Prevalence morbidity and mortality among heroin users and methadone patients
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GENERAL DISCUSSION

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In this final chapter we elaborate on the topics discussed in the previous chapters. Here we discuss how the prevalence estimates relate to other indicators of problematic drug use in Amsterdam and we describe the prevalence trends. We discuss the concept of health services coverage and we briefly discuss the chapters concerning TB and COPD. In addition, we express our view on the policy measures in place to prevent overdose mortality and we discuss the increased risk of mortality among opiate users. Furthermore, we propose future research directions for these areas.

PREVALENCE ESTIMATION AND COVERAGE

Better method, better result?

In 1997 the prevalence of problematic opiate users in Amsterdam was estimated to be 4130 ± 95% CI: 3753 - 4566. The sampling method used is an improvement on the method which was used traditionally, a 3-sample capture-recapture analysis C/RC with a three month sampling period, as opposed to a 2-sample C/RC with a one year sampling period. The 3-sample C/RC with sampling periods longer than three months resulted in statistically unstable models, inflated estimates and inflated confidence intervals. This is an indication that the results are biased, and this is most probably caused by the violation of the closed population assumption. In this section we do not present any new information, but the estimates already made are presented graphically and discussed more extensively.

Figure 1 shows the probability curves of the 2-sample and the 3-sample estimates using data samples provided by the police, hospitals and two different treatment samples. These two different treatment samples reflect the different methadone programmes in Amsterdam. Problematic opiate users are treated via low-threshold treatment, i.e. MHS, less problematic opiate users via high-threshold treatment, i.e. Jellinek or GP. Probability distributions of 2-sample C/RC estimates are normal distributions. The 3-sample C/RC estimates result in normal distributions on a log-normal scale. The peak of the probability curve represents the point estimate. As the total area under each probability curve is 1.0, smaller variances result in higher peaks.


If the low-threshold treatment sample is used, the 2-sample estimate based on the treatment/hospital sample results in a lower estimate, 3072 users, than the 2-sample estimate based on the treatment/police sample 4069 users, and the police/hospital sample, 4721 users. The best fitting model is the model which is adjusted for a positive dependency between the treatment/hospital sample. The probability curve for the 3-sample C/RC analysis reaches its peak at an estimated number of 4130 problematic opiate users - point estimate - and 95% of its surface area lies between 3753 and 4566 - 95% Confidence Interval CI.
If the high-threshold treatment sample is used, the 2-sample estimate together with the hospital sample leads to a higher estimate, 7507 opiate users, whereas the estimate with the police sample results in the extremely high estimate of 16637 opiate users. The best fitting model for the 3-sample C/RC analysis with the high-threshold treatment, police/hospital sample is the model which adjusts for the negative dependency between the police and treatment sample. The probability curve for this analysis reaches its peak at an estimated number of 6226 opiate users and 95% of its surface area lies between 4647 and 8688.

The statistical parameters indicating the fit of the model which include the likelihood ratio and Akaike’s and Bayesian information criteria, suggest that estimates using the high or low-threshold are equally valid. However, in chapter 2 we argue that estimates with the high-threshold treatment sample do not lead to valid results. The majority of high-threshold patients do not belong to the population of interest\textsuperscript{11} i.e. the group of problematic opiate users. Neither does the estimated number of 6226 opiate users reflect the size of a larger population, i.e. the total number opiate users; the hidden population of non-problematic heroin users can not be estimated by including stabilized methadone patients in one of the samples. Although both groups are opiate users, their characteristics differ tremendously.

It is important to notice that a statistically sound analysis derived from the 3-sample C/RC does not necessarily lead to a valid estimate of the number of drug users. Therefore, C/RC estimates should be treated with caution.

**Other indicators of prevalence**

In order to check the validity of our estimate of the number of opiate users in Amsterdam -4130; 95% CI 3753-4666- we compared our results to other indicators of the prevalence of \textit{problematic} heroin use. Several other indicators have been used:

- results of a population survey conducted by the University of Amsterdam\textsuperscript{12}
- number of needles exchanged in relation to the number of needles that are used per injecting drug user\textsuperscript{31}\textsuperscript{4}
- number of Dutch and Surinam OD deaths among opiate users and the estimated OD mortality incidence rate\textsuperscript{5}\textsuperscript{16}
- number of TB cases among opiate users related to the estimated TB incidence rate.\textsuperscript{17}

In a population survey the problematic heroin users are likely to be underrepresented. So, if the prevalence estimate derived from a population survey is higher than the C/RC estimate, this would either suggest that our estimate of the user numbers is a serious underestimation or that a high proportion of the Amsterdam heroin users are
non-problematic heroin users. The results of the population survey suggest that the prevalence of current heroin users is 2 per 1000 inhabitants in the age range 15-64 years. In 1997, the official Amsterdam population in the age range 15 to 64 years was 509,562. Therefore, our prevalence estimate of between 3753 and 4566 users leads to a maximum city prevalence rate of 7.4 to 9.0 per thousand inhabitants in this age category. This is a maximum estimate, because non-registered residents are counted in the numerator but not in the denominator of officially registered inhabitants. So, we may conclude that this comparison does not invalidate the C/RC estimate. Furthermore, it should be noted that our prevalence estimate is no higher than recently published prevalence estimates for other Western European cities.

We will also provide an indication of the population size of active injecting drug users. Injecting drug users are considered to be a minority of the problematic opiate users. Assuming that the number of syringes which are used in Amsterdam is equal to the number of syringes exchanged, we are able to estimate the number of injecting drug users. Recent data concerning injectors in the AIDS study cohort indicates that the average number of different syringes which are currently used by injectors in one month is 58.5. The median number of syringes was 22.5 - inter quartile range within 2.6-90. The total number of syringes exchanged in 2000 totals 334,345 which is an average of 28,695 syringes per month. If these two figures are combined the estimated number of drug users currently injecting is \( \frac{28,695}{58.5} = 490 \). Taking into account the confidence intervals of our prevalence estimate this would imply that 10 to 14% of users are injecting opiate users; a range which is consistent with other estimates. This estimate depends on the assumption that the observations among injecting drug users within the AIDS study cohort can be extrapolated to the total number in injecting drug users of Amsterdam.

In addition, we also used the number of OD deaths as an indicator of the prevalence of drug usage. We related this number to the mortality rate among low-threshold clients which is presented in section 4.1 and used a multiplier method to re-estimate the estimated number of problematic opiate users born in The Netherlands or Surinam - N = 2807 95% CI 2568-3048 - given in chapter 2. However, not all OD deaths belong to the population of problematic opiate users. There are also deaths due to drugs other than opiates, suicide with drugs among non-drug users and deaths resulting from intestinal drug smuggling. Therefore we limited the overdose deaths to those registered with the Central Methadone Register CMR. Hence, we assume that after 20 years of large scale low-threshold methadone treatment, including methadone treatment at police stations, almost all current problem-
atic opiate users are already registered with the CMR.29 Twenty-two cases have been identified in the period 1999-2001 of those born in Surinam or the Netherlands and who are registered with the CMR. Given the incidence rate of 2.7/1000 person years py, these 22 cases are expected to occur within 8148 person years of observation time. This is equivalent to a three year observation period of a population with an average size of 2716 individuals, an estimate in line with the estimate of 2807 derived in chapter 2.

Similarly, section 3.1 shows that the TB incidence rate among the MHS population is estimated as 5/1000 py. Again, this offers an opportunity to use the multiplier method as an indicator of prevalence. In the 12-year period from 1989 through 2000, 254 TB cases have been observed among drug users. This is an average of 21.2 cases each year; equivalent to an average size of a population of 4233 drug users. Again, this is consistent with the prevalence of 4130 users -95%CI 3793-4566 - estimated in chapter 2. The coherence between the incidence rates presented in sections 3.1 and 4.1 and the estimated prevalence of opiate users presented in chapter 2, seem to support each others validity.

**Trends**

Prevalence is defined as the total number of cases at a single moment in time. Prevalence trends over time are the result of the difference between the number of people entering the population and the number of users leaving the population. This is represented by:

- the number of initial heroin users and those relapsing to heroin use, releases from prison and other closed institutions and users migrating to Amsterdam less
- the number of mortalities, the number abstaining - even if this is temporary; ad missions to prison or to other closed institutions and migration out of Amsterdam.

In this section we will present indicators of prevalence trends concerning the numbers of opiate users and the drug related problems.

In chapter 2, no statistically significant dependence between quarterly low-threshold treatment and the police sample was observed. Therefore, we used the 2-sample C/RC with quarterly police and treatment samples to describe prevalence trends. Figure 2A shows the average quarterly values per annum - the average of four estimates - and the estimated values based on two sample C/RC estimates with annual police and low-threshold treatment samples which are usually reported.10 The quarterly sample estimates show a modest net decrease between 1989 and 2000. The annual sample estimates lead to a more pronounced decline of problematic opiate users. This can be explained by the reduction in the number of foreign heroin users temporarily residing in Amsterdam. This decrease results in a gradual
Figure 2  Indicators of trends in problematic drug use
reduction of the violation of the closed population assumption over time and leads to a decreasing overestimation. If the results of quarterly samples are used, a slowly decreasing trend remains.

This decrease or stabilization is also reflected in the trends of fatal OD cases in Amsterdam in the period 1976-2001. In interpreting these figures it should be noted that OD deaths other than those among opiate users are included. The number of TB cases in the period 1989-2000 shows the initial increase which is discussed in section 3.1, followed by a stable or decreasing trend. The annual number of syringes exchanged shows a major reduction over time. The number of exchanged syringes is not only influenced by the number of heroin users but also by the proportion of injectors and number of injections per injector.

Coverage and time
In chapter 2 we showed that in the first quarter of 1997 the proportion of problematic opiate users who were reached by methadone programmes coverage was 40%. If we use coverage of an intervention as an epidemiological indicator, the population which is considered to be reached by an intervention should be similar to the population which is actually affected by it. Because methadone patients form a dynamic population, the percentage which has been in contact with a methadone programme increases with the observation period. For example, the number of people reached within a month is always lower than the number reached within a year. This leaves the question of which period to choose. We state that this period should be equal to the duration of the effect of the intervention.

However, methadone treatment consists of a multitude of interventions. TB screening is considered to be effective if conducted once every six months. Therefore, the proportion reached by TB screening should be the proportion of problematic opiate users screened no longer than six months previously. The pharmacological effect of methadone will disappear soon after leaving treatment. Considering this single aspect, those who are contacted no longer than one week ago could be considered as covered. Each intervention has its own period of effectiveness, and thus its own coverage. In a dynamic patient population, preventive measures with a longer duration of effect are able to cover a higher proportion of drug users. This should be taken into account when choices are made between different types of interventions.

Methadone patients are not the only dynamic population, the total population of problematic opiate users in Amsterdam is also dynamic. Some of the opiate users who were contacted in the past no longer belong to this population, due to factors such as migration, mortality and stable abstinence. If we want to calculate the proportion
of opiate users who are contacted over a longer period of time, we should be aware that not all opiate users who have been contacted in this period still belong to the population of current opiate users. Otherwise, coverage will be increasingly overestimated with an increasing period of time. To give an extreme example: 14 717 opiate users have been in contact with some form of voluntary out-patient methadone treatment in Amsterdam since 1985. However, at the time of writing, the majority of those contacted no longer belong to the population of Amsterdam opiate users. In order to determine the real proportion of opiate users which has been covered over a longer period of time, coverage among a representative sample of the population of problematic opiate users should be studied.

Coverage and relevance
Whether we can consider 40% coverage of methadone programmes over a three month period to be a satisfactory result mainly depends on whether the relevant section of the problematic heroin user population is actually reached. If those with the most severe social and medical problems are reached, the potential benefit of methadone maintenance treatment will probably be greater than if this group is excluded from treatment.

In Amsterdam those with the more severe problems are probably over-represented among the population covered by the programme. The positive dependence between treatment and hospital admission suggests that particularly those heroin users with severe health problems are reached by methadone programmes. In addition, among a sample of heroin users arrested by the police, the main reason for not participating in methadone maintenance treatment was the absence or perceived absence of health problems.115

The low-threshold character of methadone treatment probably increases the coverage to the relevant proportion of opiate users. Individual opiate users may experience periods with fewer, less severe problems and periods with more severe problems. Apparently, not all of them need treatment all of the time. It is important that during the specific periods in which the need for treatment exists, treatment can be offered. The low-threshold service implies that heroin users can receive treatment without delay. This will probably enhance the coverage of the relevant proportion of heroin users. Nevertheless, not all opiate users with serious health problems who - according to the health and/or police services - ‘should’ apply for treatment, actually do so. This group needs to be actively approached by the health services.
Future directions of study on this topic

Continuation of the various studies to monitor the prevalence and incidence of drug usage in Amsterdam is important. However, besides the indicators of prevalence, indicators of problematic use of drugs - but also alcohol - should also be monitored. Although the subtitle of chapter 2 is 'the importance of case-definition' the term problematic opiate user which we used in this chapter is not clearly defined. The MHS treatment registration needs to be improved in order to define the concept of a problematic opiate user more specifically in terms of the frequency and kind of drugs used and additional social, physical and mental health deficits.

In addition, rather than studying a more abstract proportion of opiate users who are contacted by the health services, we should define the population of opiate users, and other groups in a similar situation, who 'should' apply for treatment but is not yet in contact with the health services. Cooperation with the police and citizens of Amsterdam is of the utmost importance to enable this population to be found. However, the public mental health services should guard against a situation in which they mainly focus on the prevention of nuisance. The reporting point for extreme nuisance to which people can report neighbours who cause a nuisance, for example with excess noise, smell or aggression, could be extended into a 'reporting point for extreme nuisance and severe care deficit'. Once a concrete population is defined, the methods used to make and maintain contact with this population - e.g. support project - should be evaluated.

Morbidity

TB

Section 3.1 describes the incidence of TB among methadone patients recorded between 1989 and 1992. At that time, TB was a possible new threat together with HIV. Similarly, with the decreasing incidence of HIV among drug users and the increasing treatment possibilities, the threat of a major TB epidemic among opiate users has declined. Although HIV prevalence among methadone patients born in Surinam or the Dutch Antilles is rare, TB incidence within this group of users was no lower than in other groups of opiate users. It is therefore expected that despite the reduction in new HIV cases, TB will continue to show a rather high prevalence within the population of opiate users. Consequently, TB screening remains important to protect other patients, health workers and the general population. TB incidence among GP methadone patients was no higher than among the general Amsterdam population. Therefore, the extension of TB screening to these patients is not necessary.
A further reduction of TB could possibly be attained by giving the highest risk group preventive treatment with tuberculostatics. The highest risk group consists of opiate users who are both HIV and Purified Protein Derivative PPD seropositive. Randomized controlled trials in HIV-infected adults have shown that preventive therapy significantly decreased the risk of TB and death in HIV and PPD positive individuals.

TB among drug users is of particular importance because their irregular lifestyle does not enhance treatment compliance. This risk factor encourages the development of multi-drug resistant strains of TB. Methadone treatment programmes provide a framework to enhance TB treatment compliance. In this respect, daily contact in the newly implemented heroin treatment facilities may offer an opportunity for Directly Observed Treatment DOT to treat TB infection in active heroin users.

**COPD**

In section 3.2 we found an impaired pulmonary function among methadone patients. In contrast to TB, COPD is likely to cause more problems in the future population of ageing and chronic heroin users. The chronic use of cigarettes is probably a major causal factor of this impairment. Consistent with other studies, we observed an extremely high prevalence and low quit rate of heavy cigarette smoking among methadone clients. Almost all patients have smoked cigarettes since they were young adolescents. Therefore, cigarette smoking could not be identified as a separate risk factor in this study.

Section 3.2 suggests that the inhalation of heroin results in additional pulmonary impairment. Moreover, the large variation in the spirometric results among most chronic heroin inhalers suggests that if the inhalation of heroin is causally related to pulmonary impairment, other risk factors will also play a role in the causal mechanism, for example a high histamine response to opiates. Although chasing the dragon might be related to lung function impairments; the health risks faced by 'chasers' are minor compared to the health risks faced by intravenous heroin users. COPD is a slow progressive disease which generally implies that these opiate users have survived decades of cigarette and heroin addiction before the disease manifests itself. Many of the health risks faced by injecting users, for example the risk of OD mortality and the risks of viral or bacterial infections, are not applicable, or are only marginally significant to those users who inhale heroin instead. Within the heroin co-prescription study, heroin was inhaled by 68% of the experimental group. Patients could change from injecting to inhaling but not the other way around. In this form of treatment the potential hazard of inhaling heroin should always be balanced against the potential gains which are obtained by treatment
with methadone and co-prescribed heroin. Other factors which may enhance or limit actual oxygen uptake may be altered due to heroin co-prescription. Therefore, based on the results of this study we can not predict whether the net effect of co-prescribing heroin for inhalation on the patients actual oxygen uptake will be positive or negative.

**Future research directions concerning TB and COPD**

Concerning TB we may conclude that the extension of TB screening to GP methadone patients is not necessary. Instead, the cost effectiveness of screening among the homeless residing in shelters with a high degree of mobility could be investigated. Concerning pulmonary function, we may consider periodical spirometry among methadone patients. This may increase the awareness of pulmonary impairment among both health workers and patients. Hence, it could be an incentive for the improvement of COPD treatment on the one hand and reduction of cigarette and drug use on the other.

Prospective studies concerning the risk factors of pulmonary impairment may disentangle the influence of inhaling heroin and cigarette smoking. Moreover, we may be able to define special risk groups at an early stage. The influence of other mechanisms affecting the pulmonary function or oxygen transport in general should also be studied. Besides heroin inhalation, attention should be paid to pneumonia and TB, nutritional status and the use of cigarettes and base-cocaine.

**Mortality**

**Higher mortality rates among heroin users**

In section 4.3 we saw that all cohorts of opiate users show a higher mortality rate than expected in the general population of the same age. This is not a surprise; in contrast to non-heroin users, heroin users are at risk from fatal poisoning by opiates, which we discussed in sections 4.1 and 4.2. In addition, opiate users risk death due to diseases caused by the contamination of the heroin itself or the paraphernalia which they use to administer the drugs. Death due to contamination of illicit heroin exists but is not a major threat. Bacterial contamination of heroin sporadically causes deaths. Moreover, lethal leuco-encephalopathy among those who inhaled heroin was probably caused by a hitherto unidentified contamination in the early 1980's. Contamination of the injection equipment used causes more deaths. Viral infection - Hepatitis B, C and HIV - cause life-threatening diseases such as liver-cirrhosis and AIDS, bacterial infections cause abscesses, sepsis and endocarditis.
Besides to the toxic effect of the drugs and the danger of contamination of drugs and the paraphernalia, we should also take into account the consequences of the psychiatric syndrome of dependence itself. As described in the introduction, the diagnosis dependence is characterized by the continual use of heroin despite the significant social and medical problems related to the use of heroin. Most probably, these consequences of dependence, such as unemployment, homelessness, prostitution, criminality and poor nutrition indirectly lead to a higher risk of mortality.

**Overdose mortality**

Sections 4.1 and 4.2 focus on death caused by the direct toxic effect of opiates: death as a result of an overdose. The number of overdose deaths in the Netherlands is low compared to the number of overdose deaths reported in other countries. We may argue that the policy in Amsterdam is likely to prevent overdose mortality. The main intervention is large-scale methadone maintenance treatment which has proven to reduce overdose mortality in international studies and in a local study among injecting opiate users. The Amsterdam methadone treatment most probably contributed to a reduction of heroine use in general and injecting heroin use in particular. Medical and social care is provided to those people who continue using heroin and the low-threshold character of the programme is important in order to reach those with the highest needs. Methadone maintenance is expected to enhance the tolerance level of the heroin users, especially because treatment compliance is increasing and higher dosages of methadone are being used. In addition, in Amsterdam detoxification treatment is mainly limited to those drug users who are expected to complete this course of treatment successfully, possibly leading to a lower proportion of relapses after detoxification treatment. Moreover, if a potentially fatal overdose occurs, the provision of professional help is not only secured by a well functioning ambulance system but also by providing an atmosphere in which witnesses, who are usually other drug users, feel free to call for professional help.

The Frankfurt policy is modelled on the Amsterdam policy. The sharp reduction of overdose deaths in Frankfurt shown in section 4.2 is considered to be the result of implementing this policy. Similar to the programme in Amsterdam, large scale methadone maintenance treatment is one of the main interventions. However, in Amsterdam OD mortality rates during treatment and after leaving methadone treatment as presented in section 4.1 do not show a significant difference. Most probably, the risk of OD is already low because the vast majority of heroin users in Amsterdam are inhalers. In this situation the potential for reducing OD mortality with methadone treatment is low. We can
therefore argue that although the drug policy as implemented in Amsterdam is likely to reduce OD mortality, the low OD mortality rate among the Amsterdam users is not singularly a consequence of this policy.

5.3.3 Sick heroin user effect

If we consider general mortality among opiate users from an epidemiological perspective there is a complicating factor that hampers a valid description of the risk which is attributable to heroin dependence. In section 4.3 we call this factor the 'sick heroin user effect', after the 'healthy worker effect' which hampers a valid description of occupational risks. The 'healthy worker effect' implies that the employed population is generally healthier than the non-employed population of the same age, and the death rate in this population group is lower than the corresponding rates for the general population. The 'healthy worker effect' can be considered as a particular kind of self-selection which is derived from a screening process and the fact that unhealthy people leave work. It causes a bias in studying occupational risks because it tends to give results which are too positive.

The 'sick heroin user effect' can also be considered as a selection process. First, a selected group starts to use heroin; for example, users of alcohol or tobacco and users of marijuana are more likely to start using heroin, and in particular, those who start using these other substances at a young age are prone to progress to the use of heroin. Most probably, the mortality risks among those who start using heroin would also have been higher even if they had not started using heroin. Additionally, we know that the majority of those who start using heroin will not end up being a chronic user. The users who continue heroin use and develop dependence are a selection of the starters. Subsequently, treatment causes an additional selection. Heroin users with psychiatric co-morbidity have less favourable treatment outcomes than those with heroin use as a single problem. Finally, relapse often occurs and contributes to the sick heroin user effect. The risk factors associated with relapse are also associated with mortality and therefore contribute to the 'sick heroin user effect'.

To summarize, the 'sick heroin user effect' encompasses the selective mechanisms at the start of heroin use, the continuation of heroin use, treatment failure and relapse to heroin use that probably results in a lower health status and higher mortality rate among opiate users than expected in the general population of the same age. Consequently, when studying the risk factor opiate dependence we tend to overestimate the number of deaths attributed to heroin dependence. The influence of the 'sick heroin user effect' may differ in
time, place and among different ethnic subgroups and may explain some of the differences in mortality rates in different periods, regions or ethnic groups.

Within the study described in chapter 4.3 it was not possible to control for the influence of the ‘sick opiate user effect’ on the total population of opiate users, nor for the potential differences in this selection process between different countries. So, we should be reluctant to attribute the total increase of mortality to the opiate dependence itself. Differential selection processes may have influenced the results. However, the differential selection bias during recruitment of opiate users by the treatment centres in different countries will probably explain a much larger part of the observed differences.

**International comparison**

Section 4.2 attempts to explain why some cities have higher numbers of OD deaths than others. A detailed description of the cities revealed that there are many factors which could possibly explain the differences. Definition and registration practices vary and the cities have differing risk profiles in terms of characteristics of drug users, the drugs used and implemented facilities.

We realise that a clear comparison was hampered by the absence of detailed information about the nature of overdose mortality, for example whether OD was accidental or intentional, whether the victim was alone or with others, what combination of drugs were detected, whether the victim was recently detoxified etc. Moreover, to quantify risk factors we had to rely on the information which was available and it was not always possible to make comparisons. Additionally, studies to evaluate the effectiveness of measures implemented to reduce OD mortality are hardly ever conducted. Therefore, the result of this study is a qualitative description addressing the potential risk factors or preventive factors in each city and any possible differences in approach. The quantitative relevance of these risk factors in relation to the OD mortality rate in each city remains under discussion.

Section 4.3 provides reference rates which can be used to calculate the SMR in mortality studies among opiate users. This study aimed to improve the comparability of mortality studies by improving the ability to adjust for differences in age and sex distribution. Within this ongoing EMCDDA project nine cohorts are constructed. Differences in mortality rates and differences in causes of death over the course of time or between different cohorts are expected to generate additional hypotheses on the topic of mortality among opiate users in the future.

Oversimplification is a pitfall in studies which are conducted to explain general differences or specific causes of mortality between different regions, as we did in section 4.2. If we attempt to explain the differences, we start with the net results, in this case, the differences
in number of OD deaths. These differences are the result of a rather complicated web of causation. Based on literature studies we are aware of certain risk factors and preventive factors. However, there will be some risk factors which have not yet been found or factors which modify the reported effects. When studying the known risk factors, it is tempting to construct a scenario which ends at its starting point: the observed differences in mortality rates. Hence, in order to reach the net result the importance of the known factors will easily be overrated or undervalued.

In order to generate a scientifically clear epidemiological study it is preferable to concentrate on a single risk factor, a clearly defined outcome parameter and a short period of observation time. Differences in the characteristics of drug users and differences in the policy measures in different cities, regions and countries do not necessarily hamper the results but may offer the possibility to construct pseudo-experimental study designs instead.

**5.3.5 Future research questions**

The continued monitoring of mortality rates among methadone patients in Amsterdam and including more information about risk factors and causes of death is recommended. Mortality rates due to pulmonary diseases are of special importance. Although OD mortality rates are low and the number of HIV infected deaths has decreased, the total mortality rate among Amsterdam methadone patients continues to increase steadily.\(^{10}\) Preferably, a national population of drug users in treatment, as registered in LADIS\(^{17}\) should be used for this purpose. The current EMCDDA study on mortality rates is designed as an open cohort - i.e. *new people may enter the study during the study period* - of drug users applying for treatment for the first time. It may be preferable to transform this study into a study which is able to monitor mortality in a dynamic cohort of opiate users too - i.e. *during the study period people may enter but also leave the cohort in order to limit the population to active drug users*.

Concerning OD mortality, it is important to gather international comparable information concerning social behaviour in relation to overdose deaths. Differences in the presence and behaviour of bystanders when an overdose occurs may explain some of the differences in overdose death statistics between different member states. In contrast to observations in the United Kingdom,\(^{16}\) OD deaths where witnesses are present are rare in Amsterdam.\(^{16}\) This suggests that professional help is more often successfully offered in a life threatening situation in Amsterdam. As mentioned in section 4.1, social factors may also explain some of the differences between males and females concerning the risk of a fatal overdose. Females may use their heroin less often alone and/or bystanders may be more willing to offer help
if a woman suffers an overdose. Other relevant topics suitable for international comparison are: the influence of prison policy - detoxification versus methadone maintenance; on relapse, non-fatal and fatal overdoses after release among various subgroups of opiate users.

Sections 4.1 and 4.2 show that similar interventions do not always lead to similar results, which implies that results of studies conducted elsewhere, predominantly among injecting heroin users, cannot always be directly extrapolated to the Dutch population of heroin users, predominantly inhaling heroin users. Considering OD mortality, both the effect of risk reducing measures and the effect of risk enhancing situations is probably lower in The Netherlands. As we have discussed earlier, an example of risk reducing measures is the stable methadone maintenance treatment, and examples of risk enhancing situations are detoxification in prison and the onset of methadone treatment. Due to the limited reproducibility of studies concerning heroin users it may be worthwhile or even necessary to reproduce studies that are conducted elsewhere.

Considering the 'sick heroin user effect', we should monitor and quantify the selection mechanisms during the start of drug usage, the continuation of drug usage, treatment and relapse in order to understand the social, physical and mental health status and thus the mortality pattern of the drug users. In our opinion different selection mechanisms will explain a part of the differences in morbidity and mortality between heroin users of different countries and between users of different kinds of drugs. In Amsterdam different research groups focus on different stages of addiction and may be able to focus on a different part of the selection process, for example contact with drugs, initial usage, continuation, treatment resistance and relapse. These differential selection processes may also be applicable when studying morbidity and mortality among other groups at the margins of society such as the homeless.
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