCBH, that – based on the current study – no major changes should be made in the definition of the target population. However, certain inclusion and exclusion criteria relevant for the trials are not very suitable or not relevant for selection and treatment allocation (e.g. minimum age 25 years; current registration in a methadone maintenance program; short life time expectancy; full command of Dutch language; oral dose of methadone higher than 150 milligram per day). It should be emphasized that the operational definition of the criterion "treatment-resistance" might change with time and with the growing insight into the role of the different treatment components in treatment effectiveness in this population. Two examples of a growing insight for the Netherlands are the upcoming results of the randomized controlled trial regarding the effectiveness of

naltrexone supported detoxification with and without anesthesia, and the results of the randomized controlled trial regarding the effectiveness of high (>85 mg per day) versus low (<85 mg per day) dosages of methadone. If dosages above 85 mg of methadone per day turn out to be more effective than lower dosages, the definition of a treatment failure and treatment-resistance should be changed accordingly. In general, a valid diagnosis of treatment-resistance can only be made, if based on a negative treatment outcome in a state-of-the-art methadone maintenance program, which includes an integrated offer of high quality pharmacotherapy (e.g. adequate dosages of methadone), somatic and psychiatric treatments, and a generous offer of counseling, psychotherapy and rehabilitation activities (Woody et al, 1984; McLellan et al, 1993; Arndt et al., 1997). The existence of high quality methadone maintenance programs is, therefore, a *conditio sine qua non* for the development of programs for the medical co-prescription of heroin.

It is also important to note, that in the German study regarding the effectiveness of the medical prescription of heroin, two target populations are studied: (a) treatment-resistant methadone maintenance patients and (b) patients (currently) not in contact with the existing treatment system. With time, the findings regarding the latter target population may warrant some reconsideration of the target population for the medical co-prescription of heroin. However, a program of supervised co-prescription of heroin is only legitimate in the presence of an appealing, accessible, and state-of-the-art methadone maintenance program.

A third action will be to determine the medical and psychosocial preconditions. Supervised co-prescription of heroin to chronic, treatment-resistant heroin dependent patients is a complex treatment with potent pharmacological compounds in patients with high levels of somatic and psychiatric comorbidity. Therefore, a state-of-the-art treatment requires adequate medical and addiction training and an adequate medical staffing in terms of both physicians and nurses. In addition, adequate drug accountability has to be secured. Finally, adequate possibilities for counseling, psychotherapy and rehabilitation should be available.

The last action should be the consolidation of the production and distribution of pharmaceutical grade heroin base and heroin HCl for medical purposes. The production of injectable heroin HCl has been rather easy, but the development of an inhalable form has created some difficulties. The current packaging of inhalable heroin base in sachets has now been sufficiently researched and standardized. However, the available techniques are rather new and the production process is not generally available. Therefore, actions should be taken to consolidate this important prerequisite for the medical prescription of heroin.

Recommendation 2.

Decide about a last-resort pharmacotherapeutic option of supervised medical co-prescription of heroin at short notice.

There are several reasons why the decision to develop a last-resort treatment offer of medically co-prescribed heroin has to be made as soon as possible. Firstly, a quick decision is necessary for those patients who were treatment responders in one of the trials and who are currently receiving medically co-prescribed heroin in the context of compassionate use. A prompt decision is necessary in order to be able to continue or to taper and discontinue their treatment with heroin. Secondly, a quick decision is necessary in order to allow new patients to enter the existing heroin dispensing and treatment units. Although the trials were clearly effective, not all patients became responders and not all responders showed substantial deterioration in the two months following heroin treatment discontinuation. As a consequence, almost all treatment units have empty

treatment slots, and therefore the treatment costs per patient are relatively high. At the same time, new candidates for a treatment with medically co-prescribed heroin are waiting for this treatment option. Recruitment of new patients to fill the open treatment slots can solve both the ethical and the health economic problems. Thirdly, a quick decision is necessary to initiate the process leading to the registration of heroin base and heroin HCl as a medicinal product, which can be marketed as such. Finally, a quick decision is necessary in order to work out the details of the financing of the treatment offer with medically co-prescribed heroin.

Recommendation 3.

Apply for the registration of heroin as a medicinal product.

Heroin is not registered for the treatment of (chronic, treatment-resistant) heroin dependent patients in the Netherlands, and the production and distribution is still based on official permits related to the scientific investigation. In order to create prescription facilities to physicians operating in special heroin treatment units and to secure regular safety monitoring of this medicine, a registration of both heroin base and heroin HCl should be obtained from the registration authorities. In order to file a request for registration, some additional studies have to be conducted and an organization has to file the request and be responsible for the safety monitoring of the medicinal product following registration.

Recommendation 4.

Develop a quality assurance system.

This recommendation is just to emphasize the issues already mentioned in the first recommendation. Recently, the addiction treatment centers in the Netherlands have taken the lead in the development of an evidence based treatment offer to alcohol and drug dependent patients and patients with a diagnosis of pathological gambling. In this initiative, quality assurance is – among others – based on the selection of proven effective treatments, which are implemented together with explicit treatment allocation procedures in order to reach the appropriate target populations and with treatment protocols in order to assure adequate treatment provision. This process of quality assurance is essential in order to obtain the same positive results in the treatment with medically co-prescribed heroin as in the trials described in this report. Again, it should be emphasized that in the treatment of treatment-resistant heroin dependent patients with co-prescribed heroin, there are no formal limitations or restrictions with regard to the offer of psychosocial treatments anymore. Psychosocial interventions have been shown to be an essential component of effective methadone maintenance programs (Woody et al, 1984; McLellan et al, 1993; Arndt et al., 1997), and are also likely to contribute to the effectiveness of medically co-prescribed heroin. Initial improvements in functioning resulting from the co-prescription of heroin may create new opportunities for psychotherapy or rehabilitation with new perspective and new long-term treatment goals. Therefore, treatment guidelines should also be developed for this component of an integrated program of medically co-prescribed heroin. Finally, the quality assurance system should include some kind of long-term monitoring system with regular assessments of the quality of methadone maintenance and heroin co-prescription programs and the potential interactions of these programs in terms of participation, mutual referrals and outcomes.

Recommendation 5.

Implement the follow-up of the current study.

In order to disseminate the main findings of the randomized controlled trials and the studies directly related to these trials, the CCBH aims to publish these findings in national and international peer reviewed scientific journals. Professionals working in addiction treatment centers in the Netherlands should also learn about the main findings of these studies. In order to reach this audience, the CCBH will distribute an executive summary of this report in Dutch. In addition, publications will be prepared for practice magazines and textbooks.

The current study on the effectiveness of the medical prescription of heroin has resulted in an evaluation with a detailed description of the study population and a high follow-up rate 12 months after randomization. However, in most cases heroin dependence is a chronic disorder with a largely unknown course after the age of 40 and with almost no data on the long-term outcome in patients treated with medically co-prescribed heroin. A long-term naturalistic follow-up of the patients of the current study can provide new information on the long-term treatment retention and on the long-term course of both responders and non-responders in the current trials. Data from this follow-up study will be unique in a scientific sense and they will be very helpful in the planning of treatment slots and treatment requirements.

A large number of questions, requests and activities are expected to result from the publication of this report and from the publication of the study findings in national and international peer reviewed journals and practice magazines. In addition, questions will arise during the development of treatment allocation procedures and treatment protocols. The process of registration of heroin as a medicinal product will also result in a variety of new research questions, and many requests for clarification and for more detailed information. Finally, many of the research projects related to the main study (see Appendix 9) still have to be finalized and published.

It is, therefore, recommended that an independent organization with enough scientific expertise and detailed knowledge of the Dutch trials should be available during the process of publication of the findings of the main study and of the additional research projects, the process of registration of heroin as a medicinal product, and the process of treatment implementation in the addiction treatment system in the Netherlands.

PART VI
REFERENCES

References

- Alterman AI; McDermott PA; Cook TG; Cacciola JS; McKay JR; McLellan AT; Rutherford MJ (2000). Generalizability of the clinical dimensions of the Addiction Severity Index to nonopioid-dependent patients. *Psychol Addict Behav*, 14 (3): 287-294.
- American Psychiatric Association (1994). *Diagnostic and statistical manual of the mental disorders (fourth edition)*. Washington DC: American Psychiatric Association.
- Armitage P; Berry G (1987, 1990). *Statistical methods in medical research*. Oxford: Blackwell Scientific Publications.
- Arndt IO, McLellan AT, Metzger D, Woodey G, O'Brien C (1997). Substitution treatment and psychological services. In: Rihs-Middel, M (editor) *The medical prescription of narcotics: scientific foundations and practical experiences*. Bern, Hogrefe & Huber.
- Arrindel WA; Ettema H (1986). *SCL-90: Handleiding bij een multidimensionele psychopathologie indicator* [Manual for a multidimensional psychopathology indicator]. Lisse: Swets & Zeitlinger.
- Bammer G; Dobler-Mikola A; Flemming PM; Strang J; Uchtenhagen A (1999). The heroin prescribing debate: Integrating science and politics. *Science*, 284 (5418): 1277-1278.
- Barendregt C; Blanken P; Christiaanse R (1995). *De achterkant van drugsoverlast* [The other side of drug-related nuisance]. Rotterdam: Stichting Odyssee.
- Benschop A; Hendriks VM; Blanken P (1997). Te verwachten effecten van experimentele heroïne-verstrekking op de toedieningswijze en het gebruik van middelen [Anticipated effects of experimental prescription of heroin on self-administration pattern and concomitant use of other substances]. *Nederlands Tijdschrift voor Geneeskunde*, 141 (6): 292-295.
- Bieleman B; Snippe J; de Bie E (1995). *Drugs binnen de grenzen: Harddrugs en criminaliteit in Nederland, schattingen van de omvang* [Drugs within the borders: Hard drugs and criminality in the Netherlands, prevalence estimates]. Groningen, Rotterdam: Intraval.
- Blanken P; Hendriks VM; Pozzi G et al. (1994). *European Addiction Severity Index EuropASI: A guide to training and administering EuropASI interviews*. European Commission: COST-A6.
- Blanken P; Barendregt C; Hendriks VM (1996a). Het cocaïneprobleem onder gemarginaliseerde opiaatgebruikers [The cocaine problem among marginalized opiate users]. *Rotterdams Bulletin voor Verslavingsonderzoek*, 1 (2): 6-7.
- Blanken P; Barendregt C; Vollemans L; Hendriks VM (1996b). *Druggebruikers in Feijenoord* [Drug users in Feijenoord]. Rotterdam: Erasmus University Rotterdam/ Addiction Research Institute.
- Blanken P; Barendregt C; Zuidmulder L (1999). The evolution of crack and basing cocaine in the Rotterdam heroin scene. *Journal of Drug Issues*, 29 (3): 609-626.
- Bronner GM (1997). *Ontwikkeling rookvorm van heroïne: Eindrapport* [Development of an inhalable form of heroin: Final report]. Amsterdam: Apotheek Slotervaartziekenhuis.
- Brussel GHA van; Buster MCA; van der Woude DH (1996). *Dovend vuur: Jaarbericht drugsafdeling 1994-1995* [Annual report drug department 1994-1995]. Amsterdam: GG&GD.
- Brussel GHA van (1997a). The morphine distribution program in Amsterdam: Practical experiences. In: Rihs-Middel M (ed.). *The medical prescription of narcotics: Scientific foundations and practical experiences*, 160-166. Seattle: Hogrefe & Huber.
- Brussel GHA van (1997b). *Evaluatieverslag Palfium behandeling voor langdurig heroïneverslaafden* [Evaluation report Palfium treatment for long-term heroin addicts]. Amsterdam: GG&GD.
- Bundesamt für Gesundheit (2000). *Heroingestützte Behandlung. Richtlinien, Empfehlungen, Information*. [Heroin-assisted treatment. Guidelines, recommendations, information]. Bern: Bundesamt für Gesundheit.
- Buster MCA; van Brussel GHA (1996). *Selectie van druggebruikers voor heroïne experiment: Een vooronderzoek* [Selection of drug users for a heroin experiment: A preliminary study]. Amsterdam: GG&GD.
- Buster MCA; Reurs H (1997). *Methadonverstrekking in Amsterdam 1997* [Methadone distribution in Amsterdam 1997]. Centrale Methadon Registratie. Amsterdam: GG&GD.

- Buster MCA, Rook L, Brussel GHA van, Ree JM van, Brink W van den (2002). Chasing the dragon, related to the impaired lung function among heroin users? *Submitted for publication*.
- Buster M, Sperati A, Brink W van den (2002). Comparing mortality rates of opiate addicts in European cities: the need for an SMR with the European population of opiate addicts as the reference category. *Submitted for publication*.
- Central Bureau of Statistics (1999). Etniciteit [Ethnicity] (www.cbs.nl).
- Central Committee on the Treatment of Heroin Addicts (1997). *Investigating the medical prescription of heroin*. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Central Committee on the Treatment of Heroin Addicts (1999a). *Investigating the medical prescription of heroin. Second, revised edition*. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Central Committee on the Treatment of Heroin Addicts (1999b). *The effectiveness of medically prescribed heroin: Statistical analysis plan*. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Central Committee on the Treatment of Heroin Addicts (1999c). *Onderzoek naar heroïne op medisch voorschrift: Addendum bij de tweede druk* [Investigating the medical prescription of heroin: Addendum of the second, revised edition]. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Central Committee on the Treatment of Heroin Addicts (2000). *Manual 'Onderzoek naar heroïne op medisch voorschrift'* [Manual 'Study medical prescription of heroin']. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Central Committee on the Treatment of Heroin Addicts (2001). *Amendments to the Statistical analysis plan*. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Cohen J (1977). *Statistical power analysis for the behavioral sciences*. New York: Academic Press.
- Cook CE; Jeffcoat AR (1990). Pyrolytic degradation of heroin, phencyclidine, and cocaine: Identification of products and some observations on their metabolism. In: Chiang CN; Hawks RL (eds.). *Research findings on smoking of abused substances*, 97-120. NIDA Research Monograph 99. Baltimore MD: National Institute on Drug Abuse.
- Cramer EASM; Schippers GM (1994). *Zelfcontrole en ontwenning van harddrugs* [Self-control and getting off hard drugs]. Nijmegen: University of Nijmegen Research Group on Addictive Behaviors.
- Cruts AAN; Ouwehand AW; van de Wijngaard GF (1997). *Trendmatig: Trendcijfers verslavingszorg 1986-1996 en prognoses voor het jaar 2006 op basis van het Landelijke Alcohol en Drugs Informatie Systeem (Ladis)* [Trends in the addiction care 1986-1996 and prognoses for the year 2006 on the basis of the National Alcohol and Drugs Information System (Ladis)]. Houten: IVV.
- Darke S; Ward J; Zador D; Swift G (1991). A scale for estimating the health status of opioid users. *British Journal of Addiction*, 86: 1317-1322.
- Darke S; Hall W; Wodak A; Heather N; Ward J (1992). Development and validation of a multi-dimensional instrument for assessing outcome of treatment among opiate users: The Opiate Treatment Index. *British Journal of Addiction*, 87: 733-742.
- D'Aunno T; Vaughn TE (1992). Variations in methadone treatment practices: Results from a national study. *Journal of the American Medical Association*, 267: 253-257.
- Derks JTM (1984). De verstrekking van injecteerbare opiaten: Doelstelling van het morfine-verstrekkingsexperiment [The distribution of injectable opiates: Objectives of the morphine dispensing experiment]. *Tijdschrift voor Sociale Gezondheidszorg*, 12: 496-498.
- Derks JTM (1990). *Het Amsterdamse morfine-verstrekkingsexperiment* [The Amsterdam morphine dispensing experiment]. Doctoral dissertation. Utrecht: University of Utrecht.
- Derks JTM (1997). The dispensing of injectable morphine in Amsterdam: Experiences, results and implications for the Swiss project for the medical prescription of narcotics. In: Rihs-Middel M (ed.). *The medical prescription of narcotics: Scientific foundations and practical experiences*, 167-180. Seattle: Hogrefe & Huber.
- Derogatis LR (1983). SCL-90-R: *Administration, scoring and procedures. Manual II*. Clinical Psychometric Research. Towsen, MD.
- Driessen FMHM (1990). *Methadonverstrekking in Nederland* [Methadone dispensing in the Netherlands]. Utrecht: Bureau Driessen.

- Driessen FMHM (1992). *Methadoncliënten in Nederland* [Methadone clients in the Netherlands]. Utrecht: Bureau Driessen.
- Driessen FMHM; Völker BGM; Kregting J; Van der Lelij B (1999). *De ontwikkeling van de situatie van methadoncliënten gedurende twee jaar* [The developments in the situation of methadone clients in the course of two years]. Den Haag, Utrecht: Bureau Driessen.
- Driessen FMHM (2000). *Effecten van hoge doses methadon in Nederlandse methadon onderhoudsprogramma's: voorlopige resultaten* [Effects of high methadone doses in Dutch methadone maintenance programs: preliminary results]. Utrecht: Bureau Driessen.
- Drucker E; Vlahov D (1999). Controlled clinical evaluation of diacetyl morphine for treatment of intractable opiate dependence. *The Lancet*, 353 (9164): 1543-1544.
- Edwards G; Arif A; Hodgson R (1981). Nomenclature and classification of drug and alcohol related problems. *Bulletin of the World Health Organization*, 59: 225-242.
- Eland-Goossensen MA (1997). *Opiate addicts in and outside of treatment: Different populations?* Doctoral dissertation. Rotterdam: Erasmus University Rotterdam/ Addiction Research Institute.
- European College of Neuropsychopharmacology (1995). Clinical relevance of response and improvement in psychopharmacology: A statement from the European College of Neuropsychopharmacology. Report of consensus meeting. *European Neuropsychopharmacology*, 5: 531-533.
- Fleiss (1981). *Statistical methods for rates and proportions*. New York: Wiley.
- Franken IHA; Hendriks VM (2001). Screening and diagnosis of anxiety and mood disorders in substance abuse patients. *The American Journal on Addictions*, 10: 30-39.
- Gageldonk A van; De Zwart W; van der Stel J; Donker M (1997). *De Nederlandse verslavingszorg: Overzicht van de kennis over aanbod, vraag en effect* [The Dutch addiction care: Overview of the knowledge with regard to availability, demand, and effect]. Utrecht: Trimbos Instituut.
- Grönbladh L; Ohlund LS; Gunne LM (1990). Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand*, 82: 223-227.
- Grund J-PC; Blanken P (1993). *From chasing the dragon to chinezen: The diffusion of heroin smoking in the Netherlands*. Rotterdam: Erasmus University Rotterdam/ Addiction Research Institute.
- Hartnoll RL; Mitcheson MC; Battersby A (1980). Evaluation of heroin maintenance in a controlled trial. *Archives of General Psychiatry*, 37: 877-884.
- Health Council of the Netherlands: Committee on Pharmacological Interventions in Heroin Addicts (1995). *The prescription of heroin to heroin addicts*. The Hague: Health Council of the Netherlands; publication no. 1995/12E.
- Hendriks VM; Kaplan C; Van Limbeek J; Geerlings P (1989). The Addiction Severity Index: Reliability and validity in a Dutch addict population. *Journal of Substance Abuse Treatment*, 6: 133-141.
- Hendriks VM (1990a). Psychiatric disorders in a Dutch addict population: Rates and correlates of DSM-III diagnosis. *Journal of Consulting and Clinical Psychology*, 58 (2): 158-165.
- Hendriks VM (1990b). *Addiction and psychopathology: A multidimensional approach to clinical practice*. Doctoral dissertation. Rotterdam: Erasmus University Rotterdam/ Addiction Research Institute.
- Hendriks VM; Van den Brink W; Blanken P; Bosman I; Van Ree JM (2001). Heroin self-administration by means of 'chasing the dragon': Pharmacodynamics and bioavailability of inhaled heroin. *European Neuropsychopharmacology*, 11: 241-252.
- Hoekstra MJ; Derks J (1991). Verslaving, verslavingszorg en verslavingsbeleid in Nederland: Een overzicht. In: Derks J; Hoekstra MJ (eds.). *Verslavingszorg: Een vak apart* [Addiction, addiction care and addiction policy in the Netherlands: An overview. In: Derks J; Hoekstra MJ (eds.). *Addiction care: A special job*]. Utrecht: NcGv.
- Hser YI; Hoffman V; Grella CE; Anglin MD (2001). A 33-year follow-up of narcotic addicts. *Archives of General Psychiatry*, 58 (5): 503-508.
- Huizer H (1987). Analytical studies on illicit heroin. V. Efficacy of volatilization during heroin smoking. *Pharmaceutisch Weekblad, Scientific Edition*, 9: 203-211.
- International Conference on Harmonisation (1994). *International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use: Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. ICH Steering Committee.

- International Conference on Harmonisation (1996). *International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use: Guideline for Good Clinical Practice*. ICH Steering Committee.
- International Conference on Harmonisation (1998). *International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use: Statistical Principles for Clinical Trials: Note for Guidance on Statistical Principles for Clinical Trials*. ICH Steering Committee.
- International Conference on Harmonisation (2000). *International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use: Good Manufacturing Practice Guideline for Active Pharmaceutical Ingredients*. ICH Steering Committee.
- IVV (Stichting Informatievoorziening Verslavingszorg) (2000). *Kerncijfers verslavingszorg 1999: Landelijk Alcohol en Drugs Informatiesysteem* [Core figures addiction treatment 1999: National Alcohol and Drugs Information System]. Houten: IVV.
- Jongerius J; Hull H; Derks J (1994). *Hoe scoort de verslavingszorg* [How does the addiction care perform] Utrecht: NcGv.
- Kokkevi A; Hartgers C (1995). European adaptation of a multidimensional assessment instrument for drug and alcohol dependents. *European Addiction Research*, 1, 208-210.
- Korf DJ (1995). *Dutch treat: Formal control and illicit drug use in the Netherlands*. Amsterdam: Thesis Publishers.
- Korf DJ; Lettink D; Bouma H (1998). *Methadondosering in Nederland: Een exploratief onderzoek onder verstrekkers en cliënten naar hoge en lage doseringen methadon* [Methadone dosages in the Netherlands: An exploratory study among dispensers and clients into high and low dose levels of methadone]. Amsterdam: Bureau voor Onderzoek en Statistiek.
- Laar MW van; Van Ooyen-Houben M; Spruit IP (1995). *Fact sheet on hard drug policy: Opiates*. Utrecht: Netherlands Institute for Alcohol and Drugs.
- Langendam MW; van Brussel GH; Coutinho RA; van Ameijden EJ (2001). The impact of harm-reduction-based methadone treatment mortality among heroin users. *American Journal of Public Health*, 91 (5): 774-780.
- Lelij B van der; Driessen FMHM (1998). *Psychosociale hulpverlening voor de doelgroep van het heroïne-verstrekkingsexperiment* [Psychosocial treatment for the target population of the heroin trial]. Utrecht: Bureau Driessen.
- Marsden J; Gossop M; Stewart D; Best D; Farrell M; Lehmann P; Edwards C; Strang J (1998). The Maudsley Addiction Profile (MAP): A brief instrument for assessing treatment outcome. *Addiction*, 93 (12): 1857-1867.
- Martindale (1997). *The Extra Pharmacopoeia: Incorporating squire's companion, 27th edition*.
- McCusker J; Stoddard A; Frost R; Zorn M (1996). Planned versus actual duration of drug abuse treatment. Reconciling observational and experimental evidence. *Journal of Nervous and Mental Disease*, 148: 482-489.
- McLellan AT, Arndt IO, Metzger DS (1993). The effects of psychosocial services in substance abuse treatment. *JAMA*, 269: 1953-1959.
- McLellan AT; Kushner H; Peters F; Smith I; Corse SJ; Alterman AI (1992). The Addiction Severity Index ten years later. *Journal of Substance Abuse Treatment*, 9: 199-213.
- McLellan AT; Luborsky L; Cacciola J; Griffith J; McGahan P; O'Brien CP (1985). *Guide to the Addiction Severity Index: Background, administration, and field testing results* (NIDA Treatment Research Monograph Series). Rockville, MD: National Institute on Drug Abuse.
- Metrebian N; Shanahan W; Wells B; Stimson GV (1998). Feasibility of prescribing injectable heroin and methadone to opiate-dependent drug users: Associated health gains and harm reductions. *Medical Journal of Australia*, 168 (12): 590-591.
- Metrebian N (2000). *The history of medically prescribed heroin in the United Kingdom*. Presentation held at the conference The prescription of heroin and reduction of harm: European experiences. France: Paris: November 16, 2000.

- Ministry of Health, Welfare and Sports (1995). *Drugs policy in the Netherlands: Continuity and change*. Ministry of Health, Welfare and Sports, Ministry of Foreign Affairs, Ministry of Justice, Ministry of Internal Affairs. The Hague: SDU Uitgeverij.
- Ministry of Health, Welfare and Sports (1998). WMO: *De wet medisch-wetenschappelijk onderzoek met mensen* [WMO: The Dutch Law on medical-scientific research in humans]. Den Haag: Ministry of Health, Welfare, and Sports.
- Mitcheson M (1994). Drug clinics in the 1970's. In: Strang J; Gossop M (eds.). *Heroin addiction and drug policy: The British system*, 178-191. Oxford: Oxford University Press.
- National Safety Committee (1998). *Rapportage Landelijke Veiligheidscommissie* [Report of the National Safety Committee]. Utrecht: November 1998.
- National Committee on Public Order and Controllability (1998). *Rapportage Landelijke Commissie Beheersaspecten* [Report of the National Committee on Public Order and Controllability]. Utrecht: November 1998.
- NDM (Nationale Drug Monitor) (2001). *Jaarbericht NDM 2001* [Annual report NDM 2001]. Utrecht: Bureau NDM.
- Parino MW (Consensus Panel Chair) (1992). *State Methadone Maintenance Treatment Guidelines*. Rockville, Maryland: U.S. Department of Health and Human Services, Center for Substance Abuse Treatment.
- Perneger TV; Giner F; del Rio M; Mino A (1998). Randomized trial of heroin maintenance programme for addicts who fail in conventional drug treatments. *British Medical Journal*, 317: 13-18.
- Pocock SG (1983, 1995). *Clinical trials: A practical approach*. New York: Wiley.
- Prochaska JO; Diclemente CC (1983). Stages and processes of self-change and smoking: Towards a more integrative model of change. *Journal of Consulting and Clinical Psychology*, 51: 390-395.
- Rehm J; Gschwend P; Steffen T; Gutzwiller F; Dobler-Mikola A; Uchtenhagen A (2001). Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. *The Lancet*, 358: 1417-1420.
- Robins LN; Wing J; Wittchen HU et al. (1988). The Composite International Diagnostic Interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, 45: 1069-1077.
- Rounsaville BJ (1993). Rationale and guidelines for using comparable measures to evaluate substance abusers: an overview. In: Rounsaville BJ, Tims FM, Horton AM, Sowder BJ (eds). *Diagnostic source book on drug abuse research and treatment*. Rockville: U.S. Department of Health and Human Services.
- Schreuder RF; Broex VMF (1998). *Verkenning drugsbeleid in Nederland: Feiten, opinies en scenarios* [Exploration of drugs policy in the Netherlands: Facts, opinions and scenarios]. Zoetermeer: STG.
- Seidenberg A; Honegger U (1998). *Methadon, Heroin und andere Opiode*. Medizinisches Manual für die ambulante opioidgestützte Behandlung. Bern: Verlag Hans Huber.
- Strang J; Ruben S; Farrell M; Gossop M (1994). Prescribing heroin and other injectable drugs. In: Strang J; Gossop M (eds.). *Heroin addiction and drug policy: The British system*, 192-206. Oxford: Oxford University Press.
- Strang J; Sheridan J; Barber N (1996). Prescribing injectable and oral methadone to opiate addicts: results from the 1995 national postal survey of community pharmacies in England and Wales. *British Medical Journal*, 313: 270-272.
- Strang J; Griffiths P; Gossop M (1997). Heroin smoking by 'chasing the dragon': origins and history. *Addiction*, 92 (6): 673-683.
- Bundesamt für Gesundheit (2000). *Heroingestützte Behandlung. Richtlinien, Empfehlungen, Information*. [Heroin-assisted treatment. Guidelines, recommendations, information]. Bern: Bundesamt für Gesundheit.
- Toet J (1990). *Het RODIS nader bekeken* [The Rotterdam Drug Information System in detail]. Rotterdam: GGD.
- Toet J (1996). *Tabellenboek RODIS: De verslavingszorg in Rotterdam van 1991 tot 1995* [Tables RODIS: The addiction care in Rotterdam from 1991 to 1995]. Rotterdam: GGD.

- Uchtenhagen A; Gutzwiller F; Dobler-Mikola A; Blätter R (1996a). *Program for a medical prescription of narcotics: Interim report of the research representatives*. Zürich: Institut für Suchtforschung in Verbindung mit der Universität Zürich.
- Uchtenhagen A; Gutzwiller F; Dobler-Mikola A (1996b). *Versuche für eine ärztliche Verschreibung von Betäubungsmitteln: Zweiter Zwischenbericht der Forschungsbeauftragten*. Zürich: Institut für Suchtforschung in Verbindung mit der Universität Zürich.
- Uchtenhagen A; Gutzwiller F; Dobler-Mikola A (1997). *Versuche für eine ärztliche Verschreibung von Betäubungsmitteln: Abschlussbericht der Forschungsbeauftragten*. Zürich: Institut für Suchtforschung in Verbindung mit der Universität Zürich.
- Uchtenhagen A; Dobler-Mikola A; Steffen T; Gutzwiller F; Blätter R; Pfeifer S (1999). *Prescription of narcotics for heroin addicts: Main results of the Swiss national cohort study*. Karger: Basel.
- Ward J, Hall W, Mattick RP (1999). Role of maintenance treatment in opioid dependence. *The Lancet*, 352: 221-226.
- Wodak A (1998). Prescribing heroin: Nothing else to fear but fear itself? Illicit drug policy based on punitive measures has failed, and it is time to seek a health care approach. *The Medical Journal of Australia*, 168: 590-591.
- Woody GE, McLellan AT, Luborsky L (1984). Severity of psychiatric symptoms as a predictor of benefits from psychotherapy: the Veterans Administration-Penn Study. *American Journal of Psychiatry*, 141: 1172-1177.
- World Health Organization (1996). *Composite International Diagnostic Interview: Version 2.0*. Geneva: World Health Organization: Mental Health Division.
- World Health Organization (1999). *Report of the external panel on the evaluation of the Swiss scientific studies of medically prescribed narcotics to drug addicts*. Geneva: World Health Organization.
- Zador D (2001). Injectable opiate maintenance in the UK: Is it good clinical practice? *Addiction*, 96: 547-553.
- Zwart WM de; van Wamel AL (1998). *Jaarboek Verslaving 1997: Over gebruik en zorg in cijfers* [Annual report addiction 1997: Figures on use and treatment]. Houten: Bohn Stafleu van Loghum.

PART VII

APPENDICES

Appendix 1

Decision on the installation of the Central Committee on the Treatment of Heroin Addicts

Appendix 2

Decision on the re-installation of the Central Committee on the Treatment of Heroin Addicts

Appendix 3

Members of the Central Committee on the Treatment of Heroin Addicts, and Observers and advisors of the Central Committee on the Treatment of Heroin Addicts.

Members of the Central Committee on the Treatment of Heroin Addicts:

Prof. dr. J.M. van Ree, chair
Dr. B.J. van Zwieten-Boot, vice-chair
Prof. dr. H.F.L. Garretsen
Drs. E. Leuw
Dr. J. van Limbeek
Prof. dr. W.A. Nolen
Drs. E.A. Noorlander
Dr. A.C.A. Paalman (until April 1999)
Dr. P.J. Roos (since May 1999)
Prof. dr. G.M. Schippers

I.A. Huijsman, LL.M., secretary

Observers and advisors of the Central Committee on the Treatment of Heroin Addicts:

Drs. A.F.W. Kok
Dr. R.J.J. Ch. Lousberg
Drs. A.A.M. Vloemans
Dr. J. Wakelin

Appendix 4

Members of the National Research Board of the Central Committee on the Treatment of Heroin Addicts

Prof. dr. W. van den Brink, director
I.A. Huijsman, LL.M., study co-ordinator
Dr. V.M. Hendriks, senior researcher
Drs. P. Blanken, researcher
H.J.F. van de Giessen-Deutschman, secretary

Appendix 5

Members of the National Safety Committee, and Members of the National Committee on Public Order and Controllability

Members of the National Safety Committee:

Prof.dr. H. Wesseling, chair

Prof.dr. F. Zitman

Drs. P.J. Geerlings

Prof. R. van Strik

Dr. B.J. van Zwieten-Boot (observer on behalf of the CCBH)

Members of the National Committee on Public Order and Controllability:

Drs. H.G. Ouwerkerk, chairman

Drs. H.J. Albert (1998-2000)

N.J.A. van der Arend, LL.M. (2000-2001)

C.K. Bakker (2000-2001)

W. Boonstra, LL.M. (1998-2000)

T.P.L. Bot, LL.M. (1998-2001)

R. Houben (since 2001)

L.H. Erkelens (since 2001)

Drs. E. Leuw (observer on behalf of the CCBH)

Appendix 6

International Advisors

Dr. Gabriele Bammer
National Centre for Epidemiology and Population Health
The Australian National University
Canberra, Australia

Prof.dr. Michael Gossop
National Addiction Centre
The Maudsley / Institute of Psychiatry
London, United Kingdom

Prof.dr. Michael Krausz
Zentrum für Interdisziplinäre Suchtforschung
Universität Hamburg
Hamburg, Germany

Prof.dr. Mary Jeanne Kreek
Laboratory of the Biology of Addictive Diseases
The Rockefeller University
New York, USA

Prof.dr. Jean Pierre Lepine
Hôpital Fernand Widal
Paris, France

Prof.dr. Charles O'Brien
Department of Psychiatry
Treatment Research Centre
University of Pennsylvania
Philadelphia, USA

Prof.dr. Ulf Rydberg
Karolinska Institute
Neurotec / Psychiatry
Stockholm, Sweden

Appendix 7

Statement of the National Safety Committee

Appendix 8

Statement of the National Committee on Public Order and Controllability

Appendix 9

Research projects related to the study

Process of change during co-prescribed heroin treatment and its acceptance by the patients

In two of the six cities participating in the heroin trials, a total of approximately 45 participants of the main study were selected for a qualitative study into the course of the process of change during the 12 months period of heroin co-prescription, and the two months following the planned discontinuation of the heroin treatment at the end of the experimental study phase. With regard to the acceptance of the treatment by the patients, all patients in the main trials who had not started the co-prescribed heroin treatment or who had left treatment prematurely were approached for a qualitative interview. The results of this study will be disseminated in future reports/ articles.

Intensity and course of heroin craving among participants of the heroin trials

In two cities participating in the heroin trials, a parallel quantitative and qualitative study was conducted into the intensity and course of heroin craving among participants of the heroin trials. In the quantitative study, heroin craving was measured every two months, by means of a structured self-report craving questionnaire and a Visual Analog Scale (VAS). In the qualitative study, an open, focussed interview was held with a selection of "high cravers" and "low cravers" at various assessment-points during the heroin trials. The results of this study will be disseminated in future reports/ articles.

Pharmacodynamics and bioavailability of inhaled heroin

In a controlled clinical study, the bioavailability and pharmacodynamics of inhaled heroin were evaluated and compared between "chasing the dragon" and inhalation from a heating device, and at three dose-levels: 25, 50 and 100 mg heroin. Between the inhalation methods, no differences were detected on any of the physiological or behavioral measures. Subjectively, the participants had a strong preference for the method of chasing. Across the three dose-levels, heroin produced a dose-related increase in subjective drug-liking, body temperature and heart rate, and a dose-related decline in reaction time. Linearly dose-related differences were found in the amount of total morphine in urine, amounting to an average of 45% of the parent heroin base received (Hendriks et al., 2001).

Contact dermatitis

Against the background of contact dermatitis occurring among some staff members in heroin treatment units, due to skin contact with small amounts of heroin base on the outside of medication capsules, a supplementary study is conducted into the incidence and severity of contact dermatitis among treatment staff and patients. In this supplementary study, special

attention will be given to delivery procedures and pharmaceutical packaging. The results of this study will be disseminated in future reports/ articles.

Effects of varying the heroin dose-level among participants of the heroin trials

In a controlled clinical study, involving heroin injecting and heroin inhaling participants in phase III of the heroin trials, pharmacokinetic parameters were determined for heroin and its metabolites 6-mono-acetylmorphine, morphine and glucuronides. In addition, the pharmacodynamic (physiological, cognitive, and subjective) effects of a – double-blind – increase and decrease of the heroin dose-level were investigated, as well as the influence of methadone dose-level on the pharmacodynamic effects of heroin. The results of this study will be disseminated in future reports/ articles.

Population pharmacokinetics of diacetylmorphine

In this study among approximately 100 participants in phase III of the heroin trials, a population pharmacokinetic model of diacetylmorphine and its metabolites, and of methadone is developed. Inter-individual differences in pharmacokinetic parameters are investigated by incorporating various co-variables into the population pharmacokinetic model. These co-variables include – among others – gender, age, weight, ethnicity, route of heroin administration, renal function, liver function, co-medication, and alcohol and cocaine use. The results of this study will be disseminated in future reports/ articles.

Psychosocial treatment for the target population of the heroin trials

To investigate if extra places had to be created for additional treatment – if patients in the co-prescribed heroin condition would express an increased need for social care during the course of their heroin treatment – a pilot study was conducted prior to the start of the trials. In each city that was selected for participation in the heroin trials, the local addiction treatment program was requested to provide an overview of their addiction care services in terms of size, structure and type of psychosocial treatment offer available for the target population of the heroin trials. The pilot study indicated, that the amount and diversity of additional psychosocial treatment places was sufficient in all participating treatment programs to handle a possible increase in treatment need, so that waiting lists were not to be expected (Van der Lelij and Driessen, 1998).

Methadone dose-levels in the Netherlands

Prior to the start of the heroin trials, an exploratory study was conducted into the way methadone dose-levels were determined in methadone maintenance treatment programs in the Netherlands. To this end, dispensers, physicians and clients of methadone programs were interviewed in four cities that were candidate for participation in the heroin trials. Among others, this exploratory study indicated that the initiative to attempt to increase the methadone dose of a client was often taken by the physician, whereas such an increase was often rejected by the client to avoid a

feeling of "being addicted to methadone", or because higher methadone dose prevented him from experiencing the euphoric effects of heroin (Korf et al., 1998).

Pulmonary problems among heroin users

To investigate the occurrence of pulmonary problems among heroin users, a study was conducted in a mixed group of 120 injecting and inhaling heroin addicts recruited from a methadone maintenance program not related to the heroin trials. In the study, pulmonary problems were assessed on the basis of self-report, and by measuring the Forced Expiratory Volume (FEV1) by means of spirometry. The study indicated that most of the patients were very heavy tobacco smokers and that inhalation of heroin was not a strong contributor to the occurrence of objective or subjective pulmonary problems (Buster et al., 2000).

Lung function among participants of the heroin trials

A supplementary study was conducted to investigate the relationship between inhalation of heroin vapors by means of "chasing the dragon" and the occurrence of pulmonary problems among participants of the heroin trials. To this end, baseline and month 12 data were collected by means of spirometry on the lung function of participants in both the injectable heroin trial and the inhalable heroin trial, in two heroin treatment sites. The results of this study will be disseminated in future reports/ articles.

Pharmaceutical forms of diacetylmorphine

A study is conducted into the development and production of different pharmaceutical forms of diacetylmorphine. For the injectable heroin, the study focuses – among others – on the characterization of the heroin HCl, development of the freeze-drying process, and stability of the final product. For the inhalable heroin, the focus is on the characterization of the heroin base, the chemical characteristics of the powder mixture, development of the production process, and stability of the final product. The results of this study will be disseminated in future reports/ articles.

Cost-effectiveness of medical co-prescription of heroin

In the present report, an analysis was presented of the costs of co-prescribed heroin treatment in a 25, 50, and 75 patient treatment unit. In a supplementary study, a cost-effectiveness analysis of the heroin treatment will be conducted. This cost-effectiveness analysis will be based on data already collected in the context of the main study. The results of the cost-effectiveness analysis will be disseminated in future reports/ articles.

Appendix 10

Publications

- Central Committee on the Treatment of Heroin Addicts (1997). *Investigating the medical prescription of heroin. A randomized trial to evaluate the effectiveness of medically co-prescribed heroin and oral methadone, compared to oral methadone alone, in chronic, treatment-refractory heroin addicts*. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Central Committee on the Treatment of Heroin Addicts (1999). *Investigating the medical prescription of heroin. A randomized trial to evaluate the effectiveness of medically co-prescribed heroin and oral methadone, compared to oral methadone alone, in chronic, treatment-refractory heroin addicts. Second, revised edition*. Utrecht: Central Committee on the Treatment of Heroin Addicts.
- Hendriks VM; Van den Brink W; Blanken P; Van Ree JM (1999). Het heroïne-onderzoek: Opzet en stand van zaken. In: *Nieuwsbrief Steun- en Informatiepunt*, 6, april 1999.
- Hendriks VM; Van den Brink W; Blanken P; Bosman IJ; Van Ree JM (2000). 'Chasing the dragon': *Bioavailability and pharmacodynamic effects of inhaled heroin*. Utrecht: Centrale Commissie Behandeling Heroïneverslaafden.
- Hendriks VM; Van den Brink W; Blanken P; Bosman I; Van Ree JM (2001). Heroin self-administration by means of 'chasing the dragon': Pharmacodynamics and bioavailability of inhaled heroin. *European Neuropsychopharmacology*, 11: 241-252.
- Hendriks VM; Van den Brink W; Blanken P; Van Ree JM (2000). Heroïne op medisch voorschrift: achtergrond en opzet van het Nederlandse onderzoek naar de effectiviteit van behandeling met heroïne bij chronische, therapieresistente methadonpatiënten. *Handboek Verslaving*. Houten: Bohn Stafleu Van Loghum.
- Hendriks VM; Van den Brink W; Blanken P; Van Ree JM (2000). Heroïne op medisch voorschrift: achtergrond en opzet. *Epidemiologisch Bulletin*, 35 (1): 13-19.
- Hendriks VM; Van den Brink W; Blanken P; Van Ree JM (2000). Heroïne op medisch voorschrift in Nederland. *Neuropraxis*, 4 (6): 195-199.
- Krausz M; Uchtenhagen A; Van den Brink W (1999) Medizinisch indizierte Heroïnverschreibung in der Behandlung Drogenabhängiger: Klinische Versuche und Stand der Forschung in Europa. *Sucht*, 45, 171-186
- Van den Brink W; Hendriks VM; Van Ree JM (1999). Medical co-prescription of heroin to chronic, treatment-resistant methadone patients in the Netherlands. *Journal of Drug Issues*, 29 (3), 587-608.
- Van den Brink W; Van Ree JM; Hendriks V (1999). The medical co-prescription of heroin to chronic treatment-resistant heroin dependent patients in methadone maintenance treatment: A randomized clinical trial in The Netherlands. In: Westermann B., Bellmann, U. & Jellinek C. (Hrsg) *Heroinverschreibung: Wirkungen und Nebenwirkungen* (pp. 31-43). Weinheim, Deutscher Studien Verlag.
- Van den Brink W; Hendriks VM; Blanken P; Van Ree JM (2000). Het Nederlandse onderzoek naar de effectiviteit van heroïne op medisch voorschrift: achtergronden, onderzoeksopzet en eerste ervaringen. *Nederlands Tijdschrift voor Geneeskunde*, 144 (3), 108-112.
- Van den Brink W; Hendriks VM; Van Ree JM (2000). Artzliche Verschreibung von Heroin an chronische, therapieresistente methadonpatienten in den Niederlanden. *Suchttherapie*, 1: 71-82.
- Van den Brink, W (2000). Die Substitutionsbehandlung mit Heroin bei therapieresistenten opiat-abhängigen Patienten in Methadonbehandlungsprogrammen: Bericht über eine Niederländische Studie. *Sucht*, 46, 195-196.