Prevalence morbidity and mortality among heroin users and methadone patients
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Heroin use emerged in Amsterdam in the autumn of 1972. Thirty years later the chronic nature of heroin addiction is still visible on its streets. In 1981 the municipality of Amsterdam adopted a pragmatic and - for its time - revolutionary drug policy. In the absence of an effective cure for all heroin users the Municipal Health Service MHS aimed to contact as many heroin users as possible to prevent social and medical problems, or at least reduce them.

This thesis reports on a number of studies being conducted at the MHS. The first study involves estimating the size of the population of problematic opiate users in Amsterdam and thus the proportion in contact with the health service. The second and third studies deal with pulmonary disease, Tuberculosis TB and Chronic Obstructive Pulmonary Disease COPD. At the beginning of the 1990s it was feared that, along with the spread of the Human Immunodeficiency Virus HIV, a TB epidemic would emerge among opiate users. Symptoms of COPD are currently a cause of concern among opiate users and health care workers. The other three studies are into mortality among opiate users. The first describes overdose OD mortality in relation to time in methadone treatment. Methadone treatment is known to prevent OD mortality. Australian researchers, however, observed high OD mortality rates during the first two weeks after the onset of treatment. The second compares four Northern European cities: Oslo, Frankfurt, Copenhagen and Amsterdam. High and rising number of OD deaths are observed in Oslo. They contacted the other three cities with lower numbers of OD cases and stable or decreasing levels to find an explanation for the difference and clues to prevent OD mortality. The last study is taking place within the framework of a broader European project initiated by the European Monitoring Centre of Drugs and Drug Addiction. This project aims to improve comparability of mortality studies of opiate users. The specific study presented here is concerned with improving the outcome parameter in mortality studies of opiate users.

The introduction situates these studies within a broader perspective, providing background information on heroin, cocaine and methadone, the characteristic substances used by this population. It also explains the difference between drug use, abuse and dependence and gives a brief history of the Amsterdam drug problem and the steps being taken by the MHS. It concludes by introducing the individual studies and addresses their importance from a public health point of view.
HEROIN, COCAINE AND METHADONE

Heroin, *diacetylmorphine*, is a semi-synthetic opiate derived from the chemical manipulation of morphine, a process first described in 1874. Morphine is one of the psycho-active components of opium, which is extracted from the opium poppy, *Papaver Somniferum*. Cocaine is a stimulant extracted from the leaves of the Erythroxylon coca bush. The process of extracting cocaine has been known since 1855. The use of the raw materials of heroin and cocaine has a long history. Stories of the ancient Greeks and the native inhabitants of Latin America refer to the use of opium and coca leaves respectively. The history of methadone is much shorter. This synthetic opioid was developed for analgesia prior to World War II in Germany.

Nowadays heroin and cocaine are predominantly used because of their euphoric effects. The nature of the effect, however, is different. The desired psychotropic effect of cocaine is an energetic, active and sociable one whereas the desired psychotropic effect of heroin is a short period of feeling high ('kick') followed by a longer period of feeling pleasant ('nothingness'). Outside medical practice methadone is used predominantly to avert withdrawal symptoms, but it also generates a euphoric effect if administered by injection.

Heroin and cocaine can be swallowed, snorted, inhaled or injected. Among the drug users that are the focus of this study, however, both cocaine and heroin are either inhaled or injected. Compared to snorting, these methods of administration result in a faster maximum concentration, a higher peak, a shorter duration of effect and probably higher addiction rates. The pharmacokinetic properties of the substances differ. When injected, the elimination half-life of cocaine is approximately 40 minutes, that of heroin about 3 hours. Methadone is a long-acting opiate with a median half-life of 33-46 hours in healthy subjects but may vary considerably between individuals.

Heroin and cocaine were introduced into official medical practice at the end of the nineteenth century. Elixirs containing heroin were considered to cure a wide variety of illnesses, including bronchitis, chronic cough, asthma and tuberculosis. Cocaine also had medical applications, for instance as a local anaesthetic for minor surgery of the eye, nose or throat. At the turn of the twentieth century the danger of heroin and cocaine addiction was already recognised as a medical problem. During the twentieth century international legislation and the availability of alternative medication gradually reduced the medical use of heroin and cocaine. In Britain physicians have been allowed to maintain addicts on heroin since the 1920s. Only recently has the prescription of heroin to heroin users experienced an upsurge, following experiments in Switzerland and the Netherlands which indicate
that this treatment is both feasible and beneficial for chronic treatment-resistant heroin addicts.\textsuperscript{14,15}

Methadone is used predominantly as a substitute for heroin. After the Second World War Isbell & Vogel found that methadone could be used effectively to take addicts off heroin. They replaced heroin with methadone and gradually reduced the dosage. After reaching abstinence from opiates, however, relapse rates of more than 90\% were observed.\textsuperscript{16} A treatment in which methadone dosages were maintained was developed by Dole and Nyswander in the 1960s.\textsuperscript{17} Daily high dosages of methadone suppress the opioid abstinence syndrome, relieve the craving for narcotics, and block the effects of heroin. Methadone maintenance treatment has been proved to reduce heroin use and criminal behaviour.\textsuperscript{18} It has become the main form of treatment for heroin addiction. In the year 2000 approximately 275,000 heroin users were treated with methadone in the member states of the European Union.\textsuperscript{19}

\textbf{Use, abuse and dependence}

The 4th Diagnostical Statistical Manual of Mental Disorders \textit{DSM-IV} distinguishes between drug use, drug abuse and drug dependence. Drug abuse is characterised by a maladaptive pattern of drug use, one in which the use of drugs repeatedly results in failure to fulfil major role obligations and consequently leads to social, interpersonal or legal problems or may put the person or others in danger - e.g. \textit{driving under influence}. Drug dependence is described as a pattern of repeated use that usually results in tolerance, withdrawal and compulsive drug-taking behaviour. A great deal of time is spend on obtaining drugs, using drugs or recovering from the use of drugs, and important social, occupational or recreational activities are given up because of drug use. Despite these significant substance-related problems the drug use continues.\textsuperscript{20} The severity of dependence not only depends on the amount and frequency of the drug being taken but also on the negative consequences of drug use. Tools to measure the severity of dependence - e.g. \textit{the Addiction Severity Index} - are designed to assess the severity of the problem in areas commonly affected in alcohol and/or drug abusers: medical condition, employment, illegal activities, family relations and psychiatric condition.\textsuperscript{21}

Once the drug is used, repeated use of heroin is more common than repeated use of other illicit drugs. A survey of Amsterdam households in 1997 revealed that, of people who reported ever having used heroin - 1.7\% of the respondents - 41\% had used it more than 25 times. The percentage of the 'ever' users who took the substances more than 25 times was 10\% among users of hallucinogens - \textit{LSD, magic mushrooms}, 18\% among users of MDMA and 27\% among cocaine users. The legal/semi-legal drugs show higher percentages of frequent users
alcohol and cigarettes both 88%; cannabis 44%. Also, compared to users of other drugs, heroin users display more medical and social problems.

In the ensuing chapters of this thesis the terms 'heroin user' and 'opiate user' are both applied. Everyone in the target population has a history of heroin use but, as most studies are conducted in the framework of methadone treatment, heroin may have been substituted for methadone and therefore the term 'opiate user' is more appropriate. Although the term 'opiate use' is utilised, the diagnosis of opioid dependence will be applicable to the vast majority of the population examined in this thesis.

Historical context of the heroin problem in Amsterdam

In the history of the heroin problem in Amsterdam there are certain milestones: the introduction of heroin in the autumn of 1972, the introduction of the mobile methadone bus in 1979, the first diagnosis of Acquired Immunodeficiency Syndrome AIDS among heroin users in 1985, the stabilisation of the heroin epidemic during the 1990s, and the introduction of heroin prescriptions in 1998. The studies described in this thesis are taking place at the MHS, hence particular attention is paid to this organisation's drug-treatment services and studies. The MHS, however, is not the only provider of services for drug users in Amsterdam. In addition treatment is provided by the Jellinek and the general practitioners in Amsterdam. Moreover there are other low-threshold services such as the street-corner work foundation, the Rainbow foundation, the AMOC and organisations for the homeless such as the Salvation Army, the HVO and the Volksbond, which provide social help, daytime activities, accommodation and/or refreshments, and user rooms or needle exchange. The MDHG - junky union- and the Mainline foundation also offer health education and information to this group.

Heroin was introduced to Amsterdam in the autumn of 1972, when the withdrawal of US forces from Vietnam forced Southeast Asian syndicates to seek new markets for their heroin production. Before 1972 opium and amphetamines had been used on a small scale. Cohen describes this drug scene as part of a deviant youth culture: the vast majority 78% of the opium users he interviewed in 1968 were under 25. After 1972 the number of heroin users and the concomitant problems escalated rapidly. Heroin was mainly injected by the - originally Dutch - users. A rapid upsurge in the number of heroin users was recorded around 1975, when Surinam became independent and many Surinamese migrated to The Netherlands. Single male Surinamese adolescents came to play a major role in the heroin street trade, and many became users themselves. As a result of initial contacts with Chinese dealers/users they administered the drugs by inhaling heroin vapour
from heated aluminium foil 'Chasing the Dragon' instead of injecting. Nowadays the vast majority of heroin users in Amsterdam and other parts of the Netherlands administer the drug by Chasing the Dragon.

Although accurate data on the prevalence of heroin use in the 1970s are not available, guestimates indicate an explosive rise. The steep increase in the number of heroin users brought an increase in public nuisance and criminality in its wake. To conquer these problems a large number of initiatives were taken by various competing organisations, the majority of which were at least partial failures.

The first mobile methadone bus on the streets of Amsterdam in 1979 was the precursor of the large-scale methadone maintenance programme subsequently implemented by the MHS. The main goal of the MHS programmes was, and still is, to contact and maintain contact with heroin users, including those who are not willing or able to stop their heroin use. With this in mind, MHS programmes are 'low-threshold', i.e. free of charge, without waiting lists, and the criteria patients have to meet are restricted to the ones necessary to run the programme safely. Patients need to be registered, screened for tuberculosis - thoracic X-ray- and undergo periodical medical check-ups. Particularly important is the fact that there are no sanctions if urine tests reveal illegal substance use. The use of high dosages of methadone is encouraged, since this is more successful in reducing heroin use. Lower dosages can be given, however, if patients so request. In such cases regular contact and the use of ancillary services are considered to be important.

The MHS targets the most problematic heroin users. More stable users should be treated by their general practitioners. Some GPs were already doing this in the 1970s, and currently half of Amsterdam GPs provide methadone treatment. In order to prevent multiple prescriptions of methadone being supplied to the same person at different locations - jellinek, pharmacy or MHS - a Central Methadone Register CMR has been set up.

In addition to the methadone treatment programmes, medical doctors from the MHS started providing methadone at police stations to prevent withdrawal symptoms among arrested heroin users. A hospital project was also established: nurses from the MHS assist with hospital admissions of heroin users and advise the physicians in charge. Again the use of methadone is recommended to prevent withdrawal and subsequent premature discharge.

After the introduction of these programmes there was no immediate reduction in the heroin problem in Amsterdam, owing mainly to foreign heroin users, predominantly Germans, who frequented Amsterdam in the first half of the 1980s. The majority of the German users took their heroin intravenously and were vulnerable to overdose OD mortality. The number of fatal ODs rose, peaking in 1984 with 73
overdose deaths. To discourage this migration, foreign drug users were given only limited access to the Amsterdam methadone treatment programmes. They could only receive methadone treatment in the case of severe health problems or prostitution - i.e. humanitarian assistance and prevention of sexually transmitted diseases. This policy of discouragement led to the MHS setting up a Foreigners and Prostitution Outpatients Clinic. The large numbers of injecting drug users visiting the city for shorter or longer periods of time probably formed the breeding ground for the next period, one dominated by the threat of HIV.

In Amsterdam, the first AIDS case among heroin users was diagnosed in 1985. That year, the MHS began a prospective cohort study of predominantly injecting heroin users to study this disease. Subsequent research revealed that 30% of injecting drug users were already infected with the virus by then. Annual mortality of HIV-positive drug users reached its peak in 1993, since when it has decreased.

Among injecting drug users needle sharing - using one another's needles - is an important route for the transmission of blood-borne viruses. A needle exchange programme was introduced by the MDHC as early as 1984 to reduce the spread of the Hepatitis B Virus HBV. A few years later the needle exchange programmes were expanded to prevent further spread of HIV. The infrastructure of methadone programmes facilitated the provision of clean needles, condoms and health education. Researchers reported a decline in risk behaviour among injecting drug users. They observed a decline in the HIV and HBV incidence rates, but a stable high incidence rate of infection with Hepatitis C Virus HCV. The behavioural change observed among injecting drug users could reduce the likelihood of becoming infected with HIV but seemed to be insufficient to lower the incidence of HCV infections.

During the nineties there was a decline in the prevalence of injecting drug use, attributed to selective migration and mortality, more people ceasing to inject and fewer people initiating or relapsing into injecting heroin use. A qualitative study of drug users who stopped injecting suggests that the main factor in cessation was health reasons - i.e. poor condition of superficial veins. The increasing methadone dosages in treatment programmes may have facilitated the reduction in risk behaviour, injecting and consequently HIV infection. Also, the increasing popularity of non-injecting use of base cocaine may have contributed to the decline in injecting use. For those opiate users who were already infected with HIV the treatment opportunities increased with the introduction of Highly Active Anti-Retroviral Therapy HAART in 1996. Evidently the main threat of an HIV epidemic among opiate users has passed.
During the 1990s there was a growing notion that the heroin epidemic was stabilising. The annual number of heroin users participating in methadone treatment decreased from 3940 in 1989 to 2912 in 2000. Meanwhile, treatment compliance of those in treatment increased and, as a result, a stable number of approximately 2000 patients participated in the various programmes each week. The median age of these patients rose from 31.7 in 1989 to 41.2 in 2000. Particularly important is the decreasing number of young people among participants in methadone programmes and among those who are arrested and receive methadone at a police station. The number of patients in methadone treatment aged under 25 decreased from 498 in 1989 to 44 in 2000, the number of young - under-25 - heroin users receiving methadone at police stations decreased from 290 in 1989 to 63 in 2000. Figure 1 shows the trend in the epidemic based on the annual numbers of clients participating in the Amsterdam methadone treatment programmes by age category. It shows the initial increase and later decrease among the younger age categories and the increasing number of older patients.
Other studies, as well as the data from the Central Methadone Register, confirm that heroin has lost its attraction for youngsters.\textsuperscript{122,149} We are, however, observing increasing consumption of MDMA, amphetamine and cocaine - administered orally or by snorting. Within the general population, the prevalence of use of these drugs is much higher than prevalence of heroin use. The demand for treatment, however, is relatively low: only 1% and 2% of the demand for outpatient drug treatment is related primarily to the use of MDMA and amphetamine respectively. Twenty-three percent of the demand was related to the use of cocaine. One-third of the demand involved snorting and two-thirds inhaling cocaine.\textsuperscript{150}

Inhaling of base cocaine is causing increasing concern. Base cocaine became popular in Amsterdam in 1981\textsuperscript{151} and its popularity increased in the course of the decade.\textsuperscript{151} At that time users themselves prepared base coke from cocaine hydrochloride. During the 1990s, however, ready-to-use base coke was increasingly available on the streets. Besides the pharmacokinetic properties of the drug, the ease of administration, availability of ready-to-use substance and relatively low cost per dose may make smoked cocaine 'crack' more likely to be abused and to contribute to the process of marginalisation.\textsuperscript{18,152}

The population of base cocaine users largely coincides with the population of heroin users. Among base cocaine users of the street drug scene in the Bijlmer district of Amsterdam, 71% reported to use heroin on a daily basis and only 10% never used it.\textsuperscript{154} Among the heroin users selected for experimental heroin co-prescription it is the other way around: 90% used cocaine during the previous month.\textsuperscript{115} Among young drug users recruited for a cross sectional study at the MHS, almost all respondents reported a history of base-coke use - 90%. Heroin or methadone was used less often.\textsuperscript{155} Key informants confirm the preference for cocaine base among marginalized groups, but they also report cocaine users slipping into heroin use.\textsuperscript{149} Despite efforts to find a pharmacological treatment that specifically targets cocaine addiction, none has yet been found.\textsuperscript{146}

In The Netherlands, the heroin epidemic now seems to be in its final phase, and the chronic nature of heroin use among those who are still using it is increasingly accepted as a fact. This does not mean, however, that the ongoing problems it brings with it are also acceptable. Social marginalization remains a major problem for both heroin users and society at large. Many heroin users remain stuck in poverty, drug use and deviant behaviour. Also, some methadone treatment clients continue using heroin compulsively despite sufficiently high dosages of methadone.

Methadone is not a panacea, and additional forms of substitution treatment have been introduced for those heroin users who have not responded satisfactorily to methadone treatment. A group of 1100
heroin users who were frequently arrested by the police were selected for heroin prescriptions as early as 1982. The prescription programme never got under way, however. A small-scale pilot scheme - N = 26 - was launched in 1983 using morphine as a substitute for heroin. The patients evaluated showed moderately positive results. The morphine substitution programme was not extended, but those subjects in whom morphine substitution led to positive results were permitted to continue with the treatment. In 1990, the MHS started a palliative treatment with prescribing intravenous methadone to severely addicted AIDS patients who were in very poor health. In 1996 a selected group of methadone clients with ongoing heroin use were treated with dextromethoramide - *Palfium*. Again the results appeared to be moderately positive, but as in the morphine study there was no comparable control group. Finally the first randomised controlled trial in which methadone was compared with methadone plus heroin co-prescription was started in 1998. The initial results show a statistically significant improvement in physical, mental and social health among heroin users. In addition to heroin co-prescription an involuntary programme has been introduced, the Penal Care Facility for Addicts *SOV*. This treatment targets chronic heroin users who are frequently arrested and is based on detoxification and rehabilitation within the correctional system. No results are available from this project yet.

**The Content of This Thesis**

This thesis contains six epidemiological studies describing the prevalence of problematic opiate use in the city of Amsterdam, focusing on two important forms of morbidity among opiate users - *tuberculosis and chronic obstructive pulmonary disease*. Three of the studies deal with mortality among opiate users. Apart from the study on pulmonary function they are based on data already available at the MHS. Data from other European cities, regions or countries are used in the last two studies in addition to the Amsterdam data.

Chapter 2 describes an estimation of the prevalence of problematic opiate users in the city of Amsterdam. This chapter focuses on the method, a three-sample capture-recapture, and emphasises the importance of case definition. As described earlier, one of the main goals of the Amsterdam treatment programmes is regular contact with the target population: the potential impact of preventive measures increases with the proportion of the target population reached. In order to know what this proportion is, the prevalence needs to be estimated. Prevalence estimations are also anchor points in the description of the heroin problem, enabling us to interpret the prevalence of heroin-related health problems - *e.g. heroin overdose mortality or TB among*
heroin users in terms of risk. A prevalence estimation also permits a quantitative comparison of the Amsterdam heroin problem with those of other cities, either in absolute terms or in relation to population size. If prevalence estimations are performed periodically, trends over time become visible.

Section 3.1 describes the incidence rate of TB among methadone clients in Amsterdam. At the start of the 1990s it was feared that the HIV epidemic among opiate users would be accompanied by a TB epidemic. TB remains a threat: opiate users suffering from TB can transmit the TB bacillus to other drug users, health care workers and the population at large.

TB is a disease of the disadvantaged and marginalized populations. Drug dependence was first suggested as a risk factor in TB by Reichmann et al. in 1979. Among drug users infected with HIV, TB often appears as the first manifestation of AIDS. Selwyn et al. describe the increased risk of TB among HIV positive drug users. The risk of the infection being transmitted is considered to be high, especially at the treatment centres. Heroin users participating in methadone programmes at the MHS are periodically screened, unlike methadone patients who attend their GPs. This study describes the incidence of TB in various treatment programmes.

Section 3.2 describes the situation as regards pulmonary function in methadone clients, focusing on chronic obstructive pulmonary disease. COPD is a cause for concern among health care providers and heroin users. It is characterised by airflow limitation that is not fully reversible. COPD has been associated with an abnormal response of the lungs to noxious particles and gases and occurs in approximately 15% of chronic cigarette smokers. The airflow limitation is usually progressive, and functional impairment presents only after 20-30 years of exposure. Chronic cigarette smoking is much more common among opiate users than in the general population.

As stated before, nowadays, the majority of the heroin users in The Netherlands inhale the substance. The influence of inhalation of heroin on pulmonary problems has not been described in the scientific literature, apart from a few case studies which report asthma attacks after inhalation of heroin. The degree of exposure to heroin by inhalation among methadone clients varies widely: some have never inhaled, others have inhaled daily for over twenty years. Based on these contrasts we attempt to find a best estimate for the effect of heroin inhalation on pulmonary function.

Section 4.1 describes overdose mortality in relation to the period during methadone treatment and after methadone treatment. Several studies indicate that methadone treatment reduces overdose mortality among heroin users. In New South Wales, however, Caplehorn and Drummer reported extremely high OD mortal-
ity rates during the first two weeks of methadone treatment - 70.4/1000 py. Rates during other periods of treatment and rates without treatment were estimated at 0.7 and 10.5 respectively.\textsuperscript{17} In Amsterdam methadone maintenance is the main treatment for heroin users. Treatment-related deaths are of particular importance because they may be preventable by modifying procedures within the methadone treatment programme.

Section 4.2 describes the differences and similarities between the situations regarding overdose mortality in four European cities - Oslo, Copenhagen, Frankfurt and Amsterdam. This study was initiated by the city of Oslo, which experienced a rising number of overdose deaths during the nineties. Although the number of opiate users in the other three cities is comparable, the number of OD deaths is lower and decreasing or stable trends are observed. A working group containing representatives from each city visited the cities, studied the available information and conducted interviews with local opiate users, police officers, social workers, paramedics, politicians and policy-makers.

At first sight the mechanism and treatment of a heroin OD do not seem to be very complicated. The main causal mechanism of a fatal heroin OD is the effect of heroin on the respiratory centre of the brain, causing respiratory depression and consequently a lack of oxygen. The vast majority of fatal ODs do not occur instantaneously,\textsuperscript{17} and death can be avoided by administering oxygen and an opioid antagonist - Naloxone.\textsuperscript{17}

In practice, however, comparing different cities is a complicated business. They may apply different procedures and definitions when it comes to recording OD mortality. Also, the breakdown of their populations of opiate users may vary, with higher or lower proportions of specific risk groups such as intravenous heroin users,\textsuperscript{17} those concurrently using alcohol and/or benzodiazepine,\textsuperscript{17} homeless heroin users,\textsuperscript{17} HIV-positive heroin users.\textsuperscript{17} Different proportions of opiate users may experience periods of higher risk such as periods following detoxification,\textsuperscript{16} incarceration\textsuperscript{16} or start of methadone treatment\textsuperscript{16} or lower risk for example during stable methadone maintenance. On top of this the way people act if they witness an overdose may differ. Bennet & Higgins reported that although most witnesses to an overdose thought that emergency help should be sought, only 44% actually contacted the emergency services.\textsuperscript{16}

The main question the study examined is whether drug policy influences OD mortality figures. Oslo's drug policy relies predominantly on abstinence and rehabilitation. Amsterdam's policy focuses on preventing and solving medical and social problems among heroin users referred to as a 'harm reduction policy'. Frankfurt developed a drug policy modelled on the Amsterdam policy at the beginning of the nineties. Copenhagen gradually moved from an abstinence and reha-
bilitation-oriented approach to one focusing on harm reduction.

Section 4.3 describes the last study, which aims to improve comparability of the outcome measure between mortality studies. This study is part of a project initiated by the European Monitoring Centre for Drugs and Drug Addiction, an organisation which aims to provide objective, reliable and comparable information at European level on drugs and drug addiction and their consequences. The project on mortality among opiate users involves multiple European countries, regions or cities and aims to improve comparability of the results by using similar enrolment criteria for drug users, follow-up procedures and methods of data analysis. The specific study presented in section 4.3 aims to improve the comparability of outcome parameters.

The main outcome parameters in general use are crude mortality rates and Standardised Mortality Ratios. The SMR corrects for differences in age and gender distribution between the study population and the reference population. Unfortunately, this does not result in full comparability between different study populations. Firstly, the SMR generally takes the population of a particular country or city at the time of the study as a reference population, so variations in mortality rates between reference populations can produce proportional variations in the SMR. Secondly, several studies suggest that rate ratios of heroin users to the general population are heterogeneous. Rate ratios are lower among the older age categories than the younger ones, and lower among males than females. The study describes this heterogeneity based on the nine European cohorts of opiate users. It also presents stratum-specific mortality rates, which can be used as a reference for calculating valid and comparable SMRs in single-group mortality studies of opiate users.

The final chapter of this thesis elaborates on the findings of the individual studies. It discusses the concept of 'coverage by drug-related services' and 'drug-related deaths' and provides additional information on trends in prevalence of drug use. It enunciates the concept of the 'sick heroin user effect', which, similarly to the 'healthy worker effect', complicates mortality studies of opiate users. It concludes by presenting the main conclusions of the studies and outlining directions for future studies on related topics.
By clinicians

The pharmacokinetics of methadone in patients with different genetic backgrounds.

The effectiveness of methadone maintenance treatment in patients with different genetic backgrounds.

When methadone is not enough: A new perspective on optimal methadone maintenance treatment.

Public Health Spain and

Necesidad de la praxis del moderno hospital.

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