Report of the External Panel on the Evaluation of the Swiss Scientific Studies of Medically Prescribed Narcotics to Drug Addicts

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The above-named evaluators represented themselves and not their governments or their places of employment. The views expressed in this report are those of the authors and do not reflect the position of the World Health Organization.

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1. Executive Summary

- This document presents the report of the external evaluation of the Swiss Scientific Studies of Medically Prescribed Narcotics to Drug Addicts that were conducted in three phases between 1995 and 1998. The Swiss Scientific Studies are hereinafter referred to as the Swiss studies.

- The Swiss studies were designed and initiated in the early 1990s as a response to difficult local problems of populations of addicts who appeared to be refractory to, and unable to engage with, the treatments then currently available.

- The Swiss Federal Office of Public Health (SFOPH) and the research team chose to conduct a direct observational study to assess the feasibility of heroin and other opioid prescription, to assess the suitability of the treatment method for heroin addicts who had failed at other treatments, and to assess the impact of such treatment on health and social outcomes.

- Unlike drug treatment systems in most other countries, the Swiss drug treatment system is highly resourced with high levels of drug-free residential and drug-free community treatment as well as high levels of oral methadone treatment.

- The Swiss studies had a very high degree of oversight involving local Canton authorities, federal authorities and researchers from the Institute for Social Research. Reports of all deaths were reviewed and none found to be related to the nature or quality of treatment. However, these reports have not been reviewed independently by the external evaluators.

- The questions and priorities for the Swiss authorities at the beginning of the project were different from those subsequently raised at an international level. The final study design was a prospective outcome study that was intended to measure the impact of the intervention but could not determine the efficacy of one intervention compared to other interventions.

- The Swiss studies were not able to examine whether improvements in health status or social functioning in the individuals treated were causally related to heroin prescription per se or a result of the impact of the overall treatment programme. Hence, from a rigorous methodological viewpoint, it was not possible to obtain internally valid results with respect to the research question of heroin prescription being causally responsible for improvements in health status or social functioning in the individuals treated.

- The external evaluation supported the study conclusions that: (1) it is medically feasible to provide an intravenous heroin treatment programme under highly controlled conditions where the prescribed drug is injected on site, in a manner that is safe, clinically responsible and acceptable to the community; (2) participants reported improvements in health and social functioning and a decrease in criminal behaviour and in reported use of illicit heroin.

- There is a need for continued scepticism about the specific benefits of one short acting opioid over others and there is a need for further studies to establish objectively the differences in the effect of these different opioids.

2. Background

The use of opioid substitution in the management of heroin and other forms of opioid dependence has been a controversial form of treatment that has been subject to extensive evaluation. According to the 30th Expert Committee on Drug Dependence Report (WHO 1998), the main objectives of treatment of opioid dependence are similar to other forms of substance use dependence treatment and they are:

- To reduce dependence on psychoactive substances
- To reduce morbidity and mortality caused by or associated with the use of psychoactive substances
- To ensure that users are able to maximise their physical, mental and social abilities and have access to services and opportunities and achieve full social integration
- To reduce costs and risks to society.

Additional objectives of treatment include a reduction in criminal and antisocial behaviour, a decrease in users' dependence on public (welfare) support, and an increase in productive legitimate activities. Since 1970 methadone maintenance treatment has grown to become the dominant form of opioid substitution treatment globally (WHO 1998, Farrell et al. 1996, EMCDDA 1998). A number of randomised controlled trials and numerous observational studies of methadone maintenance have demonstrated reductions in illicit opioid use, injecting and criminal behaviour and improvements in physical psychological and social well being (WHO 1998, Farrell et al 1994, Gossop et al 1998).

3. Introduction

Switzerland is a country of approximately seven million people that has an estimated 30,000 addicts who mainly use heroin and/or cocaine. It is estimated there are around 13,000 people in methadone treatment programmes. Therefore, the context in which these studies were undertaken is that of a country where there are significant rates of dependence and related problems, and high levels of treatment provision with oral substitution agents.

Switzerland is a party to the Single Convention of 1961. The Swiss Federal law on narcotic drugs of October 1951 (revised 1975) regulates the medical use of narcotic substances and prohibits production, trafficking, possession and consumption of drugs for non-medical purposes. Consequently, the use of heroin is restricted to the purposes of the Swiss studies[1] which were scientific studies designed to investigate the prescription of narcotics as a treatment approach for individuals who are drug dependent and with whom previous attempts with existing therapies had failed. Heroin requires exceptional authorisation by the Federal Office of Public Health for its prescription. Responsibility for the implementation of these laws lies within the Cantons, which are legally responsible for prosecution of offenders as well as the provision of treatment.

The Medical Prescription of Narcotics Project ([PROVE] acronym of Projekt zur ärztlichen Verschreibung von Betäubungsmittein), was sanctioned by the Swiss Government decree of 21 October 1992 and the research objectives and general research plan were described on 1 November 1993 (Uchtenhagen, et al. Ärztlich kontrollierte Verschreibung von Betäubungsmitteln: Grundlagen, Forschungsplan, erste Erfahrungen. Beitrag im Weiterbildungsseminar für Mitarbeiterinnen und Mitarbeiter in den Schweizerishchen Heroinabgabeversuchen, 1993). The project has since come to be called the Swiss studies and is hereafter referred to in this way in this report. Recruitment of patients started in 1994 and ended on 31 December 1996. The number of participants was initially restricted to a maximum of 700, a number that was increased to 1,000 in May 1995.

[1] Throughout this report the term **Swiss studies** is used to replace the original title SWISS STUDIES OF MEDICALLY PRESCRIBED NARCOTICS TO DRUG ADDICTS

A number of different stakeholders influenced the design, implementation and evaluation of the Swiss studies. These included policy makers, public health authorities, clinicians, social scientists, police, social welfare agencies, the general public and to some extent those who became clients of the various sites. The multiple interests of these stakeholders were reflected in the objectives of the overall programme and in the terms of reference for the evaluation teams.

3.1 External Evaluation of the Swiss Studies

In 1994 the International Narcotics Control Board (INCB) expressed concern over the Swiss Studies, particularly with regard to heroin prescription. INCB recommended in its 1994 report that "the Swiss Government should invite WHO to take part in the consideration of the medical and scientific aspects of the ongoing Swiss clinical trials." In response to this the WHO Substance Abuse Department (formerly Programme on Substance Abuse) undertook the co-ordination of an external and independent exercise, while an internal advisory group was formed, with representatives from various WHO and other UN programmes. The evaluation was divided in three phases.

In 1996 an extensive Phase I evaluation of the implementation of the trials, based on site visits and reviews of relevant material, was undertaken by a group of external evaluators. The group of sixteen international experts provided a written report on the design, ethics, and conduct of the trials noting the limitations of the design of the Swiss studies. The group was generally positive about all critical aspects of the trials. There is no evidence of any significant changes in the implementation process subsequent to that evaluation.

In Phase II, six international experts undertook site visits and interviewed sponsors and investigators of the project as part of a process evaluation, which was consolidated in a second report. The evaluation specifically addressed issues concerning measures designed to ensure the safety of study participants, especially in regard to self-injection and overdose. The group was satisfied that the clinical and research aspects of the studies were conducted with a high degree of professionalism, commitment, safety and scientific integrity.

In Phase III a group of ten experts with experience in clinical trials, public health, jurisprudence, epidemiology, treatment evaluation, quality assurance and national drug policy was invited by WHO to prepare individual written reports on the overall conduct and results of the Swiss studies. The following objectives were defined:

- To assess the scientific soundness and meaningfulness of the study results and conclusions as presented in the final report of the principal investigators of the Swiss studies (Uchtenhagen et al, 1998), with reference to its individual and public health impacts.
- To assess the overall conduct of the Swiss studies with reference to the justification and relevance (phase I of evaluation), the implementation (phase II), and results and conclusions (phase III), including a comparison of the outcomes of the studies with their original goals.
- To assess the Swiss studies in light of international research and policies on treatment approaches for opioid dependent populations.
- To develop recommendations from the Swiss studies for the future development of treatment and research policies for opioid dependent populations, both in the Swiss and the international context.

Following the conclusions of these phases, the group of evaluators met to prepare a consolidated and final report.

4. Commentary on study design, methods and analysis

4.1 Compliance with international ethical standards and Helsinki Declaration

The Ethics Committee of the Swiss Academy of Medical Sciences gave overall ethical approval for the trials. Local or regional Ethics Committees gave approval for local projects. Study physicians were required to sign a document indicating that they would bear in mind the guidelines of the Declaration of Helsinki.

Study participants were provided with detailed information about the study and the drugs that might be prescribed. They were also required to indicate informed consent by signing a detailed consent form. Participation in the study was voluntary and participants were clearly informed that they could withdraw at any time.

The confidentiality of data was assured by anonymity of all data sent to the Institute for Social Research, which conducted the analyses.

4.2 General methodological issues

A series of studies (the Swiss studies) were designed to assess the effect of intravenous heroin, intravenous morphine, intravenous methadone, alone or in combination with oral methadone on:

- the state of health of individuals treated,
- the social integration of treated individuals,
- the achievement of abstinence from drugs,
- the suitability of the treatment method for heroin addicts who have failed at previous attempts to quit,
- the efficacy of this treatment compared with those currently available, and
- the mode of action of the various narcotic substances.

Although the Swiss studies were originally designed as randomized controlled trials, they evolved into an observational open label type study in which the investigators, clinicians and participants were aware of the pharmacotherapies participants took. The investigators modified their approach as a result of a series of problems, including difficulties in recruiting individuals into the study, especially the non-heroin injectable component. As a consequence, the investigators adopted an approach which deviated from the standard of controlled clinical trials and which was similar to an action research approach.

The evaluation of the effects of prescribed opiates on health and drug use behaviours involved the use of data from a variety of sources (information from staff of treatment centres, structured interviews with patients and laboratory data). Several steps were taken to ensure the completeness and integrity of the data. The use of independent interviewers to conduct follow-up interviews reduced, to some extent, the chances of observer bias and increased the validity of self-reports.

The trials were analysed as a single group pre-post design (Cook & Campbell, 1979) by comparing different endpoints with the baseline using univariate analyses. This kind of analysis does not make full use of the data structure, and may lead to biased results because of the clustered nature of the data stemming from different, quite diverse treatment centres with different programmes. An alternative strategy of analysing the data would have been to include the treatment settings in all analyses, e.g. by making them covariates in the analyses or by using approaches like hierarchical linear models. The latter approach would have also enabled the estimation of the influence of characteristics of the treatment settings on the results.

Two provisional data analytical strategies for the non-randomised data were employed to examine the effects of heroin prescription on health status and social functioning:

- A one-group-pre-post-design comparing baseline characteristics of injectable heroin patients on admission with follow-up data after 6, 12 and 18 months, respectively (Killias & Rabasa, 1997; 1998; Uchtenhagen et al, 1998).
- A comparative analysis of the injectable heroin patients with samples of drug-free treatment and oral methadone patients from other studies that were not part of the PROVE trials (Uchtenhagen et al, 1998).

The results of these statistical analyses can be viewed as a first step. Only an analysis of the treatment intervention has been presented without a consideration of the relative contribution made by individual components of that care. Further analyses are needed to fully exploit the data available.

The Swiss studies were undertaken in a range of sites and despite the intensity of contact and range of additional interventions that were included no standardised protocol for these additional interventions was utilised. Given the complexity of the project this is understandable; however, it does increase the need to analyse the data by site to look for differences in performance across sites. Any differences between sites would lend weight to the possible contribution that the other treatment processes might have played in the overall outcome in addition to the pharmacotherapy.

The synthesis report also summarises a costing study conducted by health economists that encompassed the first seven sites involved in the study. Costs considered were: (1) direct (drugs and other medical supplies) and external medical services (laboratory tests) and (2) personnel. Evaluation of cost effectiveness was not possible using the current data and methods.

4.3 Consideration of specific methods used in the studies

4.3.1 Mode of action of various opioids

As originally conceived the Swiss studies involved three designs (double blind, non-blind randomisation and individual indication). These sought to assess the relative suitability of intravenous heroin, intravenous morphine, intravenous methadone and heroin impregnated cigarettes. The choice of opiate type substitute and the route of administration have been subject to minimal scientific enquiry. Whether one particular opiate has an advantage over another and whether particular routes of administration have an advantage for particular individuals remains a subject of substantial controversy.

The randomized controlled studies were to be three in number. The first was to compare intravenous heroin to intravenous morphine and intravenous methadone. The second was to compare intravenous heroin to intravenous morphine. A third double-blind controlled trial was to compare intravenous heroin to a waiting list control. The randomised studies proved to be difficult to conduct due to recruitment difficulties. Hence the randomised studies were limited to six weeks duration and were mainly used to determine effects and side effects of the substances. A comparison of medium and longer-term therapeutic effects was subsequently not possible.

Preliminary work was conducted to compare morphine, heroin and methadone. The synthesis report describes some small scale, clinical investigations of pharmacodynamics, pharmacokinetics and toxic effects of various forms of heroin and morphine. One important result was that heroin impregnated cigarettes are of limited clinical utility due to the low bioavailability of heroin.

4.3.2 Suitability of this treatment method for accessing heroin addicts

The Swiss studies aimed to assess the feasibility of prescribing heroin in three different clinical

contexts (1) newly established clinics, (2) existing outpatient methadone programmes and (3) a medium security prison with an inmate-run farm.

Data for evaluating the accessibility of the target group arises from the between studies comparison, using existing data from cohorts in methadone maintenance and detoxification, respectively (Uchtenhagen et al, 1998). Comparisons of patients' characteristics on admission yielded the result that injectable heroin users were on average older, used drugs for a longer period, had more unsuccessful treatment episodes and were less socially integrated than patients from methadone maintenance and from two residential, drug-free therapy programmes (Uchtenhagen et al, 1998). Interpretation of these group differences led to the conclusion that the programme's target group can be better reached through this treatment than by other treatments (Uchtenhagen et al, 1998). However, it is not a surprise that on average the injectable heroin group matches its own eligibility criteria better than other cohorts not subject to the same admission criteria.

4.3.3 Assessing health and social functioning of individuals treated

The assessment of the health parameters at both baseline and follow up used standardised instruments and the data appear to have been comprehensively collected by both clinical staff and independent research staff. Within the limitations of the overall study design this aspect of the study provided a substantial amount of data for analysis and policy consideration on the morbidity of this population.

Reporting of illicit heroin use during the heroin treatment programme was solely reliant upon self report as at the time of the study the investigators did not have an independent mechanism to differentiate licit from illicit heroin use.

The study of the effects of the heroin treatment programme on the criminal behaviour of participants was multifaceted and quite well designed. The study combined research into hidden as well as detected (officially registered) criminal activities by study participants. The method combined interviews and written questionnaires, analyses of official documents/statistics and included experiences of subjects as both offenders and victims. At this phase of scientific evaluation it seemed acceptable to focus on quantitative methods.

5. Results

5.1 Changes in health status

All participants in the Swiss studies had a comprehensive medical examination on admission. Twenty-one percent of those enrolled were considered to have either poor or very poor health. Twenty percent were considered to have poor or very poor nutritional status. 41% were considered to have either poor or very poor mental condition. 16% were found to be HIV positive, 74% had evidence of exposure to hepatitis B and 83% had evidence of exposure to hepatitis C. During the course of the study, there were three new infections of HIV, 4 new hepatitis B infections and 5 new hepatitis C infections (a total of eleven people, as one had a co-infection).

Statistically significant improvements occurred in body mass index, physical status, subcutaneous inflammation, and abscesses. Over the course of 18 months, the disease status of 18% of those diagnosed as positive for HIV/AIDS progressed.

These changes represent, within the limitations of the study design, overall meaningful improvements in health status. Those prescribed heroin (alone or in combination with methadone and other medications) evidenced significant improvement in their physical and mental health over 18 months. However, in the absence of data from an appropriate control group it is not possible to conclude that these improvements were caused or enhanced by the prescription of opioids, the provision of ancillary services, or by the combination of these interventions. Without data from a control group it is not

known if the same results would have been achieved with no intervention or could have been achieved by other means.

The reported death rates require further clarification. It was reported that there were 36 deaths among a cohort of 1146 patients. However from the description of samples (on page 44 of the synthesis report) it is not possible to determine the actual date of recruitment and to determine whether death rates were calculated by date of recruitment, or which method of calculation was used. It is important that analyses be conducted correcting for individual time in the programme. An overall death rate of 3% in the sample seems to be in accord with the limited available data on deaths in cohorts of addicts (e.g. EMCDDA, 1998, Hser et al, 1993).

5.2 Changes in social functioning

For those who remained in the Swiss studies for 18 months, the number of homeless participants reduced from 12% at entry to 1% at 18 months. Institutional accommodation reduced from 9% at entry to 2% at 18 months. Improvements in the housing situation, in the main, occurred in the first 6 months of treatment. A statistically significant reduction in unstable accommodation occurred over the 18 months with a reduction from 43% to 21% of participants.

The percentage of participants holding a job rose from 14% to 32%. The level of financial debt of study participants fell during the course of the study. While 15% were debt-free at admission, at 18 months this had risen to 34%. The proportion with substantial debts (in excess of SFr 30 000) fell from 21% at admission to 14% at 18 months.

Self-reported criminal behaviour and police reports of criminal activity involving participants fell during the course of the study. In particular, the number of shop lifting offences and the number of breaking and entry offences reported by participants or recorded by the police were reduced. The offences registered by the police reduced in excess of 50% over the time of the study. No data are provided to indicate the frequency or financial cost associated with these offences. The investigators assert that reductions in criminal behaviour persisted even after dropping out from treatment, however no data are provided to support this assertion.

Overall among participants in the Swiss studies there were significant pre-post changes in self-reported accommodation, employment, social contacts and criminal behaviour and these were all in the desired direction. The possibility that these changes could be attributable to changes in the local housing and employment situation was noted by the authors of the synthesis report (Uchtenhagen et al, 1998, page 122).

5.3 Changes in drug use

At entry 81% of the sample that remained in treatment for at least 18 months were using heroin illicitly on a daily basis. Only 6% reported almost daily illicit heroin use at six months with that reduction being maintained over the remaining months of treatment. No consumption of illicit heroin use was reported by 61% of the sample at six months and no illicit consumption was reported by 74% at 18 months.

Overall, statistically significant reductions in consumption of illicit heroin, cocaine, cannabis and benzodiazepines were reported. However it is not clear from the report whether these self reported findings are corroborated by urine test results. The major benefits were identified amongst daily consumers, whereas occasional consumers appeared to be more resistant to change. One-third of the study population continued daily consumption of cannabis at 18 months, while 6% had daily illicit heroin use, 5% had daily cocaine use and 9% had daily benzodiazepine use.

The between-studies-comparison using a weighted samples scheme (Uchtenhagen et al, 1998, p.132)

provided a methodologically sound way to evaluate retention rates for different treatment approaches. (The weighting scheme served here as a proxy for a stratified confounder analysis). According to this scheme, the 12-months retention rate was about twice as high in the heroin maintenance group compared to methadone maintenance and residential drug-free treatment samples from other studies in Switzerland.

The data presented on retention rates are among the most impressive of the Swiss studies. The dropout rates in the randomised and the double-blind studies for methadone and morphine groups were 3 to 13 times that in the heroin group. Similar retention rates were described in the early and highly structured methadone studies (Dole and Nyswander 1965).

Eighty-three of the 1035 participants switched to abstinence based therapy. On average, that occurred after 320 days of treatment. This percentage of subjects entering abstinence is in accord with the international literature.

Results of the randomised-controlled trial of a heroin maintenance programme based in Geneva have been published in a peer-reviewed journal (Perneger et al, 1998). This study had a stronger design than some others, with randomisation of subjects either to heroin maintenance or to a six-month waiting list, with encouragement of those in the waiting list condition to enrol in a treatment of their choice (usually a methadone programme).

However, since there was no control over the treatments engaged in by the comparison group, nor an attempt to assess the comparability of the non-pharmacological elements of these treatments, any differences in outcome between the two groups cannot be assumed to be attributable to heroin prescribing. This is particularly pertinent as the heroin maintenance programme offered very high levels of contact and of ancillary services. In the face of these limitations, some of the findings of this study have been somewhat over-interpreted as favourable to heroin maintenance treatment. There are a variety of alternative possible explanations to account for the impact of the experimental treatment in this particular programme.

5.4 Community attitudes

Information provided in the synthesis report (Uchtenhagen et al, 1998, page 118) and the report on public and media opinions (Boller, undated) suggests that over time the trials gained a high degree of support among opinion leaders and the general public. The synthesis report also indicates that any problems with local neighbours were resolved. There appear to be strategies for ongoing local community consultation on the impacts of the different projects.

5.5 Diversion of prescribed substances to street market

The 1996 Phase II evaluation report noted that all drugs for prescription were kept in locked safes in rooms with video surveillance. Preparations for injection were made in rooms from which patients were barred and staff observed all injections. Records were kept of all drugs delivered to the study sites and all drugs dispensed to patients. Federal authorities and local police approved all security measures.

According to the synthesis report security procedures successfully foiled three break-ins and one attempt to take prescribed heroin from the premises.

5.6 Costs of treatments studied

On average these costs were SFr. 51 per patient day or around SFr. 18,600 per patient year. They were offset to a large extent (SFr. 35) by revenues from patients, health insurance and public funds. Shortfalls were reportedly born by public funds and exceptionally by private sponsors.

6. Conclusions

6.1 Quality and cost-effectiveness of treatments compared with other services available in Switzerland

In 1993 Switzerland had 12,000 oral methadone treatment places and 1,300 places for residential treatment (Zeltner, 1997). No information is available on the quality of residential programmes. A detailed report on Swiss methadone treatment (Swiss methadone report, undated) shows that these programmes vary in important respects and that some chief medical officers have concerns about compliance with regulations. However, the report did not include any measures of quality that can be used for comparisons between methadone programmes and the Swiss studies.

A substantial report on the comparison of methadone and heroin-substitution treatment was provided (Dobler-Mikola et al, 1998). This report was in German. A brief summary of the conclusions and recommendations was translated for consideration (based on Dobler-Mikola et al., 1998, p. 171/172):

- The (psychosocial and other) adjunct therapy is very important for the group individuals who have long-term opiate dependence and considerable health and social deficits, regardless of treatment with heroin or methadone substitution.
- The fact that provision of heroin was medically feasible for those who had failed on methadone treatment does not constitute sufficient reason to enlarge the study of long term heroin treatment to other populations.
- Both heroin and methadone have only limited success especially for patients with multiple substance dependence or with a concurrent psychiatric disorder. It is not possible to give unequivocal evidence for better outcomes of either heroin or methadone treatment.
- At this time there is still a lack of a controlled clinical trial between substitution substances. Future research should examine the conduct of such a trial.
- The current practice of methadone substitution treatment in Switzerland should be improved.
- Research on medical prescription of heroin could continue under the current boundary conditions.

These cautious conclusions, especially when compared to the synthesis report (Uchtenhagen, et al, 1998) and with regard to the comparison of heroin and methadone substitution treatment are based on the uncontrolled quasi-experimental nature of the Swiss studies. The non-randomised methadone group was recruited on the basis of voluntary participation from patients of different methadone programmes with participation rates between 40% and 60% of the eligible population. In comparison, the participation in the medical prescription of narcotics programmes was mandatory.

The synthesis report does not provide evidence for the cost-effectiveness of the tested treatments compared with methadone or other treatments for the population considered. The economic evaluation notes the level of personnel resourcing on a cost per day basis. It would be useful, especially for making international comparisons, to have information as to the staff-client ratios.

6.2 The trials in the context of Switzerland's overall public health policy against drug abuse

Studies of new treatment for opioid addicts, including the studies of opioid substitution treatments are clearly consistent with Switzerland's overall approach to the drug problem. The opioid substitution trials are consistent with the four elements or pillars of the Swiss federal strategy against drug abuse in that they aim to reduce the problems associated with narcotic use and to support the survival of chronic opioid users. The overall strategy has strong political and public support. Reduction of related problems is not generally seen as a threat to the other pillars of repression, prevention and treatment.

As noted in the report of the 1998 WHO 30th Expert Committee, it is possible that one unintended

consequence of the Swiss studies might be to denigrate the value of methadone maintenance both in the eyes of the public and of opioid addicts. Long acting oral opioid agonist maintenance is by far the most successful treatment for opioid addiction. It appears that more can be done in Switzerland to improve access to existing programmes, to improve these programmes as well as to study other substitution treatments. Given the highly controlled regime associated with heroin prescription and the high cost of such delivery it is likely, if proven efficacious, that it will only be suitable for and available to a minority of heroin addicts.

6.3 Were the original goals achieved?

The Swiss studies have:

- Provided evidence that if an injectable substance is to be used for substitution therapy, the prescription of injectable heroin is feasible;
- Demonstrated that clients can be maintained on a stable dose of heroin;
- Shown that a heroin treatment programme can be delivered at treatment centres providing methadone maintenance with some modifications, and where very high levels of services are provided;
- Shown that a heroin treatment programme achieved reasonable retention levels;
- Shown self-reported improvements in the individuals' physical and mental health, social functioning (employment), and reported drug use and criminal behaviour.

An important premise of providing heroin maintenance has been that it makes it possible to attract people into treatment who otherwise would not enter into treatment. In this context it is of note that only 38% of those in the control group for the randomised treatment study in Geneva (Perneger et al., 1998) chose heroin when this was offered after the waiting period. Success on methadone was a dominant characteristic of those who declined heroin.

This result indicates that the issue of suitability for heroin prescribing is complex and this requires substantial deliberation in any future studies. This does not call into question the fact that there is a subgroup of long term heroin addicts who are prepared to engage in a restricted and controlled treatment regime in order to be maintained on an intravenous short acting opioid agonist. This choice was made in preference to a more flexible regime for a long acting oral opioid agonist.

A clear preference for intravenous heroin, either alone or in combination, was evident with 77.1% of all consumption days accounted for through this option. Only 2.1% of all consumption days were for intravenous morphine (either alone or in combination) and 3.4% were for intravenous methadone (either alone or in combination). With such small numbers meaningful within group comparisons (for the morphine and methadone arms) or between group comparisons were not possible.

Except for the small number of addicts prescribed heroin in prison and those receiving heroin from an established polyvalent outpatient clinic, the synthesis report provides no direct measures of client satisfaction with the treatments received. This is a significant omission in light of common practice in the evaluation of health services. The high retention rate for heroin maintenance could signify a high level of patient satisfaction. However, it is also possible that this reflects a high level of treatment dependence and that the requirement of frequent daily attendance might have been explored as an issue from the patients' perspective to determine how it interfered with, or facilitated, other daily activities.

6.4. Do the results support the medical prescription of narcotics to addicts?

The overall Swiss studies and their various sub-components have shown that it is medically feasible to prescribe intravenous heroin as a maintenance drug, at least under the conditions that prevailed during the studies. Few problems occurred at any site and the majority of those receiving heroin were

maintained on stable dosages of heroin, or heroin and methadone, or other opiate substitute. There was no evidence of substantial problems with dose determination, induction and stabilisation onto the injectable programme. Most of the benefits identified following entry into treatment were accrued in the initial six months of treatment. These benefits occurred in terms of health and social well-being. The retention rates were 89% at six months and 66% at eighteen months.

A variety of factors seem to have contributed to the successful implementation of heroin maintenance at the study sites and the results could be different at sites where these factors are missing:

- High level of oversight involving federal and canton authorities
- Built-in monitoring for research purposes
- Novelty of intervention and high level of public interest
- Highly qualified, multidisciplinary teams
- Ongoing staff training and development
- No take home narcotics for self-injection
- Patients required forfeiting driver's licenses (patients could not legally drive under the influence of prescribed doses of heroin)
- Provision of ancillary services
- Adequate measures to ensure the security of opioid type drugs and the safety of staff and patients.

The Swiss studies were not able to examine whether improvements in health status or social functioning in the individuals treated were causally related to heroin prescription per se or a result of the impact of the overall treatment programme. As convincing and plausible as the positive effects presented by the authors may appear, the one-group-pre-post-analyses do not allow for a causal attribution of these effects to heroin prescription. From a rigorous methodological viewpoint, it is not possible to obtain internally valid results with respect to the research question of heroin prescription being causally responsible for improvements in health status or social functioning in the individuals treated.

Alternative treatments exist for most medical conditions and, in many cases these alternatives have not been fully evaluated in comparative studies. The use of particular treatments with individual patients is largely determined by the clinical judgement of qualified medical practitioners. The main alternative to heroin is methadone and other oral opioids such as buprenorphine and LAAM. The Swiss studies suggest that heroin could be considered for patients who persistently fail on methadone. However, the studies have not provided convincing evidence that, even for persistent methadone failures, the medical prescription of heroin generally leads to better outcomes than further methadone-based treatment.

One result of the randomised control study conducted in Geneva was that two thirds assigned to a waiting list for heroin chose not to enter this treatment regime six months later. Many had since done well on methadone. This indicates the need for extreme caution in the prescription of heroin and suggests that the need to prescribe heroin can potentially be lessened if more efforts are made to engage patients in long acting oral opioid agonist programmes. There is a need for continued scepticism around the specific benefits of one short acting opioid over others and there is a need for further studies to establish objectively the differences in recognition and effect of these different opioids.

As previously noted, the Swiss studies investigated the medical prescription of narcotics under very special conditions. These included a high degree of oversight and the provision of comprehensive social and psychological services. Moreover, the studies were conducted in a wealthy country with a well-developed heath and social service system that includes a range of services for addicts. It is not known if the same results would occur if any of these conditions were different. Switzerland's unique social and political characteristics also limit the generalizability of the results of the narcotics substitution trials.

7. Implications

The results of the Swiss Studies on Medical Prescription of Narcotics to Drug Dependents have shown that prescription of heroin is medically feasible, and the consequences of this treatment to patients and society may be comparable to other forms of treatment. However, the knowledge base is not large enough to determine cost-effectiveness and the differential indications for heroin substitution treatment. There is a need to establish clear clinical guidelines and standards of care for the different forms of substitution treatment that are based on evidence derived from scientific studies and expert clinical opinion.

Basic scientific studies are essential if further understanding of the pharmacology of opioid agonist substitution treatment is to inform the debate about the choice of opioid and the choice of route of administration in the management of heroin dependence.

7.1 Implications world-wide

- Further investigation of the controlled prescription of heroin for the treatment of heroin addiction should follow ethical, medical and scientific standards, and contain appropriate legal provisions;
- Research and evaluation into the quality of different opioid substitution treatments should continue to be explored to ensure there is evidence based treatment;
- Studies of new substitution treatments should only be considered in systems where there is already an existing differentiated treatment service including long acting oral opioid agonist treatment;
- Studies of new substitution treatments should always include additional therapy including social support;
- Studies of new opioid substitution treatments should only be considered under controlled circumstances with rigorous scientific evaluations;
- Country-specific cost-effectiveness of different programmes should be explored ;
- Possible further research includes a scientifically valid controlled randomised study where the differential impact of ancillary services on treatment outcome can be evaluated.

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