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Effective treatment in patients with opioid use disorder. Prevention of somatic disease, overdose morbidity and mortality in a high-risk population

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Effective treatment in patients with opioid use disorder

Prevention of somatic disease, overdose morbidity and mortality in a high-risk population

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Effective treatment in patients with opioid use disorder

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Prevention of somatic disease, overdose morbidity and mortality in a high-risk population

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UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 25th of November at 13.00 in Agardhsalen, CRC, Malmö.

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Title and subtitle: Effective treatment in patients with opioid use disorder
Prevention of somatic disease, overdose morbidity and mortality in a high-risk population

Abstract

Background: Opioid use disorder is a chronic disorder with a high risk of relapse and an increased risk of premature overdose death and morbidity. Opioid overdose can be reversed by the use of naloxone. Broad scale implementation of overdose education and naloxone distribution (OEND) is imperative for naloxone to be present when and where overdose occur. While naloxone have the ability to solve an acute life-threatening situation, access to and retention in evidence-based opioid substitution treatment (OST) with methadone or buprenorphine reduces the risk of opioid-related morbidity and mortality. Years of opioid use is often related to less opportunity of healthy living. Injection use, homelessness, poverty, psychiatric comorbidities, polysubstance use and heavy smoking are some of the factors that have a negative impact on somatic health. Although retention in OST often stabilises health, accumulated health issues continues to be a problem, especially as this is an ageing population. In spite of a large burden of somatic symptoms healthcare is commonly not sought.

Objectives: To describe implementation and monitoring of Skåne county OEND, distribution and return rate at 30-month follow-up, description and comparison of individuals returning for refills and report having used naloxone for overdose reversals. To describe the 36-month retention of individuals with heroin addiction from a needle and syringe programme (NSP) to OST and to investigate predictors of abstinence and retention in OST. Additionally, we seek to examine OST patients' self-rated physical health, healthcare seeking, barriers thereof, and unmet healthcare needs.

Methods: OEND implementation and monitoring thereof is described in a protocol study (I). Baseline questionnaire and follow-up for trained individuals returning for all-cause naloxone refill during first 30 months after implementation. Descriptive analysis of refill cause, overdose situation and management and regression analysis of factors associated with overdose reversals (study II). Baseline intervju data, urine-samples, and days in treatment was used for discription and regression analysis (study III). A questionnaire was used for gathering data on self-rated health and healthcare seeking, using descriptive and regression analysis (study IV). Mixed methods was employed with a questionnarie combined with semi-structured interviews and thematic analysis (study V).

Results: Broad scale OEND requires a well-functioning infrastructure and coordination. Implemented in all NSPs, OSTs and addiction facilities, Skåne County OEND reaches a majority of at-risk individuals. Naloxone is more frequently used for overdose reversals by individuals with active drug use and with a higher risk of own overdose. Retention among of participants referred from Malmö NSP to OST was high. More than half of the study sample remained in OST after 36 months. Although all substance use reduced over time, apart from amphetamine use during a 30-day period before treatment start, no other variables were associated with treatment discontinuation before 36 months. Despite suffering from a large burden of physical illness OST patients refrain from healthcare seeking due to stigma, de-prioritisation/procrastination and problems navigating the healthcare system leading to a high number of unmet healthcare needs.

Conclusion: Acute risk of fatal opioid overdose can be reversed by naloxone if distributed broadly. Long-term retention in OST treatment is a prerequisite in reducing opioid related mortality and morbidity. Although patients in OST carry a heavy burden of somatic symptoms, they do not seek healthcare. To prevent somatic disease, overdose morbidity and mortality among individuals who use opioids we need to provide healthcare structures that meet their needs.

Key words: Opioid use disorder, overdose education and naloxone distribution, take-home naloxone, opioid substitution treatment, somatic symptoms, unmet healthcare needs.

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To my son Tiger

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List of papers

The thesis is based on the following papers:

I. Troberg K, Isendahl P, Blomé MA, Dahlman D, Håkansson A. Protocol for a multi-site study of the effects of overdose prevention education with naloxone distribution program in Skåne county, Sweden. BMC psychiatry. 2020;20(1):49.

II. Troberg K, Isendahl P, Blomé MA, Dahlman D, Håkansson A. Characteristics of and Experience Among People Who Use Take-Home Naloxone in Skåne County, Sweden. Frontiers in Public Health. 2022;10.

III. Troberg K, Bråbäck M, Dahlman D, Håkansson A. Malmö Treatment Referral and Intervention Study (MATRIS)—36-month follow-up on retention and substance use among patients referred from a needle exchange program to opioid substitution treatment (submitted).

IV. Troberg K, Håkansson A, Dahlman D. Self-Rated Physical Health and Unmet Healthcare Needs among Swedish Patients in Opioid Substitution Treatment. Journal of addiction. 2019; 2019:7942145.

V. Troberg K, Lundqvist K, Hansson H, Håkansson A, Dahlman D. Healthcare seeking among Swedish patients in opioid substitution treatment - a mixed methods study on barriers and facilitators. Substance abuse treatment, prevention, and policy. 2022;17(1):8.

Abbreviations

AOR	Adjusted Odds Ratio
BZD	Benzodiazepine
DRD	Drug Related Death
EMA	Emergency Medical Assistance
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
FOO	Fatal Opioid Overdose
MATRIS	Malmö Treatment Referral and Intervention Study
MMT	Methadone Maintenance Treatment
NFOO	Non-Fatal Opioid Overdose
NSP	Needle and Syringe Programme
OEND	Overdose Education and Naloxone Distribution
OR	Odds Ratio
OST	Opioid Substitution Treatment
OUD	Opioid Use Disorder
PHC	Primary Health Care
PWID	People Who Inject Drugs
PWUD	People Who Use Drugs
PWUO	People Who Use Opioids
SCS	Supervised Consumption Sites
SIOT	Supervised Injectable Opioid Treatment
SPSS	Statistical Package for the Social Sciences
SUD	Substance Use Disorder
UN	United Nations
WHO	World Health Organization

Introduction

People who are suffering from opioid use disorder (OUD) are the main focus of this thesis. Globally, approximately 40 million individuals between the ages of 15 to 64 years are suffering from OUD (1). This is a heterogenous population with a heavy burden of somatic and psychiatric morbidity, mortality, and marginalisation, compared to the general population. Around one million Europeans are presumed to be high-risk opioid users (2) and among the EU member states, including Norway, UK and Turkey, Sweden has the highest drug-related mortality per capita, of which opioids were found to be a contributing factor in 88% of these cases (3). In coherence with international research, Swedish studies show that the majority of the individuals who inject heroin report previous experience of own overdose(s) (4, 5), as well as having witnessed someone else's overdose(s) (6). Globally, naloxone has been provided to laypersons through increasingly structured programmes for more than two decades, both to those at risk of witnessing and to those at risk of own overdose, (7). In 2014, naloxone was recommended by The World Health Organization (WHO) to be made available for individuals at risk of witnessing a future overdose (8).

While naloxone is an instant response to an acute situation, opioid substitution treatment (OST) with methadone or buprenorphine is an evidence-based treatment for OUD which drastically reduces morbidity and mortality among those who enter and remain in treatment (9-13). Besides OST and overdose education and naloxone distribution (OEND), harm reduction initiatives aiming to reduce opioid related morbidity and mortality also include provision of needle and syringe programmes (NSP), safe consumption sites (SCS), low-threshold healthcare and supervised injectable opioid treatment (SIOT). Many of these facilities also provide marginalised individuals with basic somatic healthcare and connections with support services, such as addiction treatment and social services.

Although international research strongly shows the benefits of OST retention, many issues regarding somatic health will remain even after entering treatment (14-17). The OST population in Sweden, like many other European countries, (18, 19) consists not only of a growing, but an ageing population, with a high prevalence of both psychiatric (20-24) and somatic comorbidities (14-17), compared to the general population. OST has also been suggested as a natural hub for additional healthcare services to be provided on-site as regulations already require patients to visit their clinic on a regular basis (25-28).

This thesis focuses on effective treatment and interventions for people with OUD to prevent somatic disease, overdose morbidity and mortality in Skåne county, southern Sweden. The introduction begins with a brief overview of OUD, overdose mortality and morbidity, psychiatric and somatic comorbidities, followed by a summary on strategies and interventions within the harm reduction paradigm. Finally, the complexities of unmet healthcare needs and the concept of stigma is described in brief.

Opioid use disorder

OUD is a chronic condition with a high inclination of relapse. Compared to the general population, OUD significantly increases mortality and morbidity, with overdose being the main cause of death (29). Estimated prevalence of OUD varies between populations and regions and is also affected by availability of both illegal and prescription opioids. Countries with high rates of prescribed opioids also demonstrate a high prevalence of non-medical, illicit opioid use, and opioid-related mortality (30). Although OUD presupposes exposure, an interaction of genetic (31, 32), psychosocial, environmental, and structural factors, are involved in developing OUD, leaving some individuals more vulnerable than others (30). OUD involves physiological, psychological, and behavioural changes, including craving and loss of control of drug intake, which eventually become the focus of daily life and lead to failure to fulfil obligations in life. The trajectory of OUD commonly involves high-risk behaviour and inability to discontinue use despite the infliction of harm (physical or psychological) to oneself (30, 33, 34). Abrupt discontinuation of opioid intake would induce withdrawal symptoms.

Overdose mortality and morbidity

Opioid overdose is the worldwide leading cause of drug-related death (DRD). Globally, overdoses has profound consequences on all levels of society (35). Reports from European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) show an overall increase in European DRDs since 2012, where younger (<20 years) and older (>35 years) age groups, especially among those aged 50 years or older, show the highest increase. Among the DRDs in Europe, 77% were male and although most involved multiple substances, 76% involved opioids (36). The steady increase in mean age of DRDs, from 37 years in 2012 to 42 years in 2019 (36), mirrors the large proportion of ageing individuals in western European countries involved in DRD (37). Although DRDs in Sweden declined during the last two years, Sweden had the highest proportion of DRDs in EU (including UK, Norway and Turkey), in 2020 (29). As in Europe, these fatal incidents most commonly involved multiple substances, however, 88% involved opioids, with 71%

being male (3). The majority of people who use opioids (PWUO) report having previously witnessed a clinical well defined opioid overdose while 50-96% report previous experience of own non-fatal opioid overdose (NFOO) (38). Mathematical modelling indicates the ratio between fatal opioid overdose (FOO) and NFOO to be 1:20-30, suggesting that for every FOO, there are approximately between 20 to 30 NFOOs (39).

Opioid overdose is caused by respiratory depression due to reduced responsiveness of carbon dioxide by the brainstem respiratory centre. The primary clinical sign of opioid overdose is respiratory depression, with weakening respiratory activity gradually proceeding to apnoea. Unconsciousness – not responding to pain stimulation – is a result of low oxygen saturation rate, where symptoms of paleness, blue lips and fingertips evolves as blood pressure and heart rate drops, which may lead to cardiac arrest if no interventions are made (40). Differences in opioid toxicity depend on the ability of opioids to cross the blood-brain barrier and its lipid solubility (41). Instant deaths are rare, except where fentanyl is involved (42); most overdoses appear to be unintentional (43-47). The majority of the DRDs are represented by older users who have used for several years on a regular basis (48-50), and not the younger novice cohort (45, 46, 49-51). Slower tolerance of respiratory depression than that of euphoric and analgesic tolerance is thought of as one of the explanations to why long-term opioid use increases the risk of respiratory depression (52). The majority of overdose deaths involve concomitant use, most commonly of opioids, benzodiazepines (BZDs), and alcohol (48, 53) as it increases the risk of respiratory depression, and subsequently overdose death (52, 54). BZD use among patients in OST has also been associated with increased risk of poor psychosocial functioning and general health, increased anxiety and depression, and an increased polydrug use and risky injection behaviour, and poor treatment outcomes (55-60). Many illicit substances also lower the threshold for impulsivity. The increased risk of frontal lobe damage due to chronic drug use further increases impulsivity and risk behaviours. In turn, this is also one of the reasons why it may be hard to conclude whether a condition was present from substance use onset or has been brought on due to chronic substance use (61, 62).

While a study of fatal poisoning in the Nordic countries 2017 detected a median number of 4-6 different substances among the DRDs (53), during the last few years, an increase of methadone- and buprenorphine-related overdose deaths in Northern Europe has become a cause for concern, where concomitant BZD use has been reported in a majority of the cases (63, 64). Research has shown co-prescription of buprenorphine and BZDs to be associated with an increased risk of FOO (65). The "safer" profile of buprenorphine can be reduced if combined with sedatives and may lead to increased risk of serious respiratory depression (66). Concerns have been raised in regard to the effect of naloxone to reverse overdose when buprenorphine and BZD are combined, as the high μ-receptor affinity of buprenorphine may require additional naloxone doses to be administered, and may have a slower onset (67).

Direct or indirect consequences of NFOO appears to be frequently experienced by PWUO. Direct consequences, which are not uncommon, include vomiting, chest infections, seizures, and immobility during stupor, which may lead to peripheral neuropathy and temporary paralysis of the limbs (68), compartment syndrome and rhabdomyolysis, which in worst case can lead to acute renal failure (40). Liver injury can be caused by hypoxaemia or acetaminophen (paracetamol; toxicity is intensified by concomitant use) (40, 69). Indirect consequences include becoming a victim of assault, burns, traffic accidents and physical injuries from falling (68), where accidental injuries have shown to be nearly seven times more common among people with OUD compared to the general population (70).

Besides the increased risk of overdose with concurrent polydrug use (52, 54), previous experience of a NFOO is the single most common predictor of DRD (71, 72). Other overdose risk factors involve intravenous opioid use and a decrease in tolerance, even after a shorter period of abstinence, commonly seen in relation to prison (73-77), or in-patient release (78). Being older (19), suffering from mental disorder (79, 80) and somatic disease, such as liver disease, respiratory or cardiovascular complications (81), and chronic pain (82) are also risk factors connected to opioid overdose. The high prevalence of somatic disease and deterioration in this ageing population, fuelled by years of substance use, often leaves them in a more vulnerable position when it comes to overdose risk (19). Socioeconomic deprivation and having a weaker social network constitute an increased risk for overdose mortality (83, 84) as it reduces emotional and social support, which often also lead individuals with no other choice than to use drugs alone with no one there to help if overdose occurs. Also, there are those who prefer to use alone, due to convenience and safety, mistrust of others, or wanting to hide their drug use from others because of stigma and shame (85, 86).

Psychiatric and somatic comorbidities

Psychiatric comorbidities

Psychiatric comorbidities in OUD most commonly present with high prevalence of depression, anxiety, suicidality (87), antisocial personality disorder, post-traumatic stress and history of abuse or sexual trauma, polydrug and alcohol use/substance use disorder, in comparison to the general population (20, 88-91). Previous studies in Norway and Sweden show lifetime prevalence of suicide attempts among patients in OST ranging between 32-41% (4, 5, 92), which is alarmingly high compared to 8.2% among the general Swedish population (93). Psychiatric comorbidities have a major negative impact when it comes to substance use disorder (SUD) treatment outcomes (94, 95), quality of life (20, 96), and mortality (79, 80).

Somatic comorbidities

Entering OST reduces the risk of opioid overdose mortality and morbidity (9-13). Recent Danish research showed that people who use drugs (PWUD) not enrolled in OST were more likely to die from somatic causes than those in treatment (97). This coincides with previous Norwegian research which found an increased somatic morbidity during the first 12 months after OST discontinuation (98). However, years of opioid use, which often includes a lifestyle detrimental to health, is what many patients bring with them upon OST enrolment. Although over 60% of a Norwegian OST cohort considered their self-reported health to have improved since entering treatment, three quarters reported suffering from at least one chronic condition, and more than half reported seven or more somatic complaints. A small proportion reported unchanged somatic health since entering treatment, while a quarter felt that their somatic health had worsened. Reduced memory was the complaint that received the highest rating in relation to how much it was bothering them (17).

Research has shown that older adults in MMT had a higher prevalence of self-reported geriatric conditions compared with a matched cohort in the general population. MMT patients had higher prevalence of psychiatric disease, chronic lung disease, cancer, and higher percentage of hospitalisation. The MMT cohort showed a higher prevalence for all geriatric conditions except for functional impairment (99). An ageing OST population is an indicator of treatment stability, though escalating geriatric conditions with an earlier onset than the general population (99) must be taken into consideration during OST. This does imply a need for increased research concerning the aging OST population and their somatic comorbidities (17, 99, 100).

Self-reports on chronic pain have also been commonly reported by patients in MMT (101-103). Those suffering from chronic pain more frequently reported major health problems, using significantly more medications (e.g., sedatives, NSAIDs, oral narcotics and sleep medications) than those without chronic pain. Chronic pain has also been associated with mental health diagnoses, higher levels of anxiety and depression (101) .

There is limited knowledge when it comes to general somatic health, unmet healthcare needs, barriers, and facilitators within this population. This advocates a need for increased research within this field to manage the complex future healthcare needs within the OST population.

Somatic disease and its impact on mortality among OST patients

Somatic health is thought to have a major impact in preventing DRDs as these conditions are commonly found among deceased OST patients, increasingly so among those aged 45 years or older (104). Multiple organ pathology, with chronic liver disease (84%), cardiovascular disease (68%) and pulmonary emphysema (41%) was found during post-mortem examinations of Norwegian OSTs with a mean age of 48 years at the time of death (15). This corresponds to Australian findings where liver disease, especially among older individuals, were commonly found among FOOs and that the progressive burden of systemic pathology among PWUO implies an increased overdose susceptibility over time (104). Although non-DRD were more commonly reported, there seem to be an increase in methadone related fatalities among older patients (105). Methadone specific deaths were found to be three times as likely in patients aged 45 years or older than those aged 25-34 years (106).

Harm Reduction

Harm reduction is supported by the scientific literature and is strongly promoted by WHO (107) and UN (108), with recommendations that drug consumption and possession for own use should be decriminalised to enable provision of holistic healthcare to vulnerable populations without fear of discrimination. Methadone, buprenorphine and naloxone are all listed as essential medicines by the WHO (109), completed with guidelines concerning psychosocially assisted pharmacological treatment of opioid dependence (110), community management of opioid overdose (8) and on how to start and manage NSP (111).

Although opioids account for a rather small proportion of all illegal substances used, the harm related to their use accounts for a much larger proportion than that of other substances. Consequences of OUD include an increased prevalence of morbidity and mortality, homelessness, social exclusion, criminality, violence, blood-borne infections, such as HIV, hepatitis C and B, skin and deep tissue infections and endocarditis (112), compared to other substances.

When it comes to health, stigmatisation of PWUD is a public health matter as it strongly contributes to inequalities (112). Harm reduction is a set of pragmatic public healthcare strategies aiming to offer services in accordance with individual needs here and now, accepting that not all are currently capable, willing or have the means to quit their drug use. Even though abstinence is accepted as an ideal outcome (113), a drug-free society is considered unrealistic. On the contrary, punitive and repressive drug policies are thought to fuel a parallel illegal economy and feed the stigma towards an already marginalised population, building barriers towards

seeking support, healthcare, and drug treatment (114, 115). Rather than merely focusing on abstinence, harm reduction is a set of practices that aim to mitigate the negative effects of drug use on the individual.

Harm reduction interventions are dependent of the setting, type and patterns of drug use and can be adapted to suit the needs of the individual or the groups who uses drugs (116). Over the past decades there has been an increase in different types of low-threshold healthcare initiatives on an international level. Many of these out-reach units target marginalised individuals, often high-risk drug users, whose needs are not met by the services of regular healthcare facilities.

NSP

NSPs provide access to sterile needles and paraphernalia to reduce the risk of bacterial and blood-borne infections which are primarily spread by sharing and re-using injection equipment (117, 118). These establishments provide an opportunity to reach marginalised individuals, which is why additional services such as low threshold healthcare, counselling and linkage to treatment and social services often are provided through NSPs. While 11.3 million people globally are estimated to inject drugs, there are large national and regional differences in NSP availability. With a slight decrease in recent years, NSPs are available in 86 countries, with a higher proportion of people who inject drugs (PWID) in Western Europe, North America and Eurasia having access to these services, although coverage remains low even in these geographical regions (112). Public and structural stigma and discrimination against individuals suffering from SUD, particularly PWID, hinders not only the establishment of appropriate and acceptable services to the extent that is necessary, but also the implementation of needed public health policies. The result is continuously suboptimal care, failing to provide efficient harm reduction strategies and services, in which NSPs plays an essential role in providing acceptable healthcare to hard-to reach individuals (112, 119)

NSPs are available in all European countries and are for example also offered in German and Spanish prisons (112). Even though Sweden established its first two NSPs in 1986 and 1987 in Skåne county, the progress thereafter has been slow (120). More than two decades after the opening of the first two NSPs, a third was established in 2010, also in Skåne. After a HIV outbreak in Kalmar, the first NSP outside Skåne was established there in 2012. In 2013, a NSP was established in Stockholm, the capital of Sweden, while Gothenburg, the second largest city in Sweden, first opened their NSP in 2018 after law changes in 2017 which removed the municipal veto. Regulated by the needle exchange act (121) these services are now provided in 18 of 21 Swedish counties free of charge, providing services to those 18 and older.

In Skåne county, regional NSPs are run by the Department of Infectious Diseases and are located within the hospital areas of the four largest cities in the region, of which Lund and Malmö were the first NSPs established in Sweden in the mid-80s. Consisting of infection specialised physicians, registered nurses, assistant nurses, social workers and a midwife, staff has long experience in both addiction care and infectious diseases. Besides offering sterile needle, syringes, and paraphernalia, they provide visitors with OEND, counselling and referral to addiction care [Bråbäck 2016], basic and gynaecological healthcare, vaccination for hepatitis A and B as well as hepatitis C testing and treatment on-site (122). Participants are registered with their personal identification number and must submit to regular testing for blood-borne diseases.

Research has associated NSP utilisation with reduced re-use of syringes (123), sharing of injection equipment (124) and transmission of HIV, hepatitis C (118), and B (125). Studies have also shown how NSPs can serve as a platform for linkage (126) or referral of heroin dependent individuals to evidence-based treatment with methadone or buprenorphine (4, 127, 128). A manual on how to start and manage NSPs was released by WHO in 2016 (111), offering not only a theoretical background as to why more NSPs are needed, but also providing step-by-step practical guidelines on how to establish and manage NSPs, with additional services, in various settings.

SCS

SCS are legally sanctioned professionally supervised healthcare facilities where drugs can be consumed while supervised for safer and more hygienic use. These facilities aim to reduce high-risk public drug use, to promote and stabilise health among PWUD, and to reduce morbidity and mortality (129-131). Although these establishments are often seen as controversial, and are therefore closely monitored, research show SCS to be effective in reaching and staying in contact with highly marginalised individuals (132, 133), providing safer drug use (134-136) and access to health and social care, increasing access and uptake of detoxification and treatment services (129, 131). Some of these facilities also provides drug testing services, mostly to avoid unintentional overdoses through fentanyl exposure (137, 138).

International research shows SCS to be associated with a reduction in mortality (139, 140), ambulance attendance (141), harmful drug-related behaviour (142-144), injection in public places (145, 146) and HIV transmission (147). Utilisation of an unsanctioned SCS in the US was associated with reduced likelihood of ED visits, fewer visits, of being hospitalised, and reduced in-hospital treatment days (148). SCS linkage and referral increases access to treatment, recovery (149-153) and healthcare services (154), with 60-70% of the facilities providing access to primary healthcare (131). While the first drug consumption facility was opened in 1986 in

Berne, Switzerland, SCSs could be found in 12 countries by 2019. In Canada alone, more than 40 sites are found with an additional 20 volunteer-run sites. While two SCSs operate in Australia, there are more than 88 sites in European countries, including Netherlands, Germany, Denmark, France, Luxembourg, Norway, Spain, Switzerland and Portugal (112, 131).

Figure 1. Safe Consumption Site at H17, Copenhagen, Denmark.

OEND

The potent μ-receptor antagonist naloxone has a rapid onset due to its high lipid solubility, especially when administered intravenously. Naloxone can also be administered intramuscularly, subcutaneously, or intranasally. Due to being highly metabolised hepatically, oral naloxone is therefore mainly inactivated (155, 156), a quality that is utilised when combined with buprenorphine, limiting inadequate administration of the opioid. Naloxone was approved by the US Food and Drug Administration (FDA) in 1971 for intravenous, intramuscular, and subcutaneous injection for reversal of opioid overdose. For several years, the prefilled syringe, intended for intravenous or intramuscular administration was also used intranasally

by attaching a mucosal device. In 2017 FDA, and subsequently also European Commission, approved the high concentration intranasal (IN) spray.

Rapid administration of the opioid antagonist naloxone efficiently reverses opioid overdose due to its stronger affinity to μ-receptors than that of other opioids (40, 67). Naloxone does not stimulate the receptor; it simply blocks the effect of opioids whereupon breathing can be restored. Opioid withdrawal, following naloxone administration, can be extremely unpleasant, although not life-threatening. Careful titration can minimise the symptoms. Opioid withdrawal symptoms frequently present as yawning, lacrimation, rhinorrhoea, vomiting, diarrhoea, piloerection, musculoskeletal pain, and restlessness (157). These symptoms appear in various degrees upon naloxone administration and last for about 20 to 90 minutes. The half-life of naloxone is often much shorter than that of other opioid receptor agonists, which is why naloxone may require repeated administration, especially if the overdose is caused by an opioid with a longer half-life, such as methadone. This is an additional reason why calling emergency services may be crucial for complete recovery. Another reason is that injuries caused by non-fatal overdose may initially be difficult to notice clinically, though they may cause future somatic problems. As with most cases of fatal overdose, and in some cases of NFOO, pulmonary oedema is found. This is not thought to be caused by naloxone, as these findings has not increased after implementation of OEND (40).

International perspective

In the 90s, OEND programmes were mainly local responses to overdose epidemics, often run by a network of private persons offering information, training laypeople how to prevent and safely manage opioid overdoses, and distributing naloxone from the back of their private homes. These programmes have increasingly emerged to become well organised and structured programmes in a growing number of countries on a regional or national level. While Scotland and Wales implemented the first national programmes in 2011, training and distribution had been provided for 152,283 American laypersons between 1996 and 2014 who had reported managing 26,463 reversals (158). For naloxone to be available when an opioid overdose occur where a witness is present, Bird and co-workers (159) estimated that the annual THN kits distribution should be 9 to 20 times the number of the mean annual number of opioid related deaths, while research by Walley and co-workers (160) showed that annual OEND enrolment exceeding 100 trainees per 100,000 inhabitants significantly reduced mortality on a population level, compared to communities with no OEND. Although most countries have faced economic, practical, or legal barriers upon OEND implementation, a wide array of strategies have been used to overcome these hurdles. The steady increase of large-scale THN implementation globally has contributed to the growing body of evidence showing that OEND reduces opioid related mortality on a population level (161) by being safely administered by laypeople (162, 163). Also, these programmes have shown

to be cost-effective (164, 165). As of November 2021, fifteen of the EU-27 countries, Turkey and Norway, had implemented OEND on a national, regional, or local level (166). In countries where THN is part of a national strategy to reduce DRD, such as Norway (167, 168) and Scotland (169), broad scale training and distribution has also been more successful. The National Scottish Naloxone Programme issued 58,377 kits between 2011/12 and 2018/19. Since February 2022 Scottish Fire and Rescue Service are offered naloxone training and to carry naloxone (170). A pilot study in 2021 involving Scottish police officers carrying naloxone has now also led to the decision in February 2022 to train and equip 12,000 police officers with naloxone (171).

Broad-scale naloxone availability, accessibility and acceptability is crucial if the goal of reducing overdose deaths on a population level should be met. The effect of naloxone on morbidity and mortality is however complex due to several factors. One of many factors adding to the complexity is the difficulty in verifying whether an overdose would have been fatal had naloxone not been administered. The relatively low fatality rate (1:20-30) (39) in relation to NFOO is challenging when it comes to calculations regarding "lives saved", and it also requires naloxone to be distributed not only to the primary target group, but also to those at risk of becoming witnesses to opioid overdose (8). Furthermore, they must accept training on how to identify and manage an opioid overdose, carry naloxone, inform others where their naloxone is kept, and be willing to administer naloxone if needed (172-175). Also, estimating to what extent morbidity was averted due to successful overdose reversal is challenging. If naloxone had been administered earlier, would that have led to slightly less damages to internal organs? What we do know is that timely administration of naloxone, securing airways and supplying oxygen improves chances of survival and recovery. Due to the complex factors related to overdoses, there is limited understanding of the trajectory of incidents and their outcomes.

The Swedish perspective & The Regional Naloxone Project in Skåne County

In June 2017, regulations regarding the possibilities for naloxone to be prescribed to laypersons were reviewed by the National Board of Health and Welfare. The outcome stated that physicians could prescribe naloxone to individuals at risk of opioid overdose. The prefilled syringe containing 0.4 mg/ml naloxone hydrochloride was approved and available for the Swedish market in January 2018. As NSP in Stockholm decided to use the prefilled syringe; it gave them the opportunity to start at the end of January 2018, gradually switching over to IN naloxone when available for the Swedish market. The Skåne naloxone board decided that the project could start on the condition that IN naloxone was used and that the prefilled syringe was approved for IN use. When the highly concentrated IN naloxone spray containing 1.8 mg of naloxone hydrochloride was approved and available in June the same year, the regional OEND could be launched in Skåne. After the first three weeks of operation in June, the first Swedish multi-site project

had been implemented at 70% of all targeted sites in Skåne (n=24), which also meant that these NSPs and OSTs had begun OEND for their patients. At the end of the fourth year, the number of included sites had grown to 35, with more than 2,200 individuals having received nearly 3,800 kits, containing two IN naloxone doses, contributing to naloxone reportedly having been used to reverse more than 680 overdoses (Figure 2). An additional four facilities were prepared to start around June 2022, and seven had been given brief information and were aiming to start after the summer.

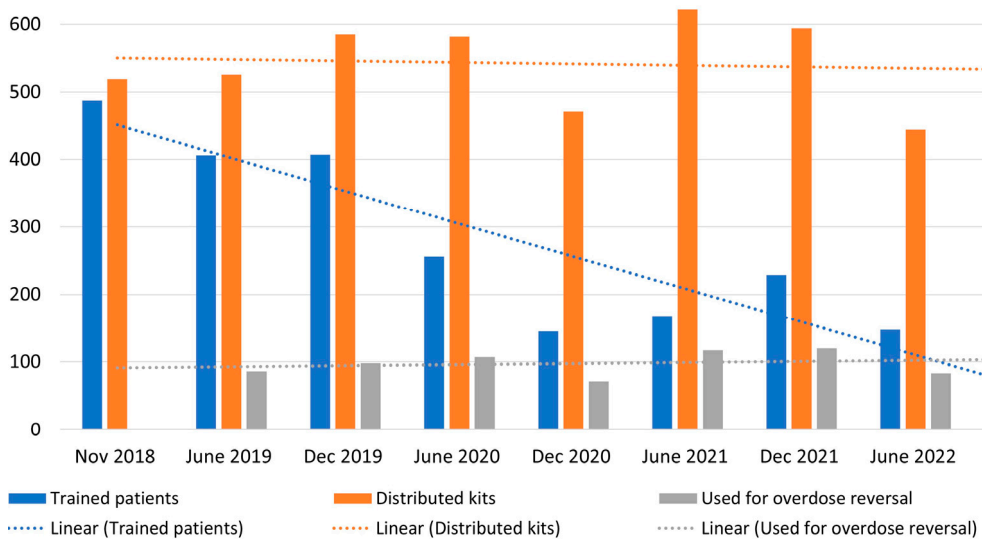

Figure 2. Overdose prevention education, naloxone distribution and reports of naloxone used for overdose reversals during 6-month intervals, Skåne county, June 2018 - June 2022 [Unpublished data, Troberg et al., 2022].

OST

Prior to the introduction of MMT in the 1960s there had been no long-term treatment for individuals suffering from OUD. While OST availability had decreased globally from 86 countries in 2018 to 84 in 2020, out of 206 (112), OST is still the only evidence-based treatment for OUD (9-12, 176, 177). Longer continuous periods of MMT have been associated with reduction in all-cause and drug-related mortality (9-13), drug use (178, 179), criminality (180-182), and high-risk behaviours, such as intravenous drug use and sharing needles, syringes and paraphernalia (183). Subsequently, OST reduces blood-borne infections, such as HIV (147, 184) and Hepatitis C (118), skin infections and endocarditis (182).

Although no other treatment approaches have the same level of proven success as OST, abstinence-oriented treatment is still more accepted in large parts of the world

(109). The stigma surrounding OST poses a threat to the health and lives of those delaying, discontinuing, or not seeking treatment at all (185). For those in OST, experiences of stigma when seeking somatic healthcare is commonly reported and poses a barrier to healthcare seeking (186, 187).

Methadone maintenance treatment (MMT)

Similar to morphine or heroin, methadone is a potent opioid analgesic, most commonly ingested orally, which reduces psychological cravings and withdrawal symptoms mainly by activating and stimulating μ-opioid receptors. The main difference is that it has a slower onset and a much longer half-life, which makes this opioid suitable for long-term medication. The half-life of a single dose varies between 10-25 hours, while a daily intake of methadone accumulates as it is retained and slowly released from the liver. Steady state will be reached after approximately 4-5 days with repeatedly daily intake of the same dose (188). Therefore, during the induction period a stepwise slow dose increase is imperative when aiming for safe medical stability without cravings and withdrawal symptoms. The effect of methadone is highly individual, as the absorption and metabolisation rates of methadone vary widely (189). Increasing the daily dose too rapidly can lead to overdose due to the effects of methadone accumulating within the body. Being highly tolerant to heroin does not guarantee a high methadone tolerance (190).

Although the oral methadone solution is used in Swedish OST, in other countries it is also available in tablet form or, in specialised clinics, as an injectable solution. The more potent methadone enantiomer levomethadone is in many countries an option in OST. In Sweden, oral levomethadone has been suggested as an option which may be considered in cases of heredity or a history of cardiovascular disease, specifically in cases where a diagnosis of Torsades de Pointes (a specific type of abnormal heart rhythm) has been verified (191).

Buprenorphine maintenance treatment

An alternative to methadone, buprenorphine, became increasingly available on the European market in the 90s. Buprenorphine combined with naloxone is theoretically a safer option. When taken sublingually the effect of naloxone will be negligible as oral absorption of naloxone is poor; whereas if injected, the antagonist effect of naloxone would cause withdrawal. In comparison with methadone, buprenorphine has the benefit of being a partial agonist. This offers a safer alternative, binding more strongly to opioid receptors, though only partially activating, and stimulating opioid receptors. The consequence of this “ceiling effect” is that to a certain point the effect flattens out, continuing to take more will prolong, but not increase, the effect (192, 193). This reduces the risk of overmedication leading to respiratory depression unless there is a contaminant use of BZDs or other central nervous system (CNS) depressants. Using CNS depressants, such as BZDs, alcohol, or z-products at the same time as opioids always increases the risk for overdose (194).

As with all opioids (except from naloxone) there is also a high risk for abuse or addiction. The recently introduced buprenorphine depot injection has become an increasingly popular alternative to the daily administered sublingual buprenorphine. The depot injection is to be administered either on a weekly or monthly basis, eliminating the risk of diversion and may also increase treatment adherence (192).

OST in Sweden

Traditionally, the Swedish experience of OST has been one of low access, unequal distribution, high thresholds when entering treatment and low thresholds when it comes to treatment discontinuation. When methadone was first introduced in Uppsala, Sweden, by Dr Lars Gunne in 1966 (195), the model constructed by Dole and Nyswander (196) was implemented. Criteria for OST enrolment stated that the applicant had to be 20 years or older and was required to have documentation confirming opioid dependence stretching back for at least four years prior to admission. There was to be no advanced polydrug use and several drug-free treatments had to be undergone before admission. Although research from this national methadone programme showed the mortality risk being 63 times higher among active heroin users compared to patients enrolled in MMT (12), these regulations applied until 2005 (197). MMT was seen as a highly controversial treatment, in total contrast to the "drug-free society" approach that began to emerge in the 1960s. This "zero-tolerance" to drug use was approved upon by majority of government representatives, and in 1988 drug use was criminalised. Initially, the punishment only implicated a fine, though from 1993 a conviction of drug use could result in imprisonment. Strong political forces declaring Sweden a drug-free society have had major repercussions for individuals suffering from SUD. In 2015 Swedish drug policies were criticised by United Nations (UN) for violating human rights (198) as the "zero-tolerance" approach stands in direct conflict with the pragmatics of harm reduction and decriminalisation of personal use and drug possession, promoted by the UN (108).

Although availability of and access to OST is continuously limited and unequally distributed on a national level (199), OST availability has increased in parts of Sweden. Regulations from 2016 state that OST can only be provided by specialised addiction treatment units which are obliged to combine the pharmacological with psychosocial treatment. Regular testing of HIV/hepatitis B and C should be offered to all patients and basic somatic healthcare must be provided by the OST unit. Patients 20 years and older who have suffered from opioid dependence for a minimum of one year are able to apply for OST treatment. Exceptions to the age-rule can be made in extenuating circumstances (200).

As of September 2013, before the implementation of free choice for OST in Skåne county, there were 99 registered OST facilities in Sweden (201). Implementation of the policy changes regarding free choice of OST in Skåne county 2014 rapidly increased OST access and availability in the county. Individuals who fulfil the OST

criteria (200) can choose between all available OST clinics, both public and private. From 2013 until June 2022 the number of patients in OSTs in Skåne more than doubled, from 992 (202) to 2,038[1], with the number of OST facilities increasing in the area from six to 26.

Implementation of OST enrolment through NSP – the Malmö Treatment Referral and Intervention Study (MATRIS) project

At the time of MATRIS implementation in 2011, patients in Skåne had been queuing for months to receive OST. Although regulated by the National Board of Health and Welfare, waiting times and requirements for entering OST varied widely on a national level. The more restrictive OSTs were requiring enrolees to have stable living conditions and to be abstinent at treatment initiation. Generally, patients had to apply for treatment, where after they were put on a waiting-list. If they changed telephone number or address, they had to inform the OST and if the treatment facility could not contact them, they would end up at the end of the list. When the patient reached the top of the list, which in some cases took years, the patient was called for a medical and social assessment. A lengthy investigation started; if documentation was insufficient in proving opiate dependence for at least one year, application would be denied. In particular, patients dependent on other opioids, and not opiates (heroin, opium or morphine), were not eligible for OST at the time of the study (203). If accepted, they were given a timeslot for in-patient detoxification and substitution medication titration. With MATRIS, the main priority was an effective referral and a safe outpatient medical stabilisation, which at the time was not general practice on a national level. Although doubted by many, with thorough information, comprehensive medical assessment and a close cooperation with the patient, the process of outpatient stabilisation was safe and effective. With the patient being medically stabilised, focus could be aimed towards other areas.

At the time of the study, regulations from the National Board of Health and Welfare stated that concomitant use of drugs or alcohol to a degree which could be regarded as a medical risk were not to be accepted for treatment. The same rule was applied if drug or alcohol use during treatment would increase to such a degree where it would be a regarded as a medical risk (203). During treatment, regulations also stated that the patient would be terminated if being absent for seven consecutive days. Upon treatment discontinuation, patients were not allowed to seek OST again within the following three months (203), thus barred from the only evidence-based treatment. This bar was lifted when the more recent regulations were implemented in 2016 (200).

[1] Naloxone statistics collected every six months from key representatives at all units in Skåne involved in OEND, by the author Katja Troberg and Pernilla Isendahl.

SIOT

While the gold-standard treatment of OUD – OST with methadone or buprenorphine – is available in all European countries, SIOT predominantly involving supervised injection with diacetylmorphine (heroin) combined with supplementary oral methadone, is offered in several European countries and Canada (204). Traditionally, this highly structured treatment is offered to patients suffering from severe opioid dependence where optimised OST alone has been insufficient (205) with heroin continually being used on a regular basis throughout treatment (206). For these treatment-refractive OST-patients, SIOT may be an option, offering reinforced medication and support. Systematic reviews have found SIOT to be associated with positive treatment outcomes, such as reduced illicit substance use and criminality and improvement in health and well-being among participants (204, 207).

Unmet healthcare needs

Australian research on health problems associated with OST treatment concluded that if problems for which patients currently would like to seek healthcare would serve as a proxy for unmet healthcare needs, a large proportion of OST patients would have health issues not appropriately addressed by service providers (208). Compared to the general Swedish population, a much higher prevalence of daily smokers is found among the OST population (>70% vs. <10%) (209, 210). This is likely to have a high negative impact on cancer-related and cardiopulmonary disease. Canadian research by Spithoff et al (211) showed OST patients to be less likely to receive cervical, breast and colorectal cancer screening compared to matched controls and were also less likely to receive diabetes monitoring. Compared to the general Swedish population where less than 10% are daily smokers, the low numbers on COPD [Unpublished data, Dahlman et al.] and circulatory diagnoses (212) in a Swedish OST population, could also indicate underdiagnosing. Spithoff et al., (211) suggest that low rates of prevention and management are most likely to be multifactorial; impaired ability to access healthcare among OST patients, high burden of frequent visits to OST clinics which may limit capacity to seek somatic healthcare elsewhere, and that the lack of integration between primary health care (PHC) and OST may be part of the contributing factors. Irish methadone patients were found to have a higher burden of chronic disease and higher rates of psychiatric, infectious, and respiratory disease than matched controls, which was also significantly associated with increased investigations, referrals, outpatient attendance, emergency visits and hospital admissions (213). In line with previous suggestions of establishing acceptable long-term primary healthcare treatment for OST patients (28, 214, 215) researchers

recommended MMTs to offer patients the same broad range of services provided by general practitioners (213).

Individuals with heroin or cocaine dependence who had not received healthcare for at least one health related problem during the last 12 months reported barriers to healthcare seeking consisting of embarrassment, rudeness, fear of diagnoses, resignation and procrastination (216). According to US research on barriers to healthcare among PWID, judgement by clinicians was reportedly the most influential barrier (217). The mere anticipation of becoming stigmatised by healthcare providers was reported as a reason for healthcare avoidance (218).

Traditionally, studies on integration of treatment for SUD and healthcare has focused on substance use outcomes, as opposed to outcomes regarding general health; additionally, geriatric medicine has not been of any greater concern when it comes to older patients suffering from SUD (219, 220). Barriers to healthcare, and the fact that OST enrolees are an ageing population, suggest that there is a continuous need for accessible and acceptable coordinated targeted services (218, 219, 221, 222) including geriatric healthcare for a vulnerable population with a large proportion of psychiatric comorbidities (223) and with many who may continue to use illegal substances (224).

Stigma

In order to more fully grasp the situation of health and healthcare seeking among individuals with OUD, it is necessary to include the concept of stigma and how stigma creates barriers, not only for healthcare seeking among those suffering from OUD, but it can also create barriers in providing available, accessible and acceptable healthcare services.

According to Goffman (225), stigma is the mark that leads to a "spoiled identity", which could either be visually obvious, e.g., the colour of one's skin (discredited stigma), or marks that can be hidden from the public, e.g., drug use before long-term use has left the individual with marks that can no longer be hidden. At that stage, discreditable stigma has become discredited stigma, whereas the manifest mark (the label) is often created through association (226). With the conceptualisation of stigma by Link and Phelan (227), the five interrelated components needed for stigma to evolve include identifying and labelling of human differences, whereupon undesirable characteristics are linked to the labelled person (stereotyping). The labelling process makes a distinction between "us" and "them" (the stigmatised group). Linking undesirable characteristics to the stigmatised group devaluate their status, leading to rejection, exclusion, and discrimination. Stigma is derived from the inequality of power, those who label others and separates us from them are the ones in power, while those discriminated against are those without power (227).

Stigmatisation relies on the devaluation of certain groups and the public acceptance of these stereotypes. Although categorising and stereotyping is a way of unconsciously categorising the complexity of everyday life, it becomes harmful when public prejudice, stereotyping, and labelling lead to discrimination where these stereotypes are accepted to be "true" (228). Stigma is recognised as a fundamental cause, and driver, of health inequities (229), providing a societal function of enforcing compliance to social norms regarding non- or moderate substance use (230). If OUD is perceived by the public to be controllable, voluntary and of being more related to a lack of moral, of which the individual is to blame, it increases intolerant judgements and attitudes towards those suffering from the disease (226, 231), fostering a regime that rather punishes than support and reduces harm.

Structural stigma (macro-level)

Structural stigma, or institutional stigma, are enacted through rules, regulations, policies, and practices, limiting resources and opportunities which contributes to an array of negative adverse health outcomes among those stigmatised (227, 232).

The brain disease model (233) is continuously debated as the multifaceted construct of stigma that "may influence stigmatising attitudes differently depending on the type of mental disorder they are provided for" (p. 96, (234)). As language intentionally and unintentionally generates stigma, appropriate use of language should be carefully considered. Language not only impacts individuals' thoughts about themselves and their ability to change their situation, but it also shapes the general public views on substance use, treatment and recovery (235). National US studies concluded that the biomedical "chronically relapsing brain disease" terminology may reduce stigmatising blame, perceived danger, and social exclusion (236, 237). Despite a growing acceptance of the brain disease model, the continuing criminalisation of drug use will likely increase public stigma towards PWUD (238-240), limiting effective public health responses in relation to drug use. Disregarding OUD as a medical condition has been associated with higher levels of stigma and the perception of people suffering from OUD of being criminals. Also, disregarding the disease model was also associated with disagreeing with policies aiming to increase access to treatment for OUD (237).

Media plays a major role in withholding structural stigma through the use of stigmatising language, by continuously portraying PWUD as dangerous and drug use as a criminal justice issue, rather than a health and social issue (241), increases the risk of further adding to macro-, meso- and micro-level stigma of PWUD. Research on media reports on OST amidst the US opioid epidemic showed that although the proportion of articles on OST for OUD was significantly higher, news coverage in states with high opioid overdose rates highlighted a larger proportion of negative consequences than positive. Theoretically, this may increase public stigma

and negativity towards evidence-based treatment and discourage individuals suffering from OUD to seek treatment (242).

Structural stigma has been identified as a great driving force behind the lack of availability and access to appropriate healthcare and evidence-based treatment of OUD (238). This does not only lead to health inequities and injustices, but it also classifies individuals suffering from SUD as undeserving of healthcare (243). Stigma has been recognised as one of the major drivers behind health disparities among individuals suffering from substance use and mental health issues (243). In regard to treatment of OUD, stigma has been identified as a major contributor to the lack of access to OST (238). OST regulations are reportedly also connected to structural stigma whereas besides entering OST was perceived as a risk of exposing their own shame, the restrictive OST regime of supervised daily dosage intake was thought of as a barrier to recovery as treatment was hard to combine with a "normal" life and a conventional job (244, 245).

Public stigma (meso-level)

Negative stereotypes endorsed and enacted in harmful and discriminatory ways by the public fuels both structural stigma and self-stigma. Organisational norms and stereotypical beliefs about patients suffering from OUD increases discrimination, leading to suboptimal treatment or even exclusion from healthcare (243, 246). A systematic review on stigma found healthcare professionals to have a general negative attitude towards individuals suffering from SUD, commonly describing patients as aggressive, manipulative and having poor motivation (247). Positive attitudes towards working with patients with SUD were more commonly found among healthcare professionals within the mental health sector or of those working within specialised addiction services (247). Addressing stigma within the healthcare system is essential as stigma creates barriers to healthcare seeking, undermines diagnosis, treatments, and its outcomes (248) which may well reduce longevity (249).

Although OST is the only evidence-based treatment for OUD, public stigma towards OST tends to equate methadone or buprenorphine with illicit drug use. When OST is merely considered as "one drug replaced by another" it poses a barrier towards seeking treatment (250). There has proven to be more stigma among PWID towards MMT participation than continuing to inject heroin. Research has also found there to be some hostility towards MMT by those in abstinence-based treatment. This constitutes a social stigma which may effectively hinder PWID from seeking OST (185, 186).

Social stigma related to substance use may also impede naloxone acceptance (175). Not considering OEND as part of public health will inevitably limit access to those not perceived to be at risk for opioid overdose (251, 252).

Experienced and anticipated stigma (micro-level)

Experienced stigma are previous actual situations in which the individual experienced discrimination, whereas anticipated stigma is the mere expectation or fear of discrimination which may lead to avoidance of these situations. Internalisation of stigma occurs when stigmatised individuals apply the negative stereotypes accepted and endorsed by the public to themselves through stages of being aware of public stigma, agreeing with it and applying it to oneself. Together with anticipated stigma, the impact of seeing oneself through the lens of stereotypes reduces self-esteem and self-efficacy, resulting in shame, avoidance, resignation, and marginalisation ("Why try?") (228, 253). Previous experience of stigma and dehumanisation in the healthcare setting was commonly reported among American PWID where the anticipation of future stigmatising experiences led to development of strategies to avoid healthcare seeking (187, 218). For people who use drugs and alcohol, stigma impedes access to healthcare (254, 255) which has a major impact on quality of life, social support and healthcare utilisation and recovery (246). As stigma discourage individuals suffering from OUD seeking OST or even encourages patients to treatment discontinuation (185, 186), stigma may also discourage individuals from accessing training and THN (252).

Stress is associated with a constant fear of being stigmatised, whereas stigma associated stress may be even more difficult for individuals suffering from a disease closely associated with stigma (227). Research by Davidson et al., (256) describes the "Goffmanian impression management" where PWID engage in trying to avoid public exposure of parts of their identity that they wish to hide. Trying to distance oneself from the stigmatised group and to avoid exposure of disease, treatment and healthcare seeking is most often delayed, or simply avoided (227, 244). Stigma and discrimination of individuals using illicit drugs, was found to be associated with both poorer mental and physical health, while alienation was associated only with poorer mental health (257).

Although beyond the scope of this thesis, it is important to recognise stigma as intersectional with multiple stigmata interwoven, such as stigma associated with ethnicity, sexual/gender minority identities, socioeconomic status, physical and mental illness. Stigmas towards PWUD can also extend to family members as they are often blamed for their relative's substance use or even relapse (258).

Aims

General aims

The main aim of this thesis was to examine interventions of OEND and OST, including long-term effects and self-rated somatic symptoms and healthcare seeking among patients in OST. These interventions all emerged from the need of investigating into and to strengthen the chain of healthcare for individuals with OUD with the aim of reducing morbidity and mortality the population.

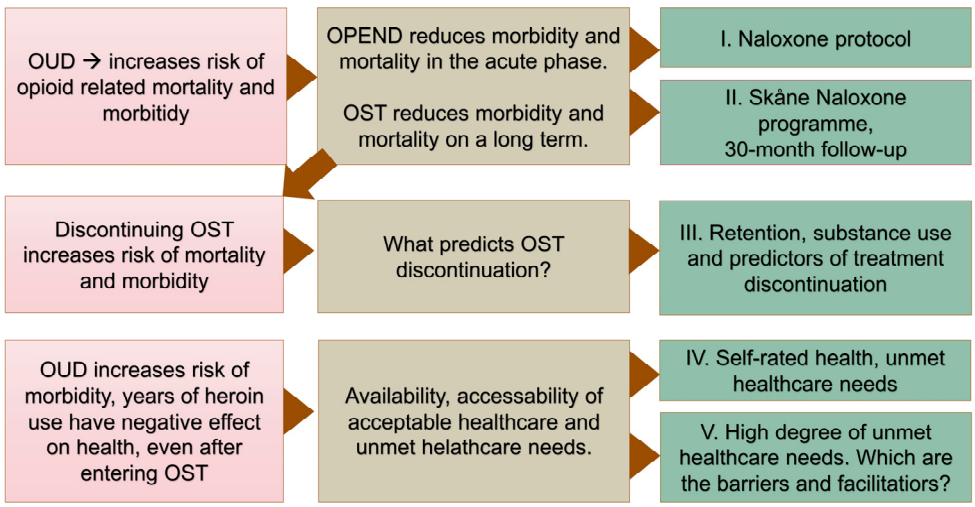

Figure 3. Clinical challenges, rational and aims of the studies included in this thesis.

Study-specific aims

Study I To describe the protocol for implementation and monitoring of the effects in relation to the overdose prevention education and naloxone distribution programme in Skåne county.

Study II To address participant characteristics and factors associated with returning for naloxone replenishment and with having used naloxone for overdose reversal, to describe self-reported reasons for naloxone replenishment and overdose experiences in which naloxone had been used for overdose reversal.

Study III To assess 36-month treatment outcomes - defined as retention and illicit drug abstinence - and predictors of OST discontinuation.

Study IV To examine OST patients' self-rated physical health, healthcare seeking behaviour and unmet healthcare needs.

Study V To identify barriers and facilitators among OST-patients seeking healthcare.

Material and methods

Apart from the protocol paper, the methods in this thesis include questionnaires with closed and open-ended questions, semi-structured interviews, and patient journal information. A methodological overview is shown in Table 1.

Study design – Paper I-V

Paper I was a protocol article, paper II and III were prospective longitudinal studies based on questionnaires, whereas paper III was combined with journal data. Papers IV and V were both cross-sectional studies, based on a questionnaire, while paper V combined a questionnaire approach with semi-structured interviews, completing a mixed method study (Table 1).

Setting and study participants

All studies were conducted in Skåne county, southern Sweden, with a population of 1.34 million inhabitants. Swedish healthcare is strongly subsidised with both public and private services being tax financed and covered by the Swedish universal health insurance. The maximum annual outpatient healthcare fee for adults (20-85 years) registered in Sweden, or with a European health insurance card, is 1200 SEK (~120 EUR) while the maximum co-payment for adults prescribed pharmaceuticals included in the benefit scheme is 2400 SEK (~240 EUR). Pharmaceuticals included in the healthcare benefit scheme are free of charge for children under the age of 18 years (259). Except for healthcare treatment that cannot be deferred, all Swedish healthcare require patients' ability to provide identification.

An increasing number of units included in the Skåne county naloxone programme providing overdose prevention and distribution free of charge. These units include all NSPs and all in-patient and out-patient addiction facilities, including both public and private OSTs. Naloxone may only be prescribed to patients who themselves are at risk of overdose, by physicians or registered nurses who have been delegated prescription permission.

Table 1. Methodological overview of paper I-V.

STUDY DESIGN	I	II	III	IV	V
TYPE OF STUDY	Protocol	Longitudinal, prospective. Cohort	Longitudinal, prospective. Cohort	Cross-sectional	Cross-sectional
FOLLOW-UP (MONTHS)	N/A	30	36	N/A	N/A
TYPE OF DATA	N/A	Questionnaire Baseline + follow-up on refill	Baseline data: structured interview. Patient record data: days in treatment, laboratory analysis of urine samples	Questionnaire	Mixed methods: Questionnaire + semi-structured interviews
N	N/A	1079	71	218	Quantitative: 218 Qualitative: 11
OUTCOME VARIABLES	N/A	Participant characteristics refill ←→ no refill, reversal ←→ no reversal. Factors associated with overdose reversal	Retention in treatment and predictors for retention: age, sex, previous suicide attempts, use of benzodiazepine and amphetamine during 30 days prior to inclusion. Abstinence from opiates and other substances over time.	Self-rated health and unmet healthcare needs among OST patients	Barriers and facilitators r/t healthcare seeking among OST patients
STATISTICS	N/A	Descriptive, Chi-2 Logistic regression (multivariate)	Descriptive, Kaplan Meier survival analysis. Logistic regression (multivariate)	Descriptive, Logistic regression (multivariate)	Descriptive (Qualitative part – no statistics)
COVARIATES TESTED FOR MULTI-COLLINEARITY	N/A	Yes	Yes	No	N/A

Study I

The protocol paper describes the implementation and monitoring of the first multi-site naloxone project in Sweden and its overall impact of OEND on mortality in the general population. Included in this thesis are the self-reported data collected from patients given their consent to take part in the study, and thus not meet the exclusion criteria, at all NSPs and addiction treatment facilities, including all OSTs, in Skåne (see detailed information in Study II below). Although not included in this thesis, future registry studies will include collecting data on the entire Swedish population, including overdose mortality data, pre- and hospital data.

Study II

This study represents the 30-month follow-up of the naloxone project in Skåne county, with respect to self-report data from included patients. Study participants were included between June 2018 and December 2020 from, at that time, 31 sites offering their patients OEND. These sites included all NSPs (n=4), OSTs (n=22) and in-patient addiction units in the county as well as out-patient addiction units (non-OST) (n=5) in Malmö.

Workshops and training of key-trainers and management representatives from all included units were performed during the autumn of 2017 and spring of 2018, preparing for immediate implementation as soon as IN naloxone was made available to the Swedish market. All units were provided with a CPR manikin, training material and naloxone kits. Although the naloxone had to be ordered by each unit, funding was provided by the county. Study recruitment started at the time of the naloxone implementation in June 2018 and continued until December 2020. The goal was for the units all over the county to start as soon as IN naloxone became available Despite the fact that implementation coincided with the start of summer holidays, 70% of all units were up and running OEND within three weeks.

Written and oral information about the study was provided upon completion of training and after having received the naloxone kit. The kit contained two doses of 1.8 mg highly concentrated naloxone hydrochloride for IN use, vinyl gloves, ventilation mask, swabs, “easy to use” instructions, training certificate and an information card which could be given to the overdose victim (Figure 4).

Figure 4. Skåne county naloxone kit.

Within the first 30 month of the study 1079 (63%) of the 1700 individuals who had received training and THN, accepted to take part in the study. Asking trainees to participate in the study after training and receiving naloxone meant that those who were not willing to take part in the study got the same treatment/services as those who did. Willingness to partake in the study should not constitute a barrier to access, as its primary goal is to equip all in need with knowledge and THN. No economic compensation was provided for study participation. Patients not able to provide an informed consent were excluded from the study.

Policy changes were made in November 2018 by The National Board of Health and Welfare, aiming to further increase access to, and prescribing of, naloxone. Registered nurses may prescribe naloxone, and pre-medic ambulance personnel were allowed to administer naloxone.

Study III

This is the 36-month follow up of the MATRIS-cohort (4) aiming to examine retention, predictors thereof, and substance use among participants with heroin dependence referred from NSP into evidence-based treatment (OST).

Malmö NSP staff began study inclusion by asking eligible patients if they would like to participate in the study in November 2011. Out of the 100 patients who were approached, 79 accepted participation and 71 were included for a 36-month follow-up. Inclusion criteria were being at least 20 years of age and having previously stated heroin to be their main drug on at least two occasions visiting Malmö NSP prior to study start. Visitors unable to understand and/or the provide an informed consent were excluded, as were individuals already enrolled in OST. Pregnant women were also excluded in this study; however, they were offered fast-track to treatment at another unit, as part of regular treatment procedures.

Establishment of OST MATRIS

A new OST unit was created solely for this study. Awaiting the new premises, the unit was located in a single room at the back of Malmö Addiction Centre. As the opening of the new facility had been delayed, the study inclusion had to be paused for five months before commencing, as it was impossible to include additional patients due to the size of the first location (Figure 5). The new permanent facility was located 3 km from the recruitment site and were renovated and re-built to fit the purpose.

Figure 5. Initial treatment facility for MATRIS.

Study IV

The PRIO project (Primary healthcare in OST) started as a response to a problem that had been observed in the clinic. As staff at OST MATRIS found that although there was a great need, it was difficult for a rather large proportion of patients to receive somatic healthcare through ordinary primary healthcare services. A collaboration with the nearby PHC facility "Granen" was implemented in 2014 where all registered nurses at OST MATRIS were trained in triage and where timeslots at PHC Granen was reserved for OST patients. An additional OST unit (the private caregiver INM) was also included in the programme. In 2016, the first evaluation of PRIO showed that even though the initiative had improved healthcare seeking, it was insufficient as nearly half of the booked patients did not turn up for their appointment. The head of staff at PHC Granen was positive to the suggestion of moving the PHC physician to OST, instead of moving the patients. The following week, on-site PHC was implemented at both MATRIS and INM. On-site PHC primarily targets patients without a functioning PHC contact. Services provided by OST staff include taking blood samples and blood pressure, keeping track of appointments, informing and reminding patients of their appointments as well as informing them about examinations. All that can be handled at the OST unit, which the patient is visiting on a regular basis, is taken care of in-house.

The first study on somatic health, healthcare seeking, and unmet healthcare needs was launched at the two sites which already offered on-site PHC, and at two additional OST public run units (Hasselgatan and Bokgatan), also in Malmö, where on-site PHC was about to be implemented. Eligible study participants were patients at these four OST units. At the time of the study, that took part from May 2017 to March 2018, there were a total number of five OST units in Malmö.

Study V

This mixed methods study consists of one quantitative and one qualitative part. The quantitative part included 210 participants and consisted of previously unpublished material from the questionnaire described above, examining healthcare seeking, access and previous experience of somatic healthcare treatment. The qualitative part was made up of semi-structured interviews with a sub-sample of 11 participants from two of the OST units described above (Matris and Hasselgatan), who had participated in study IV and had all described prior experience of unmet healthcare needs. These study participants were interviewed between February and March 2018. Participants were given a 100 SEK (~10 EUR) voucher as economic compensation for taking part in the study.

Study procedures

Study I

Methods that are used to collect data include self-reported data collected upon completion of OEND training, every 6 months thereafter and/or upon every return for naloxon refill. Data collected upon completion of initial training session and data and upon returning for naloxone refill was analysed and described in study II.

Although not included in this thesis, the overall purpose of the study was to monitor and investigate the impact of a regional naloxone programme in Skåne. Registry data will be collected from national Swedish registers. The primary outcome measure of overdose mortality in the general population will be investigated by compiling data from national registries on overdose mortality data in the general population from 2019–2023 compared with a historical control period including the years 2013–2017.

Secondary outcome measures will include a five-year timeframe on incidence of opioid overdoses attended by ambulance or emergency hospital care, premedical assessment of responsiveness with Reaction Level Scale (RLS-85) in acute brain disorders, respiratory rate and heart rate of opioid overdose survivors attended by

ambulance personnel, and naloxone administration by ambulance staff and survivors needs of transport to hospital. Secondary outcome measures will also include naloxone programme retention, incidence of witnessing overdose and bystander use of naloxone and other recommended actions related to overdose management during a three-year timeframe.

These sub-studies are – at the time of the writing of the present PhD thesis – both ongoing and waiting for further time to elapse for adequate follow-up. The study aims included in the present thesis were included and analysed in study II (see below).

Study II

This study is part of the larger naloxone study described in study I. Questionnaires that were included in this study were those collected upon completion of initial OEND training and follow-up during naloxone refills. Upon completion of training session, and having received THN, participants of the naloxone project who had provided a written consent to take part in the study were to answer an initial baseline questionnaire. The questions included demographics, previous experience(s) of the participant's own, or being a witness to someone else's, overdose(s), knowledge of overdose recognition and management, and confidence of future overdose management and the participant's own substance use during the 30 days prior to training.

Questions upon refill included information on whether the previous doses had been used, lost, stolen or given to someone else. If naloxone had been used for overdose reversal, participants were asked to provide information whether it had been used to reverse overdose on themselves, or on someone else (friend, family member, acquaintance or stranger), if the overdose had occurred in a private accommodation (their own or someone else's) or in a public place, observed overdose symptoms, number of doses administered, and if complementary overdose management strategies had been used, apart from naloxone administration.

During the autumn of 2018, digital questionnaires gradually replaced the paper forms that were used at the start of the study. Henceforth, questionnaires were answered by patients using the iPads which were provided at all units, using a Research Electronic Data Capture (RedCap) application. The paper questionnaires were manually transferred into the digital system by a research assistant at Lund University who was not involved in the project.

Study III

Baseline data for paper III was collected from the structured interview that took place at Malmö NSP after the patient had provided written consent. After the interview, study participants were randomised into case-management intervention/ no intervention groups and were handed information about their appointment for the referral to the psychiatrist at the OST clinic (4). This appointment took place within a week after the interview (Figure 6). Urine samples were collected for laboratory toxicological analysis during the initial appointment and thereafter collected continuously throughout the three-year period for follow-up, or for as long as they remained in treatment during this period. A new appointment was booked for the following Monday, four days after the initial appointment to the psychiatrist. Participants had been informed to turn up in a state where treatment initiation would be possible the same day, if the decision would be positive to treatment start.

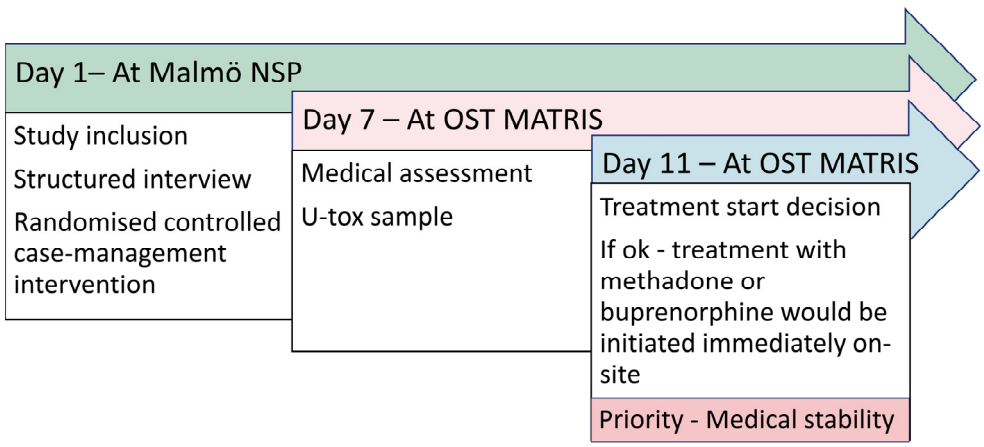

Figure 6. The referral process from Malmö NSP to MATRIS OST (4).

Study IV

A questionnaire on self-rated physical health was employed for this cross-sectional study. One of the authors (K.T.) or staff, at the four OSTs where the study was taken place, asked patients if they would be willing to take part in a study regarding their somatic health. All patients were given written and oral information about the study before committing to participating by signing the written informed consent. During the study period (4th of May 2017 – 6th of March 2018) the goal was to make sure that all patients at these units would have been given the opportunity to take part in the study, and to inform those visiting the units about possible participation in the study on a more or less frequent basis. The only exclusion criteria were severe intoxication or psychiatric condition that would prevent the patient from giving

informed consent. However, if the patient's status improved, they would be asked again if they would like to take part. Assistance was given to participants in need of help with reading and writing. For practical reasons, translation to languages other than English was not possible. Participants were not given any economic compensation.

The questionnaire included questions regarding their own physical health, healthcare utilisation and unmet healthcare needs, barriers and facilitators towards healthcare seeking and lifestyle factors having strong effects on health (e.g., physical exercise, nutrition habits, alcohol, and tobacco use). The questionnaire contained both open-ended and closed-ended questions. A sample of 218 participants answered the questionnaire partially, or in full.

Study V

Data collected during the first part of the study on somatic health, healthcare seeking and unmet healthcare needs, not previously presented, was used for the quantitative part of the study. The section used for this part of the study covered questions on healthcare seeking, and whether the study participant had refrained from seeking healthcare, and if so, reasons for refraining. Although the combination of closed- and open-ended questions applied in the section had provided a lot of information, it did also raise more questions on the subject as the material did not provide a deeper understanding of study participants thoughts, experiences and consequences of barriers towards healthcare. Qualitative methods are considered to be effective when it comes to accessing this kind of knowledge and experiences. Therefore, a mixed methods exploratory design was applied providing an opportunity of exploring different aspects within the area (260), in examining and identifying barriers towards, and facilitators to, healthcare seeking. The entire material would create an equal weights design, (QUAN→QUAL) (260) and were to consist of two separate datasets.

Although access to the quantitative material meant that the research group had a few preconceived themes which we would like to evolve, it was equally important to keep an open mind to new perspectives. To allow for a balance between these interests, the choice was made to conduct semi-structured interviews with an openness to explore other areas and perspectives that may be presented during the interviews.

Interviews were conducted to investigate three comprehensive areas covering barriers to healthcare seeking (Figure 7). Each area framed specific themes of interests.

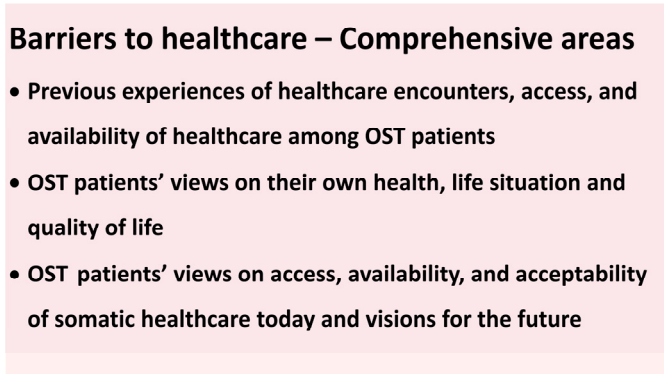

Figure 7. Barriers to healthcare – Comprehensive areas for semi-structured interviews

Trying to establish an environment where participants would feel that they could freely express themselves (261, 262) the research group thought it would best for the interviewer to have no previous healthcare provider – patient contact with the individuals who were to be interviewed, and that the interviews should be conducted in an environment familiar to the patient. This meant that neither K.T. nor D.D. could perform the interviews since they had an ongoing, or previous, healthcare contact with many of the patients. There was also a need for an additional researcher able to make separate thematic analysis. Therefore, another researcher (K.L.) conducted the semi-structured interviews for the qualitative part of the study and separately analysed the material. Participants were offered a 100 SEK (~ €10) voucher as an economic compensation.

Methods

Study I

Power was calculated in regard to the primary outcome (as described above), with a target of 80%.

The primary outcome, a year-by-year comparison of the relative risk (RR) of mortality before and after intervention in the overall cohort, will be calculated by Poisson regression, adjusting for gender and age. P-values <0.05 and confidence intervals of 95% will be considered as statistically significant applying a double-sided test.

Subgroup analysis of the RR of mortality will be presented separately for patients who received training and initial kit at an OST facility, respectively through NSPs,

whereas an interaction test will be described by the p-value. Each of the individuals included in the cohort contribute with person time, from enrolment until the end of the study, or until the date the study participant deceases. The participant can also withdraw from partaking, and if so, the data will be erased.

Aiming to separate acute drug-related deaths from those with other causes, data will be collected from the National Board of Health's Death Causes Register (mortality and cause of death), the National Drug Index (linked to the Death Cause Register, with additional information on which substance was the underlying respectively the contributing cause), the National Registry Data (interconnecting national mortality data with the presence of a F1 diagnosis), Skåne county medical and registers (diagnoses and intervention codes), ambulance data (fatal/non-fata overdose and status from regional prehospital dispatch records), and records from the emergency departments within the region (overdose events among those attending). The variables described above refer to the overall project and will not be further assessed in the present doctoral thesis.

Quantitative data obtained from initial training and thereafter every six months, or upon naloxone replenishment will be described through cohort-specific analysis and subgroup analysis by descriptive statistics, chi-square test, univariate and multivariate regression models. Variable correlation will be calculated for variables included in the multivariate regression analysis.

Study II

Descriptive data was used to display demographic and behavioural characteristics, participants returning for naloxone replenishment and of those who reported having administered naloxone for overdose reversal. Descriptive data was also used to present naloxone distribution, reasons for naloxone replenishment, settings and circumstances in which naloxone was used.

In the initial analysis of participants returning and of those who did not return Chi-square test was used. This was also the case when comparing those reporting having used previous naloxone to reverse overdose to those reporting other reasons for needing refill.

In a sub-sample analysis examining factors associated with naloxone use for overdose reversal univariate and multivariate logistic regression were employed, controlling for age, gender, initial training at NSP, prior experience of own, or being witness to someone else's, overdose.

Statistical analyses were performed using IBM SPSS Statistics, version 27.0 (263). Confidence intervals of 95%, and P-values <0.05, were considered statistically significant. Correlation analysis of variables in multiple logistic regression was employed where correlation less than 0.7 was accepted.

Study III

Longitudinal cohort study. Kaplan-Meier survival analysis was used for examining treatment retention, with the time-dependent variable set to days in treatment. Characteristics of participants remaining in treatment respectively terminating treatment before the end of 36 months were presented using descriptive data.

Descriptive data was also used to present laboratory findings of substance use in urine samples, which were collected on a regular basis. Up to eight samples per study participant were analysed every month. If one or more were positive, the whole period was noted as positive. Patient data on number of days and dates where patients were imprisoned or in a residential treatment facility were noted as periods where participants could not provide urine samples. Participants who chose not to leave any samples during the month that was studied were coded as "no sample".

Logistic regression was employed to investigate whether gender, age, previous suicide attempts at treatment start, use of BZDs or amphetamines during a 30-day period prior to treatment start were associated with treatment discontinuation. Possible association was also analysed using adjusted logistic regression. Statistical analyses were performed using IBM SPSS Statistics, version 27.0 (263). P-values lower than 0.05 were considered statistically significant. Correlation analysis of variables in multiple logistic regression with correlation less than 0.7 was accepted.

Study IV

This cross-sectional study was presented both by descriptive data and by logistic regression analysis. Statistical analyses were performed using IBM SPSS Statistics, version 24.0 (264). P-values lower than 0.05 were considered statistically significant.

Study V

This mixed methods study combined cross sectional quantitative data on physical health, healthcare seeking, and barriers related to healthcare seeking with qualitative data gathered through semi-structured interviews with a subsample of participants from the quantitative part of the study. The theoretical framework regarding healthcare access, by Penchansky and Thomas (265) was applied, together with the perspectives of micro-, meso-, and macro-levels of stigma theory (186). Thematic analysis, informed by the ideas of Braun and Clarke (266), was employed for the descriptive analysis of the qualitative data.

Two of the authors (K.L. and K.T.) analysed the qualitative material separately. The material was then compared and discussed. In case of discrepancies between the interpretations, another team member (D.D.) was consulted. Before bringing in

researcher (H.H.) with greater knowledge and competence on thematic analysis, the material was gone through with the whole team, including A.H., whereupon H.H. was involved in the process of going through all the material and the results thoroughly prior to the manuscript writing. With this process the aim was to produce an analysis with high quality and transparency. IBM SPSS Statistics, version 21.0 (267) was used for analysis of descriptive data.

Ethical considerations

Participation in these studies did not pose any known or significant health risks. The self-report of illicit substance use, mental and physical health disorders may always lead to a certain risk of discomfort and may possibly lead to stronger emotional reactions upon recalling previous distressing events. However, in all studies included here, it has been judged that the study benefits have outweighed the risks. Even the studies which do not involve formal treatment, such as those asking questions about health problems and previous overdose history, are believed to have been more beneficial to the patients' health, rather than the opposite, as a discussion on these issues may evoke self-reflection and motivational processes in patients. All interviews were performed by medical professionals with previous experience of handling distress and to offer support if needed. The studies were conducted in accordance with the Declaration of Helsinki 2013 (268) and were approved by the Regional Ethics Board in Lund, Sweden (file number 2018/300 for projects I-II, file number 2011/450 for project III, file number 2016/1105 for project IV and file number 2017/1024 for project V). Studies I-III were registered at Clinicaltrials.gov (Study I-II file number NCT03570099, Study III file number NCT01457872).

Economic compensation could provide an ethical dilemma if participants perceive this as an opportunity they cannot afford to turn down and would not otherwise want to take part in the study. It might also contribute to sampling bias, if the economic compensation offered only attracts individuals who cannot afford to say no or if their input is merely thought of as a commodification. From another perspective, participants should be compensated for their time and contribution, and we should not take their participation for granted. If they do participate, they should have the right to compensation. It is also a possibility for researchers to show gratitude towards those sharing experiences and thoughts that we as researchers need in order to increase our understanding to hopefully contribute to positive outcomes for the patient group. Participants in the semi-structured interviews in study V were offered a nominal monetary compensation, it is however doubtful that this offer was irresistible to such a degree that someone would participate against their own will.

Questions about previous overdoses and how participants had handled these might lead to feelings of guilt and shame. The questionnaire included information about

where to seek help if needed. The OEND model used here and internationally includes individuals in socioeconomically vulnerable positions who are given a 10 to 15-minute training providing them the means to intervene in highly stressful situations. In half of the reported reversals, the situation involved overdose reversal on a friend or a family member, while the other half represented strangers or acquaintances. One third of the overdoses reportedly occurred in public places while two thirds occurred in private accommodations. This variety in settings and the proximity of relationship to the victim may place a lot of responsibility on the individual (269-271). Broad-scale naloxone programmes can effectively distribute naloxone to laypersons; however, we need to secure a support system for patients involved in these situations. On the other hand, one could argue that the pressure has always been there and that OEND merely provides individuals with the tools for more safe and effective overdose management. Training and talking about these situations do provide a less stigmatised situation and serve a possibility to put overdoses and responses thereof on the agenda. The fact that OEND is a collaboration between healthcare and the individuals who choose to get involved reminds all those engaged that we need each other to save lives, and that the healthcare system is dependent on participants' willingness to get involved.

Main results

Study I

Protocol paper. No results reported.

Study II

Of the 1079 study participants the majority were male (68%) and had a mean age of 40.2 years. A majority had previous experience of own (61%) or having witnessed someone else's (81%) overdose. Almost everyone (97%) stated that they knew what to do in case of witnessing a future overdose.

Among participants returning for refill, 60% of previous naloxone kits were reported to have been used for overdose reversal, while 18% respectively 13% had been lost or given to someone else. Separating OST from NSP, the proportion of naloxone kits reported as used for overdose reversals in relation to number of all cause refill were reported more frequently at NSPs (70%), compared to the OSTs (51%).

Within the sub-sample of those reporting to have used naloxone for overdose reversals, logistic regression analysis showed that having received initial training and naloxone kit through NSP [adjusted odds ratio (AOR) = 5.18, 95% Confidence interval (CI) = 3.38–7.95)], prior experience of own overdose (AOR = 1.63, 95% CI = 1.03–2.58), having witnessed overdose (AOR = 2.12, 95% CI = 1.05–4.29), and having used sedatives during the 30 days prior to initial training (AOR = 1.56, 95% CI = 1.04–2.33) to be significantly associated with having used naloxone for overdose reversal (Table 2).

Table 2. Factors associated with use of naloxone for overdose reversals (n=235)

	Univariate analysis OR (95% CI)	p value	Multivariate analysis AOR (95% CI)	p value
Male gender	1.09 (0.74-1.61)	0.64	1.04 (0.68-1.59)	0.86
Age in years	1.01 (0.99-1.02)	0.29	1.02 (1.00-1.03)	0.09
Initial training at a needle and syringe programme	5.28 (3.57-7.82)	<0.01*	5.18 (3.38-7.95)	<0.01*
Prior experience of own overdose	1.76 (1.17-2.64)	<0.01*	1.63 (1.03-2.58)	0.04*
Prior experience of witnessing overdose	3.24 (1.66-6.29)	<0.01*	2.12 (1.05-4.29)	0.04*
Use of sedatives previous 30 days	2.41 (1.43-2.93)	<0.01*	1.56 (1.04-2.33)	0.03*

*p ≤ 0.05

Of the 200 situations where naloxone reportedly had been used to reverse someone else's overdose, two thirds had taken place in a private accommodation, while one third occurred in a public place. The majority of the victims were male (70%), half were a relative or a friend, while the other half were reported to be an acquaintance or a stranger. Only a small proportion (4%) of participants had stated that they had administered more than two doses of naloxone, while half of the remaining participants had administered one dose and the other half two. The majority (74%) reported to have applied an additional measure accept from administering naloxone. Although nearly all (96%) had stated that they would call an ambulance after initial training, only about half (46%) actually did. The most common reason for not calling was due to not considering it necessary (60%), or that the person who had suffered from overdose not wanting the rescuer to call (23%), while only a minority (14%) refrained from calling due to being afraid of police turning up. Calling the ambulance services was more common if the overdose had occurred in a public place (53%), as opposed to a private setting (39%).

Study III

Characteristics of this cohort was previously described in Bråbäck et al., (4). Participants had a mean age of 37.4 years and the majority were male (76%), born in Sweden (70%), had unstable living conditions (75%). The vast majority (94%) reported injection use during the past 30 days to inclusion, 72% reported previous own experience of overdose and 32% had previously attempted to commit suicide. During the 30 days prior to inclusion, 92% reported having used heroin and mean years of heroin use was 17 (4). Methadone and buprenorphine use was reported by 66% respectively 37%, while tramadol and other opioids had been used by 17% and 18% respectively. Other substances used during the 30 days prior to study inclusion involved amphetamine use (32%), cocaine use (14%) and cannabis use (63%).

Retention in treatment

Retention in treatment after 36 month was 51% (Figure 8), with mean days in treatment being 763, equivalent to 2.1 years. A steeper decline was prevalent during the first 600 days, whereupon the treatment discontinuation rate flattened out.

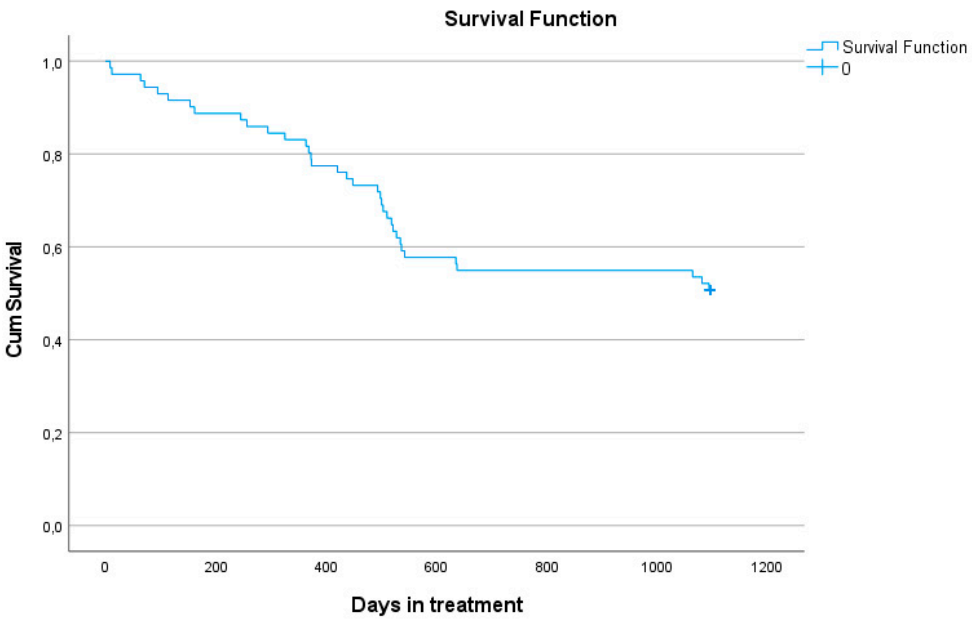

Figure 8. Retention in OST- treatment, 36-months follow-up.

Multiple logistic regression found only amphetamine use during the 30 days prior to treatment to be associated with treatment discontinuation before end of study period (AOR = 3.64, 95% CI = 1.22–10.93) whereas no correlation was found in regard to gender, age, previous suicide attempt, or BZD use during the 30 days prior to treatment start (Table 3).

Table 3. Factors associated with treatment discontinuation before 36 months

	Univariate analysis OR (95% CI)	p-value	Multivariate analysis AOR (95% CI)	p-value
Gender	0.96 (0.33-2.81)	0.95	0.72 (0.21-2.39)	0.59
Age (years)	1.01 (0.96-1.06)	0.76	0.99 (0.93-1.05)	0.76
Suicide attempt prior to treatment	0.92 (0.34-2.48)	0.86	1.09 (0.34-3.47)	0.88
Benzodiazepine use prior to treatment*	1.25 (0.43-3.67)	0.69	0.98 (0.92-1.03)	0.39
Amphetamine use prior to treatment	3.49 (1.21-10.07)	0.02**	3.64 (1.22- 10.93)	0.02**

*Z-drugs included (Zolpidem, Zopiclone)
**p ≤ 0.05

Substance use during treatment

All substances being tested for declined rapidly from inclusion. In general, the proportions of positive urine samples had a steeper decline throughout the first six months, reaching more stable levels thereafter. During the first six months, opiate-positive samples fell from 77% to 12%. The use of BZD, the second most prevalent concomitant substance, fell from 64% to 15% during the same period (Figure 9).

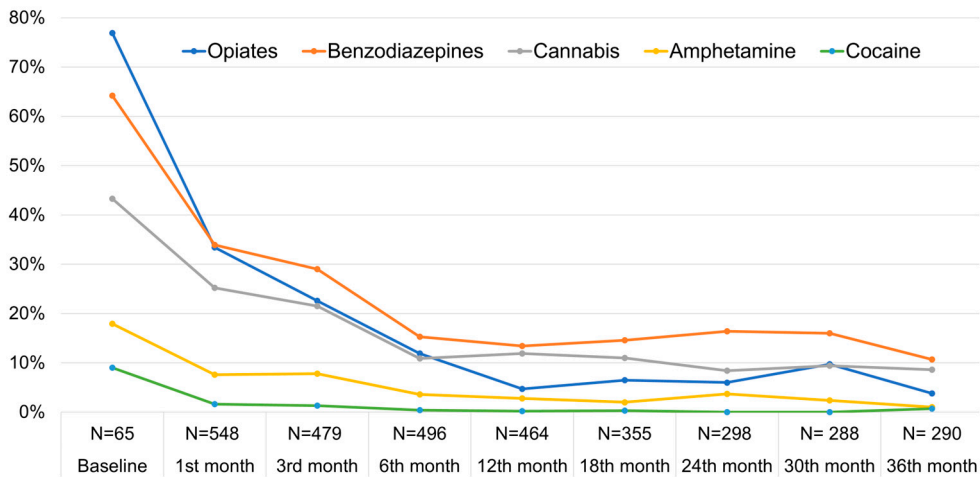

Figure 9. Substance use based on positive samples from baseline during the 36-month follow-up, 6-month intervals.

There was little difference in proportions of polydrug use at baseline between participants remaining in treatment to those who discontinued treatment before the end of the study period.

Study IV

Among the 218 included participants, median age was 43 years, 28% were women and 76% were born in Sweden. Unstable housing was reported by one fifth, while more than half (54%) received welfare and 17% being employed. Daily tobacco smoking was reported by the majority (75%).

Accept from dental symptoms (69%), the most commonly reported physical symptom was pain from extremities, back or neck (66%), followed by gastrointestinal symptoms (56%). Health problems related to airways and genitals were reported by nearly half of the participants (47% respectively) (Table 4).

Table 4. Symptoms and not seeking healthcare for these symptoms

SYMPTOM AREA	SYMPTOMS N=218 (%)	REFRAINED FROM HEALTHCARE SEEKING N (%)*
Pain (from the musculoskeletal system)	66	92 (71%)
Gastrointestinal	56	66 (66%)
Airways	47	50 (56%)
Genitals	47	74 (80%)
Dental/Oral	69	66 (52%)

*of valid

Generally, unmet healthcare needs concerning any of the areas were reported by 82%. Not seeking healthcare for genital symptoms and pain was reported by 80%, respectively 71%, while refraining from seeking healthcare for gastrointestinal symptoms were reported by 66%. Just over half (56%) had not sought healthcare for symptoms from respiratory organs or dental symptoms (52%) (Table 4).

The majority reported previous experience of discrimination and stigma due to illegal substance use, or for being enrolled in OST. Just over half (53%) of the participants had refrained from seeking needed healthcare during the past year.

In multivariate analysis, participants who reported symptoms involving pain from extremities, back or neck were associated with being older (AOR 1.04 [95% CI 1.01-1.07]), unstable housing (AOR 4.26 [95% CI 1.73-10.48]), and negatively associated with being male (AOR 0.45 [95% CI 0.22-0.91]), whereas no correlation was found of respiratory, gastrointestinal, genital, or dental symptoms.

Study V

As previously reported in study IV, the majority (72%) of participants were male, most (75%) smoked tobacco on a daily basis and had an average age of 43.8 years. Most (76%) were born in Sweden, 21% reported unstable housing, while 59% reported having an unstable income.

De-prioritising was reportedly the most common reason (49%) for refraining from healthcare seeking. Many reported fear of being stigmatised as the reason for not seeking healthcare, either described as fear of being labelled a junky and not getting helped (48%) or afraid of being treated badly (38%). Having tried to seek healthcare without success or just being resigned was reported by a quarter of the participants respectively. Refraining due to worry about having a serious medical condition or that they would not understand what the physician would tell them was reported by 17% respectively 13%. Between four and 10% had not sought healthcare due to not knowing what number to call, where they were listed or not having a phone or money for the call.

Analysis of the qualitative material provided a deeper understanding of the results from the quantitative part of the study. De-prioritisation seemed to be associated with resignation and the presumed negative outcomes involved in the healthcare seeking equation. Prior experience of stigma and discrimination, not being listened to, prior efforts not bearing fruit, worrying that they would not understand nor being able to follow advise or afford prescriptions overrode the possible positive outcomes of seeking healthcare, which resulted in resignation and de-prioritisation. Patients also fought with the internalised stigma of having caused their misfortunes themselves and that they were not worthy of seeking help. Being ashamed of the situation they were in, they preferred to wait until their physical condition nearly killed them rather than seeking help.

Analysis of the qualitative data also showed on-site PHC at an OST-clinic to be a facilitator. On-site was thought of as acceptable, as it was provided within a facility where they felt safe and listened to. It was also seen as being easily available and accessible as this was a facility which they visited on a regular basis and as they were reminded recurrently about their appointments.

Discussion

This section will discuss methodological considerations, strengths and limitations of the sample selection and recruitment of study participants, data collection and analysis, followed by an interpretation of the main findings, clinical implications, and implications for future research.

Methodological considerations

Sample selection and recruitment

All studies were located to Skåne county, Sweden. This may impact the generalisability as Skåne county is not only self-governing regarding healthcare, but the healthcare and its judicial system also differs in relation to that of international research. However, sample characteristics are similar to populations in other settings, such as of individuals in North America and Europe who suffer from severe OUD, which is also reflected by the results of the studies.

Sampling bias may occur if representatives from certain groups of individuals decline to partake in the study. Those declining to partake may have a more severe SUD, having withdrawal symptoms and not having time to stay to answer questions or wanting to "stay under the radar". Language barriers, reading and writing disabilities, and cognitive impairment may also hinder individuals' ability to answer questionnaires. Those who are willing to partake may be healthier and may have more resources than those declining. In study II there is also the possibility of eligible subjects turning down OEND entirely due to stigma and social desirability bias, not wanting others to think that they are at risk of overdose, or even socialising with individuals who are at risk. This could also be a way of avoiding suspicion, fearing that privileges such take-home doses may be discontinued. Denial of own overdose risk has also been subject to research, and it has been shown that perceiving overdose risk of others is easier than one's own, due to intragroup stigma and actor observer bias (272).

The numbers of enrolees in the naloxone study were lower than those anticipated prior to its implementation. Rapid expansion of OST establishments within the region led to a reduction in unique NSP visitors who could be included, while

numbers of patients in OST increased. Although this is great from a patient perspective, it may have a negative impact on the statistical power. An increased access to OST generally reduces the risk of overdose among prior at-risk individuals, which also adds to the complex equation on factors which could either increase or decrease drug-related mortality.

Study II-IV were all based on questionnaires, of which study III and IV contained rather comprehensive questionnaires. Study IV also included open-ended questions. There was no economic compensation for participation in study II-IV, whereas a nominal monetary compensation was offered patients taking part in semi-structured interviews in study V. After receiving training and naloxone, eligible candidates were asked if they would be willing to participate in study II. Some may have perceived the time and effort they spent on the ten-minute training to be more than enough, wanting to leave the scene as soon as possible. Even though this may have reduced the numbers of individuals willing to take part, it secured the most important aim of the project which was to provide all at-risk individuals with OEND. Also, a few months into the study, the COVID-19 pandemic also put a hard strain on healthcare. This may have inflicted co-workers to prioritise training and naloxone distribution, and not study inclusion. For ethical reasons, there were no additional advantages for taking part in the study. As Swedish COVID-19 regulations never involved lock-down or confinement measures, the possible negative impact on sample selection and recruitment in study II is thought to be limited, although this needs to be further investigated. A majority (63%) of those who received training and THN agreed to take part in the naloxone study (II), while 46% (n=218) of all patients at the four OST clinics where study IV took place were included. A minor economic compensation might have encouraged patients to take part in study IV.

Comparisons between the naloxone project in Skåne and international studies can be somewhat difficult since regulations between countries vary in regard to whom naloxone can be distributed. For instance, the Norwegian Medicines Agency allowed naloxone to be distributed without prescription, giving non-healthcare staff the possibility to more freely distribute naloxone to anyone at risk of overdose themselves, to potential bystanders at risk of witnessing future overdose, or even to those interested in receiving training and naloxone (273). Naloxone has been generously distributed in Skåne county. Patients are aware of that naloxone used, lost, given away stolen or otherwise unaccounted for will be replenished. This is likely to have contributed to naloxone reaching individuals in need outside the programme. However, the scale of this “underground distribution” remains unknown. Although creative solutions can, at least partially, make up for the inability of the programme to reach certain groups, it is not sufficient. There is an overarching risk that individuals prescribed opioids for long term treatment of non-cancer related pain, potential bystanders, police and watchmen, will continue not to be reached. Additionally, individuals receiving naloxone through “underground

distribution" will not be represented in research, which may cause a sampling bias. The naloxone programme in Skåne has however actively reached out to what we refer to as "hang-arounds". These units are provided with information and education and include premedical and acute medical units, low threshold housing, staff at clinics for non-cancer related pain, social services and other hubs where there may be an increased risk of becoming a witness to future overdoses. Different regulations and OEND design permits reaching different groups in society. OEND in Skåne are aiming at a broad-scale naloxone distribution, with an even broader information network of increased overdose knowledge and know-how, preparing and hoping for regulations to change.

Naturalistic post-hoc analysis of participants in study III showed that those who had not been approached at Malmö NSP were younger ($p=0.03$) and had significantly fewer visits to Malmö NSP than participants who were successfully referred to OST and started treatment ($p<0.001$) (4). These results indicated that a core group of older and more frequent visitors had been reached.

Although it appears to be a small risk of sampling bias when it comes to study participants referred from Malmö NSP to OST (study III) as the sample was representative to the population of individuals who inject heroin enrolled at NSPs in Skåne, it was a rather small sample size. This may limit statistical power; hence inference of associations may be undetected. A larger study sample may render significant findings when it comes to variables associated with retention and the role of abstinence.

While study II offered an analysis of OEND study participants not returning for refill, there was no analysis of individuals who turned down THN and participation in the study. Broad recruitment, aiming to provide all patients with the opportunity to take part in both study II and IV, with many patients asked repeatedly, is a challenge, though it may have presented a possibility to learn more about barriers.

Data collection and analysis

The use of self-report data in study II-V, may affect the quality due to response or *recall bias*, and answers may also be affected by social *desirability bias*. However, there are no other methods that capture study participants' experiences, thoughts and needs more accurately (274, 275). A high prevalence of cognitive impairment (276) and poor health literacy among individuals in OST (277) may also affect the results in study II and IV, as they rely on answers from questionnaires. In some cases, *reliability* in open-ended questions in study IV appeared to be low, as participant answers seemed to refer to a different question, and therefore had to be excluded from analyses.

In study II stigma, *social desirability bias* or fear of negative consequences may lead to avoidance in telling the truth when it comes to reporting what had happened

to the previous naloxone kit, especially in cases where naloxone had been used to reverse one's own overdose. In these situations, reporting previous naloxone as lost could be less problematic, leading to underreporting of overdose reversals.

The *reliability* and *specificity* of the urine-samples in study III are high. Analyses were conducted at the university hospital laboratory, and if a result would to be contested by the patient, the laboratory would perform a re-analysis of the test, including a more specified analysis. Patients were recommended to leave two urine samples weekly during the first six months, as abstinence from other substances than those prescribed would present the possibility of take-home doses. Even though patients could leave urine samples at any time, some did not leave any samples for months; in these cases, consumption was to a large extent unknown, even though the clinical impression was that most patients refraining from leaving samples had no problems of describing at least to some extent what they had consumed. However, as only laboratory samples were included in the data, missing samples lead to diminished *statistical power*.

The mixed methods design applied in study V provides a rich understanding of the subject that would not have been possible to achieve using qualitative or quantitative methods alone. To establish an interview environment where study participants feel that they can speak freely, reducing *social desirability* and *researcher bias*, and for the interviewer to be open to new perspective and insights, interviews had to be performed by someone else than the main author (K.T.), who at the time was working as a nurse and as head of one of the OST units, and who also had been working as a nurse at one of the other OST units.

To secure *trustworthiness* (261, 262, 278) the semi-structured interview instrument was constructed by research group with years of experience of working within the field and where mixed methods adds to the strengthening of *internal validity* (credibility) since questions could be constructed based on quantitative findings. *Dependability* was secured through pilot interview testing theme content and interview length followed by analysis and peer debriefing. All interviews were conducted by the same interviewer (K.L.) with researchers' *reflexivity* and influence of the research process discussed before, during, after the interviews and during analysis. Additionally, the whole material was subject to thematic analyses separately by two of the authors (K.L. and K.T.), after which the results were revised by the third author (D.D.). Aiming for *confirmability* (neutrality of data/objectivity) the results were discussed, negotiated, and re-analysed, then to be revised by the entire research group. Although the setting in which the study was conducted may differ somewhat from that of previous research within the field, the findings were likely to meet the criteria of *generalisability* (transferability).

Interpretation of main findings

- (Study II) This follow-up of the first Swedish multi-site OEND, implemented in Skåne county, adds to the growing international body of literature on broad-scale implementation. Although implementation of such a project is feasible in a Swedish setting, it requires a well-functioning infrastructure and coordination.
- (Study II) Skåne County OEND reaches the target group where naloxone is more frequently used for overdose reversals by individuals with active drug use, rather than those in OST.
- (Study III) Retention in OST treatment at 36-month follow up is considered as high although the lack of long-term studies with referral from NSP to OST makes comparison difficult. Predictors of long-term OST retention and abstinence regarding individuals referred from NSP are inconclusive. This is the first Swedish long-term follow-up on OST patients referred from NSP and, to the best of our knowledge, the first internationally.
- (Study IV) OST patients suffer from a high degree of physical symptoms. However, they do not seek healthcare which leads to a high degree of unmet healthcare needs. This is, to our knowledge, the first study on self-rated health among OST-patients in a Swedish context.
- (Study V) Within the OST-population, barriers to healthcare consist of stigma, de-prioritisation/procrastination, and problems of navigation throughout the healthcare system. Participants found on-site PHC to provide needed non-stigmatised healthcare and support by dedicated staff offered in a safe space where they felt like they were someone who matters and were taken seriously. To our knowledge, this is the first study on barriers to healthcare among OST-patients in a Swedish context.

Broad-scale OEND in Skåne effectively reaches at-risk individuals

The large proportion of participants reporting having used their previous naloxone kit for overdose reversal upon returning for refill indicates that the project was successful to a large extent in reaching the targeted population. Although regulations and settings may vary internationally or even regionally, making comparison between programmes difficult, the prevalence of naloxone use for overdose reversals among trainees matches that of international studies to a large degree (160, 167, 279-281).

Among participants in OEND Skåne 61% reported previous experience of own overdose. Having witnessed overdose was reported by 81%, which is comparable

to enrolees with active substance use, in treatment or in recovery, in a large study in Massachusetts. Here, 54% reported previous own experience of overdose, while 81% had witnessed overdose(s). In the same study, 184 individuals (9%) reported 286 (14%) overdoses reversals (160), in relation to the 140 (13%) individuals in Skåne who reported 229 (21%) overdose reversals. Participants in the Massachusetts study reported to use one respectively two doses in 48% of the cases (160). The exact same proportion was reported in Skåne county.

Between 1996 – June 2014 644 sites in USA reported having distributed naloxone to 152,283 laypersons which had rendered 26,463 (17%) reports of overdose reversals (158).

The Norwegian THN programme trained 1322 individuals likely to experience own or witnessing overdose, between June 2014 – December 2015. While a large proportion (92%) of trainees exhibited risk factors for own overdose 8% had never used opioids. In 277 (21%) cases, naloxone had reportedly been used for overdose reversal (167), which is the same proportion as that of Skåne.

In Scotland, the OEND programme had issued 11,270 kits in the community during its first three years, April 2011 - March 2014, of which approximately 90% were issued to individuals at risk of own overdose. Of these, 8657 kits were "first" supply, issued after initial training, while 767 (9%) kits reportedly had been used for overdose reversal (281).

The large proportion of participants reporting naloxone having been used for overdose reversal upon returning for replenishment, show that Skåne OEND, in comparison with international studies and reports, seem to have a high coverage when it comes to reaching the targeted population.

In situations in Skåne where naloxone was reportedly used to reverse someone else's overdose, most (62%) occurred in a private accommodation. Approximately one third occurred in one's own accommodation (29%), in someone else's (33%), or in a public place (35%), respectively. The proportion of overdoses which were reportedly occurring in a public place is rather high compared to international research as overdoses in public places ranged between 12-23% (160, 280, 282-284). In approximately half of the cases (49%), the victim was a relative or a friend, while nearly as many (48%) reported the victim being a stranger or an acquaintance. The majority (70%) of the victims being male mirrors the proportion of men among DRDs in Sweden (3).

Nearly half (46%) of study participants in Skåne replied that they had called an ambulance even though almost all (96%) stated at the end of the training that they would. Similar, and lower, numbers (10-54%) have been reported in international studies (160, 280, 282-285). The intent to call when hypothetically thinking about an overdose situation is often rated as high (167, 286), but real-life circumstances may influence overdose management, or even hinder protocol to be followed in

practice, leading to lower actual percentage of seeking EMA (287, 288). The majority (60%) of responders in Skåne county found contacting EMA to be unnecessary, 23% referred to the reason being that the victim did not want the respondent to call, while 14% respectively 4% refrained from calling due to being afraid of police or social services getting involved. Previous international studies showed refraining from calling due to being afraid of police involvement to be the most prevalent reason (167, 280, 289-291). Similar findings on refraining from calling due to not finding it necessary were also found in previous studies (280, 292), though not to the same extent as in our study.

Overdose reversal with naloxone requires bystander presence, overdose recognition and intervention. International research has shown a high prevalence of bystanders (80%) to be present when overdose occur (293), with bystanders administering naloxone primarily consisting of other PWUD (160, 282, 294). Most overdoses occur in private accommodations (160, 280, 282-284) where the victim to a great extent (75-81%) is someone close to the rescuer (friend, partner or family member) (160, 282, 283). These individuals constitute potential lifesavers who themselves may not actively use drugs. This is why broad-scale training and distribution is crucial, certifying that potential bystanders are equipped and able to intervene. A recent Swedish study conducted in Skåne before OEND implementation showed that the majority (80%) of overdoses had occurred in a private accommodation, mostly their own (58%), whereas only a small proportion (6%) occurred in a public place. In 59% of the fatalities, police reports did not note someone else being present at the scene at the time of death. Among those at the scene, 23% were in another room, while 18% had been in the same room as the deceased of which around half (8%) had been asleep. Eight percent reported hearing snoring or unnatural breathing (295), in which interventions for overdose reversal could have been performed, would the bystander had known that this is a common symptom in opioid overdose.

With OEND training in Skåne, symptoms involving snoring, irregular breathing, or no breathing at all is one of the issues that is thoroughly discussed. Although, at the beginning of implementation, there were quite a few individuals who previously had witnessed overdose, unaware of this being a cardinal symptom of overdose. Today, the clinical experience is that the number of these stories have declined throughout the years of OEND training. In coherence with international training (289), OEND in Skåne include the concern of using drugs alone as it increases the risk of overdose death, as no one can save you. The clinical impression is that this often can be problematic to patients as they may prefer to use on their own, having a weak social network, or for those who are forced to inject in public places, alone. Although only a few studies have investigated the extent and reasons for using drugs alone, Canadian research demonstrated that the majority (76%) of individuals who use drugs do so alone, of these, 73% reportedly used opioids, commonly involving poly-substance use. Convenience and comfort (44%) were most frequently reported as the reason for why they were using alone, while reasons attributed to stigma or

desire to hide drug use from others was reported by 14%. Safety, not wanting to chare drugs with others and not having anyone around was approximately reported by 10% respectively (86). A qualitative US study among PWID reported that a key reason for injecting alone was due to prioritising withdrawal avoidance and "getting well" as soon as the drug was purchased, and not the location. Respondents also frequently described shame and self-stigma, trying to hide their drug use from others to avoid stigma and embarrassment. Being afraid of legal and practical consequences of witnessing and intervening in a drug overdose also led to avoidance of being around other PWID. Not wanting to share drugs with others or not having any trusted friends were also frequently reported as reasons for using alone (85).

Also, as research has shown that individuals with own high risk of opioid overdose (older, injecting opioids more frequently) may perceive themselves as less likely to overdose (272, 296), it is imperative to equip individuals in their near environment with knowledge and naloxone. Perceiving one's own risk of overdose to be lower than that of peers in similar situations to oneself is likely to be shaped by intragroup stigma where stigmatised individuals within their group internalise societal stigma and perpetuate this to other group members. A hierarchy evolves within the group where individuals exhibiting the most negative characteristics, such as not being able to handle their drug intake and having a high risk of overdose are ranked low. Together with actor-observer bias it creates an environment where own NFOO is blamed on circumstances outside one's own power, while NFOO of others are negatively judged, seen as a weakness in character (272).

Failing to recognise the role of stigma, social determinants (297) and structural vulnerabilities of everyday life (287) of PWUO there is an imminent risk that we will continue to lose the uphill battle of eliminating overdose mortality and morbidity.

Retention in OST

To the best of the authors knowledge, there are no previous long-term follow-ups on retention of individuals with intravenous heroin use referred from NSP to OST. In relation to the 35% retention reported in a 12-month follow-up study among PWUO referred from NSP to OST (128), the 36-month retention rate of 51% among participants in MATRIS is high. Also, median retention rate of 25,1 months (763 days) widely exceeded that of 7,9 months found in a study from Baltimore (127). Our results are more similar to that of the median three-year retention rate among MMT-patients (54%) with unspecified/general referral presented in a recent systematic review. Though, when buprenorphine treatment was added to the picture, retention rate dropped to 38% (298).

Through logistic regression, the only baseline variable associated with treatment discontinuation before 36 months in MATRIS was amphetamine use during the 30

days prior to treatment start. With amphetamine being the more commonly used stimulant in Sweden, where cocaine availability traditionally has been low (299, 300), a comparison of negative effects of cocaine on retention in other parts of the world may be called for. The 12-month follow-up by Neufeld et al., (128) with patients referred from NSP, showed poorer retention to be associated with younger age and having a more extensive cocaine use at baseline. Similar findings were presented in the systematic review with general referral where cocaine use was associated to shorter retention in a majority of the included cohorts (298). Not only does these results indicate negative outcomes for individuals with concomitant stimulant use, but it may also reflect the lack of treatment alternatives for those suffering from stimulant use dependence. Previous research has shown a high proportion of ADHD among patients in MMT which was associated with greater use of stimulants, addiction severity and psychopathology (21, 301). Reduced impulse control and compliance as a consequence of untreated, maltreated and/or undiagnosed neuropsychiatric dysfunction, will likely increase the risk of treatment discontinuation.

As seen in previous research, OST is effective when it comes to reducing heroin use (183, 195, 302-306), which was also found to be the case in our cohort. Another encouraging finding was the reduction of all substances tested for over time, with a steep decline throughout the first six months, followed by a more stable phase over the following 30 months.

It was, however, surprising that no association was found between BZD use during the 30-day period prior to study inclusion as previous research has found BZD use to be associated with negative treatment outcomes and reduced retention (307-309). Specifically, BZD use at baseline have been significantly associated with reduced retention (310). Additionally, as these international research results does also reflect our clinical experiences, it certainly calls for further investigation.

Although previous research has found younger age to be associated with reduced retention (311-316) this was not found among our participants. This was however not that surprising as waiting times for enrolling in OST traditionally had been long before the start of this project. A post hoc study of patients included in the study in relation to those who were potentially eligible though not approached for participation. The results showed that being older, and having a higher number of NSP visits, was significantly associated with inclusion. This, combined with the rather lengthy mean period of time during which heroin had been used (17 years) by those included (4), may have contributed to not finding any significant association between age and treatment retention. Lengthy waiting times are no longer a problem for those suffering from OUD currently seeking treatment in Skåne county. The free choice of OST care ("Vårdval LARO") has led to a rapid increase in newly established privately run OST facilities. There is however a need for further investigation of the effect that these ever-changing regulations has on the OST-population. Factors such as psychiatric distress, being employed, unstable housing,

buying drugs for others and living further away from the treatment site has also been associated with shorter retention periods. This suggests the importance of multilevel interventions (i.e., individual, social, and environmental) to increase retention (127) and patient's wellbeing. The newly conducted Swedish comorbidity investigation suggests a comprehensive approach to tackle co-occurring psychiatric illness and SUD more effectively, which includes a majority of the patients currently in OST. Although Skåne county has witnessed a rapid OST expansion, this is not seen in the rest of Sweden where inequalities in availability and accessibility to OST is still highly prevalent in a majority of the regions (199). As no associations between drug use before treatment start was found, except for amphetamine use, this may indicate that the services provided during treatment are far more important than that of the situation before treatment start.

Self-rated health and unmet healthcare needs

Our findings show a high prevalence of self-reported symptoms and a high degree of unmet healthcare needs among OST-patients. While international research is mainly concerned of the direct consequences of intravenous drug use, HIV and hepatitis C, research on self-rated health and general health among patients in OST is scarce. A high prevalence of self-rated symptoms was also found among the long-term OST patients in a Norwegian study, with more than half of the cohort reported seven or more somatic complaints where the disease burden was associated with more chronic conditions, higher mental distress, fewer years in treatment and dissatisfaction thereof (17). Long-term use of substances and daily tobacco smoking are commonly found within this population which is one of the factors that has a high impact on physical health and wellbeing.

There has been an increased emphasis on the need of adjusting clinical focus from acute to chronic care as the OST population is an ageing population likely to require a high level of somatic healthcare in parallel to long-term OST (17, 19, 106). Only a small proportion of research articles regarding the ageing SUD population, including OUD, is being published in high impact substance or gerontology journals. This disadvantaged research representation increases the risk of insufficient or improper treatment, failing to understand the role of both psychiatric and somatic comorbidities related to the aging SUD population (223).

Airway symptoms and tobacco smoking

Nearly half of all study participants did report having airway symptoms, which is not surprising as 75% reported daily tobacco smoking, one of the main driving factors behind pulmonary disease, cancer, and cardiovascular disease (110). These numbers are however not exceptionally high compared to international studies on OST and tobacco smoking (209). Nevertheless, compared to the 6% of daily smokers among the general population in Sweden (317) the numbers are alarming,

especially since the 24-year follow-up on PWUD in California, by Hser et al., (318), found tobacco smoking contributing to mortality to a higher extent than opiate use. Studies on tobacco smoking within the SUD population (including OST) have shown that a large proportion of participants were both willing and motivated to quit (319-322). In a study among individuals suffering from SUD, including OUD, more than 75% expressed willingness to quit tobacco smoking, with 22% having a desire to quit within the following three months (322). Underestimating the consequences of tobacco smoking, in relation to consequences of drug use may lead to smoking cessation not being prioritised (323), or not delt with at all. Prevalence of COPD and asthma have shown to be substantially higher among MMT patients and apart from physical advantages of smoking cessation it may also enhance treatment outcome success (324). A systematic review and meta-analysis showed smoking cessation to increase quality of life and to reduce depression, anxiety and stress. There was no evidence of differences in effect size when comparing the general population to those suffering from physical and psychiatric disorders (325). Previous studies have shown that smoking cessation can be rather challenging when it comes to the OST population (210, 326-328). Results from a pilot study among OST patients did not only show a high willingness to quit smoking, but also a significant reduction in numbers of cigarettes smoked when applying an individually tailored intervention (329). Our results showed that not only did the majority of our participants smoke on a daily basis, but more than half of those reporting airway symptoms had not sought medical care. As smoking generally is a primary cause of preventable death, this calls for tailoring smoking reduction or cessation treatment models which matches the needs of highly dependent individuals with a long history of smoking and high prevalence of psychiatric comorbidities.

Pain

The large proportion (66%) of OST patients suffering from pain while medicating with methadone or buprenorphine is concerning. The prevalence is not unique in comparison to international studies of pain in MMT patients (101, 330, 331). However, although the vast majority (71%) of patients in our study did refrain from seeking healthcare, the etiology is to a large extent unknown, diminishing the forecast of finding a cure for the symptom. OST patients suffering from chronic pain has been associated with significantly more health problems, psychiatric disturbance, distress, and of having a greater belief of being undertreated (101, 331). This may explain, at least in part, why our patients to a large extent refrained from seeking healthcare.

Gastrointestinal symptoms

As opioids disrupt gastrointestinal mobility and secretion, opioid-induced bowel dysfunction is commonly reported among OST patients (332). Among participants in our study who reported gastrointestinal symptoms (46%) the majority (66%) had

refrained from seeking healthcare. This clearly indicates that there is a need for healthcare staff to more actively inform patients about this condition and how improvements can be accomplished, and systematically follow outcomes, as many of the underlying conditions are treatable.

Sexual health

Almost half (47%) of our study participants reported symptoms from genitals, though the vast majority (80%) had not sought healthcare for these symptoms. An international meta-analysis on sexual dysfunction among men in MMT reported a pooled prevalence of 52%, ranging between 16-84%. As with international research on women's sexuality, desire and functions are generally limited, in relation to that of men (333), research on the effects of opioids on sexual functioning among women in OST is very limited (334). A multi-centre study in Italy found that 57% of women in OST reported sexual dysfunction for at least three months, with no significant differences between participants prescribed methadone or buprenorphine (334). It is imperative that healthcare professionals inform patients, women included, of possible side effects of OST (and other) medication and available treatment options. Sexual dysfunction may have a large impact on quality of life if having a negative effect on intimate relationships. It has also been connected to an increased risk of illegal use of drugs trying to enhance sexual ability and an increased risk of treatment discontinuation (335).

Dental problems

Two thirds (69%) of patients in our study reported having dental symptoms, of which a little more than half (52%) reported having refrained from seeking care. However, these reports did not define the extent of the problem, neither did it explore of those who had sought help did commit and had followed through with all needed dental procedures. Nevertheless, numbers are consistent with international research among individuals suffering from OUD, confirming a high prevalence of dental problems most often caused by a combination poor oral hygiene, undernourishment, increased sugar consumption, homelessness, and of heroin use often being combined with other drugs and tobacco smoking (336). Xerostomia (low salivary secretion) increases caries and can be caused by an array of medications, including methadone and buprenorphine, also negatively impacted by insufficient oral hygiene and malnourishment (336, 337). The analgesic effect of opioids may also delay treatment seeking as opioids can mask pain caused by oral disease, which may unfortunately also increase problem severity further (336). As dental problems are not likely to solve themselves and are more likely to become worse if not treated there is a need for further investigation into the magnitude of these problems and how OST professionals can facilitate patients in being examined and treated for their symptoms.

Barriers to healthcare

As our research had shown a high degree of self-rated somatic symptoms and unmet healthcare needs, we were interested in exploring what these barriers to healthcare consisted of. Results from our mixed methods study on healthcare seeking showed that both individual and structural barriers reduce access to healthcare. We found de-prioritisation/resignation, fear of stigma, previous mistreatment, and difficulty in navigating the fragmentised healthcare system, to be the most common reasons for not seeking needed healthcare.

De-prioritisation seemed however more complex than not prioritising healthcare per se. Many described how low self-efficacy and self-esteem, together with the realisation that there would be a slim chance that healthcare seeking would result in a positive outcome (i.e., successfully being examined by a physician without experiencing stigmatising and judgement, where they would be listened to and where their problems would be taken seriously), led to the feeling of resignation, not even worth the effort of trying. This was explicitly expressed by interviewees suffering from pain as they reported that seeking healthcare treatment would only make healthcare professionals perceive them as prescription-hunters.

De-prioritisation had previously been found to be the most commonly presented reason for not seeking healthcare among visitors to a NSP in US. Instead, the solution by the majority was to procrastinate (80%), trying to ignore the symptoms. Similarly to our findings, de-prioritisation was described as multifaceted, referring to the Health Belief Model (338), where tension between perceived susceptibility, severity benefits, barriers, cues to action and self-efficacy could be helpful in explaining the complexities of healthcare seeking and barriers thereof (217). This coincides with previous description of low self-esteem and self-efficacy as the final stages of internalisation of stigma, with an overarching feeling of hopelessness inevitably leading to resignation ("Why try?") (228, 253). Discrimination among PWUD has been associated with poorer physical health (257), and as expressed by the majority of our participants, international research show that stigma does play a major part in healthcare seeking (339, 340). The mere anticipation of being treated badly, based on previous experiences, was rated as the barrier having the largest impact on healthcare seeking among NSP visitors in US (217).

Delaying healthcare seeking as a strategy to avoid anticipated stigma has previously been described among PWIDs (218). This was also reported among our study participants. Procrastination, trying to deal with symptoms using alternative strategies, or trying to ignore the symptoms, were ways in which the symptoms were delt with while trying to avoid healthcare seeking. Quite a few of the interviewees did however report previous situations where the severity of their problems had escalated, leaving the person with the only option of seeking emergency healthcare. In many cases these symptoms could have been dealt with at an earlier stage, which likely would have involved much less suffering. This indicates that although

enrolling in OST may reduce emergency healthcare visits and hospital admittance (341) it is still an overarching issue among our patients.

Problems with navigation throughout the healthcare system due to psychiatric comorbidity, actively using illegal substances and of the healthcare being fragmented are issues described previously in the literature. The high proportion of psychiatric comorbidities, SUD, or alcohol use disorder among patients with OUD are well documented (20, 21, 23, 80, 88, 90, 94, 301) and is likely to have a negative impact on healthcare seeking. The increasingly fragmented healthcare system described in an American context is shown to contribute greatly to inequity (342) similarly described when examining the structure of Swedish healthcare (343, 344). This becomes problematic as it demands high self-efficacy, self-sufficiency, endurance, cognitive functioning, and health literacy (342, 343) which are commonly reduced by the psychiatric comorbidities found among OST patients.

Integration of healthcare within facilities frequently visited by PWUD, such as on-site PHC at OST facilities or NSPs, have been suggested as a solution to overcome barriers to healthcare seeking (218, 345-347). Although scarcely presented in the international research, findings do indicate positive results and could offer considerable benefits in caring for vulnerable populations and their health (25, 26, 28, 212, 214, 347-351), however, more research is needed.

Main conclusions

Broad-scale OEND implementation, distribution and monitoring is feasible in a Swedish context. Although individuals with increased own risk of overdose also are those who most frequently report usage of naloxone for overdose reversal, reaching a large proportion of at-risk individuals is vital for naloxone to be present when and where opioid overdose occurs. A well-functioning network of healthcare units which independently can offer preventive overdose training and THN to its patients and coordination hereof is imperative in decreasing morbidity and mortality caused by opioid overdose.

Broad-scale OEND is generally considered to be an effective response to an acute situation (160). As methadone and buprenorphine treatment is significantly associated with all cause and overdose mortality (9), retention in treatment is essential. While the methadone induction period also increases risk of mortality, the period immediately after treatment discontinuation is strongly associated with an increased overdose risk (9). Therefore, retention and stability, as well as overdose prevention education and naloxone distribution, is imperative for positive outcomes and reductions in morbidity and mortality.

Retention in treatment among heroin-dependent individuals who were provided a fast-track referral from NSP to OST was considered to be high, in comparison with international studies. The only baseline variable associated with treatment discontinuation before end of the three-year follow-up period was amphetamine use. Substance use at treatment start may have less impact on treatment outcomes than that of offering diverse, highly professional psychiatric treatment and social support matched with individual conditions and needs throughout different stages in their lives.

Patients in OST have a large burden of self-rated somatic symptoms along with a high degree of unmet healthcare needs. Previous experience of discrimination and stigma, not being taken seriously and listened to and problems with navigation throughout the healthcare system leads to resignation, avoidance, de-prioritisation and procrastination. On-site PHC within OST facilities can offer available, accessible, and acceptable healthcare to a growing and ageing population with a high proportion of somatic disease.

Clinical implications

Preliminary findings indicate that broad-scale THN implementation in an already existing network of multiple NSPs, OST units and other addiction facilities is successful in reaching its targeted population in a setting with traditionally low level of harm reduction interventions. This calls for broader collaboration and coordination between healthcare facilities in regions where the network of NSPs and OST units are scares, to ensure that individuals at risk of opioid overdose are accessing THN.

Using NSP as a platform for rapid referral, without initial focus on social situation or drug use, seems equally effective when it comes to retention, in relation to traditional referral. Use of substances other than amphetamines during the 30-day period prior to OST enrolment does not appear to have bearing on treatment outcomes, implying that services should focus on matching patients with treatment and support to meet their individual needs throughout their life trajectories in a timely manner since this is more likely to impact recovery and treatment outcomes.

To meet the complex healthcare needs of patients with OUD, the system needs to change. Ways of providing easily acceptable non-stigmatising healthcare must be established with incentives for PHC and specialised psychiatric care units to collaborate on a whole new level. On-site PHC could be one way to override some of the barriers. Inevitably, this also implies a need to increase healthcare professionals' knowledge and experience managing people with OUD and psychiatric comorbidities in relation to somatic health and healthcare needs. Additionally, since the vast majority of OST patients smoke tobacco on a daily basis, there is an urgent need to address this issue and to implement an effective smoking cessation model within this group.

Implication for future research

Although the studies presented in this thesis did add to the limited research within these fields there is a continuous need for further investigation to be conducted, more specifically, there is a need for future research on the following:

- Investigations into the population of naloxone "super-users" are needed to assure that they receive the support they need in continuing to intervene in overdose situations, which could be studied using qualitative methods.
- There is a need to investigate why some at-risk individuals refuse to partake in OEND – what constitutes the resistance towards accepting and carrying naloxone and what does the resistance stand for? Qualitative methods are believed to be most suitable for studying this area more thoroughly.
- Long-term studies on the effect of broad-scale OEND implementation on mortality and morbidity on a population level are needed, as international research covering long-term aspects are scarce.
- Reasons behind OST patients' decisions to discontinue OST need to be further investigated and how psychosocial treatment throughout the life course can affect treatment outcomes. A mixed methods design with initial focus groups could be one way of initiating research within this field.
- Future research should include screening and physical examination, assessing somatic status of OST patients, with a special focus on older patients. There is a need to map out and objectively study the extent of somatic illness and chronic disease within this group
- There is a need for further investigation into patient-centred healthcare among OST patients and weather on-site PHC could lead to reduced symptoms and increased quality of life?
- Reasons for OST patients with somatic symptoms refraining from seeking healthcare need to be further investigated to prevent problems from developing further and to reduce seeking emergency healthcare as a result of procrastination and avoidance.
- An intervention study should be implemented to assess the effectiveness of smoking cessation, or smoking reduction, methods among OST patients.
- Designing and implementing a study on naloxone access is of great importance as it will allow us to override the inability to reach individuals outside the healthcare system, whom for varying reasons have difficulties in seeking healthcare.

Populärvetenskaplig sammanfattning

Opioidberoende medför många olika komplikationer och risker för användaren, i synnerhet vid långvarig injektion av heroin med samtidig användning av andra substanser, så som bensodiazepiner och alkohol. Den här avhandlingen handlar om olika insatser som kan minska risken för sjukdom och förtida död till följd av opioidberoende.

Död till följd av opioidöverdos utgör den största risken för förtida död bland de som lider av opioidberoende. Opioider har en andningshämmande effekt, som vid överdosering kan leda till oregelbunden och otillfredsställande andning och i värsta fall till andningsstopp och död. Naloxon är ett läkemedel som effektivt kan häva opioidöverdos, om det administreras i tid. Det är därför viktigt att både naloxon och kunskap om vad som kännetecknar en opioidöverdos och vad man bör göra för att hjälpa den drabbade sprids på bred front så att man kan agera snabbt där och då överdos inträffar, i väntan på ambulans. Även om majoriteten av Sveriges regioner uppger att de idag har naloxonprogram, så varierar tillgång och tillgänglighet stort inte bara nationellt utan även inom regionerna.

För att långsiktigt förebygga och minska risken för skador och död till följd av opioidanvändande och beroende tillgång till evidensbaserad behandling, såsom läkemedelsassisterad rehabilitering vid opioidberoende (LARO), avgörande. Eftersom riskerna för skador och död ökar till följd av avbruten behandling är det viktigt att de som går in i LARO även stannar kvar. Även om Sverige var det andra landet i världen att introducera LARO behandling så har utvecklingen traditionellt varit präglad av höga trösklar in och låga trösklar ut ur programmen. Förändringar i regelverket har över tid förbättrat behandlingssituationen, men förutom i Skåne, där vårdvalet lett till en enorm expansion av enheter, är tillgången till LARO i Sverige fortlöpande otillfredsställande och ojämlik.

De som går in i LARO har ofta ett mångårigt opioidberoende bakom sig som präglats av ett ohälsosamt, eller direkt skadligt, livsförlopp. Även om forskningen vad gäller den kroppsliga ohälsan hos personer i LARO är skral, så tyder befintliga resultat på att personer i LARO har en hög grad av kroppslig ohälsa, men att de, av olika anledningar, inte söker vård i den utsträckning som är medicinskt befogat. En åldrande LARO-population i kombination med lågt vårdsökande och en hög andel av psykiatrisk samsjuklighet kommer framöver att i ökande grad utgöra en utmaning

för hälso- och sjukvården. Därför behöver vi kartlägga upplevelsen av fysisk ohälsa i denna population och i vilken grad behoven uppfylls av den befintliga vården.

Syftet med denna avhandling är att beskriva forskningsansatsen vad gäller Sveriges första regionala naloxonprojekt och dess utveckling under de första 30 månaderna. Avhandlingen syftar även till att undersöka vad som kan påverka kvarstannandet LARO och hur substansanvändandet ser ut över tid, samt att undersöka den självupplevda fysiska hälsan och vårdbehov bland patienter i LARO, och i vilken grad detta behov tillfredsställs.

Den första studien avser att beskriva det regionala naloxonprojekt i Skåne som kom att bli det första i Sverige att på bred front erbjuda patienter som riskerar att drabbas av opioidöverdos utbildning och naloxon att bära med sig. I denna protokollartikel beskrivs de statistiska mätningar och undersökningar som avses utföras inom ramen för Region Skånes naloxonprojekt.

Den andra studien som avsåg att följa naloxonprojektets utfall under de första 30 månaderna byggde på frågeformulär som samlats in kontinuerligt vid första utbildningstillfället och därefter vid de tillfällen då tidigare erhållet kit ersattes med ett nytt. De huvudsakliga fynden visade att storskalig implementering i en svensk region varit framgångsrik vad gäller att på bred front att nå ut till individer som riskerar att drabbas av opioidöverdos. De som själva löpte större risk att drabbas var även de som främst rapporterade användning. Mest vanligt var det att överdosen inträffat i en privat bostad. I hälften av fallen var den drabbade en närstående eller vän, medan den andra hälften bestod av bekanta eller främlingar. Färre än hälften uppgav att de ringt ambulans i samband med att de gav naloxon. Den främsta anledningen till att man lät bli att ringa var att man inte tyckte att det behövdes, eller att den drabbade inte ville att man skulle ringa. Endast ett fåtal svarade att de låtit bli att ringa på grund av rädsla för att polis eller sociala myndigheter skulle ingripa.

Den tredje studien undersökte kvarstannande i LARO efter 36 månader bland heroinberoende individer som överförts från sprutbytet i Malmö. Intervjun som gjordes inför bedömning, och provtagning som ägde rum vid denna, samt de urinprover som samlades in regelbundet under de tre åren som studien pågick låg till grund för denna studie. Resultaten visade att en hög andel patienterna hade stannat kvar i behandling vid 36-månadersuppföljningen. Uppföljningen visade en minskning av opiatpositiva urinprov över tid, vilket är det huvudsakliga målet med behandlingen, men även en minskning av andra substanser. Amfetaminanvändning månaden inför överföringen till LARO var dock det enda som tycktes ha en negativ effekt på kvarstannande i behandling. Även om studiepopulationens storlek utgjorde en begränsning vad gäller tolkningen av resultatet kan man med försiktighet ändå påtala att den vård som erbjuds patienter när de väl är i behandling och de livshändelser som äger rum under behandlingstiden sannolikt spelar större roll än patientens psykosociala och medicinska status vid behandlingsstart, varför det är

viktigt att skyndsamt erbjuda individuell behandling i förhållande till patientens situation och behov.

Den fjärde studien bygger på enkäter som avsåg att undersöka självskattad hälsa bland patienter i LARO och om de sökt vård för upplevda symtom. Resultaten visar att patienter i OST har en hög grad av fysiska symtom samtidigt som de inte söker vård i den omfattning som kan anses medicinskt befogat. En majoritet av deltagarna i studien uppgav att de levde med kroppslig smärta och problem med tand- och munhåla, mer än hälften uppgav att de hade problem med magen och nästan hälften rapporterade att de hade problem med andningsorgan och genitala besvär. Smärta var vanligare bland de som rapporterat att de hade en instabil boendesituation och bland kvinnor. Till trots för den höga andelen av självrapporterade symtom var det få som sökt vård.

I den femte studien kombinerades tidigare opublicerade data med intervjuer för att på djupet undersöka varför patienter i LARO inte söker vård till trots för det stora vårdbehovet. Resultaten visade att stigma, nedprioritering/ resignation och svårigheter att navigera i sjukvårdssystemet utgjorde de främsta anledningarna till att man inte sökte vård. Tidigare erfarenheter av dåligt bemötande och diskriminering på grund av substansberoende gjorde att många undvek att söka vård. Fragmenteringen av sjukvården gjorde det svårare för de med kognitiv svikt att navigera i systemet. Detta gjorde att många gav upp, att det inte ens var lönt att försöka. Eftersom man ofta bedömde chansen att få god vård som ringa fick vårdsökandet lägre prioritering och undveks så långt det var möjligt. De som fått tillgång till primärvård ”on-site” på sin LARO-mottagning rapporterade att de nu orkade ta tag i saker som de tidigare inte haft möjlighet till, genom stöd från personal och tillgång till vård i en miljö där de inte upplevde sig stigmatiserade och diskriminerande.

Slutsatserna för avhandlingen är att överdosdödlighet kan förebyggas både på kort och lång sikt genom naloxonutbildning och utdelning på bred front, ökad tillgänglighet och retention i LARO samt genom förenklade vägar in i en vård som inte upplevs stigmatiserande eller diskriminerande.

Det behövs mer forskning vad gäller naloxonanvändning och hur vi når de individer som befinner sig i riskzonen, som vi i dagens vårdsystem har svårt att nå samt undersöka om de som ingripit vid flertalet tillfällen anser sig få det stöd de behöver för att fortsätta utgöra sjukvårdens förlängda arm. Sedan vårdval LARO 2014 har antalet patienter i behandling fördubblats, men vad som utgör god vård, vad som får individer att stanna kvar i behandling och uppnå sina mål inom vårdens ramar vet vi fortfarande för lite om, varför det är av stor vikt att studera detta mer ingående. De få studier som gjorts vad gäller LARO patienters somatiska hälsa och vårdsökande talar för att det behövs mer forskning inom området, i synnerhet då denna åldrande och växande population inte söker vård till trots för en tung sjukdomsbörda i förhållande till jämnåriga i normalbefolkningen.

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References

1. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet (London, England). 2019;394(10208):1560-79.
2. European Monitoring Centre for Drugs and Drug Addiction. Statistical Bulletin 2022 - At a glance — estimates of drug use in the European Union [Internet]. Luxembourg: Publications Office of the European Union; 2022. [cited 2022 July 28]; Available from: https://www.emcdda.europa.eu/media-library/glance-%E2%80%94-estimates-drug-use-european-union-updated-june-2022_en
3. Folkhälsomyndigheten. Den svenska narkotikasituationen [Internet]. Stockholm; Folkhälsomyndigheten; 2022. [cited 2022 July 14]; Available from: https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/d/den-svenska-narkotikasituationen-2021/?
4. Bråbäck M, Nilsson S, Isendahl P, Troberg K, Brådvik L, Håkansson A. Malmö Treatment Referral and Intervention Study (MATRIS)—effective referral from syringe exchange to treatment for heroin dependence: a pilot randomized controlled trial. Addiction. 2016;111(5):866-73.
5. Brådvik L, Frank A, Hulenvik P, Medvedeo A, Berglund M. Heroin addicts reporting previous heroin overdoses also report suicide attempts. Suicide Life Threat Behav. 2007;37(4):475-81.
6. Håkansson A, Vedin A, Wallin C, Kral AH. [Distribution of naloxone to prevent death from heroin overdose. Study of opioid dependent patients' attitudes to be part of the antidote program]. Lakartidningen. 2013;110(29-31):1340-2.
7. European Monitoring Centre for Drugs and Drug Addiction. Topic Overview. Take-home naloxone. [Internet]. Luxembourg: Publications Office of the European Union; 2021. [cited 2022 February 24]; Available from: https://www.emcdda.europa.eu/publications/topic-overviews/take-home-naloxone
8. World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee: Community Management of Opioid Overdose [Internet]. Geneva: World Health Organization; 2014. [cited 2022 February 14]. Available from: https://apps.who.int/iris/bitstream/handle/10665/137462/9789241548816_eng.pdf?sequence=1
9. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Bmj. 2017;357:j1550.

10. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009;2009(3):Cd002209.
11. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014(2):Cd002207.
12. Gronbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. Acta Psychiatr Scand. 1990;82(3):223-7.
13. Fugelstad A, Stenbacka M, Leifman A, Nylander M, Thiblin I. Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings. Addiction. 2007;102(3):406-12.
14. Clausen T, Waal H, Thoresen M, Gossop M. Mortality among opiate users: opioid maintenance therapy, age and causes of death. Addiction. 2009;104(8):1356-62.
15. Bech AB, Clausen T, Waal H, Delaveris GJM, Skeie I. Organ pathologies detected post-mortem in patients receiving opioid agonist treatment for opioid use disorder: a nation-wide 2-year cross-sectional study. Addiction. 2021.
16. Bech AB, Clausen T, Waal H, Šaltytė Benth J, Skeie I. Mortality and causes of death among patients with opioid use disorder receiving opioid agonist treatment: a national register study. BMC health services research. 2019;19(1):440.
17. Medved D, Clausen T, Bukten A, Bjørnestad R, Muller AE. Large and non-specific somatic disease burdens among ageing, long-term opioid maintenance treatment patients. Subst Abuse Treat Prev Policy. 2020;15(1):87.
18. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2017: Trends and Developments [Internet]. Luxembourg: Publications Office of the European union; 2017. [cited 2022 February 24]. Available from: https://www.emcdda.europa.eu/system/files/publications/4541/TDAT17001ENN.pdf
19. European Monitoring Centre for Drugs and Drug Addiction. Policy and practice briefings. Older people with problematic opioid use [Internet]. Luxembourg: Publications Office of the European union; 2017. [cited 2022 May 12]. Available from: https://www.emcdda.europa.eu/best-practice/briefings/older-people-with-problematic-opioid-use_en
20. Carpentier PJ, Krabbe PF, van Gogh MT, Knapen LJ, Buitelaar JK, de Jong CA. Psychiatric comorbidity reduces quality of life in chronic methadone maintained patients. Am J Addict. 2009;18(6):470-80.
21. Carpentier PJ, van Gogh MT, Knapen LJ, Buitelaar JK, De Jong CA. Influence of attention deficit hyperactivity disorder and conduct disorder on opioid dependence severity and psychiatric comorbidity in chronic methadone-maintained patients. Eur Addict Res. 2011;17(1):10-20.
22. Bråbäck M, Brantefors A, Franck J, Brådvik L, Isendahl P, Nilsson S, et al. Substance Use, Hospitalizations, and Co-Occurring Disorders among Patients Transferred from a Needle Exchange Program to Opioid Maintenance Treatment. International Journal of Environmental Research and Public Health. 2022;19(2):697.

23. Milby JB, Sims MK, Khuder S, Schumacher JE, Huggins N, McLellan AT, et al. Psychiatric comorbidity: prevalence in methadone maintenance treatment. Am J Drug Alcohol Abuse. 1996;22(1):95-107.
24. Rosic T, Naji L, Bawor M, Dennis BB, Plater C, Marsh DC, et al. The impact of comorbid psychiatric disorders on methadone maintenance treatment in opioid use disorder: a prospective cohort study. Neuropsychiatr Dis Treat. 2017;13:1399-408.
25. Umbricht-Schneiter A, Ginn DH, Pabst KM, Bigelow GE. Providing medical care to methadone clinic patients: referral vs on-site care. Am J Public Health. 1994;84(2):207-10.
26. Selwyn PA, Budner NS, Wasserman WC, Arno PS. Utilization of on-site primary care services by HIV-seropositive and seronegative drug users in a methadone maintenance program. Public Health Rep. 1993;108(4):492-500.
27. Friedmann PD, Alexander JA, Jin L, D'Aunno TA. On-site primary care and mental health services in outpatient drug abuse treatment units. The journal of behavioral health services & research. 1999;26(1):80-94.
28. Gourevitch MN, Chatterji P, Deb N, Schoenbaum EE, Turner BJ. On-site medical care in methadone maintenance: associations with health care use and expenditures. J Subst Abuse Treat. 2007;32(2):143-51.
29. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2020: Trends and Developments [Internet]. Luxembourg: Publications Office of the European Union: 2020. [cited 2022 April 12]. Available from: https://www.emcdda.europa.eu/system/files/publications/13236/TDAT20001ENN_web.pdf
30. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid use disorder. Nature reviews Disease primers. 2020;6(1):3.
31. Wang JC, Kapoor M, Goate AM. The genetics of substance dependence. Annu Rev Genomics Hum Genet. 2012;13:241-61.
32. Saxon AJ, Oreskovich MR, Brkanac Z. Genetic determinants of addiction to opioids and cocaine. Harvard review of psychiatry. 2005;13(4):218-32.
33. Bolshakova M, Bluthenthal R, Sussman S. Opioid use and misuse: health impact, prevalence, correlates and interventions. Psychology & health. 2019;34(9):1105-39.
34. Saunders JB. Substance use and addictive disorders in DSM-5 and ICD 10 and the draft ICD 11. Curr Opin Psychiatry. 2017;30(4):227-37.
35. Word Health Organization. Opioid overdose. [Internet]. Geneva: World Health Organization; 2021 [cited 2022 February 24]; Available from: https://www.who.int/news-room/fact-sheets/detail/opioid-overdose
36. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2021: Trends and Developments [Internet]. Luxembourg: Publications Office of the European Union; 2021. [cited 2022 May 5]. Available from: https://www.emcdda.europa.eu/system/files/publications/13838/TDAT21001ENN.pdf

37. European Monitoring Centre for Drugs and Drug Addiction. Drug-related deaths and mortality in Europe: update from the EMCDDA expert network. Technical report [Internet]. Luxembourg: Publications Office of the European Union; 2021. [cited 2022 May 5]. Available from: https://www.emcdda.europa.eu/system/files/publications/13762/TD0221591ENN.pdf
38. Martins SS, Sampson L, Cerdá M, Galea S. Worldwide Prevalence and Trends in Unintentional Drug Overdose: A Systematic Review of the Literature. Am J Public Health. 2015;105(11):e29-49.
39. Darke S, Mattick RP, Degenhardt L. The ratio of non-fatal to fatal heroin overdose. Addiction. 2003;98(8):1169-71.
40. Boyer EW. Management of opioid analgesic overdose. The New England journal of medicine. 2012;367(2):146-55.
41. Sporer KA. Acute heroin overdose. Ann Intern Med. 1999;130(7):584-90.
42. Darke S, Duflou J. The toxicology of heroin-related death: estimating survival times. Addiction. 2016;111(9):1607-13.
43. Darke S, Duflou J, Torok M. The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. Drug Alcohol Depend. 2010;106(1):1-6.
44. Darke S. Heroin overdose. Addiction. 2016;111(11):2060-3.
45. Darke S, Ross J, Zador D, Sunjic S. Heroin-related deaths in New South Wales, Australia, 1992-1996. Drug Alcohol Depend. 2000;60(2):141-50.
46. Davidson PJ, McLean RL, Kral AH, Gleghorn AA, Edlin BR, Moss AR. Fatal heroin-related overdose in San Francisco, 1997-2000: a case for targeted intervention. J Urban Health. 2003;80(2):261-73.
47. Maloney E, Degenhardt L, Darke S, Nelson EC. Are non-fatal opioid overdoses misclassified suicide attempts? Comparing the associated correlates. Addict Behav. 2009;34(9):723-9.
48. Darke S, Zador D. Fatal heroin 'overdose': a review. Addiction. 1996;91(12):1765-72.
49. Bird SM. Over 1200 drugs-related deaths and 190,000 opiate-user-years of follow-up: Relative risks by sex and age group. Addiction Research & Theory. 2010;18(2):194-207.
50. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011;106(1):32-51.
51. Hickman M, Carnwath Z, Madden P, Farrell M, Rooney C, Ashcroft R, et al. Drug-related mortality and fatal overdose risk: Pilot cohort study of heroin users recruited from specialist drug treatment sites in London. Journal of Urban Health. 2003;80(2):274-87.
52. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999;94(7):961-72.
53. Simonsen KW, Kriikku P, Thelander G, Edvardsen HME, Thordardottir S, Andersen CU, et al. Fatal poisoning in drug addicts in the Nordic countries in 2017. Forensic science international. 2020;313:110343.

54. Macleod J, Steer C, Tilling K, Cornish R, Marsden J, Millar T, et al. Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records. PLoS medicine. 2019;16(11):e1002965.
55. Darke SG, Ross JE, Hall WD. Benzodiazepine use among injecting heroin users. The Medical journal of Australia. 1995;162(12):645-7.
56. Ford C, Law F. Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice, Substance Misuse Management in General Practice, London. 2014.
57. Lader M. Benzodiazepine harm: how can it be reduced? British journal of clinical pharmacology. 2014;77(2):295-301.
58. Brands B, Blake J, Marsh DC, Sproule B, Jeyapalan R, Li S. The impact of benzodiazepine use on methadone maintenance treatment outcomes. J Addict Dis. 2008;27(3):37-48.
59. Lavie E, Fatséas M, Denis C, Auriacombe M. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: correlates of use, abuse and dependence. Drug Alcohol Depend. 2009;99(1-3):338-44.
60. Vogel M, Knöpfli B, Schmid O, Prica M, Strasser J, Prieto L, et al. Treatment or "high": benzodiazepine use in patients on injectable heroin or oral opioids. Addict Behav. 2013;38(10):2477-84.
61. de Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addiction biology. 2009;14(1):22-31.
62. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl). 1999;146(4):373-90.
63. Tjagvad C, Clausen T, Handal M, Skurtveit S. Benzodiazepine prescription for patients in treatment for drug use disorders: a nationwide cohort study in Denmark, 2000-2010. BMC psychiatry. 2016;16:168.
64. McAuley A, Matheson C, Robertson JR. From the clinic to the street: the changing role of benzodiazepines in the Scottish overdose epidemic. International Journal of Drug Policy. 2022;100:103512.
65. Park TW, Larochelle MR, Saitz R, Wang N, Bernson D, Walley AY. Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine. Addiction. 2020;115(5):924-32.
66. Dahan A, van Lemmen M, Jansen S, Simons P, van der Schrier R. Buprenorphine: a treatment and cause of opioid-induced respiratory depression. Br J Anaesth. 2022;128(3):402-4.
67. Strang J, McDonald R, Campbell G, Degenhardt L, Nielsen S, Ritter A, et al. Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health Application of an Emergency Medicine. Drugs. 2019;79(13):1395-418.
68. Warner-Smith M, Darke S, Day C. Morbidity associated with non-fatal heroin overdose. Addiction. 2002;97(8):963-7.

69. McClain CJ, Price S, Barve S, Devalarja R, Shedlofsky S. Acetaminophen hepatotoxicity: An update. Curr Gastroenterol Rep. 1999;1(1):42-9.
70. Larney S, Tran LT, Leung J, Santo T, Jr., Santomauro D, Hickman M, et al. All-Cause and Cause-Specific Mortality Among People Using Extramedical Opioids: A Systematic Review and Meta-analysis. JAMA psychiatry. 2020;77(5):493-502.
71. Stoové MA, Dietze PM, Jolley D. Overdose deaths following previous non-fatal heroin overdose: record linkage of ambulance attendance and death registry data. Drug Alcohol Rev. 2009;28(4):347-52.
72. Caudarella A, Dong H, Milloy MJ, Kerr T, Wood E, Hayashi K. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. Drug Alcohol Depend. 2016;162:51-5.
73. Farrell M, Marsden J. Acute risk of drug-related death among newly released prisoners in England and Wales. Addiction. 2008;103(2):251-5.
74. Merrall EL, Kariminia A, Binswanger IA, Hobbs MS, Farrell M, Marsden J, et al. Meta-analysis of drug-related deaths soon after release from prison. Addiction. 2010;105(9):1545-54.
75. Binswanger IA, Blatchford PJ, Mueller SR, Stern MF. Mortality after prison release: opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. Ann Intern Med. 2013;159(9):592-600.
76. Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, et al. Release from prison--a high risk of death for former inmates. The New England journal of medicine. 2007;356(2):157-65.
77. Bukten A, Stavseth MR, Skurtveit S, Tverdal A, Strang J, Clausen T. High risk of overdose death following release from prison: variations in mortality during a 15-year observation period. Addiction. 2017;112(8):1432-9.
78. Merrall EL, Bird SM, Hutchinson SJ. A record-linkage study of drug-related death and suicide after hospital discharge among drug-treatment clients in Scotland, 1996-2006. Addiction. 2013;108(2):377-84.
79. van Draanen J, Tsang C, Mitra S, Phuong V, Murakami A, Karamouzian M, et al. Mental disorder and opioid overdose: a systematic review. Soc Psychiatry Psychiatr Epidemiol. 2021:1-25.
80. Bogdanowicz KM, Stewart R, Broadbent M, Hatch SL, Hotopf M, Strang J, et al. Double trouble: Psychiatric comorbidity and opioid addiction-all-cause and cause-specific mortality. Drug Alcohol Depend. 2015;148:85-92.
81. Zedler BK, Saunders WB, Joyce AR, Vick CC, Murrelle EL. Validation of a Screening Risk Index for Serious Prescription Opioid-Induced Respiratory Depression or Overdose in a US Commercial Health Plan Claims Database. Pain medicine (Malden, Mass). 2018;19(1):68-78.
82. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. Pain medicine (Malden, Mass). 2016;17(1):85-98.
83. Dahlman D, Ohlsson H, Edwards AC, Sundquist J, Håkansson A, Sundquist K. Socioeconomic correlates of incident and fatal opioid overdose among Swedish people with opioid use disorder. Subst Abuse Treat Prev Policy. 2021;16(1):73.

84. van Draanen J, Tsang C, Mitra S, Karamouzian M, Richardson L. Socioeconomic marginalization and opioid-related overdose: A systematic review. Drug Alcohol Depend. 2020;214:108127.
85. Winiker AK, Tobin KE, Gicquelais RE, Owczarzak J, Latkin C. "When You're Getting High… You Just Don't Want to Be Around Anybody." A Qualitative Exploration of Reasons for Injecting Alone: Perspectives from Young People Who Inject Drugs. Subst Use Misuse. 2020;55(13):2079-86.
86. Papamihali K, Yoon M, Graham B, Karamouzian M, Slaunwhite AK, Tsang V, et al. Convenience and comfort: reasons reported for using drugs alone among clients of harm reduction sites in British Columbia, Canada. Harm Reduct J. 2020;17(1):90.
87. Darke S, Ross J, Lynskey M, Teesson M. Attempted suicide among entrants to three treatment modalities for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence and risk factors. Drug Alcohol Depend. 2004;73(1):1-10.
88. Brooner RK, King VL, Kidorf M, Schmidt CW, Jr., Bigelow GE. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. Arch Gen Psychiatry. 1997;54(1):71-80.
89. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. The Journal of clinical psychiatry. 2006;67(2):247-57.
90. Kidorf M, Solazzo S, Yan H, Brooner RK. Psychiatric and Substance Use Comorbidity in Treatment-Seeking Injection Opioid Users Referred From Syringe Exchange. J Dual Diagn. 2018;14(4):193-200.
91. Meier A, Lambert-Harris C, McGovern MP, Xie H, An M, McLeman B. Co-occurring prescription opioid use problems and posttraumatic stress disorder symptom severity. Am J Drug Alcohol Abuse. 2014;40(4):304-11.
92. Vold JH, Løberg EM, Aas CF, Steier JA, Johansson KA, Fadnes LT. Prevalence and correlates of suicide attempts in high-risk populations: a cross-sectional study among patients receiving opioid agonist therapy in Norway. BMC psychiatry. 2022;22(1):181.
93. Folkhälsomyndigheten. Statistiken för suicidförsök [Internet]. Stockholm; Folkhälsomyndigheten; 2021. [cited 2022 February 14]; Available from: https://www.folkhalsomyndigheten.se/suicidprevention/statistik-om-suicid/
94. Roncero C, Barral C, Rodríguez-Cintas L, Pérez-Pazos J, Martinez-Luna N, Casas M, et al. Psychiatric comorbidities in opioid-dependent patients undergoing a replacement therapy programme in Spain: The PROTEUS study. Psychiatry research. 2016;243:174-81.
95. Zhu Y, Mooney LJ, Yoo C, Evans EA, Kelleghan A, Saxon AJ, et al. Psychiatric comorbidity and treatment outcomes in patients with opioid use disorder: Results from a multisite trial of buprenorphine-naloxone and methadone. Drug Alcohol Depend. 2021;228:108996.
96. Muller AE, Skurtveit S, Clausen T. Many correlates of poor quality of life among substance users entering treatment are not addiction-specific. Health and quality of life outcomes. 2016;14:39.

97. Nielsen M, Kruckow L, Buch AK, Olsen KB, Banner J. Characterization of deceased drug users in Denmark based on treatment status: A nationwide retrospective autopsy study. Drug Alcohol Depend. 2022;230:109146.
98. Skeie I, Brekke M, Clausen T, Gossop M, Lindbaek M, Reinertsen E, et al. Increased somatic morbidity in the first year after leaving opioid maintenance treatment: results from a Norwegian cohort study. Eur Addict Res. 2013;19(4):194-201.
99. Han BH, Cotton BP, Polydorou S, Sherman SE, Ferris R, Arcila-Mesa M, et al. Geriatric Conditions Among Middle-aged and Older Adults on Methadone Maintenance Treatment: A Pilot Study. J Addict Med. 2022;16(1):110-3.
100. Sharif B, Nosyk B, Sun H, Marsh DC, Anis A. Changes in the characteristics and levels of comorbidity among new patients into methadone maintenance treatment program in British Columbia during its expansion period from 1998-2006. Subst Use Misuse. 2013;48(8):671-82.
101. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. Journal of pain and symptom management. 2000;19(1):53-62.
102. Dhingra L, Masson C, Perlman DC, Seewald RM, Katz J, McKnight C, et al. Epidemiology of pain among outpatients in methadone maintenance treatment programs. Drug Alcohol Depend. 2013;128(1-2):161-5.
103. Dunn KE, Brooner RK, Clark MR. Severity and interference of chronic pain in methadone-maintained outpatients. Pain medicine (Malden, Mass). 2014;15(9):1540-8.
104. Darke S, Kaye S, Duflou J. Systemic disease among cases of fatal opioid toxicity. Addiction. 2006;101(9):1299-305.
105. Gao L, Dimitropoulou P, Robertson JR, McTaggart S, Bennie M, Bird SM. Risk-factors for methadone-specific deaths in Scotland's methadone-prescription clients between 2009 and 2013. Drug Alcohol Depend. 2016;167:214-23.
106. Pierce M, Millar T, Robertson JR, Bird SM. Ageing opioid users' increased risk of methadone-specific death in the UK. Int J Drug Policy. 2018;55:121-7.
107. Word Health Organization. The public health dimension of the world drug problem: How WHO works to prevent drug misuse, reduce harm and improve safe access to medicine [Internet]. Geneva: Word Health Organization; 2019. [cited 2022 February 17]. Available from: https://www.who.int/publications/i/item/WHO-MVP-EMP-2019.02
108. UNAIDS. Health, Rights and Drugs. Harm reduction, decriminalization and zero discrimination for people who use drugs [Internet]. Geneva: UNAIDS Joint United Nations Programme on HIV/AIDS; 2019. [cited 2022 February 17]. Available from: https://www.unaids.org/sites/default/files/media_asset/JC2954_UNAIDS_drugs_report_2019_en.pdf
109. Word Health Organization. Model List of Essential Medicines – 22nd List [Internet]. Geneva: World Health Organization; 2021. [cited 2022 February 18] Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02

110. Word Health Organization. WHO report on the global tobacco epidemic 2021: addressing new and emerging products [Internet]. Geneva: World Health Organization; 2021. [cited 2022 February 18]. Available from: https://www.who.int/publications/i/item/9789240032095
111. Word Health Organization. Guide to starting and managing needle and syringe programme [Internet]. Geneva: World Health Organization; 2007. [cited 2022 February 18]. Available from: https://www.who.int/westernpacific/publications-detail/guide-to-starting-and-managing-needle-and-syringe-programmes
112. Harm Reduction International. The Global State of Harm Reduction 2020 [Internet]. London: Harm Reduction International: 2020. [cited 2022 February 18]. Available from: https://www.hri.global/files/2021/03/04/Global_State_HRI_2020_BOOK_FA_Web.pdf
113. Marlatt GA. Harm reduction: come as you are. Addict Behav. 1996;21(6):779-88.
114. Csete J, Kamarulzaman A, Kazatchkine M, Altice F, Balicki M, Buxton J, et al. Public health and international drug policy. Lancet (London, England). 2016;387(10026):1427-80.
115. Soussan C, Kjellgren A. Alarming attitudinal barriers to help-seeking in drug-related emergency situations: Results from a Swedish online survey. Nordisk alkohol- & narkotikatidskrift : NAT. 2019;36(6):532-41.
116. European Monitoring Centre for Drugs and Drug Addiction. Health and social responses to drug problems: a European guide [Internet]. Luxembourg: Publications Office of the European Union; 2021. [cited 2022 May 21]. Available from: https://www.emcdda.europa.eu/publications/health-and-social-responses-a-european-guide_en
117. Clarke K, Harris D, Zweifler JA, Lasher M, Mortimer RB, Hughes S. The Significance of Harm Reduction as a Social and Health Care Intervention for Injecting Drug Users: An Exploratory Study of a Needle Exchange Program in Fresno, California. Social Work in Public Health. 2016;31(5):398-407.
118. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database of Systematic Reviews. 2017(9).
119. Tsai AC, Kiang MV, Barnett ML, Beletsky L, Keyes KM, McGinty EE, et al. Stigma as a fundamental hindrance to the United States opioid overdose crisis response. PLoS Med. 2019;16(11):e1002969-e.
120. Karlsson N, Berglund T, Ekström AM, Hammarberg A, Tammi T. Could 30 years of political controversy on needle exchange programmes in Sweden contribute to scaling-up harm reduction services in the world? Nordic Studies on Alcohol and Drugs. 2020;38(1):66-88.
121. Socialstyrelsen. Lag om Utbyte av Sprutor Och Kanyler. Stockholm: Socialstyrelsen, SFS 2006:323.
122. Blomé MA, Bråbäck M, Alsterberg S, Jerkeman A. Hepatitis C treatment at a Swedish needle exchange program, a successful model of care – the ACTIONNE study. International Journal of Drug Policy. 2021;96:103407.

123. Bluthenthal RN, Malik MR, Grau LE, Singer M, Marshall P, Heimer R. Sterile syringe access conditions and variations in HIV risk among drug injectors in three cities. Addiction. 2004;99(9):1136-46.
124. Kerr T, Small W, Buchner C, Zhang R, Li K, Montaner J, et al. Syringe sharing and HIV incidence among injection drug users and increased access to sterile syringes. Am J Public Health. 2010;100(8):1449-53.
125. Alanko Blomé M, Björkman P, Flamholc L, Jacobsson H, Widell A. Vaccination against hepatitis B virus among people who inject drugs - A 20year experience from a Swedish needle exchange program. Vaccine. 2017;35(1):84-90.
126. Brooner R, Kidorf M, King V, Beilenson P, Svikis D, Vlahov D. Drug abuse treatment success among needle exchange participants. Public Health Rep. 1998;113 Suppl 1(Suppl 1):129-39.
127. Havens JR, Latkin CA, Pu M, Cornelius LJ, Bishai D, Huettner S, et al. Predictors of opiate agonist treatment retention among injection drug users referred from a needle exchange program. J Subst Abuse Treat. 2009;36(3):306-12.
128. Neufeld K, King V, Peirce J, Kolodner K, Brooner R, Kidorf M. A comparison of 1-year substance abuse treatment outcomes in community syringe exchange participants versus other referrals. Drug Alcohol Depend. 2008;97(1-2):122-9.
129. Hedrich D, Kerr T, Dubois-Arber F. Drug consumption facilities in Europe and beyond', in Rhodes, T. and Hedrich, D. (eds), Harm reduction: evidence, impacts and challenges. Publications Office of the European Union, Luxembourg; 2010.
130. Kennedy MC, Karamouzian M, Kerr T. Public Health and Public Order Outcomes Associated with Supervised Drug Consumption Facilities: a Systematic Review. Current HIV/AIDS Reports. 2017;14(5):161-83.
131. European Monitoring Centre for Drugs and Drug Addiction. Drug consumption rooms: an overview of provision and evidence [Internet]. Luxembourg: Publications Office of the European Union; 2018. [cited 2022 May 5]. Available from: https://www.emcdda.europa.eu/system/files/publications/2734/POD_Drug%20consumption%20rooms.pdf
132. Hedrich D, Kerr T, Dubois-Arber F. Drug consumption facilities in Europe and beyond', in Rhodes, T. and Hedrich, D. (eds), Harm reduction: Evidence, impacts and challenges.; 2010.
133. Potier C, Laprévote V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: what has been demonstrated? A systematic literature review. Drug Alcohol Depend. 2014;145:48-68.
134. Small W, Wood E, Lloyd-Smith E, Tyndall M, Kerr T. Accessing care for injection-related infections through a medically supervised injecting facility: a qualitative study. Drug Alcohol Depend. 2008;98(1-2):159-62.
135. Small W, Van Borek N, Fairbairn N, Wood E, Kerr T. Access to health and social services for IDU: the impact of a medically supervised injection facility. Drug Alcohol Rev. 2009;28(4):341-6.
136. Lloyd-Smith E, Wood E, Zhang R, Tyndall MW, Montaner JS, Kerr T. Determinants of cutaneous injection-related infection care at a supervised injecting facility. Annals of epidemiology. 2009;19(6):404-9.

137. Karamouzian M, Dohoo C, Forsting S, McNeil R, Kerr T, Lysyshyn M. Evaluation of a fentanyl drug checking service for clients of a supervised injection facility, Vancouver, Canada. Harm reduction journal. 2018;15(1):46.
138. Young S, Fairbairn N. Expanding supervised injection facilities across Canada: lessons from the Vancouver experience. Canadian journal of public health = Revue canadienne de sante publique. 2018;109(2):227-30.
139. Marshall BD, Milloy MJ, Wood E, Montaner JS, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. Lancet (London, England). 2011;377(9775):1429-37.
140. Kennedy MC, Hayashi K, Milloy MJ, Wood E, Kerr T. Supervised injection facility use and all-cause mortality among people who inject drugs in Vancouver, Canada: A cohort study. PLoS medicine. 2019;16(11):e1002964.
141. Salmon AM, van Beek I, Amin J, Kaldor J, Maher L. The impact of a supervised injecting facility on ambulance call-outs in Sydney, Australia. Addiction. 2010;105(4):676-83.
142. Kerr T, Tyndall M, Li K, Montaner J, Wood E. Safer injection facility use and syringe sharing in injection drug users. Lancet (London, England). 2005;366(9482):316-8.
143. Petrar S, Kerr T, Tyndall MW, Zhang R, Montaner JS, Wood E. Injection drug users' perceptions regarding use of a medically supervised safer injecting facility. Addict Behav. 2007;32(5):1088-93.
144. Milloy MJ, Wood E. Emerging role of supervised injecting facilities in human immunodeficiency virus prevention. Addiction. 2009;104(4):620-1.
145. Wood E, Kerr T, Small W, Li K, Marsh DC, Montaner JS, et al. Changes in public order after the opening of a medically supervised safer injecting facility for illicit injection drug users. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2004;171(7):731-4.
146. Kinnard EN, Howe CJ, Kerr T, Skjødt Hass V, Marshall BD. Self-reported changes in drug use behaviors and syringe disposal methods following the opening of a supervised injecting facility in Copenhagen, Denmark. Harm Reduct J. 2014;11(1):29.
147. Aspinall EJ, Nambiar D, Goldberg DJ, Hickman M, Weir A, Van Velzen E, et al. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis. Int J Epidemiol. 2014;43(1):235-48.
148. Lambdin BH, Davidson PJ, Browne EN, Suen LW, Wenger LD, Kral AH. Reduced Emergency Department Visits and Hospitalisation with Use of an Unsanctioned Safe Consumption Site for Injection Drug Use in the United States. J Gen Intern Med. 2022:1-8.
149. Folch C, Lorente N, Majó X, Parés-Badell O, Roca X, Brugal T, et al. Drug consumption rooms in Catalonia: A comprehensive evaluation of social, health and harm reduction benefits. Int J Drug Policy. 2018;62:24-9.

150. Gaddis A, Kennedy MC, Nosova E, Milloy MJ, Hayashi K, Wood E, et al. Use of on-site detoxification services co-located with a supervised injection facility. J Subst Abuse Treat. 2017;82:1-6.
151. Wood E, Tyndall MW, Zhang R, Montaner JS, Kerr T. Rate of detoxification service use and its impact among a cohort of supervised injecting facility users. Addiction. 2007;102(6):916-9.
152. Wood E, Tyndall MW, Zhang R, Stoltz JA, Lai C, Montaner JS, et al. Attendance at supervised injecting facilities and use of detoxification services. The New England journal of medicine. 2006;354(23):2512-4.
153. Kimber J, Mattick RP, Kaldor J, van Beek I, Gilmour S, Rance JA. Process and predictors of drug treatment referral and referral uptake at the Sydney Medically Supervised Injecting Centre. Drug Alcohol Rev. 2008;27(6):602-12.
154. Toth EC, Tegner J, Lauridsen S, Kappel N. A cross-sectional national survey assessing self-reported drug intake behavior, contact with the primary sector and drug treatment among service users of Danish drug consumption rooms. Harm Reduct J. 2016;13(1):27.
155. Ling W, Smith D. Buprenorphine: blending practice and research. Journal of substance abuse treatment. 2002;23(2):87-92.
156. Sporer KA. Buprenorphine: a primer for emergency physicians. Annals of emergency medicine. 2004;43(5):580-4.
157. Handelsman, L., et al., Two New Rating Scales for Opiate Withdrawal. Am J Drug Alcohol Abuse, 1987;13: 293-308.
158. Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. MMWR Morbidity and mortality weekly report. 2015;64(23):631-5.
159. Bird SM, Parmar MK, Strang J. Take-home naloxone to prevent fatalities from opiate-overdose: Protocol for Scotland's public health policy evaluation, and a new measure to assess impact. Drugs (Abingdon, England). 2015;22(1):66-76.
160. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. Bmj. 2013;346:f174.
161. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction. 2016;111(7):1177-87.
162. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Injury epidemiology. 2015;2(1):10.
163. Winstanley EL, Clark A, Feinberg J, Wilder CM. Barriers to implementation of opioid overdose prevention programs in Ohio. Subst Abus. 2016;37(1):42-6.
164. Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities. J Med Econ. 2013;16(8):1051-60.

165. Langham S, Wright A, Kenworthy J, Grieve R, Dunlop WCN. Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom. Value Health. 2018;21(4):407-15.
166. European Monitoring Centre for Drugs and Drug Addiction. Infographic. Availability of take-home naloxone programmes in Europe [Internet]. Luxembourg: Publications Office of the European Union; 2021. [cited 2022 May 4]. Available from: https://www.emcdda.europa.eu/node/14249_me
167. Madah-Amiri D, Clausen T, Lobmaier P. Rapid widespread distribution of intranasal naloxone for overdose prevention. Drug Alcohol Depend. 2017;173:17-23.
168. Seraf, UiO. Nalokson - Nesesprayen som redder liv [Internet]. Oslo: Universitetet i Oslo, Senter for rus- og avhengighetsforskning; 2021 [cited 2022 April 20]. Available from: https://www.nalokson.uio.no/
169. Alcohol and drugs. Policy actions: National mission [Internet]. Edinburgh: Cabinet Secretary for Health and Social Care, Scottish Government; 2021 [cited 2022 April 20]. Available from: https://www.gov.scot/policies/alcohol-and-drugs/national-mission/
170. Scottish Drugs Forum. Scottish Fire and Rescue Service to Carry Naloxone [Internet]. Glasgow: Scottish Drugs Forum; 2022. [cited 2022 20 April]. Available from: https://www.sdf.org.uk/scottish-fire-and-rescue-service-to-carry-naloxone/
171. Scottish Drugs Forum. Police Roll Out Naloxone After Successful Pilot [Internet]. Glasgow: Scottish Drugs Forum; 2022. [cited 2022 20 April]. Available from: https://www.sdf.org.uk/police-roll-out-naloxone-after-successful-pilot/#:~:text=Police%20officers%20across%20Scotland%20will,in%20a%20pilot%20in%202021
172. Madah-Amiri D, Gjersing L, Clausen T. Naloxone distribution and possession following a large-scale naloxone programme. Addiction. 2019;114(1):92-100.
173. McAuley A, Munro A, Bird SM, Hutchinson SJ, Goldberg DJ, Taylor A. Engagement in a National Naloxone Programme among people who inject drugs. Drug Alcohol Depend. 2016;162:236-40.
174. Reed M, Wagner KD, Tran NK, Brady KA, Shinefeld J, Roth A. Prevalence and correlates of carrying naloxone among a community-based sample of opioid-using people who inject drugs. Int J Drug Policy. 2019;73:32-5.
175. Bennett AS, Freeman R, Des Jarlais DC, Aronson ID. Reasons People Who Use Opioids Do Not Accept or Carry No-Cost Naloxone: Qualitative Interview Study. JMIR formative research. 2020;4(12):e22411.
176. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, García de Olalla P, de la Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. Addiction. 2005;100(7):981-9.
177. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. Subst Use Misuse. 1996;31(2):177-96.
178. Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. J Subst Abuse Treat. 2005;28(4):321-9.

179. Hser YI, Zhu Y, Fei Z, Mooney LJ, Evans EA, Kelleghan A, et al. Long-term follow-up assessment of opioid use outcomes among individuals with comorbid mental disorders and opioid use disorder treated with buprenorphine or methadone in a randomized clinical trial. Addiction. 2021.
180. Russolillo A, Moniruzzaman A, McCandless LC, Patterson M, Somers JM. Associations between methadone maintenance treatment and crime: a 17-year longitudinal cohort study of Canadian provincial offenders. Addiction. 2018;113(4):656-67.
181. Teesson M, Mills K, Ross J, Darke S, Williamson A, Havard A. The impact of treatment on 3 years' outcome for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). Addiction. 2008;103(1):80-8.
182. Teesson M, Marel C, Darke S, Ross J, Slade T, Burns L, et al. Long-term mortality, remission, criminality and psychiatric comorbidity of heroin dependence: 11-year findings from the Australian Treatment Outcome Study. Addiction. 2015;110(6):986-93.
183. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2011(8):Cd004145.
184. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. Bmj. 2012;345:e5945.
185. O'Byrne P, Jeske Pearson C. Methadone maintenance treatment as social control: Analyzing patient experiences. Nursing inquiry. 2019;26(2):e12275.
186. Paquette CE, Syvertsen JL, Pollini RA. Stigma at every turn: Health services experiences among people who inject drugs. Int J Drug Policy. 2018;57:104-10.
187. Garpenhag L, Dahlman D. Perceived healthcare stigma among patients in opioid substitution treatment: a qualitative study. Subst Abuse Treat Prev Policy. 2021;16(1):81.
188. Baxter LE, Sr., Campbell A, Deshields M, Levounis P, Martin JA, McNicholas L, et al. Safe methadone induction and stabilization: report of an expert panel. J Addict Med. 2013;7(6):377-86.
189. Ferrari A, Coccia CP, Bertolini A, Sternieri E. Methadone--metabolism, pharmacokinetics and interactions. Pharmacol Res. 2004;50(6):551-9.
190. Grissinger M. Keeping patients safe from methadone overdoses. P t. 2011;36(8):462-6.
191. Läkemedelsrådet. Regional riktlinje för läkemedelsbehandling inom LARO, Region Skåne [Internet]. Malmö: Läkemedelsrådet, Terapigrupp Psykiatri; 2022. [Accessed 2022 July 18]. Available from: https://vardgivare.skane.se/siteassets/1.-vardriktlinjer/lakemedel/riktlinjer/lakemedelsriktlinjer/laro-lakemedelsbehandling.pdf
192. Bell J, Strang J. Medication Treatment of Opioid Use Disorder. Biological psychiatry. 2020;87(1):82-8.
193. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clinical Pharmacology & Therapeutics. 1994;55(5):569-80.

194. Mégarbane B, Buisine A, Jacobs F, Résière D, Chevillard L, Vicaut E, et al. Prospective comparative assessment of buprenorphine overdose with heroin and methadone: clinical characteristics and response to antidotal treatment. J Subst Abuse Treat. 2010;38(4):403-7.
195. Gunne LM, Grönbladh L. The Swedish methadone maintenance program: a controlled study. Drug Alcohol Depend. 1981;7(3):249-56.
196. Dole, V.P. and M. Nyswander, A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. Jama, 1965. 193: p. 646-50.
197. Socialstyrelsen. Socialstyrelsens föreskrifter och allmänna råd om läkemedelsassisterad underhållsbehandling vid opiatberoende. Stockholm: Socialstyrelsen; HSLF-FS 2004:8.
198. Sveriges Radio. UN: Swedish drug rules violate human rights [Internet, press release November 11, 2015]. [Accessed 2022 May 22]. Available from: https://sverigesradio.se/artikel/6299618
199. Printz, A., et al., 2021. Från delar till helhet. En reform för samordnade, behovsanpassade och personcentrerade insatser till personer med samsjuklighet. Stockholm: Socialdepartementet, Statens Offentliga Utredningar, SOU.
200. Socialstyrelsen. Socialstyrelsens föreskrifter och allmänna råd om läkemedelsassisterad behandling vid opioidberoende. Stockholm: Socialstyrelsen; HSLF-FS 2016:1.
201. Socialstyrelsen. Kartläggning av verksamheter som bedriver läkemedelsassisterad behandling vid opiatberoende. Stockholm: Socialstyrelsen; 2015.
202. Rådet för Kommunalekonomisk Forskning och Utbildning, KEFU. Delrapport 3: Vårdvalets och ersättningsmodellens effekter för Läkemedelsassisterad rehabilitering vid opiatberoende. Region Skåne; 2015.
203. Socialstyrelsen. Socialstyrelsens föreskrifter och allmänna råd om läkemedelsassisterad underhållsbehandling vid opiatberoende. Stockholm: Socialstyrelsen; SOSFS 2009:27.
204. Bell J, Belackova V, Lintzeris N. Supervised Injectable Opioid Treatment for the Management of Opioid Dependence. Drugs. 2018;78(13):1339-52.
205. Lintzeris N. Prescription of heroin for the management of heroin dependence: current status. CNS Drugs. 2009;23(6):463-76.
206. van den Brink W, Hendriks VM, Blanken P, Koeter MW, van Zwieten BJ, van Ree JM. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Bmj. 2003;327(7410):310.
207. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. Cochrane Database Syst Rev. 2011;2011(12):Cd003410.
208. Winstock AR, Lea T, Sheridan J. Patients' help-seeking behaviours for health problems associated with methadone and buprenorphine treatment. Drug Alcohol Rev. 2008;27(4):393-7.
209. Zirakzadeh A, Shuman C, Stauter E, Hays JT, Ebbert JO. Cigarette smoking in methadone maintained patients: an up-to-date review. Current drug abuse reviews. 2013;6(1):77-84.

210. Okoli CT, Khara M, Procyshyn RM, Johnson JL, Barr AM, Greaves L. Smoking cessation interventions among individuals in methadone maintenance: a brief review. J Subst Abuse Treat. 2010;38(2):191-9.
211. Spithoff S, Kiran T, Khuu W, Kahan M, Guan Q, Tadrous M, et al. Quality of primary care among individuals receiving treatment for opioid use disorder. Canadian family physician Medecin de famille canadien. 2019;65(5):343-51.
212. Bäckström E, Troberg K, Håkansson A, Dahlman D. Healthcare Contacts Regarding Circulatory Conditions among Swedish Patients in Opioid Substitution Treatment, with and without On-Site Primary Healthcare. International Journal of Environmental Research and Public Health. 2021;18(9):4614.
213. O'Toole J, Hambly R, Cox AM, O'Shea B, Darker C. Methadone-maintained patients in primary care have higher rates of chronic disease and multimorbidity, and use health services more intensively than matched controls. The European journal of general practice. 2014;20(4):275-80.
214. Islam MM, Topp L, Day CA, Dawson A, Conigrave KM. The accessibility, acceptability, health impact and cost implications of primary healthcare outlets that target injecting drug users: a narrative synthesis of literature. Int J Drug Policy. 2012;23(2):94-102.
215. Islam MM, Topp L, Conigrave KM, Day CA. Opioid substitution therapy clients' preferences for targeted versus general primary health-care outlets. Drug Alcohol Rev. 2013;32(2):211-4.
216. McCoy CB, Metsch LR, Chitwood DD, Miles C. Drug use and barriers to use of health care services. Subst Use Misuse. 2001;36(6-7):789-806.
217. Miller-Lloyd L, Landry J, Macmadu A, Allard I, Waxman M. Barriers to Healthcare for People Who Inject Drugs: A Survey at a Syringe Exchange Program. Subst Use Misuse. 2020;55(6):896-9.
218. Biancarelli DL, Biello KB, Childs E, Drainoni M, Salhaney P, Edeza A, et al. Strategies used by people who inject drugs to avoid stigma in healthcare settings. Drug Alcohol Depend. 2019;198:80-6.
219. Han BH. Aging, multimorbidity, and substance use disorders: The growing case for integrating the principles of geriatric care and harm reduction. Int J Drug Policy. 2018;58:135-6.
220. Rosen D, Engel RJ, Hunsaker AE, Engel Y, Detlefsen EG, Reynolds CF, 3rd. Just say know: an examination of substance use disorders among older adults in gerontological and substance abuse journals. Soc Work Public Health. 2013;28(3-4):377-87.
221. Arnold-Reed DE, Brett T, Troeung L, O'Neill J, Backhouse R, Bulsara MK. Multimorbidity in patients enrolled in a community-based methadone maintenance treatment programme delivered through primary care. Journal of comorbidity. 2014;4:46-54.
222. Mofizul Islam M, Topp L, Day CA, Dawson A, Conigrave KM. Primary healthcare outlets that target injecting drug users: opportunity to make services accessible and acceptable to the target group. Int J Drug Policy. 2012;23(2):109-10.

223. Rosen D, Smith ML, Reynolds CF, 3rd. The prevalence of mental and physical health disorders among older methadone patients. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2008;16(6):488-97.
224. Gfroerer J, Penne M, Pemberton M, Folsom R. Substance abuse treatment need among older adults in 2020: the impact of the aging baby-boom cohort. Drug Alcohol Depend. 2003;69(2):127-35.
225. Goffman E. Stigma: Notes on the Management of Spoiled Identity: Prentice Hall; 1963.
226. Corrigan P, Schomerus G, Shuman V, Kraus D, Perlick D, Harnish A, et al. Developing a research agenda for understanding the stigma of addictions Part I: Lessons from the Mental Health Stigma Literature. Am J Addict. 2017;26(1):59-66.
227. Link BG, Phelan JC. Stigma and its public health implications. Lancet (London, England). 2006;367(9509):528-9.
228. Corrigan PW, Nieweglowski K. Stigma and the public health agenda for the opioid crisis in America. Int J Drug Policy. 2018;59:44-9.
229. Hatzenbuehler ML, Phelan JC, Link BG. Stigma as a fundamental cause of population health inequalities. Am J Public Health. 2013;103(5):813-21.
230. Phelan JC, Link BG, Dovidio JF. Stigma and prejudice: one animal or two? Soc Sci Med. 2008;67(3):358-67.
231. Corrigan P, Markowitz FE, Watson A, Rowan D, Kubiak MA. An attribution model of public discrimination towards persons with mental illness. Journal of health and social behavior. 2003;44(2):162-79.
232. Hatzenbuehler ML. Structural stigma: Research evidence and implications for psychological science. The American psychologist. 2016;71(8):742-51.
233. Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. The New England journal of medicine. 2016;374(4):363-71.
234. Kvaale EP, Gottdiener WH, Haslam N. Biogenetic explanations and stigma: a meta-analytic review of associations among laypeople. Soc Sci Med. 2013;96:95-103.
235. Broyles LM, Binswanger IA, Jenkins JA, Finnell DS, Faseru B, Cavaiola A, et al. Confronting inadvertent stigma and pejorative language in addiction scholarship: a recognition and response. Subst Abus. 2014;35(3):217-21.
236. Kelly JF, Greene MC, Abry A. A US national randomized study to guide how best to reduce stigma when describing drug-related impairment in practice and policy. Addiction. 2021;116(7):1757-67.
237. Taylor BG, Lamuda PA, Flanagan E, Watts E, Pollack H, Schneider J. Social Stigma toward Persons with Opioid Use Disorder: Results from a Nationally Representative Survey of U.S. Adults. Subst Use Misuse. 2021;56(12):1752-64.
238. Wakeman SE, Rich JD. Barriers to Medications for Addiction Treatment: How Stigma Kills. Subst Use Misuse. 2018;53(2):330-3.

239. Fischer B. Some notes on the use, concept and socio-political framing of 'stigma' focusing on an opioid-related public health crisis. Subst Abuse Treat Prev Policy. 2020;15(1):54.
240. Corrigan P, Schomerus G, Smelson D. Are some of the stigmas of addictions culturally sanctioned? Br J Psychiatry. 2017;210(3):180-1.
241. McGinty EE, Kennedy-Hendricks A, Baller J, Niederdeppe J, Gollust S, Barry CL. Criminal Activity or Treatable Health Condition? News Media Framing of Opioid Analgesic Abuse in the United States, 1998-2012. Psychiatric services (Washington, DC). 2016;67(4):405-11.
242. Kennedy-Hendricks A, Levin J, Stone E, McGinty EE, Gollust SE, Barry CL. News Media Reporting On Medication Treatment For Opioid Use Disorder Amid The Opioid Epidemic. Health Aff (Millwood). 2019;38(4):643-51.
243. Livingston JD. Structural stigma in health-care contexts for people with mental health and substance use issues: A literature review. Mental Health Commission of Canada. 2020.
244. Radcliffe P, Stevens A. Are drug treatment services only for 'thieving junkie scumbags'? Drug users and the management of stigmatised identities. Soc Sci Med. 2008;67(7):1065-73.
245. Frank D, Mateu-Gelabert P, Perlman DC, Walters SM, Curran L, Guarino H. "It's like 'liquid handcuffs": The effects of take-home dosing policies on Methadone Maintenance Treatment (MMT) patients' lives. Harm Reduct J. 2021;18(1):88.
246. Knaak S, Christie R, Mercer S, Stuart H. Stigma and the opioid crisis -- Final report. Mental Health Commission of Canada. 2019.
247. van Boekel LC, Brouwers EP, van Weeghel J, Garretsen HF. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: systematic review. Drug Alcohol Depend. 2013;131(1-2):23-35.
248. Nyblade L, Stockton MA, Giger K, Bond V, Ekstrand ML, Lean RM, et al. Stigma in health facilities: why it matters and how we can change it. BMC Med. 2019;17(1):25.
249. Wogen J, Restrepo MT. Human Rights, Stigma, and Substance Use. Health Hum Rights. 2020;22(1):51-60.
250. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. The Mount Sinai journal of medicine, New York. 2000;67(5-6):347-64.
251. Fomiatti R, Farrugia A, Fraser S, Dwyer R, Neale J, Strang J. Addiction stigma and the production of impediments to take-home naloxone uptake. Health (London, England : 1997). 2020:1363459320925863.
252. Fomiatti R, Farrugia A, Fraser S, Dwyer R, Neale J, Strang J. Addiction stigma and the production of impediments to take-home naloxone uptake. Health (London, England : 1997). 2022;26(2):139-61.
253. Corrigan PW, Larson JE, Rüsch N. Self-stigma and the "why try" effect: impact on life goals and evidence-based practices. World Psychiatry. 2009;8(2):75-81.

254. McCradden MD, Vasileva D, Orchanian-Cheff A, Buchman DZ. Ambiguous identities of drugs and people: A scoping review of opioid-related stigma. Int J Drug Policy. 2019;74:205-15.
255. Lloyd C. The stigmatization of problem drug users: A narrative literature review. Drugs: Education, Prevention and Policy. 2013;20(2):85-95.
256. Davidson PJ, Lozada R, Rosen PC, Macias A, Gallardo M, Pollini RA. Negotiating access: social barriers to purchasing syringes at pharmacies in Tijuana, Mexico. Int J Drug Policy. 2012;23(4):286-94.
257. Ahern J, Stuber J, Galea S. Stigma, discrimination and the health of illicit drug users. Drug Alcohol Depend. 2007;88(2-3):188-96.
258. Corrigan PW, Watson AC, Miller FE. Blame, shame, and contamination: the impact of mental illness and drug dependence stigma on family members. J Fam Psychol. 2006;20(2):239-46.
259. Region Skåne. Det här betalar du för i vården [Internet]. Kristianstad: Region Skåne; 2022. [Accessed 2022 July 25]. Available from: https://www.1177.se/en/Skane/other-languages/other-languages/soka-vard/det-har-betalar-du-for-varden-i-skane/
260. Hesse-Biber SN. Mixed Methods Research. Merging theory with practice. New York: Guilford Publications; 2010.
261. Polit DF BC, Hungler BP. Essentials of nursing research: methods, appraisal, and utilization, 5 ed. New York and Baltimore: Lippincott; 2001.
262. Nyirenda L, Kumar MB, Theobald S, Sarker M, Simwinga M, Kumwenda M, et al. Using research networks to generate trustworthy qualitative public health research findings from multiple contexts. BMC Med Res Methodol. 2020;20(1):13.
263. IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.
264. IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.
265. Penchansky R, Thomas JW. The concept of access: definition and relationship to consumer satisfaction. Medical care. 1981;19(2):127-40.
266. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
267. IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.
268. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.
269. Buchman DZ, Orkin AM, Strike C, Upshur REG. Overdose Education and Naloxone Distribution Programmes and the Ethics of Task Shifting. Public Health Ethics. 2018;11(2):151-64.
270. Farrugia A, Fraser S, Dwyer R, Fomiatti R, Neale J, Dietze P, et al. Take-home naloxone and the politics of care. Sociology of health & illness. 2019;41(2):427-43.
271. Faulkner-Gurstein R. The social logic of naloxone: Peer administration, harm reduction, and the transformation of social policy. Soc Sci Med. 2017;180:20-7.

272. Behar E, Chang JS, Countess K, Matheson T, Santos GM, Coffin P. Perceived Causes of Personal versus Witnessed Overdoses among People who Inject Opioids. Subst Use Misuse. 2019;54(12):1929-37.
273. Madah-Amiri D, Clausen T, Lobmaier P. Utilizing a train-the-trainer model for multi-site naloxone distribution programs. Drug Alcohol Depend. 2016;163:153-6.
274. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. Medical care research and review : MCRR. 2006;63(2):217-35.
275. Bombak A. Self-Rated Health and Public Health: A Critical Perspective. Frontiers in Public Health. 2013;1(15).
276. Darke S, Sims J, McDonald S, Wickes W. Cognitive impairment among methadone maintenance patients. Addiction. 2000;95(5):687-95.
277. Dahlman D, Ekefäll M, Garpenhag L. Health Literacy among Swedish Patients in Opioid Substitution Treatment: A Mixed-Methods Study. Drug Alcohol Depend. 2020;214:108186.
278. Gunawan J. Ensuring Trustworthiness in Qualitative Research. Belitung Nursing Journal. 2015;1:10-1.
279. Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health. 2010;87(6):931-41.
280. Banjo O, Tzemis D, Al-Qutub D, Amlani A, Kesselring S, Buxton JA. A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program. CMAJ open. 2014;2(3):E153-61.
281. Barnsdale, L (Ed.) 2014. National Naloxone Programme Scotland – Naloxone kits issued in 2013/14 and trends in opioid-related deaths. Edinburgh: Public Health Scotland.
282. Rowe C, Santos GM, Vittinghoff E, Wheeler E, Davidson P, Coffin PO. Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program. Addiction. 2015;110(8):1301-10.
283. Doe-Simkins M, Quinn E, Xuan Z, Sorensen-Alawad A, Hackman H, Ozonoff A, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC public health. 2014;14:297.
284. Ambrose G, Amlani A, Buxton JA. Predictors of seeking emergency medical help during overdose events in a provincial naloxone distribution programme: a retrospective analysis. BMJ open. 2016;6(6):e011224.
285. Bennett AS, Bell A, Tomedi L, Hulsey EG, Kral AH. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. J Urban Health. 2011;88(6):1020-30.
286. Khatiwoda P, Proeschold-Bell RJ, Meade CS, Park LP, Proescholdbell S. Facilitators and Barriers to Naloxone Kit Use Among Opioid-Dependent Patients Enrolled in Medication Assisted Therapy Clinics in North Carolina. North Carolina medical journal. 2018;79(3):149-55.

287. Chang JS, Behar E, Coffin PO. Narratives of people who inject drugs on factors contributing to opioid overdose. Int J Drug Policy. 2019;74:26-32.
288. McAuley A, Munro A, Taylor A. "Once I'd done it once it was like writing your name": Lived experience of take-home naloxone administration by people who inject drugs. Int J Drug Policy. 2018;58:46-54.
289. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med. 2014;8(3):153-63.
290. Koester S, Mueller SR, Raville L, Langegger S, Binswanger IA. Why are some people who have received overdose education and naloxone reticent to call Emergency Medical Services in the event of overdose? Int J Drug Policy. 2017;48:115-24.
291. Wagner KD, Harding RW, Kelley R, Labus B, Verdugo SR, Copulsky E, et al. Post-overdose interventions triggered by calling 911: Centering the perspectives of people who use drugs (PWUDs). PloS one. 2019;14(10):e0223823.
292. Pollini RA, McCall L, Mehta SH, Celentano DD, Vlahov D, Strathdee SA. Response to overdose among injection drug users. Am J Prev Med. 2006;31(3):261-4.
293. Strang J, Powis B, Best D, Vingoe L, Griffiths P, Taylor C, et al. Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability. Addiction. 1999;94(2):199-204.
294. Bennett AS, Bell A, Doe-Simkins M, Elliott L, Pouget E, Davis C. From Peers to Lay Bystanders: Findings from a Decade of Naloxone Distribution in Pittsburgh, PA. J Psychoactive Drugs. 2018;50(3):240-6.
295. Andersson, L. and B. Johnson, [Fatal opioid overdoses usually occur without anyone being present and able to intervene. Knowledge of the presence of witnesses is important for how naloxone programs should be designed]. Läkartidningen, 2022. Jan 25;119:21121. Swedish. MMID: 35077567.
296. Rowe C, Santos GM, Behar E, Coffin PO. Correlates of overdose risk perception among illicit opioid users. Drug Alcohol Depend. 2016;159:234-9.
297. Park JN, Rouhani S, Beletsky L, Vincent L, Saloner B, Sherman SG. Situating the Continuum of Overdose Risk in the Social Determinants of Health: A New Conceptual Framework. The Milbank quarterly. 2020;98(3):700-46.
298. O'Connor AM, Cousins G, Durand L, Barry J, Boland F. Retention of patients in opioid substitution treatment: A systematic review. PloS one. 2020;15(5):e0232086.
299. European Monitoring Centre for Drugs and Drug Addiction and Europol (2011). EMCDDA-European joint publications No 3. Amphetamine: A European Union perspective in the global context. Europe [Internet]. Luxembourg: Publications Office of the European Union; 2011. [cited 2022 May 2]. Available from: https://www.emcdda.europa.eu/system/files/publications/621/EMCDDA-Europol_Amphetamine-joint-publication_319089.pdf
300. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2017: Trends and Developments [Internet]. Luxembourg: Publications Office of the European Union; 2017. [cited 2022 May 2] Available from: https://www.emcdda.europa.eu/system/files/publications/4541/TDAT17001ENN.pdf

301. Abel KF, Skjærvø I, Ravndal E, Clausen T, Bramness JG. Perceived Self-Control is Related to Mental Distress in Patients Entering Substance Use Disorder Treatment. Subst Use Misuse. 2018;53(9):1454-62.
302. Goldstein A, Herrera J. Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. Drug Alcohol Depend. 1995;40(2):139-50.
303. Dole VP, Nyswander ME. The use of methadone for narcotic blockade. Br J Addict Alcohol Other Drugs. 1968;63(1):55-7.
304. Newman RG, Whitehill WB. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. Lancet (London, England). 1979;2(8141):485-8.
305. Simpson DD, Joe GW, Broome KM, Hiller ML, Knight K, Rowan-Szal GA. Program diversity and treatment retention rates in the Drug Abuse Treatment Outcome Study (DATOS). Psychology of Addictive Behaviors. 1997;11(4):279-93.
306. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. Lancet (London, England). 1999;353(9148):221-6.
307. Peles E, Schreiber S, Adelson M. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. Drug Alcohol Depend. 2010;107(2-3):141-8.
308. Peles E, Linzy S, Kreek M, Adelson M. One-year and cumulative retention as predictors of success in methadone maintenance treatment: a comparison of two clinics in the United States and Israel. J Addict Dis. 2008;27(4):11-25.
309. Peles E, Schreiber S, Sason A, Adelson M. Similarities and changes between 15- and 24-year survival and retention rates of patients in a large medical-affiliated methadone maintenance treatment (MMT) center. Drug Alcohol Depend. 2018;185:112-9.
310. Peles E, Adelson M, Schreiber S. Benzodiazepine usage during 19.5 years in methadone maintenance treatment patients and its relation to long-term outcome. Isr J Psychiatry Relat Sci. 2014;51(4):285-8.
311. Bukten A, Skurtveit S, Waal H, Clausen T. Factors associated with dropout among patients in opioid maintenance treatment (OMT) and predictors of re-entry. A national registry-based study. Addict Behav. 2014;39(10):1504-9.
312. Busch M, Klein C, Uhl A, Haltmayer H, Cabanis M, Westenberg JN, et al. Retention in the Austrian opioid agonist treatment system: a national prospective cohort study. Harm Reduct J. 2021;18(1):25.
313. Burns L, Randall D, Hall WD, Law M, Butler T, Bell J, et al. Opioid agonist pharmacotherapy in New South Wales from 1985 to 2006: patient characteristics and patterns and predictors of treatment retention. Addiction. 2009;104(8):1363-72.
314. Darker CD, Ho J, Kelly G, Whiston L, Barry J. Demographic and clinical factors predicting retention in methadone maintenance: results from an Irish cohort. Ir J Med Sci. 2016;185(2):433-41.
315. Krawczyk N, Williams AR, Saloner B, Cerdá M. Who stays in medication treatment for opioid use disorder? A national study of outpatient specialty treatment settings. J Subst Abuse Treat. 2021;126:108329.

316. Magura S, Nwakeze PC, Demsky SY. Pre- and in-treatment predictors of retention in methadone treatment using survival analysis. Addiction. 1998;93(1):51-60.
317. Folkhälsomyndigheten. Tobaksrökning, daglig [Internet]. Stockholm: Folkhälsomyndigheten; 2022. [cited 2022 July 14]; Available from: https://www.folkhalsomyndigheten.se/fu-tobaksrokning
318. Hser YI, Anglin D, Powers K. A 24-year follow-up of California narcotics addicts. Arch Gen Psychiatry. 1993;50(7):577-84.
319. Mendelsohn CP, Wodak Am A. Smoking cessation in people with alcohol and other drug problems. Australian family physician. 2016;45(8):569-73.
320. Nahvi S, Richter K, Li X, Modali L, Arnsten J. Cigarette smoking and interest in quitting in methadone maintenance patients. Addict Behav. 2006;31(11):2127-34.
321. Clemmey P, Brooner R, Chutuape MA, Kidorf M, Stitzer M. Smoking habits and attitudes in a methadone maintenance treatment population. Drug Alcohol Depend. 1997;44(2-3):123-32.
322. Cookson C, Strang J, Ratschen E, Sutherland G, Finch E, McNeill A. Smoking and its treatment in addiction services: clients' and staff behaviour and attitudes. BMC health services research. 2014;14:304.
323. Richter KP. Good and bad times for treating cigarette smoking in drug treatment. J Psychoactive Drugs. 2006;38(3):311-5.
324. Baca CT, Yahne CE. Smoking cessation during substance abuse treatment: what you need to know. J Subst Abuse Treat. 2009;36(2):205-19.
325. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. Bmj. 2014;348:g1151.
326. Richter KP, Gibson CA, Ahluwalia JS, Schmelzle KH. Tobacco use and quit attempts among methadone maintenance clients. Am J Public Health. 2001;91(2):296-9.
327. Stein MD, Caviness CM, Kurth ME, Audet D, Olson J, Anderson BJ. Varenicline for smoking cessation among methadone-maintained smokers: a randomized clinical trial. Drug Alcohol Depend. 2013;133(2):486-93.
328. Nahvi S, Adams TR, Ning Y, Zhang C, Arnsten JH. Effect of varenicline directly observed therapy versus varenicline self-administered therapy on varenicline adherence and smoking cessation in methadone-maintained smokers: a randomized controlled trial. Addiction. 2021;116(4):902-13.
329. Cooperman NA, Lu SE, Richter KP, Bernstein SL, Williams JM. Pilot Study of a Tailored Smoking Cessation Intervention for Individuals in Treatment for Opioid Dependence. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2018;20(9):1152-6.
330. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. Jama. 2003;289(18):2370-8.

331. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. The Journal of clinical psychiatry. 2009;70(9):1213-8.
332. Haber PS, Elsayed M, Espinoza D, Lintzeris N, Veillard AS, Hallinan R. Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment. Drug Alcohol Depend. 2017;181:132-9.
333. Petherick A. Sexual arousal: Sex matters. Nature. 2017;550(7674):S2-s3.
334. Zamboni L, Franceschini A, Portoghese I, Morbioli L, Lugoboni F. Sexual Functioning and Opioid Maintenance Treatment in Women. Results From a Large Multicentre Study. Front Behav Neurosci. 2019;13:97.
335. Xia Y, Zhang D, Li X, Chen W, He Q, Jahn HJ, et al. Sexual dysfunction during methadone maintenance treatment and its influence on patient's life and treatment: a qualitative study in South China. Psychology, health & medicine. 2013;18(3):321-9.
336. Robinson PG, Acquah S, Gibson B. Drug users: oral health-related attitudes and behaviours. British dental journal. 2005;198(4):219-24, discussion 4.
337. Titsas A, Ferguson MM. Impact of opioid use on dentistry. Australian dental journal. 2002;47(2):94-8.
338. Janz NK, Becker MH. The Health Belief Model: a decade later. Health education quarterly. 1984;11(1):1-47.
339. Motavalli D, Taylor JL, Childs E, Valente PK, Salhaney P, Olson J, et al. "Health Is on the Back Burner:" Multilevel Barriers and Facilitators to Primary Care Among People Who Inject Drugs. J Gen Intern Med. 2020.
340. Muncan B, Walters SM, Ezell J, Ompad DC. "They look at us like junkies": influences of drug use stigma on the healthcare engagement of people who inject drugs in New York City. Harm Reduct J. 2020;17(1):53.
341. Lewer D, Freer J, King E, Larney S, Degenhardt L, Tweed EJ, et al. Frequency of health-care utilization by adults who use illicit drugs: a systematic review and meta-analysis. Addiction. 2020;115(6):1011-23.
342. Sofaer S. Navigating poorly charted territory: patient dilemmas in health care "nonsystems". Medical care research and review: MCRR. 2009;66(1 Suppl):75s-93s.
343. Statens offentliga utredningar (SOU) [The Governments Official investigations]. Effektiv vård [Effective healthcare]. Stockholm: SOU; 2016:2.
344. Nilsson, F. Vägen till en patientprocessorienterad sjukvård. Kristianstad: Utvecklingscentrum Region Skåne; 2008.
345. Hassan R, Roland KB, Hernandez B, Goldman L, Evans KN, Gaul Z, et al. A qualitative study of service engagement and unmet needs among unstably housed people who inject drugs in Massachusetts. J Subst Abuse Treat. 2022:108722.
346. Millson PE, Challacombe L, Villeneuve PJ, Fischer B, Strike CJ, Myers T, et al. Self-perceived health among Canadian opiate users: a comparison to the general population and to other chronic disease populations. Canadian journal of public health = Revue canadienne de sante publique. 2004;95(2):99-103.

347. Carr S, Goldberg DJ, Elliott L, Green S, Mackie C, Gruer L. A primary health care service for Glasgow street sex workers--6 years experience of the "drop-in centre', 1989-1994. AIDS care. 1996;8(4):489-97.
348. Burr CK, Storm DS, Hoyt MJ, Dutton L, Berezny L, Allread V, et al. Integrating health and prevention services in syringe access programs: a strategy to address unmet needs in a high-risk population. Public Health Rep. 2014;129 Suppl 1:26-32.
349. Friedmann PD, Hendrickson JC, Gerstein DR, Zhang Z, Stein MD. Do mechanisms that link addiction treatment patients to primary care influence subsequent utilization of emergency and hospital care? Medical care. 2006;44(1):8-15.
350. Islam MM, Taylor A, Smyth C, Day CA. General health of opioid substitution therapy clients. Intern Med J. 2013;43(12):1335-8.
351. Laine C, Lin YT, Hauck WW, Turner BJ. Availability of medical care services in drug treatment clinics associated with lower repeated emergency department use. Medical care. 2005;43(10):985-95.

AMONG OPIOID DEPENDENT INDIVIDUALS, opioid related overdose is the worldwide leading cause of premature deaths. Sweden has the highest rates of overdose deaths in Europe. Opioid overdoses are, to a large extent, preventable. Brief overdose training and access to the antidote naloxone is associated with a reduction of overdose mortality. The first regional Swedish overdose education and naloxone distribution (OEND) programme was implemented in Skåne County in 2018, now including over 40 units, educating and distributing naloxone to individuals at risk of an opioid overdose.

Opioid substitution therapy (OST) is an evidence-based treatment for opioid dependence, proven to efficiently decrease morbidity and mortality. Since OST is associated with such benefits, focusing on incentives which increase access to and retention in treatment is of great importance.

Years of substance use, and associated factors such as stigma, psychiatric comorbidity, physical trauma, tobacco smoking and poor socioeconomic status are all likely to have negative physical health impact. Interventions such as OST, OEND and available and accessible somatic healthcare are all important interventions when it comes to addressing somatic and psychiatric morbidity and reducing premature mortality and morbidity within the population.

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