European Monitoring Centre
for Drugs and Drug Addiction

TECHNICAL REPORT

Balancing access to opioid substitution treatment with preventing the diversion of opioid substitution medications in Europe: challenges and implications

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About this report

Opioid substitution treatment (OST) is a key evidence-based tool in managing opioid dependence across Europe, but increasing reports of the diversion and misuse of prescription OST medications are a cause of concern. This report reviews how OST is implemented in European countries and examines the public health consequences of the diversion and misuse of prescription OST medications. It looks at how OST medications are diverted to the illicit market, the motivations behind diversion and misuse, and considers the measures to prevent diversion and how they must ensure that the treatment remains available and accessible for those who need it.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 25 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

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Statement regarding the United Kingdom

This report covers a reference period until 2019. The United Kingdom had left the European Union as of 1 February 2020. Unless stated otherwise, for the purpose of this report, the term ‘Member States’ includes the United Kingdom.

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Abstract

Opioid use and its consequences represent a serious global public health concern, with high levels of opioid-related deaths. Compelling scientific evidence has been accumulated over recent decades regarding the benefits of opioid substitution treatment (OST) in treating opioid dependence and in ameliorating its associated health and social consequences. It is estimated that in 2018 nearly half of the 1.3 million high-risk opioid users in the European Union were receiving this treatment.

However, recent years have seen increasing debate about the worrying levels of diversion and misuse of OST medications, which appear to be playing an increasing role in the European drug problem. For example, nearly 15 % of clients entering specialised drug treatment for an opioid problem in recent years in the European Union, Norway and Turkey sought treatment for problems associated with the misuse of an OST medication. Available European data indicate that diverted prescription OST medications originate principally from domestic supplies. In Europe, the primary sources for high-risk opioid users to acquire OST medications for non-medical use are friends and family (who generally obtain them through legitimate medical supply), drug dealers and their own legitimate medical prescriptions. Cross-border trafficking and the internet appear to play a lesser role in supply.

The large majority of individuals misusing prescription OST medications in the European Union are long-term high-risk opioid users with a history of opioid dependence and past treatment experiences. Two out of three treatment entrants for primary methadone misuse reported having been in OST before. According to European studies, not being in OST remains, however, one of the most important factors in the misuse of prescription OST medications and, in this case, OST medications may be used primarily for self-medication purposes. Clearly, it is a challenge for, but also a responsibility of, the stakeholders involved in the provision of OST to ensure the availability and accessibility of this effective treatment while developing and implementing effective anti-diversion policies.

To improve our understanding of the underlying factors associated with the increasing levels of misuse of OST medications in Europe, the current report analyses various dimensions of the history, availability, diversion and misuse of OST medications in European countries. The objective is to explore, at a systemic level, the relationship between these dimensions and to identify potential implications for policy and practice at national and European levels.

1. Introduction

Opioid use and its consequences represent a serious global public health concern and, in recent years, a number of new policy and public health concerns have emerged, including high levels of drug-related deaths. Opioid substitution treatment (OST) represents the main approach to the treatment of opioid dependence and is part of a wider range of treatment options available to heroin users.

It is estimated that nearly half of the 1.3 million problem opioid users in the European Union are receiving this treatment, a considerably higher rate than in most other world regions (EMCDDA, 2019a). The wide use of this treatment is supported by scientific evidence accumulated over recent decades regarding the benefits of OST in treating opioid dependence and in ameliorating its associated health and social consequences.

In spite of these clear benefits, recent years have seen increasing debate about the worrying levels of diversion and misuse of OST medications in Europe (EMCDDA, 2019a), which appear to be playing an increasing role in the European drug problem. In 2017, 19 European countries reported that more than 10 % of all opioid clients entering specialised services presented for problems primarily related to opioids other than heroin, most commonly problems associated with the misuse of methadone or buprenorphine (EMCDDA, 2019a). A rise in overdose deaths associated with methadone and buprenorphine, although not necessarily diverted, has also been observed in recent years in Europe (EMCDDA, 2019a). These deaths currently represent a substantial proportion of overdose deaths in some European countries.

In addition to increases in mortality rates, the consequences of the misuse of OST medications may include poor adherence to treatment, negative-impact treatment outcomes, somatic complications associated with injection of the medication and a risk of contracting blood-borne viruses. Diversion of OST medicines has also been associated with increases in crime, has had a negative impact on prescribers' practice, has threatened the reputation of treatment services and has compromised public acceptance of the long-term treatment of opioid-dependent individuals (Alho et al., 2015; Wright et al., 2016; Reimer et al., 2016). The consequences of the diversion and misuse of prescription OST medications in Europe are a continuing public health concern and require heightened vigilance, particularly in light of the recent opioid epidemics in the United States.

In this context, it is a challenge for but also a responsibility of the stakeholders involved in the provision of OST to ensure the availability and accessibility of this effective treatment while developing and implementing effective anti-diversion policies. Therefore, it is important that the principle of balance (Box 1) is applied.

Box 1. Principle of balance (WHO, 2011)

The World Health Organization (WHO) considers the public health outcome of controlled medicines, including OST medications, to be at its maximum (or to be 'balanced') when the optimum is reached between maximising access for rational medical use and minimising substance abuse. All countries have a dual obligation with regard to these medicines based on legal, political, public health and moral grounds. The dual obligation is to ensure that essential medicines such as methadone and buprenorphine are safely accessible and available for medical purposes while protecting populations against the harms derived from the abuse and misuse of, and dependence on, these medicines. Countries should aim for a policy that ultimately achieves both objectives, in other words a 'balanced policy'.

1.1. Aim and objective of the report

To improve our understanding of the underlying factors associated with the increasing levels of misuse of OST medications in Europe, the current report analyses various dimensions of the history, availability, diversion and misuse of OST in European countries. The objective is to explore, at a systemic level, the relation between these dimensions and identify potential implications for policy and practice at national and European levels. This should in turn inform national efforts in implementing balanced and evidence-based OST and anti-diversion policies.

1.2. Background

Prevalence of opioid use and related harms

It is estimated that, globally, 53 million people used opioids (i.e. persons who used opiates and persons who used prescription opioids for non-medical purposes) in 2017, corresponding to 1.1 % of the global population aged 15-64 years (UNODC, 2019). In the European Union, the prevalence of high-risk opioid use among adults (15-64 years) is estimated to be 0.4 % of the EU population, the equivalent of 1.3 million high-risk opioid users in 2017. High-risk opioid use is defined by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as 'injecting drug use or long duration/regular use of opioids' (EMCDDA, 2019b). Heroin remains the most common opioid used among high-risk opioid users in Europe, and opioids were found in 78 % of the total 8 238 overdose deaths involving at least one illicit drug in the European Union in 2017 (EMCDDA, 2019a). In addition to drug-related deaths, the consequences of opioid use include dependency, a high risk of infection with HIV and viral hepatitis through sharing of injecting equipment, engaging in risky sexual behaviours, criminal activity, a loss of social and family cohesion, and economic costs for societies (Best et al., 2003; Fischer et al., 2006; Donmall et al., 2012).

Evidence base for opioid substitution treatment

A large evidence base exists for the health and cost benefits of OST, especially when it is combined with psychosocial and other interventions. These benefits include reductions in the risk of HIV and other blood-borne infections (in particular when combined with needle and syringe exchange interventions), risky sexual behaviours, the risk of overdose, participation in criminal activity and illicit drug use. The evidence also indicates that OST is associated with increased levels of retention in treatment and social reintegration (Mattick et al., 2004; Amato et al., 2005, 2011; Gowing et al., 2008, 2011; Lawrinson et al., 2008; ECDC and EMCDDA, 2011; Havnes et al., 2012; MacArthur et al., 2012).

Opioid substitution treatment goals and outcomes

Over the past three decades, the introduction and scaling-up of OST has been a key response geared towards reducing the number of opioid-related deaths, the levels of high-risk opioid use and the number of HIV infections among injecting drug users in Europe (Hedrich et al., 2008).

A range of OST outcomes and goals exist, including the reduction and management of drug-related problems, abstinence and social integration by facilitating employment and greater social cohesion (WHO, 2009a; Rao et al., 2014).

At the start of OST, initial treatment goals are generally aimed at enabling clients to control opioid withdrawal symptoms and cravings, addressing any medical or psychosocial crisis faced by clients, and establishing a rapport with clients and educating them about the treatment process. After the initial stage, goals generally focus on maintaining clients on adequate doses of OST medication, addressing other substance use by the client, if any, and preventing clients from shifting to use of another substance; motivating clients and referring them to other services, including HIV and hepatitis C virus diagnosis and treatment; helping clients in regaining occupational, financial and familial stability; retaining clients in treatment and helping them to adhere to the treatment regime; and helping clients to prevent relapse to opioid use.

There is no specified duration for clients to be maintained on OST. OST may last for months or years. The endpoint is generally reached when the client achieves the treatment goals decided mutually by the client and the service provider during the initiation of OST. The treatment goals are not limited to the client stopping drug use; they also include successful reintegration of clients into their family, society and work.

The achievement of these outcomes depends greatly on the motivation and circumstances of each individual and on the quality and effectiveness of the treatment delivered, as well as on the wider treatment, health and social services supporting the recovery of the client in OST. It is important to acknowledge that pharmacological treatment by itself will not enable an individual to achieve a full range of outcomes (ACMD, 2015).

Number of clients in opioid substitution treatment and coverage in Europe

In 1993, the estimated number of clients in OST in the 15 countries that were EU Member States at the time ([1]) was about 73 000 and, by 2005, the number for the same countries had risen to above half a million. The provision of OST in the 28 Member States of the European Union in 2017 reached its peak in 2010-2011, with about 700 000 cases. The latest figures show that an estimated 654 000 high-risk opioid users received OST in the European Union in 2017 (EMCDDA, 2019a).

A comparison with current estimates of the number of high-risk opioid users would suggest that one in two high-risk opioid users receive this treatment in the European Union, but large variations between countries exist, ranging from 10 % in Latvia to over 80 % in France (EMCDDA, 2019a). Differences in OST coverage between the countries can be explained by variation in the availability of and access to OST. As with any other medical or pharmacological treatment, the accessibility, availability, affordability and acceptability have an impact on how many individuals in need have access to this treatment. Multiple factors determine this,

([1]) Timeline of the European Union's enlargement by country and year of joining the European Union: Belgium, Germany, France, Italy, Luxembourg and the Netherlands (1957); Denmark, Ireland and the United Kingdom (1973); Greece (1981); Spain and Portugal (1986); Austria, Finland and Sweden (1995); Czechia, Estonia, Cyprus, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia (2004); Bulgaria and Romania (2007); and Croatia (2013).

including the impact of past drug epidemics, drug policies, geographical availability, health service funding, health insurance reimbursement schemes and legal prescribing frameworks (Vranken et al., 2014; Hedrich and Pirona, 2017).

1.3. Methods

For this report, a non-systematic review of the international literature was carried out. Primary analyses, including not previously published analyses, used national epidemiological data submitted by the Reitox national focal points to the EMCDDA. The main national datasets used in this report were the treatment demand, health and social responses, overdose deaths, seizures of drugs and problem drug use datasets published annually in the EMCDDA's Statistical Bulletin. Previously published data were also used, namely from the EMCDDA's European Drug Report, EMCDDA-Europol EU Drug Markets Report and Statistical Bulletin. Data sources are referenced in the report where necessary. Further national information on the history, availability, accessibility and affordability of OST, as well as on the misuse and diversion of OST medications at the national level, was collected through a dedicated survey among national focal points from Czechia, Germany, Ireland, France, Austria, Poland and Finland.

2. Access to opioid substitution treatment in Europe

Access to OST can be understood as a general concept that includes a set of more specific dimensions describing the fit between the patient and the system providing OST. These dimensions include availability and accessibility, but also the affordability and acceptability of OST (see the **Glossary**). In a country, these dimensions are affected by moderating factors, each of which can have an impact on one or more of the dimensions. For example, legal frameworks or national regulations will determine which OST medications can be prescribed for the treatment of opioid dependence and which medical professionals are allowed to prescribe them. Limitations in one or more of these dimensions will have an impact on the overall level of access to OST in a country (or region or city) (Figure 1).

Figure 1. System dimensions and their moderating factors affecting access to opioid substitution treatment

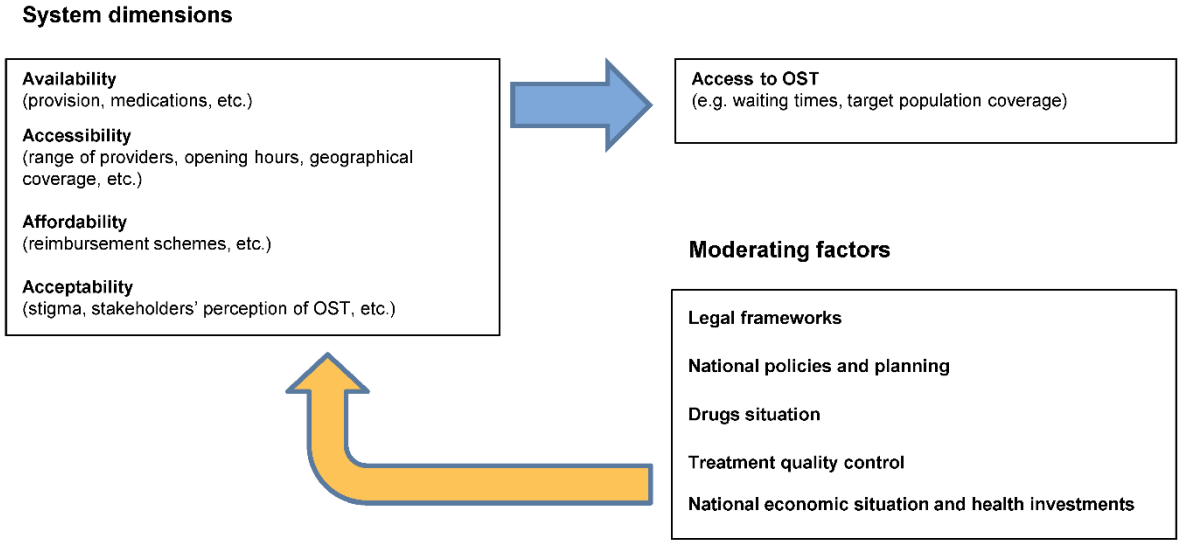
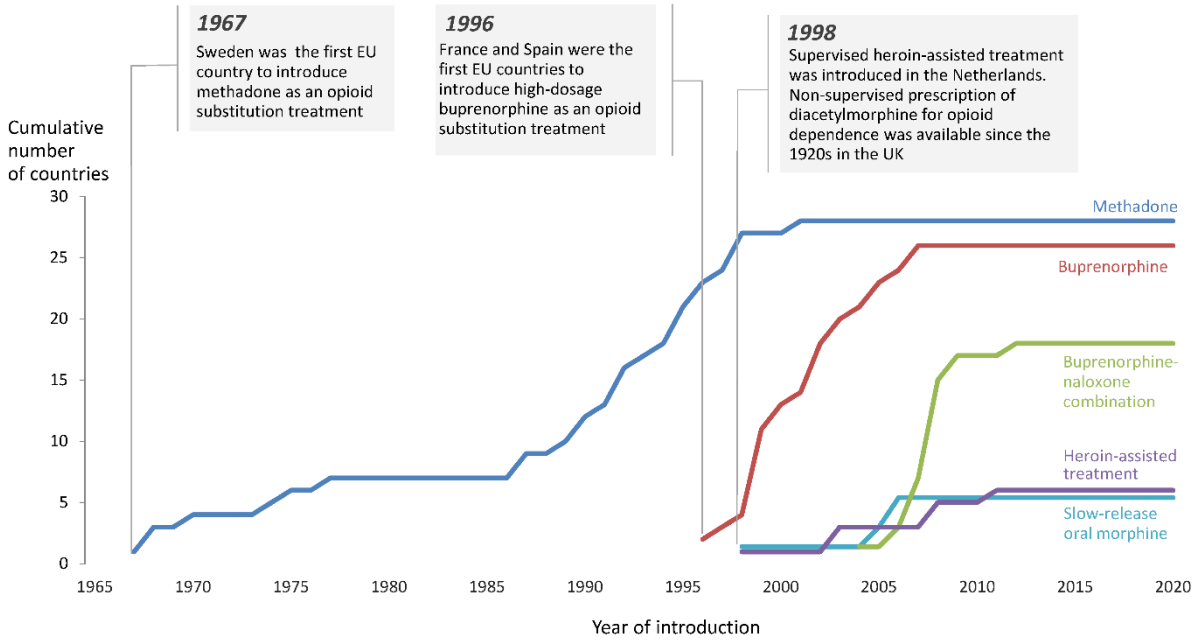


Figure 2. Year of introduction by OST medication in EU Member States, Norway and Turkey



Source: EMCDDA (2019c) (see Appendix Table A1).

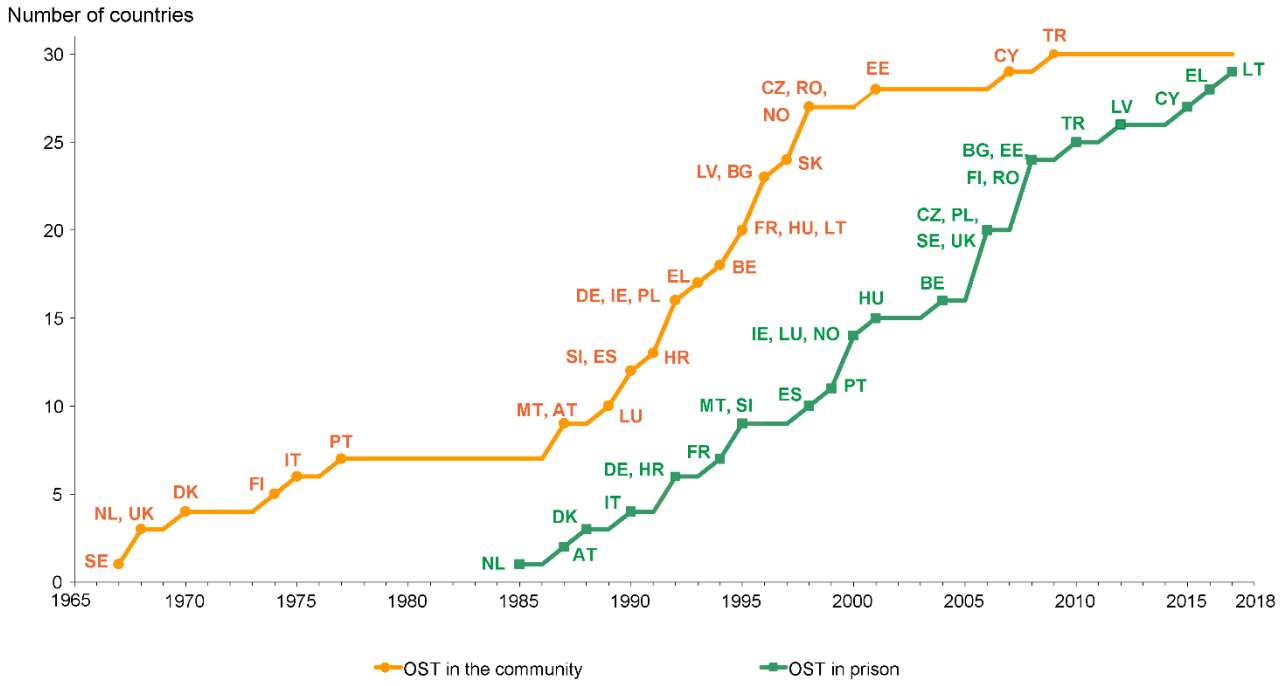
2.1. Availability of opioid substitution treatment medications in Europe

A wide range of medications are available in Europe for the treatment of opioid dependence. Methadone (as well as levo-methadone) and buprenorphine (as well as the combination buprenorphine-naloxone) are the two main medications prescribed for this purpose in Europe and, by 2005, they were available in nearly all Member States (see Figure 2). Slow-release morphine, codeine, dihydrocodeine and diacetylmorphine are also used in some of the countries. Large differences in the availability and provision of these medications exist between countries owing to historical, economic and legal reasons.

Methadone

Methadone as a treatment for opioid dependence was pioneered in Europe by Denmark, the Netherlands, Sweden and the United Kingdom in the late 1960s and the early 1970s (Hedrich et al., 2008). Over the course of the 1980s, levels of heroin use and injecting drug use rose in many western European countries. In 1985, HIV antibody tests were introduced, leading to the discovery of high rates of infection in numerous western European cities among people who inject drugs. The fear and realisation of an HIV/AIDS epidemic, as well as concern over crime and public safety, meant that drugs became a political priority at both the national and the EU levels, leading to a wider diffusion of harm reduction interventions, including OST (Figure 3). This diffusion is reflected in an acceleration of the introduction rate at which methadone became an official treatment modality in other European countries in the mid-1980s. Some countries adopted harm reduction policies that led to an increase in the availability of methadone maintenance treatment quite rapidly. It should be noted that these developments occurred almost entirely in western Europe; the countries of central and eastern Europe, most of which were under Soviet influence until the fall of the Berlin Wall in 1989, were barely affected by the increased opioid use observed elsewhere. Of these countries, all of which joined the European Union in or after 2004, only a few embraced OST as a harm reduction measure and most continued to emphasise high-threshold, often abstinence-oriented treatment services (Cook et al., 2010).

Figure 3. Year of introduction of OST in the community and in custodial settings in Europe



Source: EMCDDA (2019c) (see Appendix Table A1).

Buprenorphine

A breakthrough occurred in the early 1990s with the development of high-dosage buprenorphine treatment. Owing to its unique pharmacological profile, buprenorphine has, in principle, a number of advantages over methadone for use as an opioid substitution medication. For example, buprenorphine is not as potent as a full mu agonist, such as methadone, and has less analgesic and euphoric ('high') effects than methadone, but nonetheless ameliorates withdrawal symptoms. As a partial agonist, buprenorphine has a 'ceiling effect', that is, after a certain point, taking more will not increase any of the effects of the drug. In addition, buprenorphine has a high affinity for the mu receptor, which means that it reduces the effects of additional opioid use. Buprenorphine causes less respiratory depression than methadone owing to its ceiling effect and, thus, has a lower overdose potential. This particular pharmacological profile of buprenorphine makes it safer to use on an outpatient basis and this has encouraged non-addiction specialists, such as general practitioners, to be involved in the prescribing and scaling-up of OST to opioid-dependent patients in some countries. However, when used in combination with other respiratory depressants, such as alcohol or benzodiazepines, buprenorphine use can result in sedation, coma and death. In addition, patients who use additional opioids to seek a 'high' are at risk of an overdose when the effects of buprenorphine wear off. High-dosage buprenorphine treatment became available first in Spain and France in 1996 and was rapidly introduced in more countries thereafter.

As rising concerns emerged about the potential of diversion, misuse and harms caused by available OST medications, an abuse-deterrent form of buprenorphine was introduced in 2004 in Europe. This medication combines two active ingredients, buprenorphine and naloxone, with the latter being an opioid receptor antagonist. With sublingual administration, the pharmacodynamic effect of the buprenorphine-naloxone combination is comparable to that of buprenorphine alone, because naloxone is only minimally absorbed by that route or not at all. However, when the combination is administered by the intravenous or nasal routes, naloxone

binds to the opioid receptors more rapidly than buprenorphine, which precipitates withdrawal (Mendelson and Jones, 2003). To date, half of the Member States have introduced the combination buprenorphine-naloxone. It should be noted that a wide range of formulations of the active substance, such as buprenorphine, may be available in a country. In France, for example, over 61 buprenorphine-based medications for the treatment of opioid dependence are available with different dosages (0.4 mg, 1 mg, 2 mg, 4 mg and 8 mg) including 42 generics, five original products for buprenorphine alone and four original products for the combination buprenorphine-naloxone.

Diacetylmorphine and slow-release morphine

Diacetylmorphine (pharmaceutical-grade heroin) has been available for supervised provision to a small number of individuals since 2006 in the Netherlands, 2008 in Denmark, 2009 in Germany, 2012 in the United Kingdom and 2017 in Luxembourg. Trials have been conducted in Belgium and Spain (see EMCDDA, 2012a, for further information on supervised heroin-assisted treatment in Europe). It should be noted that unsupervised provision of diacetylmorphine as an option in the treatment of opioid dependence has been available in the United Kingdom since the 1920s (EMCDDA, 2012a).

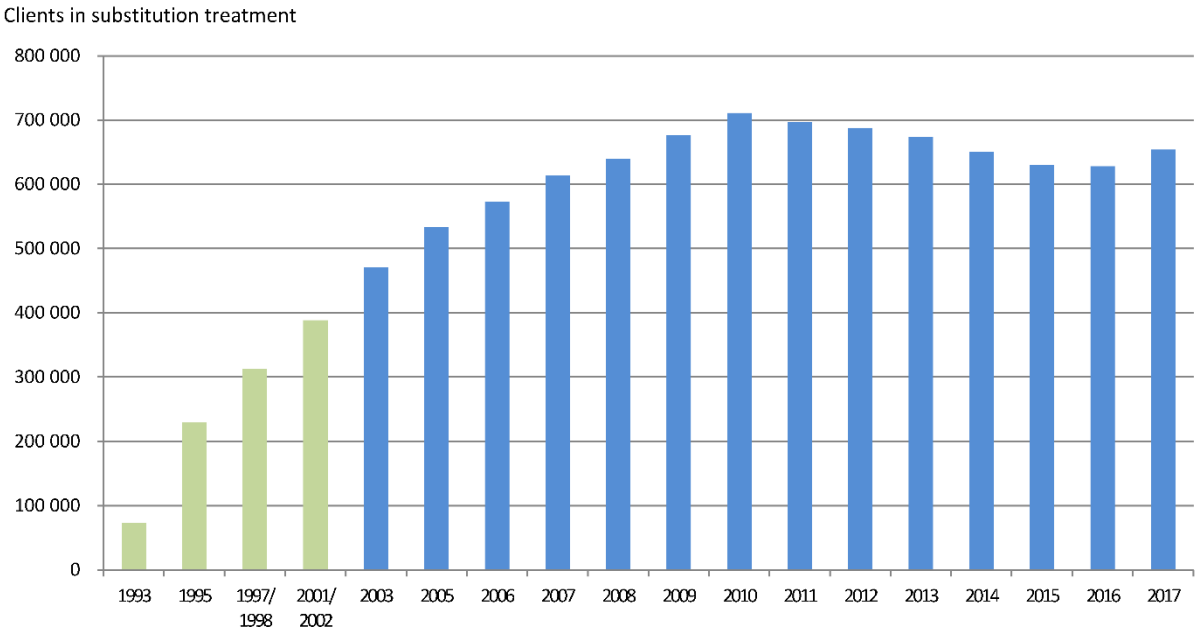
Slow-release morphine is a legal medication used in substitution treatment in only seven countries (Bulgaria, Germany, Luxembourg, Austria, Poland, Slovenia and Slovakia), where it has been introduced over the past 15 years, apart from Austria, where it has been available since the late 1990s.

Current levels of provision of opioid substitution treatment in the European Union

OST remains the most common treatment for opioid dependence in the European Union. An estimated 654 000 opioid users received substitution treatment in 2017. The European OST client cohort is ageing, with the majority of clients now being over 40 years old, predominantly male, most commonly prescribed methadone and typically receiving treatment for more than 2 years (EMCDDA, 2019a).

Figure 4 shows historical trends in the provision of substitution treatment in the European Union and Norway over 24 years. The current total estimated number of clients in OST is down from the peak in the provision of OST in the EU and Norway, which was 710 000 clients in 2010. The period prior to this peak reflects the scaling-up process of OST in the majority of EU Member States. A decline was observed between 2010 and 2015, which may have been due to several factors, including changes in estimation methodologies and shrinking cohorts of ageing opioid users in larger western European countries. Between 2015 and 2017, increases were observed in 17 Member States, including Sweden (an increase of 21 %), Romania (21 %) and Italy (16 %).

Figure 4. Trends in OST in the European Union and Norway (1993-2017)



Note: Until 2001/2002, the data include only EU-15 countries (orange bars). Data from the United Kingdom were available only from 2005 onwards.
Source: EMCDDA (2019c).

Proportions of opioid substitution treatment medications prescribed

Owing to its earlier introduction and lower cost than buprenorphine, methadone is currently the most commonly prescribed opioid substitution medication in the European Union, provided to around two thirds (63 %) of all patients in OST. A further 34 % of patients in OST are prescribed buprenorphine-based medications (high-dosage buprenorphine treatment and/or buprenorphine-naloxone combination). Slow-release morphine and diacetylmorphine (heroin-assisted treatment) are less commonly prescribed for OST.

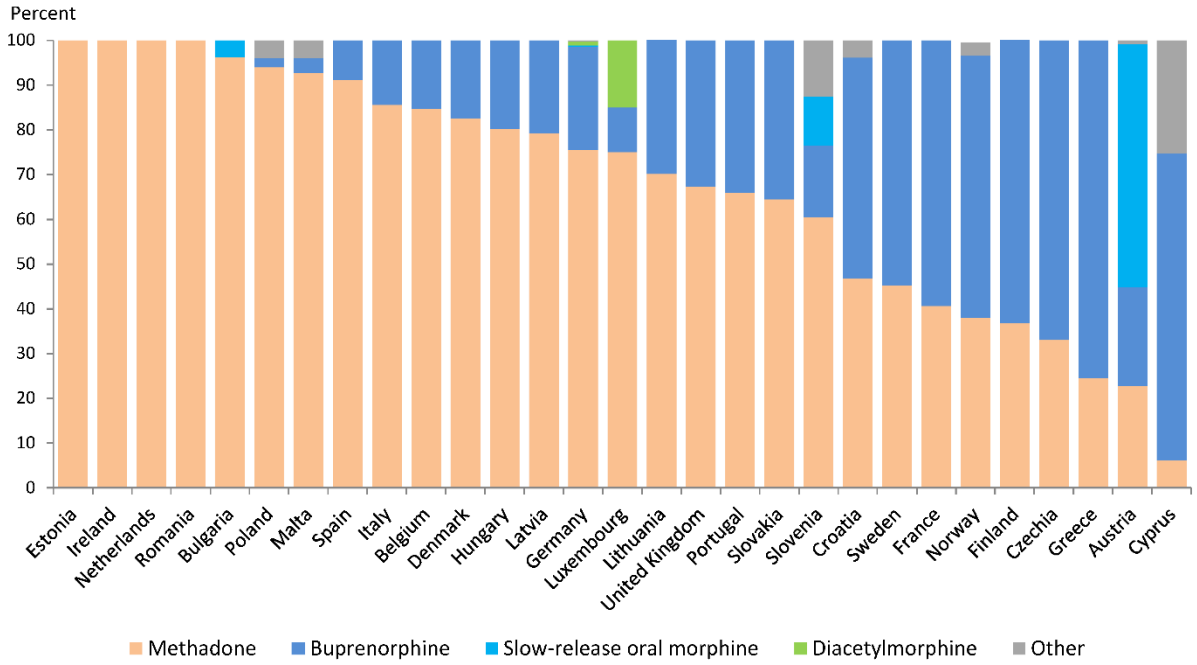
Although both methadone- and buprenorphine-based OST medications are legally available for prescription in all EU Member States, data on the proportions of OST medications provided in the EU Member States show large differences in terms of the predominance of a particular medication. Note that WHO recommends that both methadone and buprenorphine should be available and offered to patients (see Box 2). In some countries, methadone is the only medication prescribed for OST. In 20 of the 28 Member States in 2017, methadone was provided to over 50 % of all OST clients (Figure 5). In eight of those Member States, methadone was prescribed to more than 90 % of all clients, including Estonia, Ireland, the Netherlands and Romania, where all or nearly all clients were prescribed methadone. In eight Member States, buprenorphine-based medications were prescribed to 50 % or more of all clients, ranging from 50 % (Croatia) to 75 % (Greece). In Austria, slow-release morphine was the most commonly prescribed OST medication (54 %).

Box 2. WHO recommendations on the availability of OST medications

If countries are able to afford it, it is best to have both methadone and buprenorphine available for opioid agonist maintenance treatment. Having both treatment options available means that patients who experience adverse effects of one of the medications, or fail to respond, can try the alternative. This situation may increase the proportion of people with opioid dependence staying in opioid agonist treatment; it may also increase the effectiveness of treatment through better matching of treatments to patients.

Source: WHO, 2009a.

Figure 5. Proportion of clients receiving different types of prescribed opioid substitution medication in 2017



Note: In the Netherlands, about 10 % of clients receiving methadone are also prescribed diacetylmorphine. In Finland, buprenorphine includes the medication alone or combined with naloxone. UK data are for Wales only.
Source: EMCDDA (2019c).

Country examples shed some light on factors influencing the prominence of one OST medication over another. For example, 96 % of the 2 685 clients in OST in Poland were prescribed methadone, 4 % were prescribed buprenorphine-based medications and less than 1 % were prescribed slow-release morphine. Although all of the above medications are available in Poland, in practice, methadone is the most commonly prescribed owing to its low cost. The National Health Fund (NHF) provides fixed budgets for OST programmes regardless of the medications prescribed (all costs connected with OST are incurred by the NHF). As a result, OST programmes prescribe the medication that is the cheapest, to keep the costs low and serve as many patients as possible.

In Ireland, almost all clients receive methadone as their opioid substitute, not necessarily for economic reasons but because historically this has been the first-choice drug for treating opioid dependency. In 2011, an expert group concluded that methadone should remain the first-choice drug for treating opioid dependency, but that buprenorphine-naloxone may be appropriate for some patient cohorts in certain circumstances. Since November 2017, Suboxone (buprenorphine and naloxone in combination) has been available for patients when clinically appropriate, but so far it has been prescribed to a very low number.

2.2. Accessibility of opioid substitution treatment

According to WHO guidelines, OST should be accessible to all those in need and therefore treatment programmes should be designed to be as accessible as possible; for example, programmes should be physically accessible, open at convenient times, have no undue restrictions on accessibility and have the capacity to be expanded to accommodate the likely demand. National laws usually define who is permitted to prescribe OST and thereby directly influence availability and accessibility of OST in a country.

Legal frameworks and provision models of opioid substitution treatment in Europe

The scope of the legal framework for OST varies considerably between Member States. In some countries, OST is covered by a specific parliamentary law, such as Belgium and Finland and, in the latter, the implementation of OST is based on a decree of the Ministry of Social Affairs and Health. In other countries, however, such as Cyprus, OST implementation is subject to interpretation of the laws on controlled substances. The national laws normally designate those substances that can be used for substitution treatment. In most cases, only methadone or only methadone and buprenorphine can be prescribed; however, in a few countries, other medications such as slow-release morphine or diacetylmorphine are permitted. National laws normally also designate which medical professionals are allowed to prescribe OST medications and under which conditions (e.g. only those with a specific accreditation or with a specialisation in addictive behaviours). In some countries, such as Czechia, France and Luxembourg, any medical doctor is allowed to prescribe OST medications (for an overview of legal frameworks in Europe, see the legal framework datasets of the EMCDDA Statistical Bulletin's health and social responses dataset (EMCDDA, 2019c)).

In Europe, various OST provision models exist, but, overall, nearly all OST in the European Union is provided on an outpatient basis. A common feature of these models is the role of outpatient specialised drug treatment centres as access points to OST. In all EU countries, OST is available in specialised outpatient drug treatment centres; however, the importance of these centres varies greatly, from being the only access point to OST (e.g. in Italy and in nearly all eastern EU countries) to being only moderately involved in OST (e.g. in Germany, France, Luxembourg and Austria).

Another provision model that is nearly exclusively observed in western European countries is the provision of OST in low-threshold agencies and in primary healthcare settings. Unless specialised treatment centres are widely available and accessible, the involvement of primary healthcare and low-threshold points greatly increases the geographical coverage of OST, especially in rural areas. Treatment numbers have increased rapidly in countries that have adopted models based on primary healthcare involvement. According to WHO guidelines, treatment in primary care also has the advantage of integrating medical and psychiatric addiction services into mainstream services and reducing the stigma of addiction and the professional isolation of medical staff. On the downside, primary healthcare settings are

generally not equipped to address psychiatric comorbidities or to provide psychosocial counselling. WHO guidelines underline that primary care practitioners will usually need support from the specialist system through mentoring, training, consultation and referral. Only a few European countries provide OST as a treatment option in inpatient settings.

2.3. How good is the overall access to opioid substitution treatment in Europe?

As described at the beginning of this section, the overall access to treatment in a country is dependent on various dimensions, such as availability, accessibility, affordability and acceptability. For example, a treatment may be highly available and accessible, but not affordable. As a result, access to treatment will be low. These dimensions are, however, hard to quantify for evaluation purposes owing to their qualitative nature, their complexity and often a lack of reliable data. As an alternative, waiting times and treatment coverage may be used as proxy measures of the overall level of access to OST in a country.

Waiting times to enter opioid substitution treatment

Because of the severity of the health risks associated with opioid dependence, waiting times to enter OST should be minimised. According to data reported to the EMCDDA by the Reitox national focal points, average national waiting times for OST vary greatly between countries. It should be noted that, in many cases, reported national waiting times are based on expert opinion of the national situation and may hide important variations within countries. In nearly one third of the Member States, no waiting times are reported for clients wanting to enter OST. In six Member States, national average waiting times are estimated to be less than 2 weeks, while, in five countries, waiting times can reach up to 1 month. In four countries, national waiting times exceed 1 month and can reach up to 6 months. According to national experts, the main causes of lengthy waiting times are limited service availability and insufficient professional or financial resources to provide OST. In some countries, waiting times are primarily due to the formal procedures required prior to accessing OST.

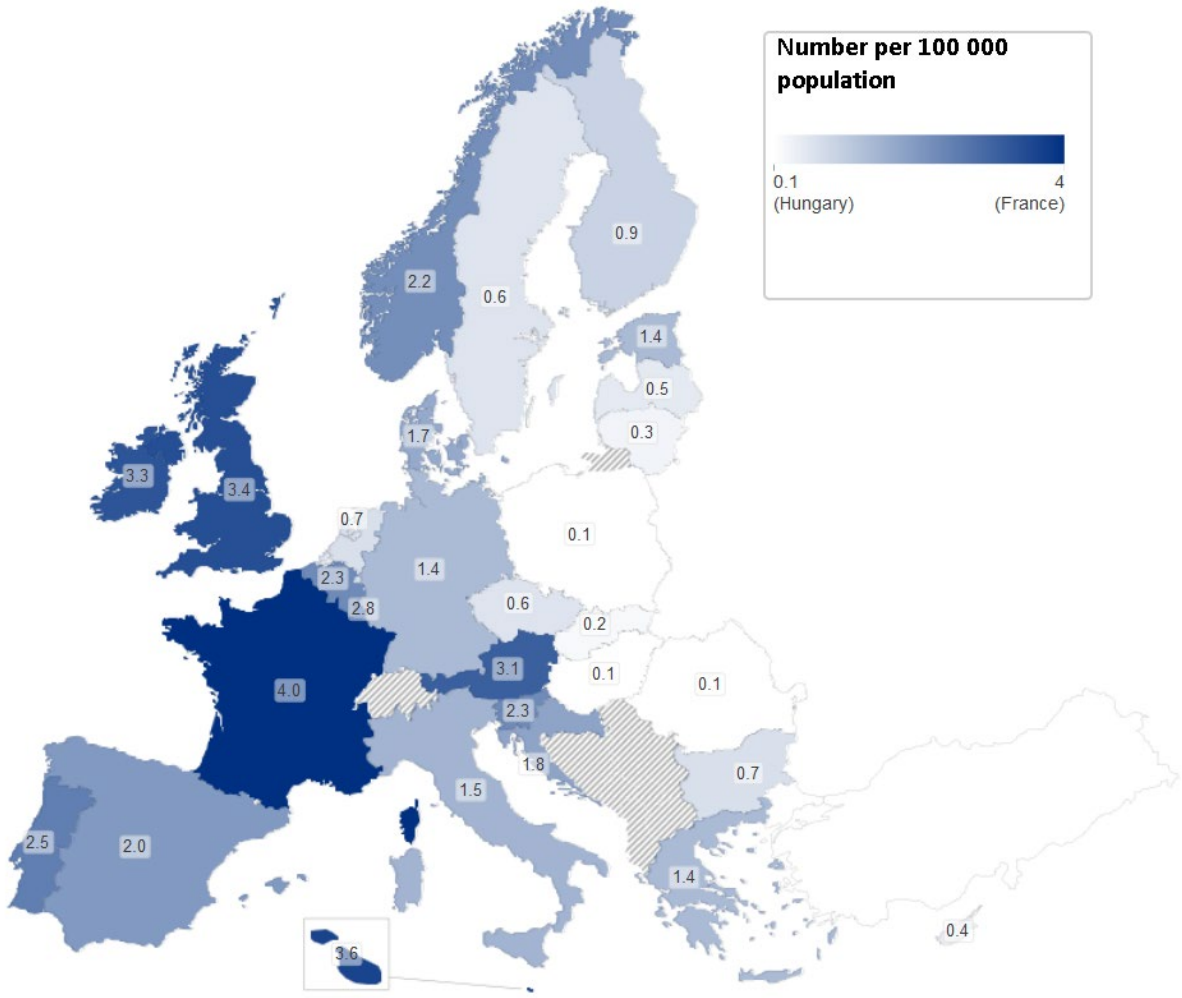
In Poland, it is estimated that the waiting times are approximately 1 to 2 weeks before starting OST, while in Ireland the average waiting time is 28 days from assessment to accessing OST (or removal from the waiting list). However, waiting lists for OST in Ireland may be longer outside the main urban areas, and clients living in more rural areas may have difficulties travelling to clinics owing to limited public transport infrastructure. In Austria, clients receiving OST from general practitioners should, in theory, not experience waiting times, but this varies from region to region because of differences in the availability of medical doctors eligible for prescribing OST. Those receiving OST in specialised treatment centres in Austria often do experience waiting times, but this also varies from region to region. According to national Finnish experts, the total waiting time between the first request for OST and the start of OST in Finland might be several months owing to formal procedural processes (assessment and formal medical decision).

Coverage of opioid substitution treatment in Europe

The coverage of OST is considered the most informative indicator of the overall level of access to treatment. The coverage of a specific treatment is generally calculated by assessing the proportion of people in need of the treatment who actually receive it. In addition, coverage data alongside other data can provide information on potential shortcomings within the system. For example, short waiting times but low coverage levels in a country may indicate that the acceptability of OST among clients is problematic, as they do not seek this particular treatment.

Not all European countries produce estimates of the number of people in need of OST (e.g. estimates of the number of high-risk opioid users). Therefore, a first analysis of the coverage of the total number of people receiving OST in a year (see Appendix Table A2) per 1 000 population in each Member State provides a first indication of the level of access to OST. Results show that Member States in western Europe, primarily the 15 countries that had joined the European Union by 1995, tend to have higher rates of OST provision than countries in eastern Europe (Figure 6). Sweden, the Netherlands and Finland appear to be exceptions within this group, with lower rates (<1 per 1 000 population) than other EU-15 countries. On the other hand, countries that have joined the European Union since 2004 generally show lower rates, with several countries presenting rates below 0.3 per 1 000 population (see Figure 6). Among these countries, Croatia and Estonia show rates similar to most EU-15 countries. These first results are in line with the historical developments described earlier about the differences in OST implementation between western and eastern EU countries.

Figure 6. OST provision: number of people receiving OST per 1 000 in the general population in 2017



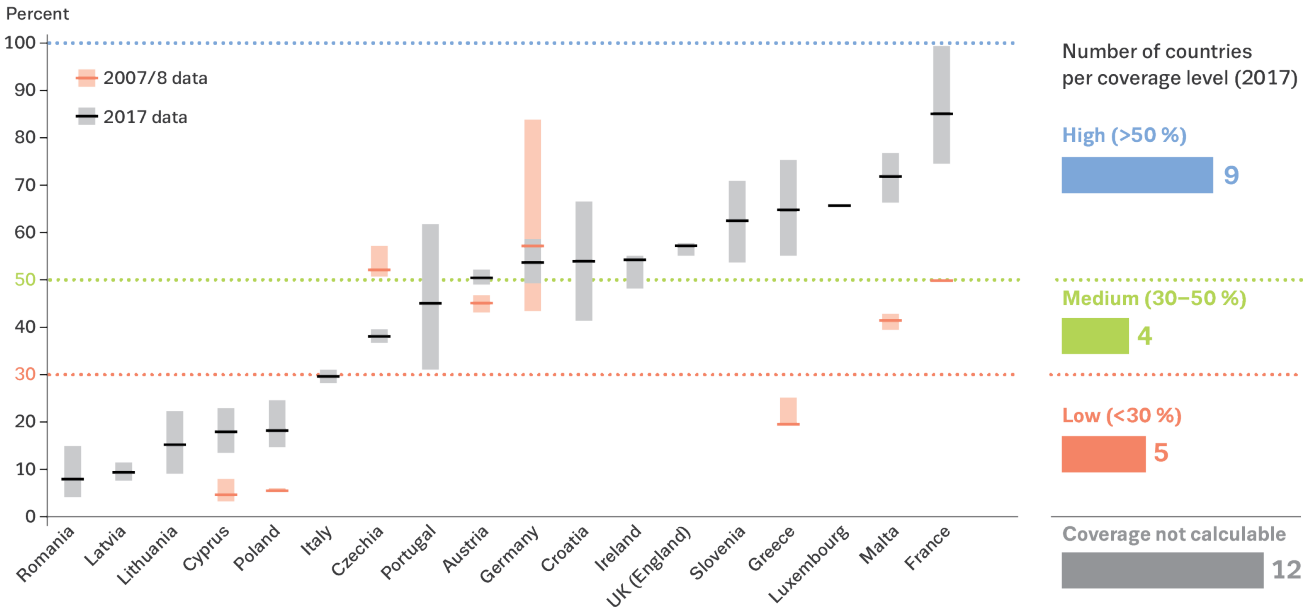
Sources: Eurostat and EMCDDA (2019c).

However, OST coverage calculations based on general population figures are influenced by a number of factors, among which are differences between countries in the size of the high-risk opioid user population who are in need of this particular treatment.

Therefore, a more accurate indication of the level of coverage of OST is to calculate how many high-risk opioid users (in need of treatment) are actually receiving OST.

To assess the size of the population in need, countries produce estimates of the high-risk opioid user population. These estimates can be found on the EMCDDA Statistical Bulletin's health and social responses web page (EMCDDA, 2019c). Thus, an analysis of the total number of people receiving OST as a percentage of the estimated high-risk opioid user population in a country shows that in 10 of the 18 EU countries where recent data are available, the coverage is considered high, according to United Nations targets for universal access to HIV prevention, treatment and care (WHO, 2009b). In these 10 countries, it is estimated that more than once every second a problem opioid user (>50 % coverage) receives OST, with France reaching coverage levels above 80 %, which represents four out of five high-risk opioid users receiving OST at the national level (Figure 7). Medium coverage levels, of between 30 % and 50 %, are reported in Italy, Czechia and Portugal. Suboptimal (low) coverage levels (below 30 %) are observed in Poland, Cyprus, Lithuania, Latvia and Romania, with the two latter countries reporting that only about 10 % of their high-risk opioid user population receives OST.

Figure 7. Coverage of OST (percentage of estimated high-risk opioid users receiving the intervention) in 2017 or in the most recent year and in 2007/2008



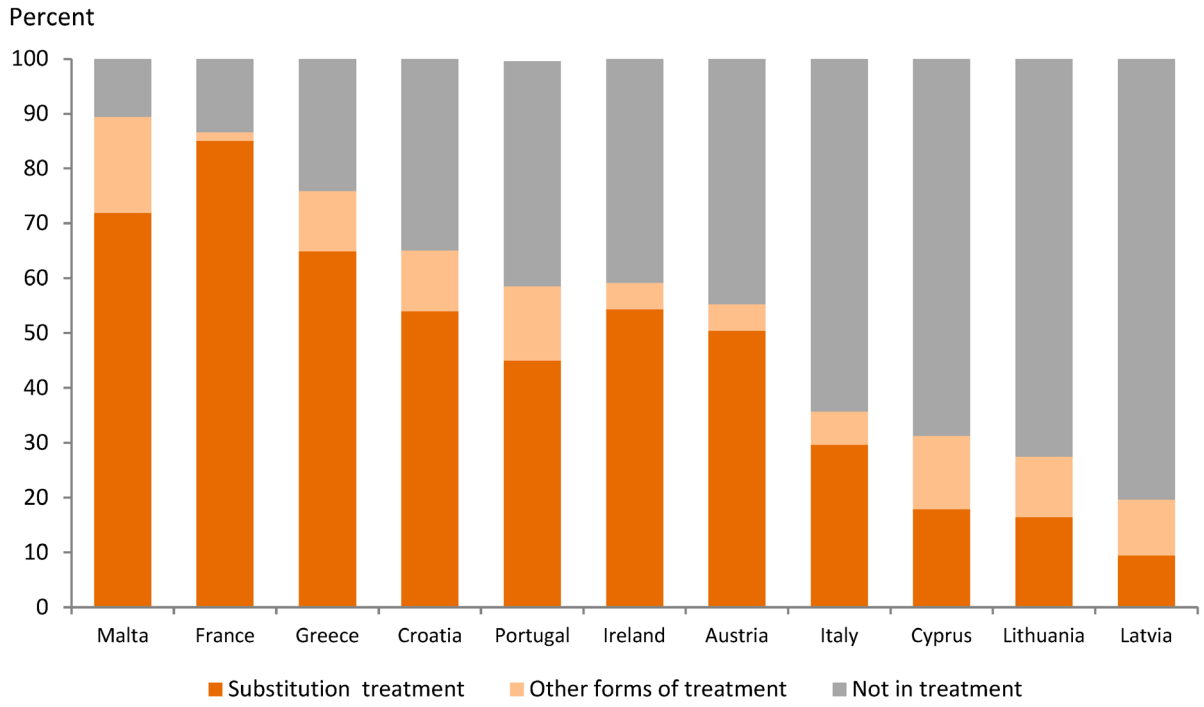
Note: Data are displayed as point estimates with uncertainty intervals.
Source: EMCDDA (2019c,d).

It could be argued that people already receiving OST should not be included in the overall estimate of the high-risk opioid user population, as the majority of these are in recovery and should no longer be considered high-risk opioid users. However, as with any other medical chronic disorder requiring long-term treatment, the calculation of the coverage of a medical treatment applies to the overall population in need of continuous, long-term treatment, whether they are currently in or out of treatment. A practical implication of this principle involves the planning, commissioning and funding of OST required in a given year. In simple terms, the

funding to be earmarked for the next financial year would need to consider the individuals already in treatment and a proportion of those out of treatment who may possibly access OST in the future. This coverage calculation also allows the number in need who have not yet been reached with OST to be determined.

Furthermore, data on the overall number of high-risk opioid users in any kind of drug treatment are available for 11 countries (Figure 8). An analysis of the data of all high-risk opioid users in any kind of treatment and in OST shows that OST is the treatment of choice in all countries. Between 2 % and 17 % of all opioid users in treatment receive interventions not involving opioid substitution (Figure 8). In addition, these data show that, in low OST coverage countries (Cyprus, Lithuania and Latvia), but also in Italy, the overall treatment coverage beyond OST is estimated to be low, with a significant proportion of high-risk opioid users not in drug treatment.

Figure 8. Overall estimated number of high-risk opioid users in treatment (in OST and other treatments) as a percentage of the estimated number of high-risk opioid users in 2017 in selected countries



Source: EMCDDA (2019c,d).

3. Diversion and misuse of prescription opioid substitution treatment medications

The diversion and misuse of opioid substitution medications is of particular concern in Europe. The demand for specialised treatment related to the misuse of OST medications and the number of deaths associated with these medications have been increasing over the past decade. This growing problem requires close monitoring and adequate interventions. For this reason, it is important to describe and understand the national contexts, groups and drivers behind these observed increases.

First, it is important to clarify the terminology pertinent to such analysis and to draw a distinction between prescription opioids and prescribed opioids. Prescribed opioid medications, such as

methadone and buprenorphine, are prescribed by a physician to a patient and dispensed by a pharmacy. Prescription (or prescriptible) opioids refer to opioid medications that are intended to be prescribed as medicines and that can be diverted anywhere in the system without necessarily being prescribed (Scholten, 2017). For example, it is estimated that about 75 % of fatal overdoses from prescription opioids in the United States (primarily opioids used for pain relief) occur in people who have not been prescribed opioids during the 3 months preceding their deaths (Scholten and Henningfield, 2016). The majority of these people probably obtained these prescription opioids on the illicit market. Thus, the diversion of prescription opioid medications, such as buprenorphine and methadone, refers to the act of redirecting these medications from legitimate sources to illegitimate or illegal ones.

3.1. Seizures of prescription opioid substitution treatment medications

In the European Union, heroin remains the most common opioid seized by law enforcement agencies, with 37 000 seizures, amounting to 5.4 tonnes, being reported in 2017. Prescription methadone and buprenorphine represent a small fraction of all non-heroin opioids seized (see Table 1), but in some countries these represent an important proportion of the national illicit opioid market. Over three quarters (77 %) of all buprenorphine tablets seized in Europe in 2017 (i.e. 45 637 tablets) were reported by Sweden and Finland alone (see EMCDDA, 2019e for detailed national breakdowns). Similarly, Greece reported 57 % of all European seizures of methadone in solid form (kilograms) and Italy reported 71 % of all European seizures of methadone in liquid form (litres) in 2017 (EMCDDA, 2019e). This may indicate that, during that year, large quantities were seized at the wholesale or retail level in these countries. The number of seizures across the reporting countries for these two medications indicates that trafficking and diversion at the retail level is not negligible.

Table 1. Seizures of opioids other than heroin in the European Union, Norway and Turkey in 2017

Opioid	Number	Quantity				Number of countries
		Kilograms	Litres	Tablets	Patches	
Methadone	1 428	17.2	26.4	30 381		18
Buprenorphine	2 649	0.5	0.01	58 682		17
Tramadol	4 290	13.8	0.1	118 935 898		11
Fentanyl derivatives	940	14.3	1.9	10 551	2 291	13
Morphine	358	246.0	1.3	9 337		13
Opium	1 837	2 177.9				17
Codeine	522	0.1		18 475		8
Dihydrocodeine	21			1 436		4
Oxycodone	560	0.0001		18 035		8

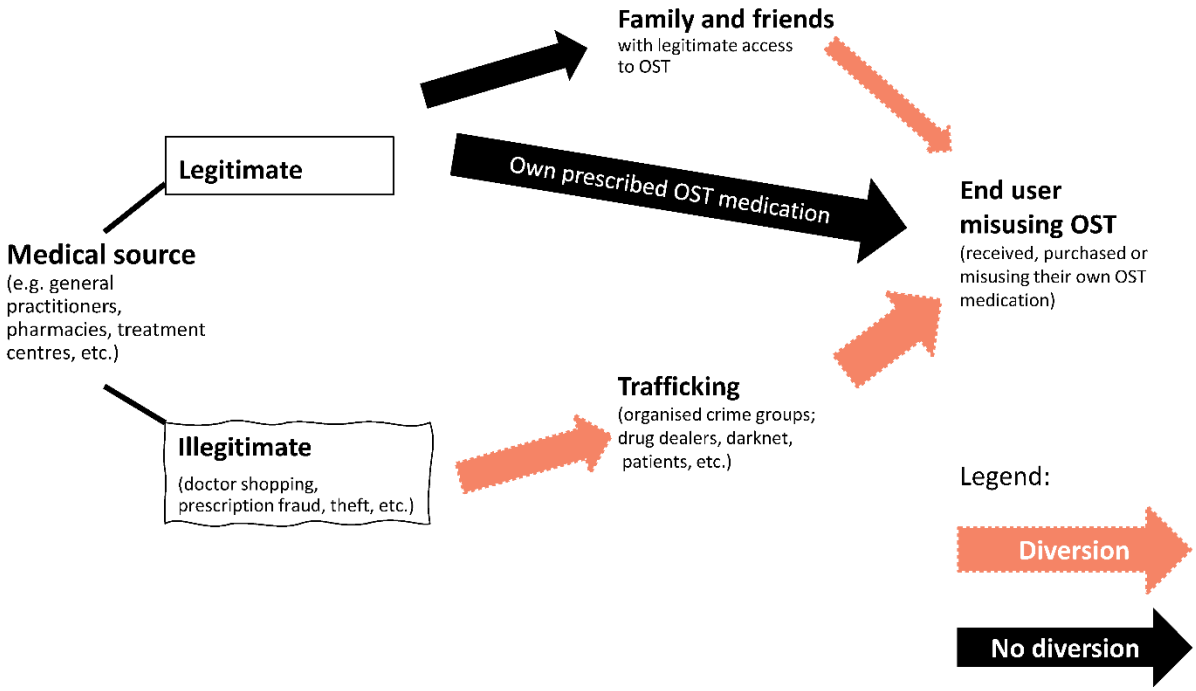
Source: EMCDDA (2019e).

3.2. Sources and mechanisms for diverting prescription opioid substitution treatment medications

Studies on the sources and mechanisms for diverting prescription OST medications within European countries are scarce. Available international and European studies indicate that diverted prescription OST medications originate principally from domestic supplies and, to a lesser extent, from cross-border trafficking. The role of the internet (darknet and surface web) for acquiring OST medications appears to be very limited (Hulme et al., 2018; EMCDDA and Europol, 2019; EMCDDA, 2020).

Domestic supply channels used by end users to illicitly obtain OST medications can be divided into two main interlinked categories: non-medical sourcing and medical sourcing of prescription OST medications (Hulme et al., 2018) (Figure 9).

Figure 9. Main pathways of misused prescription OST medications



Non-medical sourcing

Friends and relatives are the most common and predominant source for high-risk opioid users to obtain these medications in an illegitimate manner. These are generally gifted rather than traded or sold. High-risk opioid users regularly socialise with other users in OST programmes with ready access to medications (a legitimate medical source). Within these communities, informal medication sharing occurs and is often driven by altruistic motives or the desire to help another who may be experiencing the effects of withdrawal or have no access to treatment. The exchange of OST medications for money (and other medications or illicit drugs) may also take place between high-risk opioid users. Diversion, in this case, occurs when friends and relatives who have access to legitimate OST medications divert their own medications.

Drug dealers are also a common source for obtaining OST medications, which are most often part of a wider range of products on offer to potential consumers (pharmaceuticals and illicit

drugs) (Rigg et al., 2012; Vuolo et al., 2014). Little is yet known about where drug dealers are obtaining their supplies of OST medications. Investigations have revealed that organised crime groups in Finland are operating through large-scale cross-border trafficking of buprenorphine medications, which supplies the national illicit market.

Medical sourcing

Legitimate medical sourcing is also a relatively common channel for end users to obtain prescription OST medications for non-medical use. Medications are obtained legitimately by the end user (e.g. in the context of a treatment programme), but partial or excess supplies of medications are not used according to clinical guidance (e.g. injected) or are stockpiled for later use. Studies have also shown the occurrence of diversion of supervised OST doses such as methadone, whereby clients have removed all or part of their dose at the time of administration (Tompkins et al., 2009; Winstock et al., 2009a,b; Larance et al., 2011). This is commonly done for the purpose of saving medications for later personal use (Larance et al., 2011), but it has also been documented that others may coerce treatment clients to share or sell their doses (Green et al., 2013; Allen and Harocopos, 2016).

Illegitimate medical sourcing refers to the sourcing of OST medications through the medical system by faking opioid dependence, prescription forgery or doctor shopping. According to the available literature, these practices are relatively uncommon, as they require considerable time and effort to gather medical knowledge, identify the most amenable practitioners to target, develop a particular profile or appearance, and build rapport with practitioners (Worley and Thomas, 2014; Van Hout and Hearne, 2016; Rönkä and Katainen, 2017). Doctor shopping and prescription fraud are more likely in countries with fewer regulations and incomplete or limited patient registration systems. Illegitimate medical sourcing is a common phenomenon in Czechia, where high-risk opioid users sell parts of the illegally obtained buprenorphine medications to finance their own use for self-medication purposes. As a consequence, large quantities of this medication enter the illicit market via this diversion mechanism.

Country examples of the main sources of diverted prescription opioid substitution treatment medications

European data reveal that the importance of these different sources for acquiring diverted prescription OST medications differs between countries.

The large quantities of buprenorphine seized in Finland and Sweden in 2017 indicate that organised crime groups are involved in the trafficking of these substances. According to national experts and the last EU Drug Markets Report (EMCDDA and Europol, 2019), large-scale smuggling and distribution of mono-preparations of buprenorphine into Finland is primarily organised by Finnish, West African, Lithuanian and Estonian nationals. Evidence from law enforcement agencies suggests that the majority of the buprenorphine seized in Finland originates from within the French healthcare system. Individuals with legitimate access to treatment in France sell their doctor prescriptions to individuals called ‘collectors’. They also use stolen health insurance cards to collect buprenorphine prescriptions. These collectors collect up to 10 prescriptions a day, which can amount to over 1 000 buprenorphine tablets daily (112 tablets per prescription). Strips of seven tablets are then being sold for EUR 10 each to wholesalers who are then selling them to smugglers for EUR 15 each. These smugglers are then reselling them to dealers at the retail level for EUR 35 per seven tablets. The final price in the capital region around Helsinki is between EUR 30 and 50 per tablet. In December 2017, a Europol-supported operation dismantled a trafficking ring that had smuggled high-dose buprenorphine tablets (Subutex) from France to Finland in significant quantities (EMCDDA and Europol, 2019).

Information on the origin and the destination of large quantities of buprenorphine tablets recently seized in Sweden is not known. However, a recent Swedish study investigated the sources of non-prescribed OST medications among patients in OST who reported having ever used non-prescribed OST medications (Johnson and Richert, 2019). Most respondents had bought or received the substances from other Swedish patients in OST, but dealers were also a significant source of non-prescribed methadone and buprenorphine. Another group of Swedish patients stated that they had purchased methadone from Danish patients and/or dealers in Denmark, smuggling small amounts for personal use. There was no corresponding cross-border trade for buprenorphine, which has historically not been much used in Danish OST programmes (see Figure 5).

Findings from a 2015 study in England and Wales showed that during the 5-year study period (2007-2012), only negligible amounts of prescription OST medications were seized by UK customs, about 4 000 methadone doses, while the average annual number of methadone doses prescribed over the same period exceeded 38 million doses (Marteau et al., 2015). There were also no reports of detection of any illegal manufacture of methadone or buprenorphine in the United Kingdom during that period. The authors concluded that domestic diversion was the probable source of black-market OST medications implicated in the observed increase in prescription methadone- and buprenorphine-related deaths in England and Wales. Another UK study indicated that large proportions of participants had obtained illicit methadone for use in the last year, with smaller proportions doing so in the last month. The proportions of participants buying and being given methadone were similar. The exchange of methadone primarily took place between friends and associates, with established dealers rarely involved (Duffy and Baldwin, 2012).

In Germany, two studies were conducted on the misuse and diversion of prescription OST medications (Casati et al., 2014; Schulte et al., 2016). An analysis of 422 police records of seizures of OST medications found that the amounts seized averaged from three to four daily dosages and the persons found dealing were mostly drug users. There were no indications of larger amounts entering the illicit market or involving organised crime groups. Austrian national focal point experts participating in the current study indicated that prescription OST medications were mainly diverted from patients in treatment. According to Goulão and Stöver (2012), survey data showed that 28 % of OST patients in Austria reported having given their prescribed OST medication to others, exchanged it or sold it at least once.

In France, the low-threshold access to prescription OST medications through general practitioners and pharmacies results in domestic diversion being the probable main source of illicit-market OST medications (Milhet and Cadet-Taïrou, 2017). In Czechia, a recent study indicated that the majority of the large-scale misuse of buprenorphine among injecting drug users originates from domestic distribution channels through doctor shopping and re-selling of buprenorphine tablets on the illicit market (Mravcik et al., 2018).

3.3. Recent trends in the misuse of prescription opioid substitution treatment medications

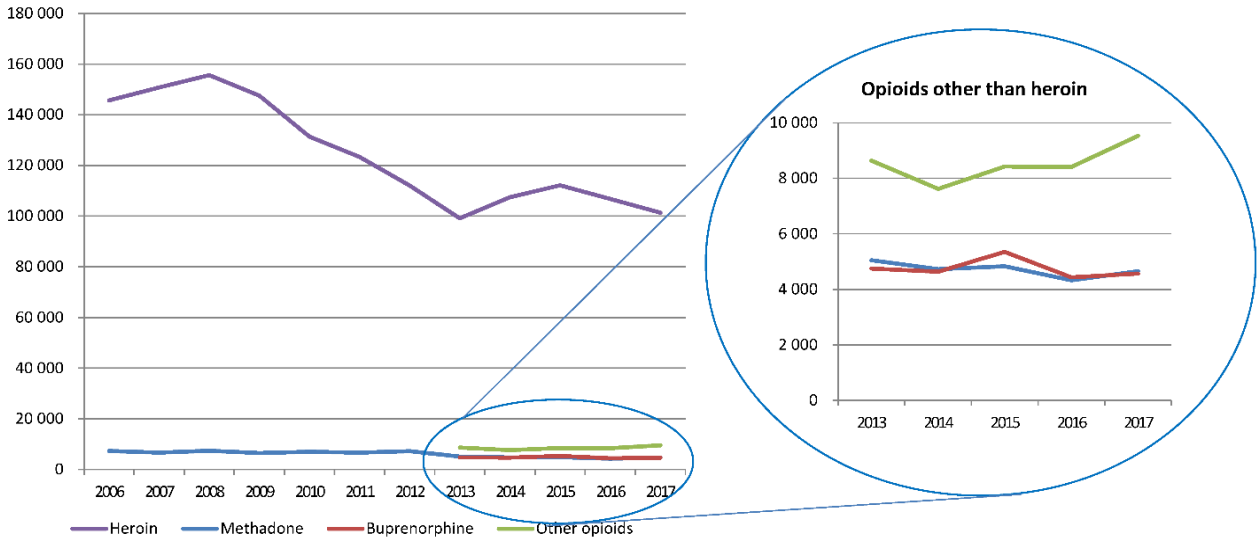
Some insight into the characteristics of individuals with problematic use of prescription OST medications can be obtained from the European treatment demand indicator. It should, however, be noted that data from the treatment demand indicator do not provide information on the source of the OST medications (legitimate or illegitimate medical sourcing).

Overall, trends among clients entering treatment for the misuse of OST medications in Europe follow closely the trends of clients entering treatment for heroin. A decrease in numbers for both groups is observed up to 2013, followed by a stable trend. The number of treatment entrants for problems with other opioids such as tramadol and fentanyl has been increasing in recent years, highlighting the dynamic nature of the opioid market in Europe within a relatively contained group of high-risk opioid users.

However, heroin remains the opioid for which most people seek treatment in Europe. Between 2006 and 2017, the annual number of persons in the European Union who were admitted to treatment with a primary heroin problem decreased from 145 000 to 101 000 (Figure 10). During the same period, the number of treatment entrants citing misuse of methadone as the primary problem decreased from 7 275 in 2006 to 4 644 in 2017. The number of admissions for misuse of buprenorphine in the European Union remained stable, with 4 740 treatment entrants in 2013 and 4 560 in 2017. Overall, 78 % of all clients entering specialised drug treatment services with an opioid problem did so for heroin, while 22 % sought treatment for problems associated with opioids other than heroin, including for problems associated with the misuse of methadone (9 %) and buprenorphine (5 %) (EMCDDA, 2019a).

National treatment demand data for 2017 show that the highest proportion of all opioid-related treatment entrants citing misuse of methadone as the primary drug were reported by Germany (33 %), Denmark (19 %), Bulgaria (13 %), the Netherlands (11 %) and Estonia (10 %). Finland (83 %), Czechia (22 %) and Germany (12 %) reported the largest proportions of treatment entrants citing misuse of buprenorphine as the primary drug among all opioid-related treatment entrants (see Appendix Table A3). In France, the proportion of treatment entrants citing misuse of methadone (8 %) and buprenorphine (10 %) among all opioid-related treatment entrants amounted to 18 %. The remaining countries reported that less than 10 % of treatment entrants were related to misuse of prescription OST medications.

Figure 10. Trends in the number of clients entering treatment for heroin and for opioids other than heroin in the European Union (2006-2017)



Note: Available data from 22 countries were used for the heroin trends (2006-2017) and for opioids other than heroin trends (2013-2017). Data are not available prior to 2013 for buprenorphine and other opioids due to the revision of the EMCDDA TDI data collection protocol (EMCDDA, 2012b). Data are for clients entering treatment during the calendar year who report an opioid as their main problem drug.
Source: EMCDDA (2019f).

3.4. Characteristics of clients seeking treatment for misuse of prescription methadone, buprenorphine and/or heroin

In comparison with individuals entering treatment in the European Union, Norway and Turkey in 2017 for either heroin or misuse of buprenorphine as the primary drug, individuals citing misuse of methadone as the primary drug tended to be slightly older and were more likely to be first admissions (Table 2).

All three groups of treatment entrants have a high mean age, reflecting the overall ageing opioid-using population in the European Union. The initiation of misuse methadone or buprenorphine tends, however, to be on average 5 years later than that of heroin. This could indicate that the misuse of OST medications has developed after a heroin problem, rather than individuals initiating an opioid problem through prescription OST medications. Additional data reveal that 67 % of treatment entrants for primary methadone misuse reported having been in OST before, while this is true of 57 % of entrants with primary buprenorphine misuse.

Table 2. Characteristics and main secondary drugs among clients entering treatment for heroin, misuse of methadone or misuse of buprenorphine in the European Union in 2017

	Primary drug problem for entering treatment		
	Heroin	**Methadone misuse**	**Buprenorphine misuse**
Mean age	37.8 years	39.4 years	37.1 years
Mean age of first use	22.8 years	27.7 years	27.4 years
Previously treated (any drug treatment)	81 % (*n* = 89 663)	71 % (*n* = 3 661)	75 % (*n* = 3 657)
Ever been in OST	71 % (*n* = 49 216)	67 % (*n* = 2 129)	57 % (*n* = 1 867)
Never previously treated	16 % (*n* = 18 118)	21 % (*n* = 1 067)	18 % (*n* = 891)
Main secondary drugs reported	Cannabis (17 %) Powder cocaine (10 %) Benzodiazepines (9 %) Alcohol (7 %) Other opioids (3 %) Methadone misuse: (4 %); Buprenorphine misuse: (2 %) Crack cocaine (32 %) - (5 % when excluding UK data) (total *n* = 86 549)	Heroin (48 %) Cannabis (11 %) Alcohol (10 %) Benzodiazepines (9 %) Other opioids (6 %) Powder cocaine (5 %) (Buprenorphine misuse: 2 %) (total *n* = 4 251)	Heroin (20 %) Cannabis (17 %) Alcohol (12 %) Benzodiazepines (12 %) Powder cocaine (7 %) Amphetamines (5 %) (Methadone misuse: 2 %) (total *n* = 3 900)

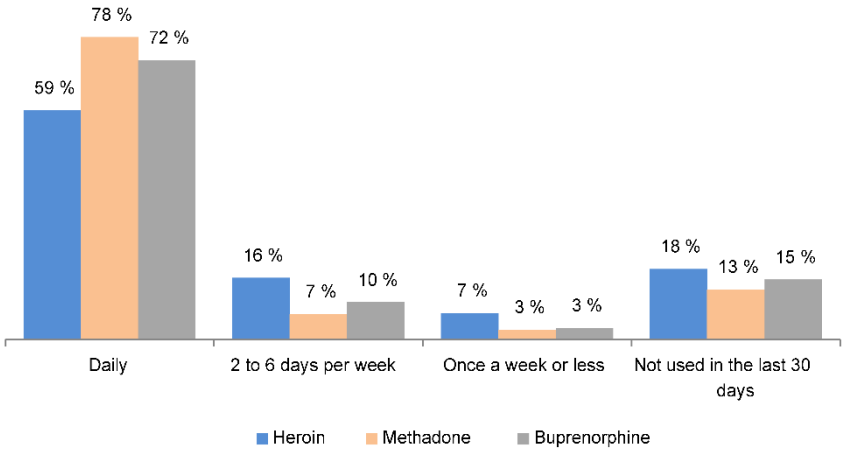
Source: EMCDDA (2019f).

Treatment entrants reported different patterns in terms of their secondary problem drugs. For those with a primary heroin problem, cannabis, powder cocaine and benzodiazepines were the three most common secondary problem drug (Table 2). The majority of those with a primary problem of misuse of methadone mentioned heroin (48 %) as a secondary drug, followed by cannabis (11 %) and alcohol (10 %). A slightly different pattern of secondary drugs characterises those with primary problems with misuse of buprenorphine. These people were less likely than the methadone group to report heroin as a secondary drug (20 %). These data suggest that methadone could be primarily misused or develop as a primary problem in the context of an existing heroin dependence. On the other hand, the misuse of buprenorphine may develop into the main opioid problem within an overall highly problematic polydrug use pattern.

Information on the frequency of use indicates that the majority of treatment entrants across these three groups use the primary drug for which they seek treatment on a daily basis, with individuals citing misuse of methadone with the highest daily use (78 %) (Figure 11). Information on the route of administration reflects primarily the form available of each substance (Figure 12). Thus, among treatment entrants with heroin, which is available most commonly in powder form, as the primary problem, 36 % reported injecting as the main route of administration, while 52 % reported inhaling/smoking as the primary route of administration. Nearly all clients seeking treatment for misuse of methadone (93 %) reported drinking the medication as the main route of

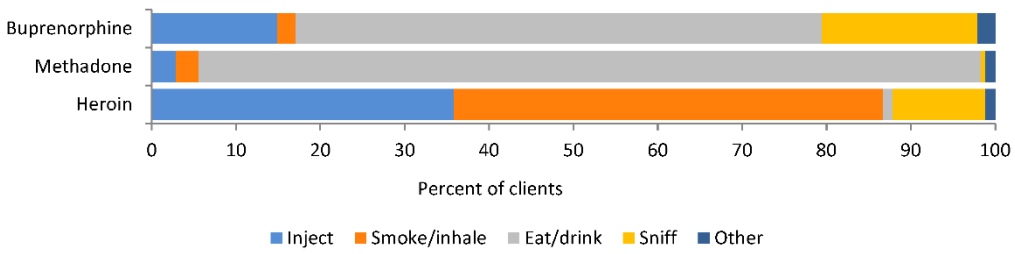
administration — in most Member States, methadone as an OST medication is most commonly available and prescribed in liquid form. In addition, 65 % of treatment entrants reporting misuse of buprenorphine as the primary problem reported eating, swallowing or sublingual administration of buprenorphine, which is available most commonly in tablet form, as the primary route of administration, while 11 % reported sniffing the substance and 20 % reported injecting it. These two latter routes of administration generally involve crushing the tablet into powder. Furthermore, of the total number of treatment entrants in the European Union reporting that they inject buprenorphine, 34 % are reported by Finland alone, where injecting is reported by about 80 % of all clients entering treatment for the misuse of buprenorphine.

Figure 11. Frequency of use of the primary drug among all clients entering treatment for heroin, misuse of methadone or misuse of buprenorphine in the European Union in 2017



Source: EMCDDA (2019f).

Figure 12. Route of administration of the primary drug among all clients entering treatment for heroin, misuse of methadone or misuse of buprenorphine in the European Union in 2017



Source: EMCDDA (2019f).

The misuse of medications, including OST medications, refers to their use outside legitimate therapeutic guidance. It is important to stress that among those that misuse prescription OST medications, there are also individuals who are under therapeutic supervision but, from time to time, use their medication not as intended (or not as prescribed). The misuse of prescribed OST

medication while under therapeutic supervision may include consumption of higher doses than prescribed and injecting or sniffing prescribed take-home medications. Although they are often referred to interchangeably in the literature, a distinction should be made between individuals who misuse diverted prescription OST medications and are not in treatment and those that misuse their prescribed OST medication while under therapeutic supervision.

A German study compared prevalence levels of use of non-prescribed (diverted) OST medications among three groups of high-risk opioid users: (1) a group not in OST and attending drug consumption rooms, (2) a group in legitimate OST and attending drug consumption rooms and (3) a group in OST under therapeutic supervision in a doctor's practice (Schulte et al., 2016). Results showed that recent use of non-prescribed OST medications decreased significantly depending on individuals' treatment status, with prevalence levels of misuse of diverted OST medications in the last 30 days among these three groups as follows: 47 %, 25 % and 3 %, respectively. These results confirm the findings of other studies that have shown that not being in OST remains one of the most important factors of misuse of non-prescribed OST medications.

French survey data from low-threshold centres indicated that 35 % of clients participating in the survey reported having used buprenorphine in the last month and that only 18 % of these obtained it without prescription. In addition, 34 % of clients participating in the survey reported having used methadone in the last month, of whom 20 % obtained it without prescription. Finally, 77 % of those who used buprenorphine and had a prescription reported that they were undergoing treatment under medical supervision. The authors estimated that about 52 % of buprenorphine users (and 7 % of methadone users) misused it at some point while being under medical supervision (Milhet and Cadet-Taïrou, 2017).

3.5. Why do individuals misuse prescribed and non-prescribed opioid substitution treatment medications?

Understanding the underlying motives for the non-medical use of prescription OST medications is crucial for developing adequate responses. European data and national studies show that the large majority of individuals misusing prescribed and/or non-prescribed OST medications in Europe are generally long-term high-risk opioid users with a history of opioid dependence and past treatment experiences. These user characteristics are in line with findings from studies showing that users tend to use OST medications outside therapeutic guidance primarily for self-medication purposes, as a replacement for their drug of choice, while a smaller percentage of individuals tend to use them for euphoric purposes.

The most common reason reported in the literature for misusing OST medications is for the intended therapeutic purpose of OST medications (whether with methadone or buprenorphine). This includes to avoid or ease withdrawals, to maintain abstinence from heroin (self-managed OST) and to try weaning oneself off illicit drugs (Roche et al., 2008; Gwin Mitchell et al., 2009; Schuman-Olivier et al., 2010; Yokell et al., 2011; Lofwall and Walsh, 2014; Richert and Johnson, 2015). A Swedish study investigated buprenorphine misuse among injecting drug users in a survey of 350 attendees of needle and syringe exchange programmes. Among heroin users, 87 % reported having misused buprenorphine in the last year for withdrawal treatment or self-detoxification and 11 % reported having done so for euphoria (Johnson and Richert, 2019).

Similar findings were reported by low-threshold users in France, where 66 % of those who had used buprenorphine in the last month reported doing so for self-therapeutic purposes (to reduce consumption or maintain abstinence), while 13 % reported doing so for euphoria and 8 % to

ease withdrawal. Self-managed OST with diverted OST medications involves regular use of roughly equal amounts of diverted medication taken daily for an extended period with the primary aim to abstain from other opioids, primarily heroin. Such suboptimal treatment practices have been documented in several studies (e.g. Peterson et al., 2010; Schuman-Olivier et al., 2010; Stöver, 2011; Richert and Johnson, 2015).

A recent German study showed that the most frequent motives reported by opioid users for misusing OST medications were insufficient substitution dosage and barriers to accessing OST (Schulte et al., 2016). Thus, patients in OST may acquire diverted medications to supplement legitimately prescribed OST medications in order to eliminate withdrawal symptoms resulting from an inadequate dose. A German multicentre study carried out in 2014 found that 41 % of OST patients experienced inadequate substitution dosage according to the Opiate Adequacy Scale (Reimer et al., 2014). Inadequate or conservative OST dosages (not in line with recommended doses in clinical guidelines) have been documented in a number of European countries and have recently been suggested as one of the factors associated with increases in opioid-related deaths observed in Scotland (House of Commons Scottish Affairs Committee, 2019).

It is well established that prescribing lower doses than clinically recommended (under-prescribing) is not effective in reducing opioid withdrawal symptoms and cravings (WHO, 2009a). Suboptimal prescribing practices may contribute to increasing demand for diverted OST medications among patients to ‘top up’ and achieve effective opioid levels in the body. Prescribing low doses may be the result of doctors’ apprehension to prescribe higher doses to patients suspected of using illicit substances. This becomes a circular problem, as misuse and low doses become both the cause and the consequence of one another. Doctors may be reluctant to prescribe higher doses out of fear of direct harm to the patient, of investigations for malpractice and potentially of legal consequences in the case of serious harm.

Lack of access to OST has also been documented as a driver for the misuse of OST in other European studies. Common barriers to OST include difficulties in accessing treatment (strict admission criteria, limited availability or demanding assessment processes), difficulties in adhering to treatment (involuntary discharge owing to relapsing, frequent urine testing, medical expectations and treatment protocols not in line with individuals’ real-life circumstances) and a reluctance to seek treatment (stigma or fear of disciplinary actions) (Johnson and Richert, 2019).

Economic factors acting as barriers to accessing OST have also been documented as playing a role in the misuse of prescription OST medications. A recent study by Mravcik et al. (2018) on the underlying drivers of large-scale diversion and misuse of buprenorphine in Czechia indicated that most legitimately prescribed buprenorphine in the country is not covered by current national health insurance schemes. Fewer than 300 of the nearly 4 000 patients enrolled in buprenorphine programmes had the cost of their medication reimbursed, while the monthly average cost for the remaining patients at 8 mg/day was estimated to be EUR 70 for Suboxone and EUR 220 for buprenorphine mono-preparations. Considering the legal minimum monthly wage of EUR 370 in Czechia, the authors concluded that the affordability of this treatment, especially at effective therapeutic dosages, constituted a major barrier to accessibility. As a result, large-scale doctor shopping is observed, with the primary aim being to obtain prescriptions of higher amounts in order to re-sell some of the medications on the illicit market at a higher price to finance one’s own medication (Nechanská et al., 2012; Malinovská and Mravčik, 2017).

Economic motives are also reported to play a role in the non-prescribed use of diverted methadone or buprenorphine, when these are available at lower prices than heroin on the illicit market (Jenkinson et al., 2005; Aitken et al., 2008; Schmidt et al., 2013) or when they are used as a replacement for heroin during heroin shortages, namely when heroin prices are high or when it is difficult to access a supplier (Rettig and Yarmolinsky, 1995). In this context, the reason for the misuse of OST medications may be to avoid withdrawal symptoms induced by the absence of heroin or potentially for euphoric purposes. The latter is a less common motive than the former, at least in studies with experienced drug users whose main drug is heroin or other opioids (Roche et al., 2008; Yokell et al., 2011; Schulte et al., 2016), but it may be more common among high-risk users of other substances. A Swedish study on this topic showed that 62 % of primary amphetamine users misusing buprenorphine did so for euphoric purposes, while only 11 % did so among primary heroin users (Hakansson et al., 2007). The misuse of buprenorphine for euphoric purposes may, however, be more common in countries where it has become the predominant illicit opioid, especially among individuals misusing OST medications with no past heroin experience, as reported in Finland (Simojoki and Alho, 2013; Uosukainen et al., 2013).

Different routes of administration can also provide some insight into the motives for use, as well as the availability, of different formulations. Oral administration of methadone and sublingual use of buprenorphine are the most common routes for the administration of these drugs in a self-medication context (Daniulaityte et al., 2012; Harris and Rhodes, 2013; Bretteville-Jensen et al., 2015). Among the reasons for injecting prescription OST medications are the fact that withdrawal symptoms are alleviated more quickly if the drugs are injected and that injecting is the most economic route of administration (less product is required for similar effects). For long-term injectors, the very ritual of injecting can be closely associated with pleasure and can make the habit extremely hard to break, regardless of the motive for misuse (McBride et al., 2001; Horyniak et al., 2007). However, these reasons seem to be connected not to a particular substance, but rather to the injecting culture and customs among high-risk opioid users in certain European regions or cities.

3.6. What is the public health impact of the misuse of prescription opioid substitution treatment medications in Europe?

The public health burden of the diversion and misuse of opioid substitution medications includes an excess of mortality, an increased risk of contracting blood-borne viruses such as HIV and hepatitis C virus, increased somatic complications associated with injecting OST medications, negative impacts on treatment outcomes (associated with poor adherence to recommended treatment), a negative impact on prescribers' practice, and a threat to the reputation of treatment services and compromised public acceptance of OST (Alho et al., 2015; Reimer et al., 2016).

Hospital emergency data can provide an insight into acute drug-related harms and the public health impact of the use of drugs in Europe. Drug-related acute toxicity presentations to 26 (sentinel) hospitals in 18 European countries are monitored by the European Drug Emergencies Network (Euro-DEN Plus; EMCDDA, 2019a). In 2017, the hospitals recorded 7 267 drug-related acute toxicity presentations; heroin was the second most commonly involved drug in presentations after cocaine. Presentations involving methadone (the 11th most common drug) and buprenorphine (the 19th most common drug) represented, respectively, 3 % and 1 % of all presentations. The overall trend for the 14 centres from the eight countries that reported data for 2014-2017 shows a decrease in the number of presentations related to heroin and

buprenorphine, while the number of presentations involving methadone remained stable during this period. The origin and use of the OST medications (misused or not) involved in the hospital presentations is, however, not known.

According to the 2019 European Drug Report, opioids, mainly heroin and its metabolites, are found in the majority of drug-related deaths in Europe (EMCDDA, 2019a). Methadone and to a lesser extent buprenorphine, are among the non-heroin opioids regularly found in toxicological reports. It should be noted that national data submitted to the EMCDDA do not indicate or provide information on the treatment status of the deceased or whether the role of the OST medication in the death was causal, contributing or independent. In 2017, there was mention of methadone in 17 % of all overdose deaths in 13 countries that reported a breakdown by substance. In some countries, methadone was present in a substantial number of overdose deaths, often in combination with other drugs. The percentage of overdose deaths mentioning methadone in 2017 reached 66 % in Romania, 42 % in Portugal, 38 % in Luxembourg, 37 % in France, 32 % in Latvia, 22 % in Lithuania, 15 % in Hungary and below 15 % in the remaining countries. Data provided to the EMCDDA on drug-related deaths from six major Spanish cities in 2016 indicated that methadone was mentioned in 30 % of all drug-related fatalities in these six cities.

In 2017, buprenorphine was mentioned among all drug-related fatalities reported to the EMCDDA in only four countries: Finland (55 %), France (8 %), Germany (2 %) and Austria (1 %). Comparison with the 2010/11 data in these same countries shows little change. Buprenorphine was mentioned among all drug-related deaths in 2010/11 in Finland in 54 % of cases, in 3 % of cases in France and in 1 % of cases in both Germany and Austria. However, there are a number of challenges in interpreting drug-related deaths data mentioning prescription OST medications (Box 3). One of the main challenges is related to the lack of information regarding the origin and usage of the OST medication (i.e. whether it was misused or not) detected in the post mortem toxicology report.

Box 3. Main challenges in interpreting drug-related deaths data mentioning prescription OST medications (Rettig and Yarmolinsky, 1995)

There are three main caveats when using mentions of prescription OST medications in drug-related deaths data (as well in emergency data) to infer the extent of the diversion or misuse problems in a country, and more so at the European level.

First, with typical maintenance dosing, methadone has a half-life of about 24 hours. As with all opioids, toxicity is thought to be the result of respiratory depression due to decreased sensitivity of the brain's respiratory centre to the stimulatory effect of carbon dioxide. There is, however, no clear definition of what constitutes a toxic or fatal blood methadone level. One reason for the difficulty of determining a toxic blood methadone level is drug interaction. A given blood methadone level may or may not be toxic depending on the presence of other drugs, which may augment or counteract any toxic effects of methadone.

Another factor that complicates establishing a toxic methadone level is individual variability in susceptibility to methadone's effects. Opioid tolerance is a major determinant of this variability. As opioid users develop tolerance, they need progressively higher doses to achieve the desired effect. The rate at which tolerance develops depends in part on the pattern of use. Some patients who are highly tolerant to methadone suffer no toxic effects at blood methadone levels that would be toxic to a person lacking tolerance. Therefore, because of the phenomena of drug interactions and tolerance, considerable overlap exists between therapeutic and toxic blood methadone levels.

Finally, the number of deaths in which methadone has been detected in the body is a direct function of the number of people who are enrolled in methadone or buprenorphine treatment. As the number of methadone patients increases, so will the number of deaths in which methadone is detected. If all heroin users were enrolled in methadone and other types of treatment programmes and if these treatment programmes were successful in greatly reducing, if not eliminating, heroin use, then long-acting methadone would be detected in virtually all deaths involving opioid (Wright, 1992).

The sharp increase in methadone-related deaths in France may be an illustration of this phenomenon. Between 2008 and 2017 in France, the percentage of deaths involving methadone increased from 29 % to 37 % of all drug-related deaths, exceeding the greatest percentage of heroin-related deaths since 2010. However, the number of clients enrolled in methadone maintenance treatment increased two-fold during the same period, from 37 000 in 2008 to 74 000 clients in 2017. This is why any sophisticated analysis of methadone's involvement in drug-related deaths (or in emergency room mentions) should include the treatment status of the deceased and a clinical assessment of whether the presence of methadone in the deceased was causal, contributing or independent.

3.7. What are the treatment options for people who seek treatment for the misuse of opioid substitution treatment medications?

Although the scientific literature is limited, it recommends that individuals with a history of misuse of OST outside therapeutic guidance be encouraged to access treatment and be provided OST as the first-line treatment (e.g. Clinical Guidelines on Drug Misuse and

Dependence Update 2017 Independent Expert Working Group, 2017). The main difficulty for patients who are using non-prescribed OST medications is that it is not possible for doctors to accurately predict equivalent therapeutic doses in most cases at the start of treatment. This is especially true for street methadone or buprenorphine, as the purity is variable, or when past dosages are unknown. It is also problematic to convert the dosage from one medication to another when the half-lives are not equivalent (e.g. between methadone and buprenorphine). Clinicians must therefore apply careful clinical judgement and monitor the progress of treatment carefully, especially during the early stages of treatment. The initial OST dose should aim to achieve an effective level of comfort, both physical and psychological, while minimising the likelihood of overdose.

4. Prevention of diversion of opioid substitution treatment medications

OST medications such as methadone and buprenorphine are controlled drugs for medical (and scientific uses) and can be obtained only by prescription from a doctor. Depending on the country, specialised doctors (e.g. psychiatrists or accredited medical doctors) or non-specialised doctors (e.g. general practitioners) can prescribe these medications (for an overview, see EMCDDA, 2019b). These controlled medications are subject to strict record keeping and storage in pharmacies, either at community pharmacies or at OST treatment centres. Despite these precautions, the diversion of prescription OST medications for non-medical use remains a common problem in Europe.

European countries have implemented a number of strategies at the national level to control and prevent the diversion of OST medications (EMCDDA, 2016). These include providing training for clinicians and patients, implementing strategies to assure therapeutic compliance by appropriate prescription of dosing, the use of electronic medicine dispensers and employing control measures such as patient toxicology tests, pill counts and unannounced monitoring. Monitoring of prescribing practices can take place through registers of patients and/or pharmacy transactions and the enforcement of appropriate prescribing through disciplinary measures or administrative sanctions. Other control measures include legal restrictions on the medical professions and clinical settings and dispensaries of pharmaceuticals that are allowed to prescribe and/or dispense OST medications, pre-authorisation procedures, the use of special prescribing forms and regulations stipulating that administration of doses must be under direct supervision in specialised treatment centres or pharmacies.

One strategy to prevent the diversion of OST medications is to register patients receiving OST and, in some countries, one central register records all patients at the national level. This has a number of advantages, as it prevents patients from receiving methadone, buprenorphine or other OST medications from more than one source. It can be used to limit access to other controlled medicines requiring central approval, such as other opioids, and it can provide more accurate data on treatment numbers than would be available in situations in which central registration is not used. A potential disadvantage, however, of the central registration of patients is that it can risk breaches of privacy, and this may deter some patients from entering treatment. According to WHO guidelines, safe and effective treatment of opioid dependence can be achieved without central registration. Because such registration could cause harm if privacy is breached, it should be used only if government agencies have effective systems for maintaining privacy and personal data security. In addition, in most Member States, especially in eastern European countries, medical doctors have to use special prescription forms, often in multiple copies, to inform the central registration system. These forms are not always free of charge, and

complex reporting requirements can be applicable to medical doctors authorised to prescribe, which was reported to delay the commencement of treatment and deter practitioners from engaging in OST prescribing (Vranken et al., 2014, Radbruch et al., 2012).

According to information provided by the Reitox national focal points to the EMCDDA, the majority of Member States and Norway (22 countries) have one specific registry recording OST patients. Six Member States have two registers in which OST patient data are recorded, while the Netherlands has three registers. These registers are often maintained by national health departments or institutes or at national medicines agencies. In 11 countries, OST patient data are recorded as part of the general national drug treatment monitoring register, which is where, for example, data on treatment demands for all patients entering drug treatment are recorded. In four countries, a data flow exists between the OST register and other drug treatment monitoring databases as a result of the existence of unique client identification codes, which allows the merging of the databases. In seven countries, there is no flow of data between databases owing to the absence of unique identifiers.

4.1. The need for country-specific anti-diversion measures

While European countries may have some commonalities, certain patterns of use, motives, and drivers for misuse or diversion appear to be country specific. For example, in some countries where access to the treatment is limited, OST medications are mentioned in relatively high numbers of drug-related deaths or seized in significant quantities by law enforcement agencies. Large-scale OST provision and low-threshold OST programmes are therefore unlikely to be the main drivers of diversion and misuse in these countries. On the other hand, the diversion and misuse of these medications may be facilitated by high OST accessibility or liberal therapeutic supervision and limited prescribing monitoring in other countries.

As a consequence, ‘one size fits all’ recommendations and policies to prevent diversion and reduce the levels of misuse will most likely be ineffective in addressing specific national causes of the observed problems. In each country, the design and implementation of such measures will present difficult trade-offs, as the advantages of offering easily accessible, effective and user-customised treatment for a large group of individuals must be weighed against the negative effects of diversion. The fact that the end users on the illicit market mainly consist of opiate- or opioid-dependent individuals, many of whom appear to be using these substances for self-medication purposes and are generally out of treatment, needs to be taken into account in those trade-offs.

The current literature on responses to the misuse and diversion of OST medications focuses primarily on improving treatment quality (e.g. optimal dosing), the supervision of patients (urine testing, supervised dispensing), monitoring prescribing practices to prevent doctor shopping and improving the availability of abuse-deterrent formulations such as the buprenorphine-naloxone combination (Reimer et al., 2016; Wright et al., 2016). It should be noted that most of the literature on anti-diversion measures originates from countries with long-established and highly available OST programmes. Therefore, these anti-diversion measures assume that a majority of high-risk opioid users are effectively accessing OST. The data presented in this report show that in nearly half of the Member States for which data are available (8 out of 18), the coverage levels of OST remain below 50 % of the target population. In a number of countries, primarily eastern EU countries, coverage levels are even below 20 % of the target population.

4.2. Would stricter anti-diversion policies and higher thresholds for opioid substitution treatment be effective?

Stricter anti-diversion policies may seem an intuitive choice when facing domestic diversion or misuse of non-prescribed OST medications. However, increased control of treatment procedures and prescribing modalities in low-coverage countries runs the risk of further limiting access to OST or deterring users from accessing this treatment. Such measures may subsequently result in unintended consequences, namely further fuelling demand on the illicit market for non-prescribed OST medications or other opioids. In contrast, policies that aim to increase availability and facilitate access by removing structural barriers linked to legal prescribing requirements, increased affordability, geographical coverage and easing contractual treatment obligations of OST patients may prove, in some instances, to be a more effective solution (Pompidou Group, 2017). Such policies should address high-threshold inclusion criteria; long waiting times; arduous and bureaucratic admission processes; negative attitudes towards OST by the public, users and professionals; fear of stigmatisation and disciplinary actions — which all constitute further barriers to seeking OST. Increasing access to attractive OST programmes as an anti-diversion strategy in some countries could encourage out-of-treatment users of non-prescribed OST medications to engage with legitimate therapeutic processes and thereby improve overall treatment quality and outcomes and reduce harms and demand associated with non-prescribed OST on the black market.

In medium- to high-OST coverage countries, which are characterised by high availability and accessibility to treatment and where domestic diversion and trafficking are problematic, the policies described in the literature that aim for greater scrutiny of prescribing practices and improved treatment adherence may be more appropriate. The French National Health Accreditation and Assessment Agency has issued recommendations for prescribers and dispensers on a range of factors associated with the diversion and misuse of OST in the country. These recommendations address prescribing and dispensing modalities, the assessment of patients' motivations, the monitoring of prescriptions, and initial and continuous training of health professionals (Milhet and Cadet-Taïrou, 2017).

4.3. The role of the criminal justice system

The criminal justice system and law enforcement agencies, in collaboration with health authorities and stakeholders, can also play an important role in the prevention of diversion and in the reduction of misuse of prescription OST medications. Illegal possession of controlled medications without proper prescription constitutes an offence in European countries, with legal and financial consequences. Individuals caught with diverted prescription OST medications with the intent to use them may benefit from proactive referral to treatment that would support efforts to engage individuals in the legitimate treatment system. Coordinated law enforcement operations can also be beneficial in reducing cross-border trafficking between Member States, especially from high- to low-OST coverage countries. In December 2017, a Europol-supported operation dismantled a trafficking ring that was smuggling high-dose buprenorphine tablets from France to Finland in significant quantities (EMCDDA and Europol, 2019).

It is, however, important to understand that illicit methadone and buprenorphine markets rely on a highly controlled system, in which substances are produced and commercialised by pharmaceutical companies, prescribed by medical doctors and distributed by pharmacies. In contrast with international and domestic markets trafficking illicit drugs, illicit methadone and buprenorphine markets are more decentralised and unorganised, with many small actors selling

or distributing smaller quantities of medications that generally they have themselves been prescribed (Fountain et al., 2000; Fountain and Strang, 2003; Cicero and Inciardi, 2005; Mravcik et al., 2018). These are comparatively closed systems of current opioid users and patients undergoing OST (Spunt et al., 1986; Johnson and Richert, 2015). Small quantities of OST medications are re-sold or handed over for free between family members, friends and acquaintances with similar drug experiences (Johnson and Richert, 2015). Among some groups of high-risk opioid users, it may be considered morally right to share one's medication with those who do not have access to OST programmes and are at risk of experiencing withdrawal symptoms (Havnes et al., 2013). Effective anti-diversion policies will necessarily require an understanding of these morally driven transactions at the local level.

5. Discussion

European countries have experienced unprecedented health and social consequences of increasing heroin use and drug injecting that emerged in the 1980s, in particular rising HIV/AIDS and overdose deaths, as well as crime and open drug scenes. Today, remarkable improvements have been documented in many countries, where comprehensive drug policies incorporating scaled-up OST programmes with methadone and buprenorphine have been implemented (Hedrich and Pirona, 2017). Substantial progress has been made towards the elimination of new HIV infections among people who inject drugs, and high availability of OST has been instrumental in this achievement. Across the European Union, which in 2017 had over 500 million citizens, just 1 046 newly reported HIV cases were attributed to drug injecting. In many cities, crime and public order problems related to drug use have also diminished substantially. OST has been a contributing factor in reducing the social cost of heroin use and improving the life expectancy of heroin users, and we are now observing ageing cohorts in their 40s and 50s while, at the same time, the number of younger heroin-naive users is at an all-time low. These data provide some reassurance that Europe is currently not facing a similar opioid crisis as that recently observed in the United States.

At the same time, the use of and harms associated with opioids other than heroin, primarily among experienced and older high-risk opioid users, are providing cause for concern. Signals from law enforcement agencies and health data indicate growing issues with tramadol and fentanyl and fentanyl derivatives, while data presented here reveal that the scale of domestic diversion and misuse of prescription OST medications is not negligible in several countries.

5.1. Addressing harms

Currently, methadone remains the predominant medication prescribed for OST in two thirds of the EU Member States. It is therefore also the one most commonly mentioned among opioid-related deaths involving OST medications. WHO guidance recommends that different opioid substitution medications be made available for treatment. Increasing the range of available buprenorphine-based OST medications, including the abuse-deterrent combination buprenorphine-naloxone, could reduce the risk of mortality associated with non-prescribed methadone. As a partial agonist, buprenorphine-based medications present a safer toxicological profile than methadone, which is a full agonist and increases the risk of overdose when used outside therapeutic guidance. A recent study in the United Kingdom examined the population-wide overdose risk emerging from the prescription of methadone and buprenorphine for OST in England and Wales (Marteau et al., 2015). This analysis of the relative safety of buprenorphine and methadone for OST revealed that buprenorphine was six times safer than methadone with regard to the overdose risk among the general population.

Unfortunately, the number of recent national studies on the nature and the health consequences of the misuse of prescription OST medications in Europe remains limited. Further national studies are necessary to gain a better understanding of the adverse consequences within a national context. In addition, it would be of particular interest to investigate which factors or determinants other than the pharmacological properties of the medication can explain the observed differences in terms of drug-related deaths involving OST medications between countries with large-scale misuse of buprenorphine medications, such as Finland (high mortality) and France and Czechia (low mortality). Study results could provide valuable information to develop tailored harm reduction responses (Box 4).

Box 4. Similar problem, different outcomes: the cases of Czechia and Finland

The scale of diversion and misuse of OST medications becomes particularly worrying when it reaches levels at which prescription OST medications become the drug of choice among the majority of high-risk opioid users in a country. In Finland, for example, a decrease in heroin supply resulted in a significant increase in diverted buprenorphine supply between 2000 and 2004, which resulted in a sharp decrease in heroin-related deaths and an increase in death rates associated with the misuse of diverted prescription buprenorphine during the same period (Simojoki and Alho, 2013). That study showed that the use of diverted prescription buprenorphine was, for a large proportion of current Finnish high-risk opioid users, their first opioid experience. During the same time period, a decreasing rate of opioid-induced mortality was observed in Czechia when a significant shift occurred on the illicit market from heroin to diverted buprenorphine. Surprisingly, no fatalities associated with buprenorphine have been recorded in Czechia despite similar large-scale buprenorphine injecting among high-risk opioid users (Mravcik et al., 2018). These contrasting phenomena point to buprenorphine-related deaths being less of a function of the pharmacological properties of the medication and more a result of a variety of contextual factors. Social and drug-related contextual factors characterising the high-risk opioid user population in a country may include the extent and severity of polydrug use, especially involving alcohol and benzodiazepines, and the role of buprenorphine within this polydrug use pattern (Rönkä et al., 2015; Rönkä and Katainen, 2017). Users' age, levels of marginalisation, the duration of their experience with opioids and their motives for using non-prescribed buprenorphine are some of the factors to be investigated to understand and interpret the observed differences in fatalities between these two countries.

5.2. Implications for monitoring

There are a range of implications for monitoring highlighted in this report. Monitoring of the diversion and misuse of pharmaceutical products, including prescription OST medications, remains a challenge owing to the large number of actors involved. These include the European and national medicines regulatory agencies; the producers, prescribers and retailers (e.g. pharmacies) of a legitimate pharmaceutical product; and reimbursement agencies. Access to commercial and medical data from the private sector is particularly difficult. In addition, the EU-wide pharmacovigilance system coordinated by the European Medicines Agency does not cover the monitoring of diversion or misuse of medications; its primary role is to monitor adverse effects or other medicine-related problems. Current indicators of drug epidemiology, such as the treatment demand indicator and drug-related deaths data, provide some insight into the extent

of misuse of these products, while law enforcement agency data on drugs seizures provide information on trafficking and diversion at the wholesale and retail levels.

To gain a more accurate understanding of the nature of and relationship between access to OST and the misuse and diversion of OST medications, current epidemiological tools require fine tuning, while their limitations must be acknowledged. For example, the source of the OST medication reported to be misused by clients entering treatment would be useful information to understand the provenance of the medication. This information would allow an understanding to be gained of whether the misuse involved legitimately prescribed OST medications or diverted OST medications. In addition, the duration of the problematic use of OST medications would provide useful information on the nature of the dependence associated with the misuse of these medications.

In relation to drug-related deaths data, two main pieces of information would clarify the role and risks of non-prescribed OST medications. First, a clear definition would be needed about the main cause of death when prescription OST medications are detected in the post mortem toxicology, and it would need to be determined if the fatality could be attributed solely to the medication, if the medication was a contributing factor or if it was not implicated. Second, information on the treatment status of the deceased should be provided. These are important pieces of information that would clarify whether, when there are 'mentions of OST medications' in reported fatalities (or in emergency room mentions), the clients were in or out of treatment at the moment of death. This information would also clarify whether changes in the number of 'mentions' of OST medications in opioid-related deaths are associated with growing diversion and misuse in the country or are a direct function of the number of people who are enrolled in legitimate OST. As mentioned earlier, as the number of patients in OST increases, so will the number of deaths in which prescribed OST medications are detected. Linkages between databases, like in Ireland, namely between the mortality register and the central OST register, can provide an indication of whether the deceased was prescribed the medication or whether it originated from diversion.

Improvements in national and European instruments and mechanisms for monitoring the diversion and misuse of pharmaceutical products, including prescription OST medications, are therefore paramount for developing effective anti-diversion policies.

6. Conclusion

The consequences of the diversion and misuse of prescription OST medications are a continuing public health concern and require heightened vigilance in light of the recent opioid epidemics in the United States. Another important concern presented here is the continued, and likely increased, involvement of OST medications in drug-related deaths in some countries. However, there is also a need to maintain focus on the importance of OST as an effective treatment option. In this context, encouraging the implementation of and adherence to evidence-based guidance, such as WHO policy guidelines, will contribute to the prevention of diversion without hindering access for legitimate patients.

It is also important that any policies and responses are in line with international conventions and treaties emphasising human rights and the right to health in the field of opioid dependence treatment. The international guiding principles for legislation and regulation of opioid agonist treatment (Pompidou Group, 2017) highlight that, from a normative point of view, anyone with a diagnosis of dependence syndrome must have access to treatment based on the latest scientific and medical knowledge, that obligations for physicians should be limited to what is strictly

necessary and proportionate to ensure the effectiveness of the treatment and its security to third parties, and that authorities should ensure that treatment is paid for and that healthcare professionals are duly remunerated.

The implementation of effective anti-diversion strategies while maintaining adequate access to effective treatment requires accurate evaluation of the individual and systemic determinants of the phenomenon in each country. Importantly, some European countries still need to improve access to OST to those in need in order to achieve adequate coverage levels. The development of responses should include all stakeholders involved in the provision of OST and in the prevention of diversion and misuse, as well as patients, with the ultimate goal of reducing the harmful use of opioids, improving overall access to and the quality of OST, and reducing drug-related deaths.

Glossary

Accessibility: the degree to which a medicine is obtainable for those who need it at the moment of need with the least possible regulatory, social or psychological barriers.

Affordability: the degree to which a medicine is obtainable for those who need it at the moment of need at a cost that does not expose them to a risk of serious negative consequences, such as not being able to satisfy other basic human needs.

Availability: the degree to which a medicine is present at distribution points in a defined area for the population living in that area at the moment of need.

Benzodiazepine: a class of drugs that have a hypnotic and sedative action; they are prescribed mainly as tranquillisers to control symptoms of anxiety, but are also used for recreational purposes.

Controlled medicines: medicines containing controlled substances, namely the substances listed in the international drug control conventions.

Diacetylmorphine (the principal psychoactive constituent of heroin): a short-acting opiate agonist. Illicit (‘street’) heroin may be smoked or solubilised with a weak acid and injected.

Diversion: the act of redirecting a prescription medication (e.g. an OST medication) from legitimate sources to illegitimate or illegal sources.

Doctor shopping: the practice of visiting multiple physicians to obtain multiple prescriptions.

Essential medicines: those medicines that are listed in the *World Health Organization model list of essential medicines*. This list presents a list of minimum medicine needs for a basic healthcare system, listing the most efficacious, safe and cost-effective medicines for priority conditions.

Misuse of medications (including OST medications): the use medications outside legitimate therapeutic guidance.

Morphine: a naturally occurring alkaloid extracted from opium; it is a powerful narcotic substance with a strong analgesic (painkilling) action and it has other significant effects on the central nervous system.

Opiate: one of a group of alkaloids derived from the opium poppy (*Papaver somniferum*) with the ability to induce analgesia, euphoria and, in higher doses, respiratory depression and coma. The term excludes synthetic opioids.

Opioid: a generic term applied to alkaloids from the opium poppy (*Papaver somniferum*), their synthetic analogues and compounds synthesised in the body that interact with specific receptors in the brain and have the ability to induce analgesia, euphoria (a sense of well-being) and, in higher doses, respiratory depression and coma.

Opioid agonist: any morphine-like substance that produces effects that mimic the action of the naturally occurring substance, including pain relief and respiratory depression.

Opioid antagonist: a substance (e.g. naloxone and naltrexone) that blocks mu, kappa or delta opioid receptors, used primarily in the treatment of opioid-induced respiratory depression.

Opioid substitution treatment (maintenance treatment): a treatment for opioid dependence that uses relatively stable doses of long-acting opioid agonists (usually methadone or buprenorphine) prescribed over prolonged periods of time (usually more than 6 months), which stabilises brain functions and prevents craving and withdrawal.

Overdose: an accidental or intentional use of any drug in an amount that produces acute adverse physical or mental reactions — transient or lasting — or death; the lethal dose of a particular drug varies depending on the individual and the circumstances.

Prescribed opioid medications (e.g. methadone and buprenorphine): medications that are prescribed by a licensed physician to a patient and dispensed by a pharmacy.

Prescription (or prescribable) opioids: opioid medications that are intended to be prescribed as medicines and that can be diverted anywhere in the system without necessarily being prescribed.

Withdrawal syndrome: the occurrence of a complex syndrome of uncomfortable symptoms or physiological changes caused by an abrupt discontinuation or a dosage decrease after repeated administration of a pharmacological agent. Withdrawal syndrome can also be caused by the administration of an antagonist.

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Appendix

Table A1. Year of introduction of opioid substitution treatment medications in the European Union

Country	Methadone	High-dosage buprenorphine	Buprenorphine -naloxone combination	Diacetylmorphine (including pilots)	Slow-release oral morphine
Austria	1987	1998	2008	NA	1998
Belgium	1994	2003	2008	2011	NA
Bulgaria	1996	NA	(2008)	NA	2006
Croatia	1991	2004	2009	NA	NA
Cyprus	NA	2007	2008	NA	NA
Czechia	1998	2000	2008	NA	NA
Denmark	1970	1999	NA	2008	NA
Estonia	2001	(2003)	NA	NA	NA
Finland	1974	1997	2004	NA	NA
France	1995	1996	2012	NA	NA
Germany	1992	2000	2007	2003	2015
Greece	1993	2002	2006	NA	NA
Hungary	1995	NA	2007	NA	NA
Ireland	1992	(2002)	(2006)	NA	NA
Italy	1975	1999	2007	NA	NA
Latvia	1996	2005	NA	NA	NA
Lithuania	1995	2002	NA	NA	NA
Luxembourg	1989	2002	NA	NA	2006
Malta	1987	2006	NA	NA	NA
Netherlands	1968	1999	NA	1998	NA
Poland	1992	2014	2008	NA	NA
Portugal	1977	1999	NA	NA	NA
Romania	1998	(2007)	2008	NA	NA
Slovakia	1997	(1999)	2008	NA	2005
Slovenia	1990	2005	2007	NA	2005
Spain	1990	(1996)	NA	2003	NA
Sweden	1967	1999	NA	NA	NA
United Kingdom	1968	1999	2006	1920s	NA

Note: Years in brackets indicate that the treatment substance was legally available in the country but there were no reported clients. NA stands for 'not applicable'.
Source: EMCDDA (2019c, dataset: opioid substitution treatment — year of introduction — OST).

Table A2. Total number of clients in opioid substitution treatment in European countries (1993-2017)

Country	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2006	2007
Austria	18632	18222	17599	17272	16989	16892	16782	15798	14202	11551	8656	10503
Belgium	16546	16560	16681	17026	17482	17351	17701	17622	16317	–	–	–
Bulgaria	3247	3338	3423	3404	3568	3445	3452	3012	2930	2315	1124	1378
Croatia	4792	4256	5061	5180	5238	5311	5127	5035	3812	2296	1951	2016
Cyprus	209	229	252	178	180	239	290	294	286	50	–	71
Czechia	5000	5000	4000	4000	4000	4000	4500	4500	4300	4000	3700	3800
Denmark	–	–	7050	–	–	–	–	7515	7384	7418	6012	7327
Estonia	1186	1248	1116	919	1166	1157	1076	1064	1012	1008	–	1044
Finland	–	–	3329	3000	–	–	2439	–	1800	1500	1000	1200
France	178665	178560	167571	163922	165597	162406	160096	155944	150363	139945	124069	131607
Germany	78800	78500	77200	77500	77300	75400	76200	77400	74600	72200	64500	68800
Greece	9388	9974	10201	10277	9973	9878	6783	6264	5360	5045	3950	–
Hungary	–	–	669	745	786	672	715	1031	992	802	–	807
Ireland	10316	10087	9917	9764	9640	9419	9243	9266	9047	8718	8089	8429
Italy	69642	62868	60047	75964	94376	97312	98636	103564	98493	93059	91503	95973
Latvia	669	647	609	518	424	355	277	237	189	164	100	134
Lithuania	1136	1231	1393	1036	592	452	513	676	562	512	381	395
Luxembourg	1142	1085	1078	1121	1126	1254	1128	1248	1212	1050	1044	1092
Malta	1025	1030	1026	1013	1078	1094	1107	977	977	1046	1094	1087
Netherlands	–	–	5241	7421	8292	9148	10017	10147	9918	8592	9818	8968
Norway	7622	7554	7445	7433	7055	7038	6640	6015	5383	4913	4166	4542
Poland	2685	2601	2564	2586	2455	2213	2181	2129	1951	1525	1221	1230
Portugal	16888	16368	17011	16587	16858	24027	–	29325	28708	–	–	24312
Romania	1530	1480	1268	1457	953	851	857	555	323	60	–	639
Slovakia	620	642	600	660	408	459	484	610	700	600	534	500
Slovenia	–	3042	3261	3190	3282	3427	3490	3526	3324	3332	2689	2957
Spain	–	58749	59264	61859	61954	69111	76263	82372	77811	81390	78503	81706
Sweden	4468	4136	3679	3502	3425	3697	3708	3574	3454	3150	2600	2898
Turkey	–	–	–	–	–	–	12500	2067	–	–	–	–
United Kingdom	149420	152823	142484	146327	148139	149000	152412	155801	150511	142322	116684	129680

Table A2 (continued)

Country	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995	1994	1993
Austria	8656	7585	6594	5718	4883	4303	3892	3311	–	–	–	–	–	–
Belgium	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Bulgaria	1124	920	670	380	–	–	–	–	–	–	–	–	–	–
Croatia	1951	995	2944	1743	–	–	–	–	–	–	–	–	–	–
Cyprus	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Czechia	3700	3200	2700	1800	900	440	210	100	20	0	0	0	0	50
Denmark	6012	6589	5887	5630	3378	2656	1919	1062	764	505	284	–	–	–
Estonia	–	500	253	60	–	–	–	–	–	–	–	–	–	–
Finland	1000	–	725	550	425	225	150	–	–	–	–	–	–	–
France	124069	116143	102005	–	–	–	–	–	–	–	–	–	–	–
Germany	64500	61000	57700	52700	46000	–	–	–	–	–	–	–	–	–
Greece	3950	3596	3336	2293	1616	1146	1120	966	666	304	400	0	0	0
Hungary	–	766	–	750	–	–	–	–	–	–	–	–	–	–
Ireland	8089	7756	7270	6852	6609	5930	5039	4354	3689	–	–	–	–	–
Italy	91503	83109	81277	84211	87796	83472	83873	80740	77776	74776	69618	66444	55161	47762
Latvia	100	91	54	67	–	88	107	90	94	100	–	0	0	0
Lithuania	381	402	436	332	322	344	322	–	–	–	–	–	–	–
Luxembourg	1044	1084	1065	1056	1040		1002		989	–	–	–	–	–
Malta	1094	968	807	733	–	–	–	–	–	–	–	–	–	–
Netherlands	9818	10416	10199	9924	–	–	–	–	–	–	–	–	–	–
Norway	4166	3614	3003	2431	1984	1503	1074	719	204	–	–	–	–	–
Poland	1221	750	–	700	1000	–	–	–	–	–	–	–	–	–
Portugal	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Romania	–	570	–	400	–	–	–	–	–	–	–	–	–	–
Slovakia	534	525	448	457	519	443	292	171	154	19	–	–	–	–
Slovenia	2689	2401	2128	1814	1559	1347	1348	1198	1034	926	–	–	–	–
Spain	78503	83374	86017	88700	90488	84731	78806	72236	63030	55813	42230	28806	18027	15398
Sweden	2600	–	858	796	750	716	636	599	581	514	480	460	432	424
Turkey	–	–	–	–	–	–	–	–	–	–	–	–	–	–
United Kingdom	116684	99149	–	–	–	–	–	–	–	–	–	–	–	–

Source: EMCDDA (2019c, dataset: opioid substitution treatment — clients — all clients).
Note that '–' corresponds to 'no information available' and '0' to 'no clients reported'.
Czechia: until 2006, the estimates were based on the distributed volume of buprenorphine and average daily dose (3 mg) plus methadone clients in specialised centres. Later, the estimates are based on surveys among general practitioners and newly implemented annual aggregated reporting for general practitioners and psychiatrists.
Germany: the data refer to clients in OST on a given day.
Estonia: the data on clients in OST are estimated.
France: the data on clients in OST are estimated based on the number in OST in prison (estimate), in OST on health insurance (estimate based on registry data) and in treatment centres (Centres de soins, d'accompagnement et de prévention en addictologie, registry data).
Italy: the data on clients in OST before 2014 are estimated, so caution should be made when interpreting trends in OST clients in Italy.
Latvia: point prevalence data (on 31 December of the respective year).
Lithuania: the data before 2014 are not comparable with data from more recent years.
Hungary: the methodology of OST data collection changed from 2010 to 2011.

Netherlands: the data for 2015 are incomplete.
Slovakia: the data on clients in OST are estimated.
Finland: the data on clients in OST are estimated.
Norway: the data on clients in OST are estimated.
United Kingdom: all data are for England and Wales.

Table A3. Total number of clients entering treatment for opioid-related problems in 2017 in European countries

Country	Year of treatment	All opioids	Heroin	Methadone	Buprenorphine	Fentanyl	Other opioids
Austria	2017	1 793	1 455	41	57	0	240
Belgium ([1])	2017	2 493	2 082	129	19	12	144
Bulgaria	2017	1 136	966	151	0	1	18
Croatia ([2])	2017	5 773	5 292	169	254	1	57
Cyprus	2017	212	114	–	1	–	97
Czechia	2017	799	443	32	175	9	140
Denmark	2017	587	241	113	27	–	206
Estonia	2016	271	10	29		226	6
Finland ([4])	2017	363	6	7	300	0	50
France	2017	12 899	8 674	1 049	1 263	66	1 847
Germany	2017	16 177	–	–	–	–	–
Greece	2017	2 593	2 342	4	112	0	135
Hungary ([3])	2017	192	154	12	0	0	26
Ireland	2017	3 837	3 241	88	1	2	505
Italy	2017	20 095	19 265	286	82		462
Latvia	2017	399	300	12	14	16	57
Lithuania	2017	1 448	1 334	68	9	0	37
Luxembourg	2017	109	104	5			
Malta	2017	1 274	1 274	–	–	–	–
Netherlands	2015	1 262	949	139	2	1	171
Norway	2017	973	–	–	–	–	–
Poland	2017	1 122	831	27	16	13	235
Portugal	2017	1 247	1 177	14	10		46
Romania	2017	918	865	25	0	0	28
Slovakia	2017	760	607	2	3	13	135
Slovenia	2017	211	183	4	17	1	6
Spain	2016	12 235	10 807	509	18	70	831
Sweden ([5])	2017	9 387	–	–	–	–	–
Turkey	2017	6 817	6 738	3	31	5	40
United Kingdom	2017	57 430	48 360	2 235	2 505	63	4 267

Note that '–' corresponds to 'no information available' and '0' to 'no clients reported'.
([1]) In the Belgian protocol, there is the possibility to choose an 'Unknown' category if the specific substance is not known; therefore, the number of clients for the category 'All opioids' is not equal to the sum of the specific substances.
([2]) All clients **in** treatment are considered for the data for all clients **entering** treatment; therefore, caution should be made when comparing Croatia with other countries for all clients entering treatment.

([3]) The data are in line with treatment demand indicator protocol 2.0. A new treatment demand indicator protocol was published in 2013, namely treatment demand indicator 3.0. For more information, see EMCDDA (undated).
([4]) Coverage of the Finnish Drug Treatment Information System is low. Reporting is voluntary for treatment units. There is no overall register of treatment units; therefore, the coverage is unknown.
([5]) The data for clients entering treatment refer only to hospital-based and specialised outpatient care facilities.