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Injectable heroin substitution treatment for opioid dependency

See page 1417

As the American baseball sage Yogi Berra once observed, “It’s déjà vu all over again”. It took 50 years for medical practice to change from short-acting injectable opioids (morphine and heroin) to longer-acting oral methadone for maintenance treatment of narcotic addiction.^{1,2} And it has taken almost another 50 years to return to medically controlled prescription of injectable heroin for cases of chronic opioid dependency refractory to methadone and other usual treatments. So the wheel turns again.

The Swiss heroin trial, the large scale provision of a heroin-assisted substitution treatment, began in 1994 as part of a national comprehensive treatment and prevention strategy. Over 75% of all Swiss heroin users are enrolled in a drug-treatment programme, whereas in the USA only about 25% are. Given social and public-health imperatives at that time, the Swiss trial did not use a randomised design,³ unlike studies now underway in the Netherlands⁴ and planned for North America.⁵ But the Swiss trial is a carefully constructed and closely monitored observational study of an important cohort of patients. In this issue of *The Lancet*, Jürgen Rehm and colleagues report on the feasibility, safety, and efficacy of injectable heroin to treat patients with history of multiple failures on other forms of addiction treatment. These findings are an important addition to the data available about treating this most difficult group.

Rehm and colleagues assessed 1969 patients seen between Jan, 1994, and March, 1995. At 12 months the treatment retention rate in the programme was 70%. And 60% of the patients discharged went on to other treatments, such as the previously spurned methadone (37%) and, surprisingly, 22% went into an abstinence-oriented treatment. This finding should dispel fears that the availability of heroin undermines interest in drug-free treatment. Social behaviour and health were assessed in a subgroup of 237 patients who stayed at least 18 months in the programme: all measures improved within the first year. There was a sharp decline in illicit “addictive behaviour”—for example, daily use of street heroin and cocaine were down from 82% to 6% and 29% to 5–7%, respectively. Not surprisingly, these substantial declines were associated with a decrease in criminal activities, which was confirmed by independent review of judicial records.

Although these findings have by now been presented at many scientific meetings and other data on this cohort have been published in non-English European journals, in book form,⁶ and in several detailed and authoritative

reports,⁷ the principal findings of the Swiss trials are finally in a widely circulated English-language medical journal. But why now—almost 5 years after the end of the study?

One explanation is that the Swiss trials are the modern fulcrum of a great historical debate about substitution (narcotic maintenance) treatment of people dependent on opioids—a debate that has persisted within medicine and public health for over a century. In the UK, the rulings of the 1926 Rolleston Commission allowed general practitioners and psychiatrists to prescribe maintenance opioids as “humane” care for patients who could not shed their addiction. With many changes over the decades, physicians in the UK have continued to prescribe these drugs to a small number of patients—a few hundred at most.² By contrast, the early morphine maintenance programmes in the 1920s in the USA (Shreveport LA, Jacksonville FL, and New York, NY)¹ fell victim to the prohibitory fervour of that age, were publicly reviled, and were widely rejected as valid medical practice by the US Supreme Court. Soon they were shut down and, with the full support of the American Medical Association¹ the care of addicts was consigned to the tender mercies of law enforcement, where, by and large, it remains today.⁸

Something has to give. The effective medical treatment of drug addiction inevitably clashes with its demonisation and—more to the point—with the continued criminalisation of the drug user. The chorus of poorly informed criticism and misinformation⁹ that has greeted the Swiss heroin trials in the USA reveals the depth of this old conflict and underscores the importance of this report. As the biological sciences identify the mechanisms of neurotransmission and the specific brain structures that underpin drug actions, the ability to treat addiction (and soon, possibly, to predict and prevent it) will surely improve. As this occurs one would hope for some diminution of the therapeutic nihilism that has characterised the medical treatment of people with drug addictions for so long. The Swiss heroin trials, and the others now underway and in the planning stage, are milestones on this long journey.

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Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study

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Summary

Background Heroin-assisted substitution treatment for severely opioid-dependent drug users has been available in Switzerland since 1994. Our aim was to ascertain the feasibility, safety, and efficacy of this treatment.

Methods We did a cohort study in 21 community outpatient treatment centres. We assessed 1969 opioid-dependent drug users, who began heroin-assisted substitution treatment between January, 1994, and December, 2000, to ascertain admission and discharge patterns, and patient characteristics. We also followed up a subset of 237 patients who began treatment between Jan 1, 1994, and March 31, 1995, and who stayed with the programme for at least 18 months. We used questionnaires, interviews, and medical examinations done at entry and after 6, 12, and 18 months to assess somatic and mental health, social integration, and treatment outcomes.

Findings More than 70% (1378) of patients remained in treatment for more than a year. Treatment showed positive effects with respect to health and social outcomes. A long stay in treatment was related to a higher chance of starting abstinence-oriented therapy than a short stay.

Interpretation: Heroin-assisted substitution treatment might be an effective option for chronically addicted patients for whom other treatments have failed.

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See *Commentary page 1385*

Introduction

In Switzerland in the 1980s and early 1990s there was an increase in problems related to heroin use. These problems were partly caused by the easy availability of drugs and the negative public attitudes towards open drug scenes.¹ Drug use also aided the spread of infectious disease, resulting in increased health costs.² In response to the situation, public health authorities implemented various measures, which were integrated and combined into successive national programmes.³ The main aims of these initiatives were to reduce the number of drug consumers and addicts, to increase the number of addicts who become abstinent, to reduce opioid-associated health consequences and the social discrimination and stigmatisation of consumers and addicts, to protect society against drug-related harm, and to counter drug-related organised crime.⁴ Repression, prevention, treatment, and risk reduction measures remain the four corner-stones of the Swiss drug policy framework.⁵

Over the past 15 years the methods of treatment of drug addiction became effective, and a relatively high proportion of addicts were reached by the Swiss programmes compared with those in other countries.^{6,7} However, some addicts could not be helped with traditional abstinence-oriented and methadone-maintenance treatments.⁸ A Swiss research project was therefore established in 1994 to ascertain the efficacy of different prescription narcotics in the treatment of drug addiction. Soon after the project was established, however, its focus altered, and it became a cohort study on heroin-assisted substitution treatment.⁸ Here, we present an overview of the results of 6 years of heroin-assisted treatment in Switzerland. Our aim is to ascertain the feasibility, safety, and efficacy of injectable prescription heroin as a treatment for opioid addicts.

Methods

Study population

We assessed all patients admitted to 21 centres for heroin-assisted treatment⁸ between January, 1994, and December, 2000 (n=2166 cases corresponding to 1969 patients). The Swiss Academy of Medical Sciences' supraregional ethics committee approved the study, and the Swiss Federal Office of Public Health individually assessed every patient before they were admitted to a clinic. An independent group of experts supervised the study. All patients gave written informed consent.

Study protocol

All patients were given opioid-assisted substitution treatment, and received psychosocial counselling. They all had access to medical services. In addition to heroin, patients were given methadone as a replacement drug when needed. The mean daily dose of intravenous heroin administered was 474.0 mg (SD 206.1) with administration of an average 2.6 (SD 1.0) applications a day.⁹

We assessed outcome variables in a subgroup of 237 patients who entered the programme between Jan 1, 1994, and March 31, 1995, and who stayed for at least 18 months. 128 patients discharged before 18 months of treatment were excluded from analyses.⁸ A team of health-care professionals examined and interviewed patients when

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	Number	Men	Women	Patients in treatment in December, 2000
Patients admitted				
Total	1969	1418 (72%)	551 (28%)	..
1 admission	1788	1287 (72%)	501 (28%)	894 (50%)
2 admissions	165	119 (72%)	46 (28%)	84 (51%)
3 admissions	16	11 (69%)	5 (31%)	9 (56%)
Patients discharged				
Total	1071	760 (71%)	311 (29%)	..
1 discharge	974	692 (71%)	292 (30%)	78 (8%)
2 discharges	90	69 (77%)	21 (23%)	9 (10%)
3 discharges	7	3 (43%)	4 (57%)	..

Table 1: **Patients admitted and discharged from heroin-assisted treatment centres in Switzerland, 1994–2000**

they were first admitted to a clinic and after 6, 12, and 18 months. We obtained data on the use of narcotics and on the patients' social circumstances by use of questionnaires consistent with the European Addiction Severity Index and the Symptom Check List-90 rating scales. At discharge, we asked patients why they were leaving.

Statistical analyses

We based survival curves on Kaplan-Meier estimates, and did residual analyses on categorical variables. We used Cochran's Q test to ascertain the overall significance of outcome variables of the treatment subsample. To avoid potential bias we used last observation carried forward

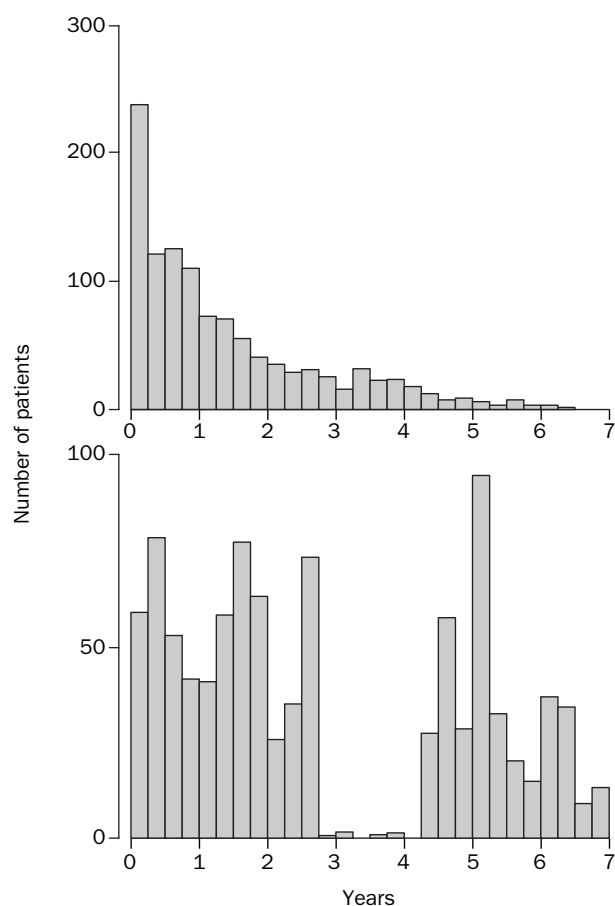


Figure 1: **Length of stay in years for patients who were (upper) and were not (lower) discharged from treatment**

The gap in the lower figure between 2.75 and 4.25 years reflects the stop in admissions to heroin-assisted treatment between July 1, 1996, and April 1, 1998, for administrative reasons.

	Patients		
	Discharges (n=1175)	Treatment remainders (n=991)	All (n=2166)
Characteristics			
Men	834 (71%)	723 (73%)	1557 (72%)
Age at treatment entry (mean [SD]) (years)*	31.1 (8.1)	32.0 (5.9)	31.5 (7.2)
Duration of heroin addiction before treatment entry (median [25th and 75th percentiles]) (years)†	10.0 (7.0–14.0)	10.0 (8.0–14.0)	10.0 (7.0–14.0)
Consumed cocaine on an almost daily or daily basis before treatment entry‡	411 (35%)	287 (29%)	715 (33%)
HIV-1 positive at treatment entry§	247 (21%)	129 (13%)	368 (17%)

Data unknown for *six, †249, ‡269, §290 patients.

Table 2: **Characteristics of patients**

where values were missing. Because the study was observational and had multiple related endpoints, significance values are provided only as an indication of a causal effect.¹⁰ Furthermore, we made no adjustments for multiple testing of effects, since our aim was to show effects of heroin-assisted treatment in different outcome categories rather than to formally and strictly test them.

Results

1969 patients addicted to opioids began heroin-assisted treatment. Table 1 shows the number of patients admitted and discharged from clinics by sex. 177 (9%) patients were admitted more than once. Neither sex was admitted more frequently than the other. Figure 1 shows that patients who were discharged were treated for a significantly shorter time than those who were not, and table 2 shows that patients who left the treatment centres were slightly younger, were more likely to have consumed cocaine on a daily or almost daily basis, and had higher rates of HIV-1 infection than those who remained in treatment. The proportion of men, and the duration of heroin dependence, however, did not affect discharge rates.

Figure 2 shows that treatment retention for heroin-assisted substitution treatment is relatively high, with 1693 (86%) patients continuing with the programme for at least 3 months, 1378 (70%) for at least a year, 985 (50%) for at

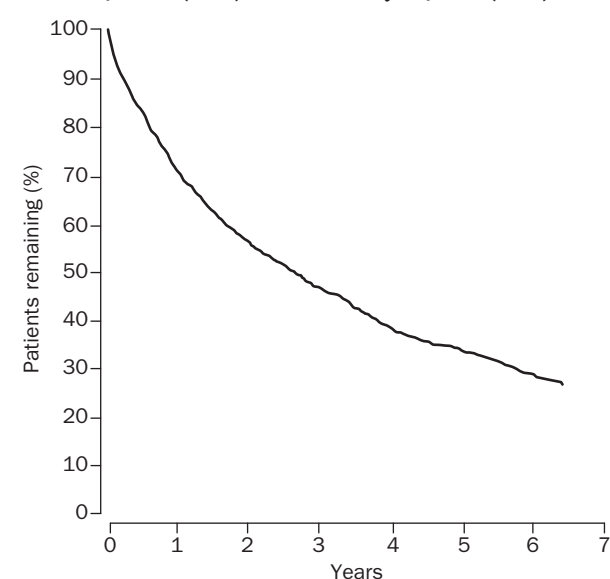


Figure 2: **Proportion of patients in treatment over time**

	Time to discharge				Total
	≤4 months	>4 months to 1 year	>1 year to 3 years	>3 years	
Reason for discharge					
Abstinence treatment	21 (9%)	74 (22%)	82 (27%)	47 (29%)	224 (22%)
Methadone-maintenance treatment	79 (35%)	128 (38%)	112 (37%)	60 (38%)	379 (37%)
Other treatment	3 (1%)	3 (1%)	14 (5%)	8 (5%)	28 (3%)
Death	4 (2%)	12 (4%)	10 (3%)	4 (3%)	30 (3%)
Violence or illegal trafficking	20 (9%)	32 (9%)	25 (8%)	10 (6%)	87 (8%)
Imprisonment	7 (3%)	15 (4%)	6 (2%)	6 (4%)	34 (3%)
Health reasons	12 (5%)	9 (3%)	12 (4%)	8 (5%)	41 (4%)
Treatment break off, refusal, lack of compliance	68 (30%)	51 (15%)	29 (9%)	6 (4%)	154 (15%)
Other	11 (5%)	15 (4%)	17 (6%)	11 (7%)	54 (5%)
Total	225	339	307	160	1031

Data are number of patients (column %) unless underwise indicated. Number of missing values=144.

Table 3: Reasons for discharge

	Admission	6 months	12 months	18 months	p*
Severe somatic problems†	52 (22%)	26 (12%)	29 (13%)	29 (13%)	0.0010
Severe mental problems‡	88 (37%)	44 (20%)	37 (17%)	43 (19%)	<0.0001
Body-mass index <20§	79 (35%)	46 (20%)	48 (21%)	55 (24%)	<0.0001

Data are number of patients (% of patients with valid data at admission).

*Based on last observation carried forward. Number of data missing at admission, and at 6, 12, and 18 month follow-up, respectively: †11, 19, 18, 47; ‡15, 14, 16, 46; §9, 17, 15, 43.

Table 4: Medical data for treatment cohort at time of admission and during follow-up (n=237)

least 2.5 years, and 669 (34%) for 5 years and longer. However, some patients drop out, and the peaks on figure 1 suggest that there are particular points at which patients are more likely to leave the programme than at others. Furthermore, there is a clear relation between length of stay and reasons for discharge ($p < 0.001$, table 3). 619 (60%) patients discharged left treatment to start another treatment, generally methadone maintenance or abstinence treatment. Less than 100 patients left treatment because of lapses in medication or lack of compliance. If lack of patient cooperation was a reason for discharge it was more likely to happen early on in treatment—ie, 15% of all discharges over the entire treatment period were due to lack of compliance, whereas, over the first 4 months non-compliant behaviour was the reason for 30% of discharges. On the other hand, switching to abstinence-based treatment or treatments other than methadone tended to happen later in heroin-assisted treatment: the longer the duration of treatment, the higher was the chance of switching to abstinence-based treatment. Thus, whereas only 9% of the discharges during the first

4 months switched to abstinence treatment, this proportion more than tripled for discharged patients after 3 years of treatment (29%). All other reasons for discharge were quite evenly distributed over time.

In the subset of patients that we followed for 18 months, the health of those with severe somatic or mental problems at the start of treatment improved, and those with a low body-mass index began to put on weight (table 4). Other health variables that were positively affected by heroin-assisted substitution treatment included skin infections, anxiety states, delusional disorders, and need for somatic and mental treatment (data not shown).^{11-14, 8} The patients' social situation also improved (table 5). The reduction in criminality shown in our study was corroborated by objective judicial data in an independent investigation.¹⁵ Finally, the proportion of patients needing daily or almost daily doses of street heroin, cocaine, or benzodiazepines was significantly reduced (table 6) after treatment.

Discussion

Heroin-assisted substitution programmes in Switzerland have a high rate of treatment retention, closely similar to that seen with methadone-maintenance treatment when it was first introduced.¹⁶⁻¹⁸ Furthermore, the treatment is often a success, with many of those discharged going on to either methadone-maintenance or abstinence therapy. Our findings suggest that patients who give up on their treatment after only a few months do so mostly because of difficulties they encounter with the rules and regulations imposed by clinics or because of lack of compliance. A high proportion of those leaving treatment at a later stage, however, manage to go into abstinence. This finding contradicts previous assumptions that long-term drug

	Admission	6 months	12 months	18 months	p*
Unstable housing situation	102 (43%)†	74 (31%)	57 (24%)	49 (21%)	<0.0001
Homeless	42 (18%)	19 (8%)	3 (1%)	3 (1%)	<0.0001
Unemployed	173 (73%)	113 (48%)	104 (44%)	106 (45%)	<0.0001
Receiving disability pension	51 (22%)	53 (22%)	60 (25%)	65 (27%)	0.001
Receiving welfare payments	149 (63%)	143 (60%)	145 (61%)	129 (54%)	0.035
No debts	61 (26%)‡	61 (26%)§	64 (27%)	77 (33%)¶	0.026
Illegal income	164 (69%)	40 (17%)	32 (14%)	25 (11%)	<0.0001
No visit to illegal drug scene last month	33 (14%)*	107 (46%)	120 (52%)††	137 (59%)‡‡	<0.0001

Data are number of patients (% of patients with valid data at admission). *Based on last observation carried forward. Number of data missing: †1; ‡4, §4, ¶6, ¶2, **4, ††1, ‡‡1.

Table 5: Socioeconomic status of treatment cohort at time of admission and during follow up (n=237)

	Admission	6 months	12 months	18 months	p*
Cocaine†‡	69 (29%)	16 (7%)	9 (4%)	12 (5%)	<0.0001
Street Heroin§	192 (82%)	22 (9%)	10 (4%)	13 (6%)	<0.0001
Benzodiazepine	44 (19%)	29 (12%)	35 (15%)	22 (9%)	0.0020

Data are number of patients (% of patients with valid data at admission). *Based on last observation carried forward. Number of data missing at admission, and at 6, 12, and 18 month follow up, respectively. †Self reported data, corrected by results of urinalysis: ‡2, 10, 13, 13; §2, 13, 21, 7; ||1, 12, 14, 15.

Table 6: Nearly daily consumption of psychoactive substances for treatment cohort at time of admission and during follow up (n=237)

substitution has a negative effect on motivation to abstinence,¹⁹ resulting in policies to exclusively allow short-term methadone-maintenance treatment.²⁰

In view of these results, a promising strategy might be to persuade addicts to persevere with heroin-assisted substitution programmes for at least 1 year before encouraging abstinence. To retain patients in their care, clinics might need to be more tolerant than at present with respect to rule breaking early in treatment. Treatment modules to deal with non-compliance during the first few months and reluctance to leave among those still receiving treatment after several years need to be researched and developed.

Our findings also suggest that heroin-assisted treatment programmes are cost-beneficial to Swiss society, since patients often show great improvements in medical and social variables, including criminality.^{21,22} In other words, the financial benefits from less criminality, less health-care use, and improvements in social variables are higher than the costs of treatment.

The WHO assessment of the first 4 years of the Swiss study on the prescription of narcotics stated that the results seen could be due to the substance, the extensive psychosocial counselling and care, or the combination of both.²³ Our study was not able to ascertain which of these factors, if any, affected treatment outcome. Furthermore, we cannot say whether or not heroin-assisted treatment is more effective and more cost-effective than well-designed methadone-maintenance treatment.²⁴ Ongoing Dutch²⁵ and German heroin prescription trials might answer these questions. Finally, one important question remains unanswered: which addicts profit the most from which types of treatment?²⁶

Although our results are encouraging, the role of heroin-assisted treatment should be considered within the overall spectrum of available treatments for opioid addiction.²⁷ More than 60% of opioid addicts in Switzerland are thought to receive treatment, with 2100 patients on inpatient abstinence-oriented treatments, more than 15 000 on methadone-maintenance treatment, and more than 1000 on heroin-assisted treatment.²⁸ In the Netherlands, where another large study²⁵ on heroin-assisted treatment is in progress, more than 70% of estimated opioid users are in treatment, with heroin-assisted treatment constituting only a small fraction of the overall system. Heroin-assisted treatment in both countries is provided as an addition to a well-developed and versatile treatment system, and any study results, should be considered against this background.

Contributors

Jürgen Rehm wrote the report and analysed the data. Patrick Gschwend designed the monitoring system of heroin-assisted treatment, collected data for analysis, and helped write the report. Thomas Steffen designed the follow-up section of the study. Anja Dobler-Mikola participated in overall design and implementation of the study. Felix Gutzwiller and Ambros Uchtenhagen designed the Swiss study on the prescription of narcotics; they also participated in and supervised this work and helped write the report.

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