Prevalence morbidity and mortality among heroin users and methadone patients
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INTRODUCTION

This thesis consists of a number of studies that have been conducted in collaboration with colleagues in- and outside the Municipal Health Service in Amsterdam. The studies refer to heroin users and, particularly, those participating in methadone treatment. The studies are predominantly based on data gathered up from 1985. As, in Amsterdam heroin became popular in 1972, they refer to the second half of the 'heroin epidemic'.

The introduction briefly describes the history of the heroin epidemic and the implementation of methadone treatment. Methadone, a synthetic opiate, is used to prevent the withdrawal syndrome, to decrease heroin use and hence, improve the quality of life of the heroin user. Methadone treatment can be utilised in order to obtain total abstinence of opiates - by gradual reduction of the methadone dose and after-care - but has proven to be mainly successful if a constant high dosage - \( \geq 60-80 \text{ mg} \) - is administered. In Amsterdam, however, lower dosages of methadone are prescribed too. Although these lower dosages are less effective to decrease heroin use, frequent contacts with the treatment service provide an opportunity to solve, diminish or prevent other social and health problems. Contacting heroin users is of the utmost importance to reduce the social and health problems among them.

When large scale methadone treatment was introduced during the onset of the 1980s, heroin problems did not diminish right away. In contrast, the attraction of Amsterdam - probably due to the introduction of methadone treatment - on predominantly German drug users initially resulted in an increasing number of heroin users and fatal overdose deaths. The overdose figures peaked in 1984 \( \cdot 73 \text{ fatal cases} \). Next to a higher number of OD fatalities, heroin-tourism turned out to be an important breeding ground for the spread of the Human Immuno-deficiency Virus HIV. Since the second half of the 1980s, prevention of further spread of the virus and treatment and care for HIV infected heroin users has been an important topic. During the last few years, it becomes increasingly clear that the heroin epidemic is shrinking and especially intravenous use of heroin is decreasing. A decreasing number of young drug users are reported and mortality among chronic heroin users is relatively low. As a result, the average age of the population of heroin users rises rapidly.

The studies that are presented here refer to an ageing, chronically opiate dependent population. Gaining more knowledge on morbidity and mortality among this population is of the utmost importance, not only for Amsterdam and The Netherlands were the heroin epidemic seems to be in her last phase, but also for cities and countries that may encounter similar developments in the future.
PREVALENCE PROBLEM DRUG USE, COVERAGE OF TREATMENT SERVICES

The first study estimates the number of problem opiate users in Amsterdam and the proportion of the population that is reached by the Amsterdam methadone treatment services. A three sample Capture-Recapture method has been used to conduct this estimation. The three samples consist of registered opiate users that have been treated by physicians and/or nurses of the Municipal Health Service at police offices, methadone treatment outposts or hospitals in Amsterdam. Based on the number of opiate users that are registered and the extent of overlap between the different registers, the size of the population that has not been registered anywhere has been estimated. The model shows that the estimated number of problem opiate users is 4130 ± 95% confidence interval 3753; 4566.

Repeating this method with methadone patients treated at general practitioners or abstinence oriented treatment results in a much higher estimation. Based on statistical criteria, it can not be established which estimation resembles the real figure most. This question can be answered by a critical contemplation of the assumptions of the Capture-Recapture method. One of these assumptions states that characteristics of samples that are used to conduct these estimations should be similar to the hidden population that we intend to estimate. This assumption is violated if patients are included who are treated with methadone at their general practitioner or abstinence oriented treatment. These patients are less 'problematic' than the 'hidden population' of interest. The violation of this assumption results in an over-estimation.

An estimated 40% of the problem drug users is reached by methadone treatment programmes. The discussion of this thesis elaborates more on the concept of coverage -proportion of the population that is reached with treatment-. In this study, a 3-months period is used to define coverage; the period in which the samples are recruited. In a dynamic population, the number of drug users reached increases with increasing period of effect of the intervention. In order to make a proper estimation of the coverage of an intervention, the period used to express coverage should reflect the period of effectiveness of the intervention. Methadone treatment, however, consists of a range of preventive measures with different periods of effect. Hence, the Coverage of methadone treatment does not exist.

Continuous coverage of the total population of opiate users is not possible nor necessary. The low threshold character of Amsterdam methadone treatment services enhances the coverage of the relevant population -those with health problems-. It enables opiate users to
participate in treatment when they feel that this is necessary. This way, the relevant population is largely reached spontaneously. Nevertheless there are opiate users who, according to the health authorities, should participate in treatment but who are not reached. Recently, new initiatives to reach and maintain contact with these people in a more active way have been developed. The effectiveness of these initiatives should be evaluated.

**MORBIDITY**

**Tuberculosis**
The chapter 3.1 discusses the incidence of tuberculosis among the opiate users. It answers the question how many new cases of active tuberculosis are diagnosed per 1000 methadone patients per year. Using methadone registers between 1989 and 1992 methadone patients are ‘followed up’ annually from the date of first contact until the end of that particular year, or in case TB is diagnosed, until date of TB diagnosis. The number of new cases appeared to be 3.86/1000 personyears. This is a ten times higher figure than that observed among the general population of Amsterdam that, on its turn, shows a four times higher figure than observed among the total population of The Netherlands.

Twice a year, opiate users at the Municipal Health Service are checked on TB by X-Thorax screening. In Amsterdam, methadone patients treated by their general practitioners are excluded from this periodical screening. This policy appears to be justifiable because incidence figures found among methadone patients of the general practitioners were much lower - 0.6/1000 personyears - compared to those of the methadone outposts of the Municipal Health Service - 5.1/1000 personyears. TB incidence among patients of the Prostitutes and Foreigners Outpost of the Municipal Health Service appeared to be highest - 7.3/1000 personyears.

Furthermore, TB incidence increases with increasing age, length of treatment and is higher among male methadone patients. HIV infection appears to be important; 53% of the TB cases were HIV infected whereas the percentage of HIV infection among all methadone patients of the Municipal Health is estimated to be 14%.

**Chronic Obstructive Pulmonary Diseases**
Other pulmonary diseases that are cause for concern at the Municipal Health Service are Chronic Obstructive Pulmonary Diseases *COPD* which may lead to shortness of breath, disability or even death. A questionnaire has been administered among methadone patients of the Municipal Health Service to investigate the pulmonary problems
and the exposure to tobacco, cannabis, base-cocaine and heroin. Moreover, spirometry was performed to assess the pulmonary function. The main outcome parameter was based on the Forced Expiratory Volume; the maximally expired volume during the first second of expiration - FEV₁. Effects of chasing the dragon of heroin - inhaling heroin in vapour through a straw - are the central topic in this study. COPD among 'heroin chasers' has not been studied before. Medical literature concerning the effects of inhaling heroin is limited to some case descriptions of sometimes fatal asthmatic attacks.

88% of the methadone patients in the study ever used heroin by chasing the dragon, 52% did so during the last month. In contrast, 41% ever injected heroin and 13% did so during the last month. Based on period and frequency of 'chasing', methadone patients were subdivided in six categories of approximately equal size.

Compared to the general population, a higher percentage of methadone patients experiences serious shortness of breath - 1% versus 13% respectively. Spirometry revealed that the lung function was lower than 80% of expected value among 26% of the patients and less than 50% of the expected value among 5% of the patients. More serious complaints of shortness of breath correlated with lower spirometric results. No doubt that cigarette smoking - 98% of the patients smokes cigarettes, average period 26 years - contributed to this poor pulmonary function. Besides, a higher exposure to heroin was related to a lower pulmonary function and a higher prevalence of shortness of breath. It was striking that spirometric results varied widely among the highest heroin exposure groups. Possibly, chasing heroin leads to a decreasing lung function among a vulnerable subgroup of heroin users only. This is also the case with cigarettes.

It should be stated that spirometry only measures one of the factors that are important in the mechanism of oxygen transport. Other factors - e.g. decreased diffusion, anaemia, weakness of expiratory muscle - are briefly discussed in the general discussion. Within the treatment practice more attention should be paid to the diagnosis and treatment of pulmonary problems. Moreover, efforts to decrease or quit smoking of cigarettes among methadone patients deserve special attention.

MORTALITY

OD mortality versus period in treatment
The remaining three studies all deal with mortality related to opiate use. Two of them are specifically focussed on mortality as a result of overdose of opiates OD. The first study describes OD mortality in relation to time in methadone treatment. Methadone treatment has proven
to prevent OD fatalities. However, an Australian publication concluded that mortality rates during the first two weeks of treatment were extremely high. The Amsterdam Central Methadone Register creates the opportunity to find out whether in Amsterdam the OD mortality rates in different periods are similar to those observed in Australia. Using this register, all first, second, third week etc. of all patients' methadone treatment were identified. Then, specific OD mortality rates per 1000 personyears were calculated by relating the number of observed OD fatalities occurring during these treatment periods with the total amount of time that was spend in the specific treatment periods. Similar to the Australian findings, OD mortality rates during the first two weeks were higher than the rates during other periods of treatment. Rate Ratio 2.9 95%CI 1.4-5.8. There are several possible explanations for this. On the one hand the increase of OD mortality can be explained by the toxic effect of methadone itself, on the other hand it can be related to the specific circumstances of the opiate user at the time treatment is demanded. Probably a period of crisis. Striking are the large difference between the figures reported in Australian and Amsterdam during the first two weeks of treatment. 9 OD deaths/1000 personyears in Amsterdam and 70/1000 personyears in Australia. This difference between the two studies shows that the OD mortality rates observed at the start of the methadone treatment can not be generalized to all methadone patients.

In Amsterdam OD mortality rates among methadone patients are low during methadone treatment but also after leaving treatment 2.3 versus 2.5/1000 personyears. This findings seem to contradict other studies among injecting drug users showing a protective effect of methadone treatment. The most plausible explanation is that injecting drug users are only a small minority among methadone patients in Amsterdam. Hence, OD mortality after treatment is low too and therefore, a clear additional reduction of OD mortality as a result of methadone treatment can not be observed anymore.

**Overdose mortality in four European cities**
The second study concerning OD mortality compares the differences of the absolute numbers of OD fatalities and the observed trends in four European cities. This study has been initiated by Oslo - Norway. Although the cities' estimated number of opiate users is roughly similar, the number of OD fatalities that are registered in 1999 is higher in Oslo - 104 - compared to Copenhagen - 44 -, Amsterdam - 28 - or Frankfurt - 26 -. Moreover, trends in Oslo rose during the 1990s. This in contrast to the decreasing or stable trends in the other cities. To explain the differences between the cities, information from all four cities has been studied and interviews have been conducted with opiate users, people who contact opiate users professionally. - police offic-
cers, paramedics, social workers· and key persons in the area of
drug policy ·drug treatment service, police, policy makers, municipal
council· Next, it has been investigated whether the differences in OD
mortality between the cities could be explained by differences in the
definitions used, trends in heroin use, characteristics of the drug cul-
ture ·e.g. the route of administration· and drug policy ·regarding
health and police policy· Although there are differences in definitions and in the process col-
lecting OD mortality figures its influence is insufficient to explain the
large differences between the four cities. Furthermore, these differ-
ences could not explain the different trends in OD mortality. Trends in
prevalence of heroin use appeared to be different. Heroin has been
introduced in the early 1970s in all cities. However, the number of
heroin users increased up to the first halve of the 1980s in
Copenhagen and Amsterdam whereas in Frankfurt the prevalence
increased dramatically during the second halve of the 1980s and in
Oslo the number of heroin users especially increased during the
1990s. Striking is that the OD peak in Amsterdam, Frankfurt and Oslo
coincides with a period of migration of heroin users from other towns
or other countries. Especially in Frankfurt this migration resulted in
the appearance of a large scale 'open drug scene'. In Oslo, a similar
development is observed recently.

Amsterdam is the only city where 'chasing the dragon' is the
dominant route of administration of heroin. Moreover, in Oslo, injec-
tion of a combination of heroin and benzodiazepines ·such as
Rohypnol· is widespread. This habit provides another explanation of
the high mortality figure in Oslo.

Considering drug policy there is large difference between Oslo
and the other three cities. In Oslo, drug services are dominated by
abstinence oriented therapeutic communities and small scale
methadone treatment under strict conditions. Professional treatment
is available as long as no additional heroin is used. Consequently pub-
lic health and nuisance appears in the streets and the police is main-
ly responsible for the problem. In contrast, in Amsterdam and
Frankfurt police and health services co-operate and share their
responsibility for the drug problem in the municipality. Considering
the reduction of OD mortality the results of the Frankfurt policy
·which is modelled after that of Amsterdam· are most impressive.
Probably, co-operation between police and health services, prevention
and reduction of the open drug scene, offering alternatives such as
large scale, low threshold methadone treatment and discouragement
of migration of drug users from outside Oslo will also help to reduce
OD mortality in Oslo.
Mortality Reference Rates for Opiate Users

The final study is conducted in co-operation with the EMCDDA - European Monitoring Centre of Drugs and Drug Addiction. This organisation aims to provide objective, reliable and comparable information at European level on drugs, drug addiction and their consequences. This study is based on data from cohorts of opiate users from nine different European cities, regions or countries. It describes the relation between age, gender and mortality among opiate users and the general European population.

Mortality studies among opiate users generally describe mortality figures within specific populations of opiate users. Age and gender distribution of these populations may differ and, therefore, crude mortality figures - number of deaths per 1000 personyears - are not always comparable. To adjust for differences in age and sex distribution, the Standardized Mortality Ratio SMR is often reported. This study, however, shows that the widely used SMR still does not lead to comparable outcome figures.

Here, the figures of the population of opiate users in Dublin and Amsterdam are presented. Within the cohort of Dublin a mortality rate of 10.9/1000 personyears and in Amsterdam a mortality rate of 14.2 is found. Hence, the crude mortality figure of the Amsterdam cohort is 1.3 times that of Dublin. However, opiate users studied in Dublin are younger than those observed in Amsterdam - mean age 27.5 and 37.2 years respectively - and the percentage of females is higher in Dublin - 27% - than it is in Amsterdam - 22%. According to the mortality figures of the general population of the European Community, a mortality rate of 1.05 could be expected in Dublin and a rate of 1.83 per 1000 personyears could be expected in Amsterdam. Hence, the SMR of the Amsterdam cohort - SMR = 7.7 - is 0.75 times that of the Dublin cohort - SMR = 10.4.

In this case both cohorts are compared to a similar reference population. Normally, the population from the region and calendar time as the study population will be used as a referent population. Then, differences between two SMRs can both be explained by differences in mortality figures between the study population and differences between the referent populations. However, although a similar referent population is used, the comparison between the two cohorts is still not valid. This is because relative mortality risks are not equal for all strata of age and gender; in comparison with the general population relative mortality risks among young drug users are higher than those among older ones, moreover, relative mortality risks among females are higher than those among males.

The reference values that are proposed in chapter 4.3 are based on the cohorts of opiate users. If these reference values are used the bias due to the heterogeneity disappears. Then, the mortality figures
of the Dublin cohort appear to be 0.56 times and the Amsterdam cohort 0.49 times the mortality expected among opiate users. Compared to Dublin the Amsterdam figures are 0.88 times lower.

The original adjustment of the figures resulted in an over-adjustment. Use of specific reference values for opiate users as presented in section 4.3 will enhance the comparability of mortality figures in single group mortality studies among opiate users.

**Explaining higher mortality rates among heroin users**

The general discussion elaborates more on mortality among heroin users. Mortality rates among all cohorts were higher than those expected in the general European population -15-50 years. This increase is due to the toxic effect of heroin itself - Overdose - , contamination of drugs or paraphernalia - HIV and Hepatitis B and C virus - and the consequences of addictive behaviour. Considering epidemiological research, selection of the population on factors that increase the risk of mortality is of special importance - such as smoking of cigarettes, psychopathology and social circumstances -. Several risk factors are related to the risk of initiation or continuation of heroin use, related to treatment outcome or to relapse after a period of abstinence. This negative variant of the 'healthy worker effect' is introduced as the 'sick heroin user effect' in section 4.3. The hypothesis is posed that differences in morbidity and mortality rates among users of different kinds of drugs or opiate users originating from different countries can partly be explained by differences in the process of selection.

**International co-operation**

The drug problem is a politically sensitive topic. This enhances the development of prejudices and may restrict the outlook of researchers too. Causal relations between important indicators of drug problems - such as prevalence of drug use and mortality due to drugs - and drug policy are easily drawn. Sections 4.2 and 4.3 show that the situation concerning drugs and drug use among different countries differs widely and that a similar drug policy may lead to different effects. These differences hamper a simple explanation of differences in number of drug related deaths or mortality rates among drug users, let alone the influence of drug policy. However, the similarities and differences among the drug users of different countries, among services and drug policy also provide new opportunities for research. The similarities and differences create pseudo-experimental situations that are waiting to be studied by epidemiologists. Showing these differences and similarities is a first step towards further clarification of drug related problems and ways to solve them.