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Dosage Regimes in the Prescription of Heroin and Other Narcotics to Chronic Opioid Addicts in Switzerland – Swiss National Cohort Study

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Key Words
Heroin prescription · Heroin · Diacetylmorphine · Morphine · Methadone · Addiction · Pharmacology · Dosage · Switzerland

Abstract
Aims: Within the guidelines of the research programme on medical prescription of narcotics for opioid addicts (PROVE), heroin, morphine, and methadone were prescribed to heavily opioid addicted individuals in Switzerland since 1994. This contribution analyses the course of dose levels during the treatment period. ***Design:*** Naturalistic description of consumed dosages per day and month. ***Setting and Participants:*** The study describes the dosages prescribed to all individuals who began outpatient treatment in the PROVE programme in Switzerland between 1994 and 1996. ***Measurements:*** Consumed amount of narcotics per day and the course of dosage of injectable heroin in different treatment regimes. ***Findings:*** Heroin was the most frequently prescribed narcotic. Of all consumption days, heroin had been applied in 77% as injection and in 9% in a smokeable form. The mean daily dosage was 474 mg for intravenous application and 993 mg for the smokeable form. Second most frequent was the prescription of oral methadone, in most cases in combination with heroin. The mean amount of daily consumption of oral methadone was 53 mg. There were dosage differences between treatment regimes. During the course of treatment the mean dosage for injectable heroin per day decreased significantly and, depending on the treatment regime, almost linearly. ***Conclusions:*** The significance of heroin dosages in heroin-assisted therapy for treatment outcome should be further explored, especially in the light of the markedly higher dosages in Switzerland compared to the UK. During the treatment period, dosages did not increase but generally decreased, indicating no further increase in tolerance.

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Introduction

Background and Swiss Drug Policy

In the 1980s and 1990s Switzerland experienced an increase in opiate users and, as a consequence, a marked increase in health and social problems. The onset of AIDS

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and the formation of an open drug scene raised public awareness of drug problems and public pressure was brought on policy makers to take appropriate action [1]. The Swiss government launched a comprehensive programme, the aims of which were as follows: to reduce the number of new drug consumers; to increase the number of addicts who become abstinent; to reduce opiate-associated health consequences and the social discrimination and stigmatisation of consumers and/or addicts, and to protect society against drug-related harm and fight against drug-related organised crime [2]. Different measures were implemented to reach these goals. The present strategy integrates prevention, abstinence treatment, harm reduction and repression in equal proportions [2, 3].

Treatment Options for Heroin Addicts

A wide variety of therapeutic protocols were established to treat opiate-dependent patients. In the early 1990s there were about 1,300 residential treatment places available for abstinence therapy for patients who had been detoxified earlier. Additionally, roughly 10,000 patients received methadone within the framework of maintenance therapies [2].

Even though Switzerland had a wide variety of drug treatment programmes, it became clear that there was no suitable therapeutic option for a group of severely addicted individuals and poly-drug users. Specifically, these were drug addicts in their thirties who had tried, to no avail, a variety of outpatient and inpatient treatments, including oral methadone programmes. To the general public the drug users were a particular burden because of their criminal activities to generate income, including prostitution. From a public health perspective this group of drug users was particularly important because they were at high risk of HIV infection or overdose. For these reasons the government decided in 1991 to launch a research programme to investigate whether these marginalised drug addicts could be integrated into another treatment programme that would lead to improved health conditions, social rehabilitation, and finally to abstinence [2].

This research programme on medical prescription of narcotics for opioid addicts (PROVE) began in 1994. Approval of the study was obtained from the Swiss Academy of Medical Sciences' supra-regional ethics committee. The intervention consisted of opioid maintenance treatment together with psychosocial and medical support. Heroin, morphine, and methadone were given as substitution agents. The medical prescription of narcotics for the opioid addicts programme was evaluated by social, medical, pharmacological, economical and criminological studies and showed positive results [4, 5]. Based on the positive experiences in Switzerland, a randomised controlled clinical trial has been conducted in the Netherlands (www.ccbh.nl) and various initiatives are under way in a few Western countries [6–8].

Dosages

Several studies [9–15] have pointed to the positive correlation between dosage and treatment success in methadone maintenance programmes. As an example, participants with a sufficiently high methadone dosage showed lower dropout rates and reduction in illegal side consumption when compared to participants with low methadone dosages. Publications on dosing in heroin maintenance programmes can be found far less often than publications on methadone substitution. Nevertheless, there are some studies by British researchers where heroin dosages had been described. It should be noted, however, that some of these studies have been conducted at an earlier stage of the heroin epidemic in Europe.

For instance, Gardner and Connell [16] reported on 107 opioid addicts who had been patients at a drug dependence clinic between March 1968 and February 1969. Based on addiction severity at treatment onset, patients were divided into 5 groups according to the doses consumed before therapy, with dosages ranging from 60 to 610 mg. Two patients with very high doses of 1,200 mg and 1,500 mg were included. During treatment patients were given either the same or, to a large degree, a lower dose than the one they were accustomed to. No mean dose was reported. In addition to heroin, oral methadone was prescribed, usually in doses between 10 and 20 mg.

In another study, Mitcheson [17] examined both heroin and methadone dosages in specialised treatment clinics between 1977 and 1984. Even though the number of patients increased during that time from 982 to 1,081, the number of patients given heroin-assisted treatment decreased from 239 to 82, as did the mean dosage of heroin. If heroin was the only substance given, the daily dose decreased from 250 mg in 1977 to 181 mg in 1984. When prescribed in combination with methadone, the daily dosage was 158 mg in 1977 and 130 mg in 1984.

In a controlled randomised study the acceptance of heroin for intravenous application was compared with oral methadone and the effects of these different treatment models were analysed [18]. Patients admitted to the programme were those who wished to continue substitution treatment with heroin but had been denied participation in other treatment programmes. Patients with psy-

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chotic diseases were excluded. Of the 96 heroin addicts who started the treatment programme, 52 were assigned to participate in a treatment programme with oral methadone and 44 were assigned to participate in a treatment programme with intravenous heroin. After 12 months, 29% of the patients in the methadone treatment programme and 74% of those in the heroin treatment programme were still participating in the trial. Daily dosages used in this programme were 10–120 mg oral methadone and 30–120 mg intravenous heroin.

Another British study examined the scope and practice of opioid prescriptions by physicians in the year 1995 [19]. For this purpose, data from a quarter of the 10,616 public pharmacies in England and Wales had been collected; 3,846 of the analysed opioid prescriptions related to 3,562 methadone prescriptions and 64 related to heroin prescriptions. The daily intravenous heroin dosages were 10–500 mg, with a mean dose of 175 mg.

In their cohort study, McCusker and Davies [20] compared the outcome in the heroin prescription cohort with that in methadone-prescribed patients. They found that after 6 months, the heroin-prescribed group manifested lower levels of psychopathology and showed a higher retention rate. The use of illicit drugs was comparable across most substances. Significantly more heroin-prescribed participants reported using illicit cocaine. Besides, both groups reported greater use of illicit heroin than at the time of the first interview. The mean dosage of opiates prescribed to the heroin prescription cohort was 253 mg pharmaceutical heroin in injectable and smokeable form (unfortunately, the authors did not differentiate between the two forms) at the first interview. The mean dose in the control group was 72 mg of oral methadone. Six months later, the mean prescribed dose increased to 295 mg in the heroin group and decreased to 60 mg in the methadone group. The authors explained the increase in illegal heroin use as a result of higher tolerance. The higher doses given in the course of treatment seemed to support this argument.

The most recent survey concerning heroin dosages also took place in England and was published in 1998 [21]. The study described the feasibility of treatment programmes for opioid addicts with injectable heroin and methadone. In this trial the daily dosages of both heroin and methadone were limited to 200 mg. Thirty-seven of the 58 participants (64%) chose intravenous heroin as medication, 21 (36%) chose intravenous methadone. Within the first 3 months of treatment, the average prescription for 37 patients was 181 mg of intravenous heroin per day; the 12-month average was 185 mg per day. Fifteen participants treated with intravenous heroin reported withdrawal symptoms during the night (41% of 37). They received additional oral methadone (on average 24 mg per day).

In sum, there is little knowledge with respect to heroin dosage in substitution treatment programmes for long-term opioid addicts with severe social and medical problems. The purpose of this current analysis is to provide data on heroin dosages prescribed in the Swiss PROVE programme. Some results from experimental sub-studies on dosage within PROVE have already been published [22–25]. This contribution analyses the course of dosage of all patients in a certain time period in the main study.

Participants and Methods

Samples

The present study evaluated daily records of all 1,151 patients who entered an outpatient treatment programme between 1 January 1994 and 30 June 1996 and who received heroin, methadone or morphine as part of their treatment. The research took place from 1 January 1994 to 31 December 1996. The shortest time someone participated in the PROVE programme was 1, the longest was 1,087 days; mean duration was 433 (SD = 281) days. Thirty percent of the sample were women and 70% were men. Mean age at entry was 30.8 (SD = 5.8) years. On average, patients had consumed heroin on a regular basis for 10.4 (SD = 5.2) years.

The evaluation of the course of dosage used data from the subsample of participants who stayed at least 18 months on the programme and who had not interrupted their treatment with intravenous heroin for more than 15 days per month due to imprisonment, hospitalisation, holidays or unauthorised absence. To be on the programme for 18 months or more, the patient had to have started the heroin-supported treatment programme before July 1995. Table 1 shows the characteristics of the overall cohort and the sample used for the 18-month evaluation. As a result of the large sample size and the overlapping membership of the same individuals in both groups, no statistical tests for significant differences were made.

Narcotics

During the research period (1994–1996), the physicians on duty could prescribe intravenous and smokeable heroin as well as intravenous and oral morphine and methadone. Originally, the design called for experimental studies comparing heroin-assisted treatment with other treatment regimes [4]. However, due to the low acceptance of alternative treatment options and the frequent, severe side effects of morphine [4, 22] (which had been one of the main comparison regimes planned), the study was changed into a naturalistic cohort design with a predominant prescription of heroin [4]. As a result of this change, after May 1995 there was a maximum of 800 treatment places available for heroin prescription of a total of 1,000 treatment places for all substances. All injectable narcotics had to be consumed under supervision at the treatment centre. All data of methadone dosages refer to the use of the racemate (a mixture of the *D*- and *L*-forms), which is common in Switzerland.

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Table 1. Comparison of the entry characteristics of the overall cohort (n = 1,151) and the sub-sample, for which the course of dosage has been evaluated (n = 139)

Parameter	Overall	Sub-sample (18 months)
Socio-demographic characteristics		
Sex	1,151	139
Male	800 (70%)	89 (64%)
Female	351 (30%)	50 (36%)
Age, years, mean ± SD	31 ± 5.8	31 ± 5.3
Social integration		
Living situation	1,133 [18]	139
With parents	125 (11%)	16 (11%)
As a lodger	216 (19%)	24 (17%)
In a rented flat/house	499 (44%)	67 (48%)
In an institution	148 (13%)	23 (7%)
Homeless	146 (13%)	9 (17%)
Employment status	1,116 [35]	138 [1]
Full or part-time	182 (16%)	17 (12%)
Temporary, pension, household	462 (42%)	55 (40%)
Without work	473 (42%)	66 (48%)
Addiction-specific characteristics		
Addicts	1,130 [20]	139
Duration of addiction		
mean ± SD, years	10.5 ± 5.5	10.3 ± 5.3
Daily consumers in the last 4 weeks prior to admission of[1]		
Alcohol	198 (18%)/1,112 [39]	29 (21%)/136 [3]
Benzodiazepine	276 (24%)/1,129 [22]	27 (20%)/134 [5]
Cannabis	333 (30%)/1,094 [57]	49 (36%)/135 [4]
Cocaine	335 (30%)/1,100 [51]	48 (35%)/136 [3]
Therapy-specific characteristics		
Heroin use	1,032	139
Heroin dose, mg, mean ± SD	474 ± 206	504 ± 203

Figures in square brackets denote missing values.
[1] Self-reported data.

Dosing Practices in Different Treatment Centres

Initially, treatment centres were free to choose their own dosage regime, but by 1996 guidelines and recommendations had been worked out. In 18 treatment centres three different main dosage regimes were initially established, with small differences between the treatment regimes, as outlined below.

Partly based on experiences with computerised dispensing of methadone, two centres, both opening at least three times a day, decided to work with a computerised dispensing modus for heroin. After the initial dosing and following a discussion between the treating physician and the patient, the patient could choose dosage and application form within a maximal daily dose (calculated on the basis of past dosages to the same patient) and an individualised, maximum single dose based on his/her opioid tolerance (regime 1). This system has been developed to allow the user to choose a dosage while providing a safety framework. The reasoning and detailed operationalisation has been described in detail elsewhere [26]. Overall, this regime resulted in the highest initial doses.

One treatment centre dispensed narcotics only twice a day (regime 2). In this regime, only the treating physician could determine dosages. There were no upper limits.

The remaining 15 treatment centres used dosage regime 3, which limited the maximum daily dose for injectable heroin to 800 mg. As in treatment regime 2, dosages were fixed and could only be changed by the responsible physician. Even though there was a maximum daily dosage in this regime, there were exceptions. All the 15 treatment centres were open at least 3 times a day.

Materials

For scientific purposes and security reasons as well as for narcotics control, each dose of opioid dispensed in the treatment centres was recorded in a data-processing system developed specifically for that purpose [26].

The evaluation of the treatment data was conducted at the Addiction Research Institute, Zurich (SPSS 6.1.1. for Macintosh and SYSTAT 8.0). Repeated analyses of variance were used to estimate

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Table 2. Overview of the prescribed substances of 1,151 participants 498,073 consumption days

Substance	Consumption days, %[1]	Dispenses per day[2]	Mean daily dose, mg[3]	SD, mg
Heroin i.v. (mono or comb.)	77	2.6	474	206
Heroin i.v. (mono)	49	2.8	492	205
Heroin smoked (mono or comb.)	9	2.2	993	755
Heroin smoked (mono)	2	3.8	1,856	483
Morphine i.v. (mono or comb.)	2	2.5	372	215
Morphine i.v. (mono)	1	2.8	391	232
Morphine p.o. (mono or comb.)	4	1.4	324	254
Morphine p.o. (mono)	1	2.0	574	256
Methadone i.v. (mono or comb.)	3	1.0	111	44
Methadone i.v. (mono)	3	1.0	109	43
Methadone p.o. (mono or comb.)	30	1.0	53	44
Methadone p.o. (mono)	5	1.0	98	39

Mono = Only 1 substance in 1 application form was consumed on a given day; comb. = combined consumption.

1 Due to multiple count, the sum adds up to more than 100%.

2 Mean per consumption day, not identical with the number of cigarettes or pills.

3 Mean daily dosage of the reported substance or application form.

Table 3. Amount of heroin consumption with respect to the different dosage regimes

	Regime 1 88,610 consumption days		Regime 2 92,252 consumption days		Regime 3 317,211 consumption days	
	consumption days, %	mean daily dosage, mg (SD)	consumption days, %	mean daily dosage, mg (SD)	consumption days, %	mean daily dosage, mg (SD)
Heroin i.v. (mono or comb.)	50	573 (277)	73	487 (190)	86	455 (191)
Heroin i.v. (mono only)	20	673 (302)	28	507 (207)	62	473 (184)

Consumption days = Days with heroin consumption/all possible days (all days in treatment); mean daily dosage = arithmetic mean of heroin consumption on consumption days.

changes over time. The within-subject factor were the different time points of each individual. In addition, dosage regime (all three described) was introduced as a between-subject factor.

Results

Daily Dosages

PROVE participants consumed narcotics on 92% of 498,073 patient days. The remaining 8% they were either in hospital, in prison or otherwise absent from the treatment centre. According to the treatment plan the most frequently consumed narcotic was heroin. It was injected on 77% of all consumption days and smoked on 9%. The mean daily dosage on days that the participant received heroin was 474 mg for intravenous and 993 mg for the smokeable application. The second most frequently consumed narcotic was oral methadone (30%), however, in most cases it was taken in combination with heroin.

Table 2 shows the mean amounts of daily consumption. It also shows that heroin and morphine were injected on average 3 times a day, whereas methadone was consumed only once a day (in agreement with the pharmacokinetic characteristics of the substances).

Table 3 shows differences of heroin prescriptions according to the dosage regimes.

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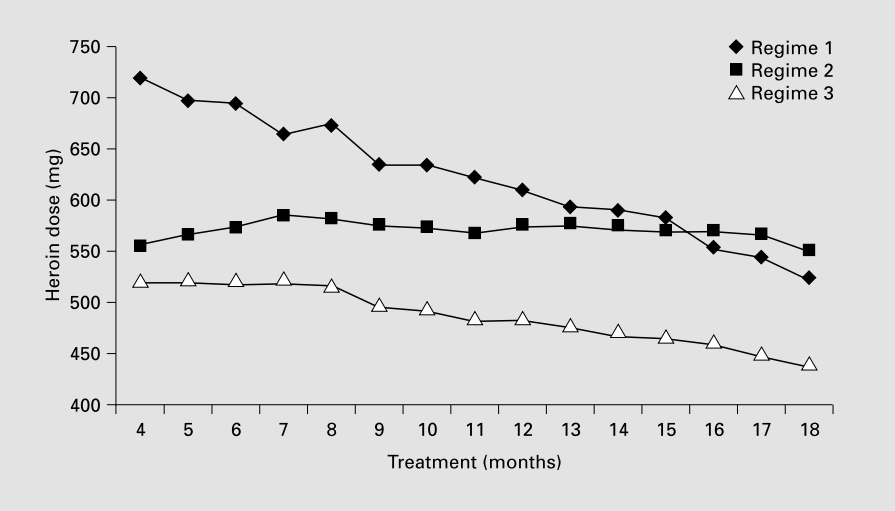

Fig. 1. Heroin dosages in the three treatment regimes. Least square estimates of heroin doses over time (regime 1: n = 22; regime 2: n = 33; regime 3: n = 84; total n = 139).

Table 4. Most frequent combinations (1,151 participants, 498,073 consumption days)

Combinations	Consumption days, %
Double combinations	
Heroin i.v., methadone p.o.	22
Heroin i.v., heroin smoked	4
Heroin i.v., morphine p.o.	2
Heroin smoked, morphine p.o.	1
Morphine i.v., methadone p.o.	1
Heroin smoked, methadon p.o.	1
Triple combinations	
Heroin i.v., heroin smoked, methadone p.o.	1

Substance and Application Combinations

Of interest was the finding on the number of combinations of narcotics or application forms that participants received. With around 22% of all treatment days, the combination of intravenous heroin and oral methadone was frequent. On around 4% of all consumption days, heroin was injected as well as smoked. In these cases, no further narcotics were used on site. Other combinations were rarely used. Table 4 shows the most frequent combinations used in PROVE.

Heroin Dosages during the Course of Treatment

Figure 1 shows the mean amount of injected heroin over the course of treatment (after the initial three months), separated by treatment regime. The first three months were excluded as they reflect the initial adjustment period where changes in dosage were quite frequent.

An inspection of the graph indicates three main effects. (1) An almost linear decline in heroin doses over time; (2) a main effect for treatment regime, with regime 1 dispensing higher mean doses than regime 2, and regime 2 dispensing higher doses than regime 3, and (3) an interaction effect, indicating different developments of dosing over time. The group under regime 1 showed the steepest decline over time, regime 2 showed no decline at all, but dosage remained stable, and regime 3 showed a decline, but not as steep as regime 1.

Repeated analyses of variance of the individual data (n = 139) revealed all these effects to be significant. The main effect for declining doses explains about 12% of the total variance within subjects ($F_{14, 1904} = 19.9$; $p < 0.001$). The mean decrease per month during the 15 months analysed was 5.9 mg of heroin.

Analyses including the intake of methadone showed that lower heroin dosages were not compensated with higher methadone dosages. An analysis of all opioids in methadone equivalents [25] revealed a highly significant decrease in consumption on all measures used ($F_{14, 1932} = 19.4$; $p < 0.001$; with Greenhouse-Geisser correction: $F_{3, 451} = 19.4$; $p < 0.001$; explained variance: 12.3%). In sum, the mean dose of heroin declined after initial adjustment of dosage without compensation with methadone.

There was also a main effect of treatment regime, i.e. the three treatment regimes differed ($F_{12, 136} = 7.78$; $p <$

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0.001). This effect explains about 11% of the variance between subjects.

Finally, there was a highly significant interaction between treatment regime and time. Regime 1 started out with the highest mean doses but also declined at the steepest rate. In the last months, regime 1 used lower heroin doses than regime 2. Regime 2 had an almost constant dosage level. Regime 3 started out lowest, but still declined, although at a lower rate than regime 1. Overall, the interaction effect accounted for about 6% of the within variance ($F_{28, 1904} = 4.9$; $p < 0.001$).

Discussion

In agreement with the treatment plan, intravenous heroin was the most frequently consumed narcotic. It was consumed exclusively on about one half of all treatment days. All other substances played only a minor role. With respect to mono consumption, the mean amount of injectable heroin used was 492 mg per day. In combination with other opioids, the mean daily amount of heroin consumption was reduced to 474 mg. According to the dosage regimes in the included treatment centres, differences could be noticed with respect to the level of dosage. In the long run, dosages seemed to converge although there were still differences at the end of the 15-month period of analysis. It is not clear whether the differences in decline between regime 1 and regime 3 are entirely due to the difference in initial dosages or whether there are other determining factors. However, it can be clearly stated that overall dosages declined, even when patients could choose their daily maintenance dosage themselves (regime 1).

The decline may be interpreted in terms of motivation of the patients to reduce their opioid dose in the long run. This would be in line with findings that the longer the participants stay on heroin-assisted treatment, the higher the chances they will enter abstinence treatment [5]. Another potential explanation for the dose reductions may be the fact that patients on tight maintenance doses of heroin do not experience the maximum flash and thus decrease dosage [25]. Whatever the reason, there was no continuous rise in heroin dosages in the long term, one of the potential threats of this type of treatment, as discussed above. Additionally, illegal drug use also decreased during participation in PROVE [4].

The daily dosages dispensed during PROVE were clearly higher than those that could be found in other studies. Five British studies used heroin dosages 2–4 times lower compared to the study presented here [17–21]. However, the samples may also be different with respect to length of opiate dependence, and different levels of somatic and psychiatric comorbidity make direct comparisons difficult. Thus questions of adequate heroin dosage for the treatment of drug addicts cannot be fully answered by the data presented here or by other currently available data. As the choice of the 'right' dosage is a central question in every substitution treatment programme, our contribution can only be seen as a basis for further studies that should try to solve the question of dosage and dosage regime using randomised controlled clinical trials.

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