‘Prescriptions of antibiotic and antiviral drugs one year prior to drug-induced death in Oslo’

- A mandatory thesis in the medical study at the University of Oslo, Norway.

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Abstract

Bacground and aims: Infectious diseases are common causes of morbidity and mortality among problem drug users. The aims of this study were to explore: prescriptions of antibiotics and antivirals to drug users during the last year prior to drug-induced death, and what this can tell about infections among these; demographic and forensic-toxicological characteristics of the deceased that were dispensed antiinfectiva; prescriptions of resistance driving antibiotics.

Methods: This retrospective registry study explored data from the Norwegian Prescription Database, and from 'Overdoses in Oslo 2006-2008', a study previously conducted at The Norwegian Centre for Drug and Addiction Research, the University of Oslo. Subjects (n=231) were deceased from drug-induced death in Oslo, from 1 January 2006 to 31 December 2008.

Results: Ninety (39%) of the deceased received antibiotics. According to type of dispensed antibiotics, the deceased suffered from skin or/and soft tissue infection (n = 65, 28%), respiratory tract infection (n = 36, 16%), and urinary tract infection (n = 9, 4%). Three (1.3%) were treated for HCV infection, and six (2.6%) for HIV infection. Compared to the general population, the deceased had increased odds to receive any antibiotics, and in particular for antibiotics commonly used for skin or/and soft tissue infections.

Conclusion: The results suggest that efforts should be made to modify well known risk factors for infectious diseases among drug users, establishment of health centres targeted to drug users, as well as to encourage problem opiate users to enroll in OMT, and to motivate recipients of OMT to continue.

1. Introduction

Illicit drug use is an important contributor to the global burden of disease by counting 20 million Disability Adjusted Life Years (DALY), and constitute 0.8% of all-cause DALYs. Opioid dependence and injecting drug use are the most significant contributors to the burden of disease, and for all types of illicit drug use there is a disproportional high representation of young men aged 20 to 29 years[1]. Problem drug use (PDU) has been defined by the EMCDDA as 'injecting drug use or long duration or regular use of opioids, cocaine, and/or amphetamines'[2]. It has been estimated to be about 1.3 million PDUs in Europe, and these have an increased mortality rate of approximately 10-20 times compared to the general population of the same age and gender[3]. Drug-induced death is the most common cause of death, and account for 28-60% of the reported deaths among PDUs[4]. Factors that are associated with drug-induced death include previous non-fatal overdose[5], injecting drugs [6, 7], poly-drug use with heroin in combination with substances such as benzodiazepines and alcohol[7, 8], recent imprisonment[9, 10], recent termination of opioid maintenance treatment (OMT)[11], being homeless[12], and Hepatitis C Virus (HCV) infection[6].

Infectious diseases are common[13], and represent nearly half of the acute presentations to hospital emergency departments among IDUs[14]. Skin and soft tissue infections account for most of the infections, followed by respiratory and circulatory infections[14-16]. Important risk factors for skin and soft tissue infections include injection of drugs, poor hand and skin cleaning prior to injection, use of unclean needles, subcutaneous or intramuscular injections, and injecting a combination of heroine and cocaine[17, 18]. Having a poor diet and being underweight has been associated with skin abscesses[19]. Many drug users are homeless, that increase the risk of both skin and respiratory infections[20, 21]. The majority of IDUs smoke cigarettes[22]. This, together with the use of alcohol and injecting drugs increase the risk of aspiration pneumonia[23]. In general, opiate users have an increased susceptibility for infections, as opiates mediate immunosuppression through a number of mechanisms of both the innate and adaptive immune system[24].

Hepatitis C Virus infection is highly prevalent among IDUs. Most countries report prevalence of HCV infection above 50%, and the trend is increasing in most countries[25]. Although treatment for HCV reduces the risk for liver disease and liver related deaths[26, 27], the treatment uptake in IDUs is low[28] and many

discontinue treatment[29]. The prevalence of HIV among IDUs is below 5% in most countries, but outbreaks have recently been reported in Greece and Romania[25].

Besides drug-induced deaths, suicide, homicide and digestive system diseases, infectious diseases are among the major causes of death among drug users. Hepatitis C infected drug users constitute a particular vulnerable group, as they have increased mortality risk for each of the other major causes[6]. About one in five deaths among opiate dependent drug users are liver related, and HCV infection is the major source of liver related deaths[30, 31]. According to the EMCDDA, about 1700 people died in 2010 of HIV/Aids attributable to intravenous drug use in Europe, and this represent a downward trend[25]. Acute infections have also been reported as a cause of death among IDUs, including endocarditis[32], pneumonia[32, 33], meningitis and sepsis[34], and spore forming bacteria such as botulism, clostridium, tetanus and anthrax[35]. Although it has been reported few cases of death due to pneumonia, it is a common infection among IDUs, and it is plausible that its negative effect on pulmonary function reduces the tolerance for the opiate-mediated respiratory depression, and hence may be a contributing factor to drug-induced death[36, 37].

The prevalence of infections among PDUs is uncertain for several reasons. Due to their preoccupation with searching drugs, they often postpone or refrain seeking health care[38]. They are also inclined to self-treatment of infections with antibiotics obtained from non-provider sources such as friends, family members or other drug users[39]. Many drug users normalize the health problem and do not perceive it serious enough to seek health care. Some refrain from health service due to unpleasant past experiences, fear of discrimination, or thinking that they might be seen as wasting health service time[40]. In the health care system, it may be challenging to arrive at the correct diagnosis and treatment[41]. Intravenous drug users often have more than one infectious disease at the same time[16]. It may be difficult to know whether a patients' intent of visiting the doctor would be to get help for a symptom or a health problem, or to obtain drugs on prescription for misuse by fraudulent presentation of disease to one or more doctors, often referred to as doctor shopping or drug-seeking behaviour. An Australian study found an increased number of doctor

visits and prescriptions of addictive drugs during the last year before overdose deaths, and suggested doctor shopping as a possible risk factor for overdose deaths[42].

Illicit drug users have increased morbidity and mortality[1]. Infections are common causes for contact with the health care system[15, 43-45], and risk factors for infections are related to the type of drug[24] and its administration[17, 18], poor lifestyle including homelessness[20, 21] and malnutrition[19]. Few other studies have explored infectious diseases among drug users residing outside institutions, and there are no other studies that provide an overall perspective on antibacterial prescriptions to this group.

The Norwegian Prescription Database (NorPD) was implemented in 2004. The Norwegian Prescription Database (NorPD) collects information on drug prescriptions that are dispensed in Norwegian pharmacies, to individuals living outside institutions. We wanted to use the NorPD to evaluate the prescriptions of anti-infectives to drug users that deceased of drug-induced death between 1 January 2006 and 31 December 2008. The aims were to find out:

- To what extent were various anti-infective drugs prescribed to the deceased, and what do this tell us about infections in this group?
- What features, such as age, gender, contact with health services, and forensic and toxicological findings, characterized the deceased that were prescribed anti-infective drugs?
- To what extent were the deceased prescribed antibiotics that may contribute to antibiotic resistance, such as broad spectrum penicillins and tetracyclines?

2. Materials and methods

2.1 Setting

Norway has the second highest rate of drug-induced deaths in Europe, with 76 deaths per million inhabitants[25]. In Oslo, the capital of Norway, with approximately 640.000 inhabitants[46], the rate of drug-induced deaths is nearly 50% higher than in the rest of the country[47]. In 2012, it was between 7200 and 10100 injecting drug users in Norway[48]. The number of patients enrolled in Opioid Maintenance Therapy (OMT) has steadily increased since its establishment in 1998[49], and by the end of 2013 there were 7055 patients in OMT, thus encompassing approximately half of the heroin using IDUs in Norway[46]**.** After a decrease from around 400 per year at the beginning of the century, the number of drug-induced deaths have remained stable between 200 and 300 annually the last years. According to a study conducted in seven norwegian cities in 2013, eighty per cent of those who used illegal opioids or central stimulating drugs the last four weeks had injected drugs during the same period[50]. Intravenous drug users were more likely to be female, younger than 44 years of age, and heroin and amphetamines were the most common drugs to inject. In 2012, thirteen per cent of those attending to needle distribution facilities in Oslo reported having shared used needles or syringes during the last four weeks[49]. A prevalence survey in 2012 among users of needle distribution programmes and drug injection rooms in Oslo, showed that 62% had a hepatitis A infection or had been vaccinated, 35% had a hepatitis B infection, and 64% had a hepatitis C infection[49]. Data on bacterial infections among drug users are insufficient in Norway. Several outbreaks of botulism have been reported in Norway[51, 52], and the most recent occurred from December 2014 to February 2015 and affected 10 IDUs in Oslo[53, 54]. Between five and ten cases of methicillin resistant staphylococcus aureus (MRSA) among drug users were reported annually the last years[49].

2.2 Subjects

This retrospective registry study explored data from the previous study ‘Overdoses in Oslo’, and the following paragraphs regarding inclusion of subjects and data sources were first formulated by Gjersing et al.[8]. The study includes deceased persons in the age between 15 and 65 years that died from drug-induced death in Oslo, in the period from 1 January 2006 to 31 December 2008. The deceased were included

according to the EMCDDA definition of drug-induced deaths: 'people who die directly due to use of illegal substances, although these often occur in combination with other substances such as alcohol or psychoactive medicines. These deaths occur generally shortly after the consumption of the substance'[55]. They were initially identified through the National Cause of Death Registry (NCDR), which is a general mortality register. The information was coded as 'underlying cause of death', and is defined as 'the disease or injury that initiated the chain of fatal events leading directly to death or the external circumstances of the accident or violence that was the cause of the fatal injury'[56]. The deceased were distributed in four age groups: 25 years or younger; 26-35 years; 36-45 years; above 45 years.

2.3 Data sources

The data obtained from the NCDR included full name, personal identification number, date of birth, date of death, postal code for the region of death, residental postal code, and whehter the person had a post-mortem examination (hospital or forensic). Vital data were cross-linked with other registries and patient/client records and anonymized for the researchers.

Data on toxicology were received from the Institute of Forensic Medicine at the University of Oslo. These data included the place of death and the postal code for the place of death. Place of death included the following variables: 'residential address', which included shelters providing long-term accommodation; 'outdoors', which included parking houses and public toilets; and 'institutions', which included hospitals, drug treatment facilities and prisons. Although only one substance was considered to be the main intoxicant by the pathologist, a person could have several other substances in their blood that may have contributed to the death. Information on both main intoxicant and other substances were collected. In this study it was created an aggregated variable for prescription opioids as the main intoxicant, which included dextromethorphan, ethylpmorphine, fentanyl, codeine, oxycodone, and tramadol.

The Norwegian Correctional Services provided the date of prison release up to 6 months before the date of death. The other social and health services provided data up to 1 year before the date of death. The number

of contacts, the type of contacts and the last contact date were collected from pre-hospital emergency services (ambulance and acute health care clinics), three hospitals that included both psychiatric and somatic wards and community care services in Oslo. Public and private drug treatment facilities, low treshold housing facilities and harm reduction facilities, such as daytime shelters and street clinics, provided contact dates, reason for contact and the last contact date. Data were also provided by the public social services in Oslo where all dates for each visit were recorded in addition to complete information on the content of each recorded visit[8]. In this study, contact with any of the three hospitals was aggregated into the variable 'contact with any hospital'.

Prescription data was extracted from the Norwegian Prescription Database (NorPD). The NorPD was established by virtue of the Norwegian Health Surveillance Act of 2001, and has collected data on all prescribed drugs dispensed in Norwegian pharmacies since 1 January 2004. It covers the entire population of approximately 5.1 million, and contains information on all dispensed drugs to individual patients living outside institutions. Each prescription record contains data variables describing characteristics regarding the patient, the prescriber, the drug, and the pharmacy. Until March 2008, indications for prescribing were not recorded, and only reimbursement codes could in some cases be used as proxies for diagnoses[57]. The prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC) system and Defined Daily Doses (DDD). The ATC system categorize the active substances according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Each active substance has a code with 6 digits and letters that contains information about the main group, subgroups and the specific active drug. A DDD is defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'. Only drugs with an ATC code have been assigned a DDD[58]. Variables that were extracted from the NorPD and used for data analyses were the encrypted patient identification number, the encrypted prescriber identification number, date of death, dispensing date, the product number, ATC-code, and Defined Daily Dose (DDD).

2.4 Data strategy and analyses

Prescription data from NorPD for each patient were linked to the data from other sources by a common pseudonymised patient identification number, constructed by a trusted third-part, the Statistics Norway. Before the files arrived at the Statistics Norway, all other data than the personal identification number and the prescribers' health personnel number were encrypted. When the encrypted files arrived at the Norwegian Institute of Public Health, they were decrypted so that all variables were available for analyses[57].

Prescription data from the last year prior to drug-related death was analysed according to 1) groups of, or specific antibiotics and antiinfective drugs, and 2) type of infection indicated by the prescribed anti-infective drugs. Main groups or specific antibiotics and anti-viral drugs include: Any antibiotics (J01), tetracyclines (J01A), penicillins (J01C), penicillins with extended spectrum (J01CA), beta-lactamase sensitive penicillins (J01CE), beta-lactamase resistant penicillins (J01CF), cephalosporins (J01D), sulphonamides and trimethoprim (J01E), macrolides (J01F), quinolones (J01M), other antibacterials excluding methenamine (J01X). When it was feasible, the active drug at ATC-7 level was used for analyses, such as phenoxymethylpenicillin (J01CE02).

Types of infections were based on common areas of use according to the Norwegian Guidelines for Antibiotic use[59], the Norwegian Drug Handbook[60], the Norwegian Pharmaceutical Product Compendium[61], and by consulting staff at Oslo University Hospital. All prescribed anti-infective drugs were cross-matched with each other and with relevant groups of somatic drugs acting in the respiratory system, alimentary tract, and dermatological system, to explore patterns that could suggest indication for prescribing antibiotics that otherwise have several possible indications according to the existing guidelines. Due to small sample size, this allowed only for few generalizations: Phenoxymethylpenicillins (J01CE02) were more likely prescribed for dermatological infections; tetracyclines (J01A) were more likely prescribed for an respiratory tract infection. The following infectious subgroups were defined according to the overmentioned strategy: Skin or/and soft tissue infection; dicloxacillin (J01CF01), cloxacillin (J01CF02), clindamycin (J01FF01), phenoxymethylpenicillin (J01CE02). Respiratory tract infection; Tetracyclines (J01AA), macrolides (J01FA), amoxicillin (J01CA04). Urinary tract infection; Pivmecillinam (J01CA08),

Sulfonamides and trimethoprim (J01E), nitrofurantoin (J01XE01). HIV-infection; lopinavir (J05AE06), atazanavir (J05AE08), didanosine (J05AF02), emitricabine (J05AF09), efavirenz (J05AG03), combination treatment of HIV (J05AR). HCV infection: Ribavirin (J05AB04). The groups are not mutually exclusive, and the deceased may appear in more than one type of infectious group.

For all analyses describing numbers of persons being dispensed an anti-infective drug or numbers of persons in an infectious subgroup, the numbers only describe how many were dispensed a drug at least once during the last year before overdose death, or how many at least had one case of an infectious condition that resulted in receiving anti-infective drugs.

2.5 Statistics

All analyses were performed with SPSS version 22.0 for Windows. Chi-Square tests were used to test for differences between groups on binominal data, and the results are described with the respective proportions in per cent, the Chi Square test statistic X^2, and the p-value. Fishers Exact test was used in comparisons of small groups. For categorical data such as age, and location of death, sub-group analyses for each category were done to reveal possible significant results. Due to not mutually exclusive groups of bacterial infections, chi-square test for each group was tested against those not being prescribed any antibiotics. Odds ratios with confidence intervals were calculated according to the logit method by Woolf[62]. A lowest significance level of 0.05 was applied for all analyses. The inhabitants of Oslo Municipality in year 2007, between 15-64 years were used as reference population in comparative analyses.

2.6 Ethics

This study was performed on data that was collected in a previous study, 'Overdoses in Oslo 2006-2008', conducted by researchers at the National Centre for Addiction Research (SERAF), the University of Oslo[63]. The Regional Committee for Medical and Health Research Ethics approved the study and granted exemption from the duty of confidentiality. All subjects included in the study were deceased, hence the information about these were outside the jurisdiction of the Personal Data Act and the Norwegian Data

Protection Authority. Data provided by the Oslo University Hospital were stored in a safe. Other collected data were stored electronically at the network of statistical analyses at the University of Oslo. Personal identification numbers of the deceased were encrypted, and the cipher key was safely stored. All data were stored in accordance with the Personal Data Act. The Director of Public Prosecution provided access to post-mortem reports, and exemption from the duty of confidentiality. After application to the Regional Committtee for Medical and Health Research Ethics, five new researchers were included to the study on 16 April 2013.

Both the society as a whole and individuals of the target group in question are beneficiaries of the study. The morbidity and mortality of problem drug users is a concerning problem, and it is of general interest to gain more knowledge that can identify targets for intervention. The society will benefit from persons that with lives saved and improved health can participate in fields such as societal activities, work, culture and politics. It is also of general interest to have knowledge on patterns of antibiotic prescriptions in such risk groups, so that resistance to antibiotics can be prevented. Individuals of the group in question may benefit directly from well-adapted health and social services that can improve their health and quality of life, and prevent overdose deaths. Employees in the social and health sector may experience more coping and success in contact with the drug users as for example more knowledge can contribute to more trust them between. A disadvantage of the study may be that problem drug users fell stigmatized from the knowledge that evolve from the research. However, the study is regarded as ethically justifiable as the above-mentioned advantages exceed the disadvantages.

3. Results

3.1 Background

Table 1 shows the demographic and forensic characteristics of the 231 persons that deceased from drug-induced death in Oslo Municipality, between 1 January 2006 and 31 December 2008. Males accounted for 77.9%, and females for 22.1% of the deceased. Sixty-eight per cent were residents of Oslo Municipality. Nearly half of the deceased were in contact with the social service or a hospital during the last year, and eight per cent were in contact with prison during the last 6 months. The most common locations of death were at a residental address (67.1%), and outdoor (17.7%). Heroin was considered as the main intoxicant in 65.8% of the deceased, and was besides benzodiazepines and hypnotics the most common drug found in forensic toxicological examinations. The mean number of substances was 2.9 (SD 1.4), and the two most common combinations of substances were heroin and benzodiazepines and/or hypnotics (n = 115, 49.8%), and heroin and stimulant drugs (n = 61, 26.4%).

3.2 Prescriptions of antibiotics and antiviral drugs

The deceased filled in total 7496 prescriptions during the last year prior to drug-induced death. Antiinfectives for systemic use (ATC J) accounted for 280 (3.7%) of the prescriptions, antibiotics for systemic use (ATC J01) accounted for 197 (3%), and antiviral drugs for treatment of HIV and HCV accounted together for 51 (0.7%) of all prescriptions.

The mean number of antibiotic prescriptions per recipient (n = 90) the last year was 2.2 (SD 2.0) and mean number of Daily Defined Doses (DDD) was 25.9 (SD 34.8). The mean number of new prescribers of antibiotics the last year was 1.6 (SD 1.0) per recipient. Figure 1a shows the mean number of filled prescriptions of antibiotics (J01) per month per recipient. The difference quotient of the trend function is -0.009, meaning that when counting backwards each month from the date of drug-induced death, the mean number of antibiotic prescriptions decreased by 0.009 times, or conversely the mean number increased by 0.009 times for each month towards the date of drug-induced death. Figure 1b shows the mean number of

new prescribers of antibiotics (J01) per month per recipient. The trend is only slightly increasing towards the date of drug-induced death, with a difference quotient of -0.005.

As shown in table 1, ninety of the deceased (39.0%) filled at least one prescription for any antibiotics during the last year prior to drug-induced death. Females more likely received antibiotics than males (51.0% vs. 35.6%, Chi Square test statistic $X^2 = 3.976$, $p < 0.05$). Those who received antibiotics were more likely to have forensic toxicological findings with benzodiazepines or/and hypnotics (77.8% vs. 63.8%, $X^2 = 5.020$ $p < 0.05$), and less likely with amphetamines (22.2% vs. 36.2%, $X^2 = 5.020$, $p < 0.05$). Heroin in combination with stimulants were less likely found among those who received antibiotics (66.7% vs. 79.4%, $X^2 = 4.708$, $p < 0.05$).

3.3 Skin and soft tissue infections

Sixty-five of the deceased (28.0%) received antibiotics commonly used for a skin or a soft tissue infection, such as dicloxacillin, cloxacillin, phenoxymethylpenicillin and clindamycin. There was no difference between genders. They were more likely to have forensic toxicological findings including cannabis (29.2% vs. 14.2%, $X^2 = 6.563$, $p < 0.05$), and benzodiazepines or/and hypnotics (78.5% vs. 63.8%, $X^2 = 4.410$, $p < 0.05$). As shown in table 2, the deceased had increased odds ratios for being dispensed phenoxymethylpenicillin (OR 2.5, 95% CI: 1.8, 3.4), beta-lactamase resistant penicillins (OR 6.2, 95% CI: 4.0, 9.8), and clindamycin (OR 3.4, 95% CI: 1.6, 7.3). Figure 2 shows that such antibiotics accounted for 51.6% of all dispensed DDD of any antibiotics to the deceased, as compared to 35.9% in the general population.

3.4 Respiratory tract infections

As shown in table 1, thirty-six (16%) of the deceased received antibiotics that are commonly used for respiratory tract infection (RTI), such as tetracyclines, amoxicillin and macrolides. Compared to those who were not dispensed any antibiotics, the recipients were more likely to be females (27.4% vs. 12.2%, $X^2 = 7.473$, $p < 0.01$), to have main intoxicants such as prescription opiates (19.4% vs. 6.4%, $X^2 = 5.950$ $p < 0.05$)

and OMT drugs (22.2% vs. 9.2%, $X^2 = 4.637$ $p < 0.05$), and less likely heroin as main intoxicant (47.2% vs. 68.8%, $X^2 = 5.821$, $p < 0.05$). They were also less likely to have the combination of heroin and stimulant drugs in the forensic toxicological findings (52.8% vs. 79.4%, $X^2 = 10.593$, $p < 0.01$). As shown in table 2, there was not significantly altered odds ratios for the deceased to be dispensed any antibiotics for a RTI, and these antibiotics all together constituted a lower proportion of the total number of prescribed DDD, as compared to the general population (36.3% vs. 52.7%).

3.5 Urinary tract infections

Nine of the deceased (4.0%) were dispensed antibiotics typically used for urinary tract infection (UTI), such as pivmecillinam, sulphonamides and trimethoprim and nitrofurantoin. Females were more likely than men to be prescribed antibiotics for an UTI (11.8% vs. 1.7%, $X^2 = 12.357$, $p < 0.01$). Compared to the general population, the deceased did not have altered odds for being prescribed any of the above mentioned antibiotics, and all together these accounted for a slightly smaller proportion of the total number of prescribed DDD of antibiotics, than in the general population (11.7% vs. 13.0%).

3.6 Blood borne infections

Three of the deceased (1.3%) were dispensed antiviral drugs for a HCV-infection, and six (2.6%) were dispensed antiviral drugs for a HIV-infection. Those who received a drug for one or both of these infections, were more likely above 45 years of age ($X^2 = 8.329$, $p < 0.05$), to be in contact with a hospital ($X^2 = 8.456$, $P < 0.01$) during the last year prior to death, and to have an institution as location of death ($X^2 = 29.294$, $p < 0.001$) (results are not shown in table 1). As shown in table 2, they had markedly increased odds ratios for being prescribed both ribavirin (OR 60.8, 95% CI: 19.1, 193.7), and anti-retroviral combination treatment for HIV (OR 15.8, 95% CI: 6.5, 38.4).

3.7 Resistance driving antibiotics

As shown in table 2, ten of the deceased (4.3%) received penicillins with extended spectrum, and they did not have significantly increased odds of being prescribed these penicililns compared to the general

population (OR 0.9, 95% CI: 0.5, 1.7). Tetracyclines were prescribed to ten of the deceased (4.3%). The deceased did not have significant higher odds than the general population for being dispensed this antibiotic (OR 1.2, 95% CI: 0.6, 2.2), but higher number of mean DDD per recipient (47.3 vs. 31.2, ratio 1.5). As shown in figure 2, both penicillins with extended spectrum and tetracyclines accounted for a smaller proportion of the total number of dispensed DDD of any antibiotics to the deceased, compared to the general population (broad spectrum penicillins: 7.2% vs. 14.4%; tetracyclines 20.3% vs. 24.8%)

4. Discussion

4.1 Discussion of the main findings

Ninety of the deceased (39%) filled at least one antibiotic prescription during the last year prior to drug-induced death, and the odds of being dispensed any antibiotics were twice as high as in the general population. The deceased that received antibiotics were more likely female, and to have post-mortem forensic toxicological findings including benzodiazepines or/and hypnotics, and less likely including amphetamines. Mean number of substances found were 2.9.

Nine of the deceased received antiviral drugs for HIV or HCV infections. These were more likely above 45 years, to have been in contact with a hospital during the last year, and to have a lower number of substances by forensic toxicological analyses. The deceased had considerably higher odds for being dispensed such antiviral drugs than the general population. However, it was surprising that only three (1.3%) of the deceased were dispensed ribavirin for HCV, while the prevalence of HCV infection among PDUs in Norway is known to be at least 65%[49]. The treatment uptake in IDUs in Norway is considerably lower than in the general population, which is probably due to serious side-effects and the need for strict follow-up[64]. According to Edlin et al., treatment is often withheld from drug users due to poor adherence to treatment regimen, side effects of treatment, risk of reinfection, and lack of urgency regarding initiation of treatment for HCV treatment[65]. However, such obstacles for treatment could be overcomed with an individualized treatment approach from understanding and respectful health care providers that refrain from making moralistic judgements, as well as treatment guidelines that take this into account. The Norwegian guidelines for treatment of HCV recommends that in particular recipients of OMT should be considered for treatment. Active IDUs are often not provided treatment due to lack of motivation and compliance, and the focus is rather on providing information about HCV. New peroral treatment with direct acting antivirals with less side-effects are soon available, and these may increase treatment uptake and compliance among IDUs, with the potential of reducing the infection pressure of HCV[66], and reduced risk of mortality due to drug-induced death, infections, digestive system diseases, homicide and suicide[6].

More than one in four of the deceased received an antibiotic commonly used for a skin or soft tissue infection. They had higher odds for being dispensed such antibiotics with odds ratios in the range from 2.5 to 6.2, and these antibiotics all together constituted 51.6% of all dispensed DDD of antibiotics, compared to 35.9% in the general population. Intravenous drug use and use of unclean needles are important risk factors for skin infections[17]. In 2013, about 80% of the users of illegal opiates, methadone or stimulating drugs in Oslo had injected drugs within the last 4 weeks[50]. Although we do not have information on intravenous drug use for the deceased in this study, we can assume that a high proportion of the deceased were injecting drugs. A low proportion have safe housing[50], which may cause poor hygiene and increased risk of skin infections[67]. Saeland et al. reported that intravenous drug users in Oslo that were malnourished had higher prevalence of abscesses[19].

One in six of the deceased received antibiotics that are often used for respiratory tract infections (RTI). Intravenous drug users have a 10 fold risk of community acquired pneumonia[68], and RTIs are among the major causes for hospital admissions in this group[15, 43, 44]. Thus, it was surprising that the deceased did not have significant higher odds for being dispensed antibiotics for RTIs, and that such antibiotics constituted a smaller proportion of the total amount of all prescribed antibiotics, than in the general population. It is important to note that phenoxymethylpenicillin was not defined as an antibiotic for RTIs in this study, which may have caused an underestimation of RTIs. Those who received antibiotics for RTIs were more likely to have prescription opiates and OMT drugs as main intoxicants, and less likely heroin. With exception for etylmorphine, it is unlikely that those presenting with symptoms of a RTI would be prescribed opiates. But one may hypothesize that the deceased that presented to the doctor with symptoms of a RTI belonged to a subgroup that had a higher burden of chronic diseases, who more frequently visited the doctor and thereby had more occasions to be prescribed opiates. Those who were treated for a RTI were less likely to have a combination of heroin and stimulating drugs in the post-mortem forensic toxicological findings. In contrast to the respiration depressive effect of opiates, stimulants such as amphetamines and cocaine increase respiration rate[69], and it is possible that combining an opiate with a stimulant drug reduce risk of aspiration pneumonia. However, we have not found any other studies that can support this.

The deceased did not have higher odds than the general population for being dispensed antibiotics known to increase antibiotic resistence, and these antibiotics accounted for a smaller proportion of the total amount prescribed antibiotics. However, they had a markedly higher mean number of DDD per user for tetracyclines, possibly because some of the deceased were high users due to recurrent infections. A study by Starrels et al. explored inappropriate patterns of antibiotic use that can contribute to antibiotic resistance among intravenous drug users[39]. The drug users often delay or avoid seeking health care due to not recognizing the health problem, they may be impatient about waiting in doctors offices or in hospitals, and previous experiences with mistreatment and discrimination. They may obtain antibiotics from non-provider sources such as friends, family or other drug users, and some rather prioritize to buy drugs instead of filling the antibiotic prescription. They have poor adherence to prescribed antibiotic treatment because of the distraction by drug use, concerns about interactions with other drugs, and having an irregular diet and concern about the requirement of taking antibiotics with food.

The mean number of prescriptions only increased slightly towards the date of drug-induced death, and we can not claim that the average recipient of antibiotics had more frequent infections towards the date of drug-induced death. Also, the mean number of new prescribers of antibiotics per month only showed a slight increase towards the date of drug-induced death, thus antibiotics are unlikely subject to doctor shopping. A study by Schistad and coworkers on the same data material showed that the mean number of new prescribers for all prescriptions increased markedly towards the date of drug induced death, and that this increasing trend was constituted by psychotropic drugs and not somatic drugs, suggesting that doctor shopping were restricted to psychotropic drugs and not somatic drugs[70].

4.2 Strenghts and limitations

There are several limitations of this study. Antibiotics are not specific for the focus of infection, but the microbial agents they are meant to conquer. The different groups of bacterial infections in this study were based on generalisations of knowledge about common areas of use, and on pattern of co-prescribing in the

data material. Antibiotics may also have been prescribed for other causes. Symptoms of infection in drug users may be unpredictable[41], and they often have more than one infection [16], so it may have been difficult for the prescriber to predict correct diagnose and treatment. The prescribers may have chosen other antibiotics than recommended due to penicillin allergy. Antibiotics may have been subject to off-label use[71]. Because the prescription records did not include indication for prescribing, this study can not assess the appropriateness of prescribing. Also we did not have any information about the deceased's compliance with the prescribed antibiotics, that is also an important determinant of developing antibiotic resistance[39].

The incidence of infections may be underestimated when prescription records are used as proxy for infectious diseases, because many drug users do not seek health care[40], and some patients that present to the doctor with a symptom of infection may be told to wait and see instead of being prescribed a drug. Some drug users will rather prioritize buying addictive drugs than filling the antibiotic prescription. Chronic drug users and IDUs have higher use of emergency rooms and are more often admitted to hospitals than non drug users[72], and numbers of infections may have been underestimated because this study did not include in-patient treatment. This can also explain why the prescription records in this study did not include antibiotics that are used for in-patient treatment of infections such as endocarditis and bacterial meningitis. The large standard deviations in the results reflect large variation in number of prescriptions and prescribed amount of DDD, as well as small sample sizes.

Unfortunately, the study did not include data on important risk factors such as injecting status or malnutrition. The study was an observational study with no control group, thus risks could not be estimated. The results must be interpreted with caution, because there are geographical variations when it comes to for example preferred drug type, injection practice and safe housing.

An important strength with this study is that it covers all deceased of drug-induced deaths within a defined urban area and time period, and included data from many institutions within the health and social sector with a high response rate, as well as prescription records on all antibiotic and antiviral drugs prescribed to the deceased. Problem drug users may be hard to study[73], but the retrospective observation design minimize the possibility of selection- and response biases.

4.3 Conclusion

The results from this study show that drug users during the last year prior to drug-induced deaths were prescribed more antibiotics and antiviral drugs than what was prescribed to the general population during a year. The deceased were prescribed more antibiotics for skin and soft tissue infections, while they were undertreated for hepatitis C and to some extent for respiratory tract infections. Actions should be taken to modify well-known risk factors for infectious diseases, such as injecting drugs, unsafe housing, poor hygiene and malnutrition. Because of the barriers to access the traditional health care services, Islam et al. emphasize the potential of IDU-targeted primary health care centres[74]. These should provide non-judgemental services with a harm-reduction framework. To increase the accessibility, the centres should be suitable located close to where the IDUs dwell, have suitable opening hours and the possibility for drop-in arrangements, be free of cost, and include or be co-located to relevant services such as needle and syringe programmes, OMT centres, and social and welfare services. In addition to the direct benefits to the IDUs by providing targeted primary health care centres, it is also likely a much more cost-effective approach compared to the costs generated by frequent use of emergency department and hospital admissions. It is important to encourage problem opiate users to enroll in OMT, and especially motivate recipients of OMT to continue, because it has been shown that interrupters have increased incidence of skin infections and systemic bacterial infections, as well as other drug related somatic health problems[75]. The results from this study may supply with valuable information about antiinfective drugs and infections among drug users, but more research is needed. Both quantitative and qualitative studies are important to elucidate both the extent and the complexity of the issue.

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6. Conflict of interst

There are none conflicts of interest to declare.

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Table 1: Demographic and forensic toxicological variables of the deceased (n=231), and numbers of deceased being treated for various types of bacterial infections. All p-values are calculated against no antibiotic collumn.

	Total (n=231)	No antibiotics	Any antibiotics (J01)	Skin or/and soft tissue infection	Respiratory tract infection	Urinary Tract Infection
Total	231 (100)	141 (61.0)	90 (39.0)	65 (28.0)	36 (16.0)	9 (4.0)
Gender						
Male	180 (77.9)	116 (82.3)	64 (71.1) *	50 (76.9)	22 (61.1)**	3 (33.3)**
Female	51 (22.1)	25 (17.7)	26 (28.9) *	15 (23.1)	14 (38.9)**	6 (66.7) **
Age						
Agegroup 1: 25 or younger:	31 (13.4)	18 (12.8)	13 (14.4)	10 (15.4)	5 (13.9)	0 (0)
Agegroup 2: 26-35:	76 (32.9)	47 (33.3)	29 (32.2)	21 (32.3)	11 (30.6)	2 (22.2)
Agegroup 3: 36-45	65 (28.1)	42 (29.8)	23 (25.6)	17 (26.2)	10 (27.8)	2 (22.2)
Agegroup 4: > 45	59 (25.5)	34 (24.1)	25 (27.8)	17 (26.2)	10 (27.8)	5 (55.6)
Oslo residents	158 (68.4)	100 (70.9)	58 (64.4)	42 (64.6)	24 (66.7)	7 (77.8)
Contact with any hospital	97 (42.0)	57 (40.4)	40 (44.4)	30 (46.2)	15 (41.7)	5 (55.6)
Contact with OMT last year	29 (12.6)	15 (10.6)	14 (15.6)	8 (12.3)	5 (13.9)	3 (33.3)
Contact with social service	108 (46.8)	68 (48.2)	40 (44.4)	29 (44.6)	15 (41.7)	5 (55.6)
Prison contact	18 (7.8)	10 (7.1)	8 (8.9)	7 (10.8)	4 (11.1)	1 (11.9)
Place of death						
Residental	155 (67.1)	96 (68.1)	59 (65.6)	40 (61.5)	26 (72.2)	5 (55.6)
Outdoors	41 (17.7)	23 (16.3)	18 (20.0)	16 (24.6)	3 (8.3)	0 (0)
Institutions	12 (5.2)	9 (6.4)	3 (3.3)	2 (3.1)	1 (2.8)	2 (22.2)
Public buildings	15 (6.5)	11 (7.8)	4 (4.4)	2 (3.1)	3 (8.3)	0 (0)
Unknown	8 (3.5)	2 (1.4)	6 (6.7)	5 (7.7) *	3 (8.3)	2 (22.2)
Main intoxicant						
Cocaine	1 (0.4)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Amphetamine/ Metamphetamine	7 (3.0)	5 (3.5)	2 (2.2)	2 (3.1)	1 (2.8)	0 (0)
Prescription opiates	21 (9.1)	9 (6.4)	12 (13.3)	7 (10.8)	7 (19.4) *	1 (11.1)
Heroin	152 (65.8)	97 (68.8)	55 (61.5)	43 (66.2)	17 (47.2) *	4 (44.4)
Morphine	11 (4.8)	9 (6.4)	2 (2.2)	2 (3.1)	0 (0)	0 (0)
OMT-preparates	25 (10.8)	13 (9.2)	12 (13.3)	6 (9.2)	8 (22.2) *	1 (11.1)
Unknown or not poisioning.	14 (6.1)	7 (5.0)	7 (7.8)	5 (7.7)	3 (8.3)	3 (33.3)*
Forensic toxicological findings						
Morphine	16 (6.9)	11 (7.8)	5 (5.6)	4 (6.2)	2 (5.6)	0 (0)
Heroin	155 (67.1)	99 (70.2)	56 (62.2)	44 (67.7)	18 (50.0) *	4 (44.4)
OMT-preparates	42 (18.2)	22 (15.6)	20 (22.2)	13 (20.0)	9 (25.0)	1 (11.1)
Amphetamines	71 (30.7)	51 (36.2)	20 (22.2)*	15 (23.1)	9 (25.0)	2 (22.2)
Cannabis	41 (17.7)	20 (14.2)	21 (23.3)	19 (29.2) *	4 (11.1)	0 (0)
Ethanol	45 (19.5)	28 (19.9)	17 (18.9)	13 (20.0)	8 (22.2)	0 (0)
Benzodiazepines /hypnotics	160 (69.3)	90 (63.8)	70 (77.8)*	51 (78.5)*	28 (77.8)	6 (66.7)
Anti-depressants/epileptics/psycotics	54 (23.4)	34 (24.1)	20 (22.2)	14 (21.5)	9 (25.0)	2 (22.2)
Strong/weak analgesics	27 (11.7)	13 (9.2)	14 (15.6)	10 (15.4)	7 (19.4)	2 (22.2)
Other	3 (1.3)	2 (1.4)	1 (1.1)	0 (0)	1 (2.8)	0 (0)
Forensic combinations						
Heroin and benzo or/and hypnotica	115 (49.8)	122 (86.5)	78 (86.7)	57 (87.7)	30 (83.3)	6 (66.7)
Heroin and stimulants	61 (26.4)	112 (79.4)	60 (66.7)*	47 (72.3)	19 (52.8)**	4 (44.4)*
Mean number of substances						
Mean (SD)	2.9 (1.4)	2.9 (1.3)	3.0 (1.5)	3.1 (1.6)	3.0 (1.5)	2.0 (1.7)

*: p-value < 0.05 **: p-value < 0.01

Table 2: Numbers of users of anti-infective drugs, and mean number of Daily Defined Doses (DDD) per user the last year before overdose death. Oslo population was used as reference. Differences between populations are presented as Odds Ratios with 95% confidence intervals, and ratios of means.

	Users of anti-infective drugs			Mean number of DDD per user		
	Deceased	Oslo population[1]		Deceased	Oslo population	
	Users (%)	Users (%)	OR (95% CI)	Mean (SD[2])	Mean	Ratio
J01 antibacterials for systemic use	90 (39.0)	95494 (24.3)	2.0 (1.5, 2.6)	25.9 (34.8)	21.0	1.2
J01AA tetracyclines	10 (4.3)	14863 (3.8)	1.2 (0.6, 2.2)	47.3 (76.3)	31.2	1.5
J01C penicillins	67 (29.0)	58335 (14.9)	2.3 (1.8, 3.1)	19.6 (16.4)	15.7	1.2
J01CA penicillins with extended spectrum	10 (4.3)	19268 (4.9)	0.9 (0.5, 1.7)	16.7 (9.9)	13.9	1.2
J01CE02 phenoxymethylpenicillin	48 (20.8)	37849 (9.6)	2.5 (1.8, 3.4)	16.5 (10.6)	15.2	1.1
J01CF beta-lactamase resistant penicillins	21 (9.1)	6192 (1.6)	6.2 (4.0, 9.8)	17.0 (20.2)	11.6	1.5
J01DB01 cefalexin	4 (1.7)	1951 (0.5)	3.5 (1.3, 9.5)	8.8 (7.5)	8.9	1.0
J01E sulphonamides and trimethoprim	7 (3.0)	9225 (2.3)	1.3 (0.6, 2.8)	29.9 (25.7)	8.9	3.4
J01F macrolides, lincosamides and streptogramins	29 (12.6)	28342 (7.2)	1.9 (1.3, 2.8)	8.9 (5.1)	10.5	0.8
J01FA macrolides	23 (10.0)	25453 (6.5)	1.6 (1.0, 2.5)	8.9 (3.9)	10.7	0.8
J01FF01 clindamycin	7 (3.0)	3532 (0.9)	3.4 (1.6, 7.3)	7.6 (4.6)	7.6	1.0
J01MA02 ciprofloxacin	4 (1.7)	3621 (0.1)	1.9 (0.7, 5.1)	8.8 (7.5)	14.4	0.6
J01XE02 nitrofurantoin	1 (0.4)	2369 (0.6)	0.7 (0.1, 5.1)	6.3	11.7	0.5
J05 antiviralsfor systemic use	16 (6.9)	4788 (1.2)	6.0 (3.6, 10.0)	186.7 (244.9)	97.0	1.9
J05AB04 ribavirin	3 (1.3)	85 (0.02)	60.8 (19.1, 193.7)	154.9 (54.4)	152.8	1.0
J05AB11 valaciclovir	5 (2.2)	2327 (0.6)	3.7 (1.5, 9.0)	43.3 (47.9)	12.8	3.4
J05AR combination ARV treatment for HIV	5 (2.2)	550 (0.1)	15.8 (6.5, 38.4)	186.0 (139.7)	363.9	0.5

[1]Reference population was inhabitants of Oslo, year 2007 (N=392789), not otherwise age or gender matched.

[2]Standard deviations (SD) could only be produced for the deceased, but not for the reference population.

Figure 1a: Mean number of prescriptions of antibiotics per recipient per month, presented as means with one standard deviation and linear trend line

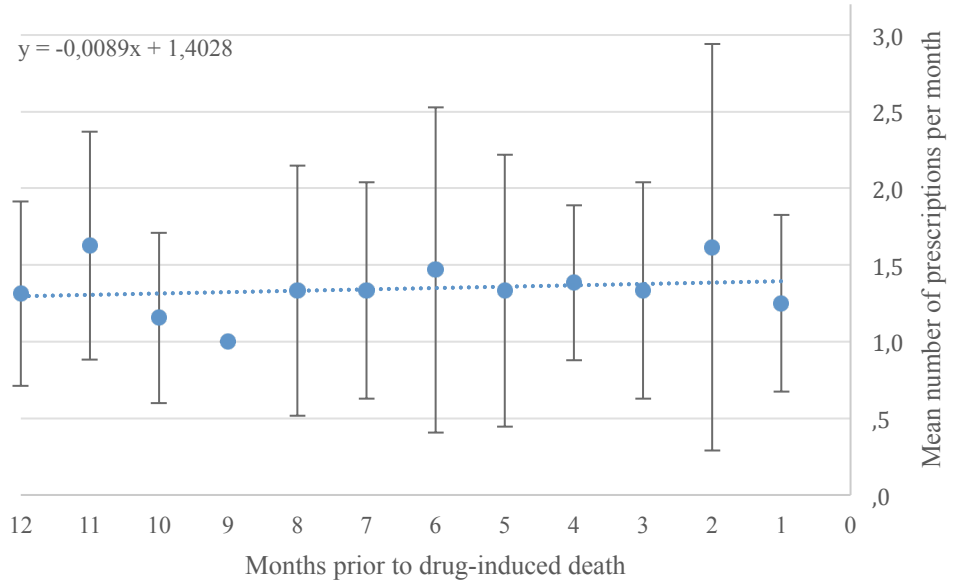

Figure 1b: Numbers of new prescribers of antibiotics (J01) per month per recipient, presented as means with one standard deviation and linear trend line

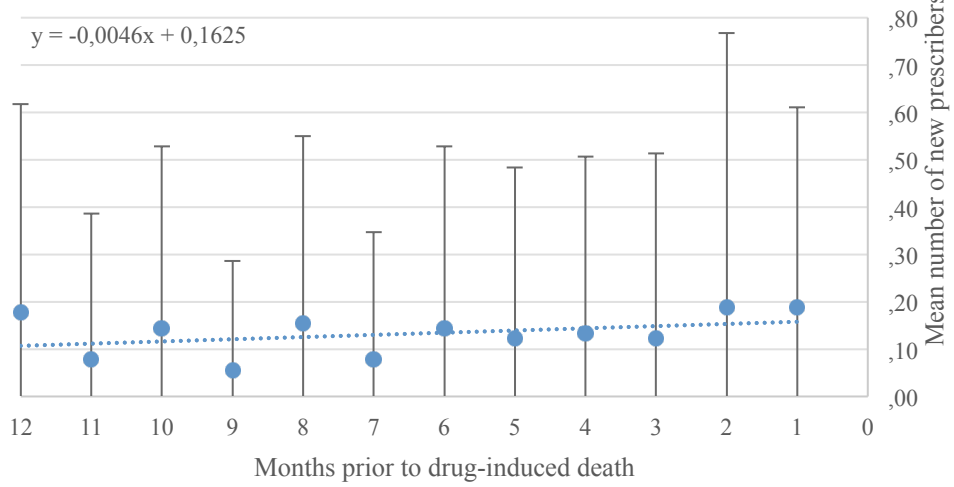

Figure 2: Distribution of prescribed antibiotics as proportion of total amount prescribed DDD, decedents and Oslo Municipality