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OPIOIDS (D FIELLIN AND J DONROE, SECTION EDITORS)

Current Opioid Access, Use, and Problems in Central and Western European Jurisdictions

Daniel Fuster[1] · Roberto Muga[1] · Olivier Simon[2] · Nicolas Bertholet[3]

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Abstract

Purpose of the Review To provide recent data on opioid use in Central and Western Europe and available treatments, with focus on Spain and Switzerland.

Recent Findings The prevalence of opioid use in Europe is around 0.4%, which represents 1.3 million individuals. Heroin use remains the main reason for treatment among patients with an opioid use disorder (> 80%). Opioid agonist treatment (OAT) is generally available, with methadone and buprenorphine being the most often used treatments. In some European countries, pharmaceutical heroin (diacetylmorphine, DAM) is also available as an OAT option.

Summary The prevalence of opioid use disorder is decreasing in Western Europe and OAT is widely available. Heroin remains the opioid of most concern but changes in the prevalence of use of other opioids should be closely monitored.

Keywords Opioids · Substance abuse · Heroin · Addiction

Introduction

Substance use is widespread throughout the world and is a major risk factor for disability and premature loss of life [1]. Tobacco and alcohol use, the two most prevalent substances, make larger contributions to disease burden than other substances, but opioids also carry a sizable impact on health [2]. Different countries are facing different challenges and consequences of opioid use. Currently, there are major differences between the USA and European situations [2], and clinicians and policy makers must take into account these differences when interpreting the international literature. The prevalence of illicit opioid use in Eastern Europe (0.85%) is more than double the prevalence of Western and Central Europe (0.37%) [2]. Comparatively, in North America, the prevalence of illicit opioid use is 0.47%, slightly higher than in Western and Central Europe [2]. Important differences also exist in terms of mode of use. The prevalence of injecting psychoactive substances is 0.22% in Western and Central Europe; it is 0.65% in North America [2, 3]. Differences also exist in the impact of the different substances on population health. Age-standardized attributable disability-adjusted life years (DALYs) for controlled substances use are 296.5 per 100,000 in Central Europe, 382.2 in Western Europe, and 1032.0 in North America [2]. Therefore, the difference in terms of DALYs is wider than the difference in prevalence of use. Compared to the USA, Western and Central Europe have lower prevalence of opioid use, lower prevalence of injection substance use, and a lower attributable burden associated with controlled substance use [2].

Despite efforts from pharmaceutical companies to expand prescription of opioid sales in many European countries, non-medical use of prescription opioids is not as alarming as that of the USA or Canada [4]. Nevertheless, the dispensing of opioid analgesics has increased significantly in Central and Western Europe between 2001 and 2013, from 3079 to 9320 defined daily doses per million inhabitants per day, respectively [5•]. In this article, we aim to summarize recent data on opioid use in Central and Western Europe and provide detailed description of available treatments in two countries, Spain and Switzerland.

This article is part of the Topical Collection on *Opioids*

✉ Nicolas Bertholet
Nicolas.Bertholet@chuv.ch

[1] Internal Medicine Service, Addiction Unit, Hospital Universitari Germans Trias i Pujol, Universitat Autonoma de Barcelona, Badalona, Spain

[2] Community Psychiatric Service, Lausanne University Hospital, Lausanne, Switzerland

[3] Alcohol Treatment Center, Department of Community Medicine and Health, Lausanne University Hospital, Beaumont 21b, P2, 02, 1011 Lausanne CHUV, Lausanne, Switzerland

Opioid Use Disorder in Central and Western Europe

There are 1.3 million individuals with nonmedical use of opioids in Europe, according to the last European Drug report [6•]. While there seems to be a steady decrease in injection substance use, lethal intoxications related to nonmedical substance use continue to be a major cause of death in young people, with 6800 deaths in 2014, representing 3.4% of all deaths in adult males under 40 [6•]. Opioids are associated with 81% of lethal intoxications related to nonmedical substance use in the European Union (EU) [6•].

In the EU, 75% of heroin consumers are concentrated in five countries (Spain, Germany, Italy, France, and UK). There have been different waves of heroin addiction in Europe, with the first wave in the mid-1970s, and, as a result, there is an aging population of individuals who use opioids. The mean age of people entering treatment has increased, from 33 years old in 2006 to 37 years old in 2015. Over the same period, the average age at nonmedical substance use-related deaths (most being related to opioids) increased by 5.5 years. This aging cohort represents a significant challenge: people with the long-term use experience the cumulative detrimental effects of substance use, frequently associated with tobacco and alcohol use, overdose, and infections. This leads to premature aging among people who use opioids with major implications in terms of public health and organization of health care and social services.

Synthetic Opioids

Recently, as in the USA, but to a lesser extent, some European countries have seen the emergence of use of highly potent synthetic opioids (fentanyl and derivatives), which are sold online and through illicit markets. Since 2012, the EU Early Warning System has seen an increase in reports of these substances, which are only needed in small volumes to produce a large number of doses. In 1997, the first cases of fatal intoxication with fentanyl were identified in Sweden and it has become a problem across Europe [7]. Estonia is particularly affected, with the number of fentanyl-related fatalities increasing to 1100 between 2005 and 2013 [8]. Comparatively, there were 160 deaths in Germany from 2007 to 2011, 70 in the UK from 2017–2012, 40 in Finland from 2008 to 2010, and 180 in Sweden from 2006 to 2013 [8].

Addiction Treatment and Harm-Reduction Strategies in Central and Western Europe

Addiction Treatment

Opioids are the third most common controlled substance after cannabis and cocaine for which patients are admitted to substance use treatment [6•]. Heroin use accounts for 79% of those who are admitted to treatment; while less than 1% are admitted for fentanyl use, 8% for methadone use, 5% for buprenorphine use, and 7% for other opioids. In Estonia, fentanyl is the most commonly used opioid among treatment entrants [6•]. In addition, there has been an increase in diversion leading to buprenorphine being the most common opioid used among treatment entrants in Finland. In the Czech Republic, addiction to other opioids (fentanyl, morphine, hydromorphone, and oxycodone) represents more than half of the patients admitted to treatment [6•].

In 2015, in the EU, 630,000 people received treatment for opioid use disorder including those who received opioid agonist treatment (OAT) [6•]. Methadone (63%) and buprenorphine (35%) are the medicines most commonly provided [9]. Pharmaceutical heroin (diacetylmorphine [DAM]) is recognized as a second line OAT and DAM is registered as a medicinal product for this indication in five European countries: Switzerland, Netherlands, Germany, UK, and Denmark. There are important variations in treatment access across Europe. The proportion of individuals with an opioid use disorder receiving OAT varies from 10% (Latvia) to 80% in France [6•]. Access to OAT has been substantially scaled up across the EU, but it remains scarce in many Eastern European countries, a region that has been severely hit by injection substance use and its associated infections, such as chronic hepatitis C virus infection (HCV), hepatitis B virus infection (HBV), and HIV [10, 11]. In Austria, levomethadyl acetate (LAAM) is still available as OAT [6•].

Harm Reduction

Supervised injection facilities, needle and syringe service programs, are associated with a decrease in the incidence of blood-borne infections like HIV or HCV as well as a decrease in deaths by overdose [12]. The use of supervised injection sites is also associated with promoting safer injection conditions and enhancing access to primary health [13]. In addition, there are anecdotal reports that have associated supervised injection facilities with a decrease in used of needle and syringe seizure by law enforcement agencies [14]. Seven countries (including Spain and Switzerland) have supervised injection facilities [13]. As of 2016, needle and syringe exchange programs were available in 19 countries (all Western Europe countries except for Iceland, Turkey, Monaco, and Andorra) [15].

Additional efforts to reduce lethal intoxications have focused on innovative ways to identify those at risk, to raise risk awareness, and to improve bystander response enabling those who witness lethal intoxications to intervene and prevent fatal outcomes [16]. Six Western European countries have take-home naloxone programs (Denmark, Germany, Italy, Norway, Spain, and the UK). A particularly important area for interventions is the improvement in transitions of care between prison and community [16, 17], with pre-release

education on overdose risks and prevention, continuation and initiation of OAT, improved referral to aftercare, and community treatment services [16].

Opioid Use Disorder Treatments in Spain

Epidemiology

Spain has a universal health care system for all citizens and most non-citizens, which is essentially free and financed by income taxes [18]. Spain experienced an injection substance use epidemic that started in the late 1970s and lasted up until mid-late 1990s [18], which fueled a devastating incidence of new HIV infections that was one of the highest in the continent, similar to what is currently seen in Eastern Europe [11, 18]. The combination between HIV infection and overdoses had an impact on life expectancy for males, which decreased in the 1993–1995 period [18]. The public response was initially of the "law and order" and "war on drugs" type [18]. In the last 20 years, the prevalence of injection heroin use has steadily decreased in Spain. In 1995, lifetime prevalence in those between 15 and 34 was 1.4%. In 2015, it was as low as 0.2%, while the lifetime prevalence of any injection substance use was 0.5% in the adult population [19]. According to a recent study, the 12-month prevalence of heroin use is 0.1% among Spaniards between 15 and 64 years, with consumption far more prevalent in males. The mean age of first heroin use is 22 years and the lifetime prevalence of use is 0.6%. There are few new individuals who inject heroin and the incidence of new cases of HIV or HCV infections related to substance use is lower than in the 1980s and 1990s [20, 21], as other complications like soft-tissue infections or endocarditis and heroin-associated overdoses [22]. However, prevalence of HCV among people who use opioids remains high [23], and HCV antiviral treatment uptake is low [24].

In 2015, heroin use was the third most common controlled substance for which people were admitted to any form of substance use treatment accounting for 11.5%, after cannabis use disorders (47%) and cocaine use disorder (35.5%) [19]. In those admitted to treatment, the main mode of heroin administration was inhaling in 83.7%, while injection and snorting accounted for 7.6% and 6.6%, respectively [19].

Currently, people who use heroin in Spain are aging and the higher prevalence of use is seen in 35 to 64 years range. Those who are admitted for heroin use disorder treatment are predominantly male, with a mean of 41 years, and most of them have already received some form of treatment. Also, 12.5% of the populations who use heroin have been in prison or jail during the prior month. Most patients use heroin daily and commonly use other substances, mainly cannabis, cocaine, and alcohol. In terms of education, in 2015, most patients with heroin use disorder (67%) have completed elementary school, while only 17.4% had completed secondary education. Conversely, 45% of those with cocaine use disorder and 42% of those with cannabis use disorder had completed secondary education [19].

In addition, there are notable differences in terms of employment status and the substance of choice, as only 17% of those treated for heroin use disorder are employed, while 41% of those with cocaine use disorder are employed. The rate of employment among those with cannabis use disorder is 23%, though this represents a much younger cohort. Also, unstable housing is much more prevalent in patients with heroin use disorder, in comparison with those with cocaine or cannabis use (5% vs. 1%).

In terms of nonmedical use of prescription opioids, there has been an increase in the dispensing of prescription opioids to treat pain in Spain [25] and in Catalonia in particular, where a 66% increase has been reported between the years 2012 and 2016 [26]. This increase is due to changes in prescribing practices for non-cancer chronic pain that have been partially fueled by influence of pharmaceutical companies, as well as patient advocacy associations [17]. However, the situation is not as alarming as what is happening in the USA [27]. In Spain, the opioids that are more commonly prescribed for pain are tramadol (62.2%), fentanyl (17.5%), and buprenorphine (6.9%) [25]. Fentanyl is mainly prescribed as a transdermal patch, which has lower abuse or diversion potential than other formulations [25].

In a survey performed among 22,000 people aged 12 and 49 in five different countries (Denmark, Germany, UK, and Sweden), Spain had the highest prevalence of non-medical use of prescription opioids, with a 12-month prevalence of 7% and a lifetime prevalence of 18%, with tramadol and codeine, the two substances most frequently misused [28].

Use of Opioid Agonist Treatment

Methadone programs started in 1985 and became more widespread after 1991 [18]. In the early years, methadone was available in the private sector, and then a network of addiction outpatient facilities was implemented [29]. Dispensing in pharmacies started in 1996, when new legislation was passed, and methadone also became available in prisons. Methadone treatment can be prescribed in different settings (hospitals, emergency departments), but is mainly prescribed and dispensed in addiction outpatient clinics [29]. Methadone programs tend to be very inclusive and low threshold in Spain and the only criteria for forced discharge are violence and/or consumption and trafficking within the treatment facility [29]. Nowadays, more than 60% of those who have an opioid use disorder receive OAT in Spain [29].

Buprenorphine is much less commonly used for OAT in Spain. While buprenorphine/naloxone has been available

for more than a decade, its price is not fully covered by the health system.

Needle exchange programs and safe injection sites opened in the mid-1990s [18]. There have been pilot trials of DAM, but this approach is not well-established [18].

In summary, the situation of opioid use disorder in Spain is characterized with a decreasing prevalence of injection substance use, mainly driven by fear of blood-borne infections and overdose risks by the general population and by public health measures, with robust availability of OAT and harm-reduction programs, and a well-established network of outpatient addiction facilities. However, given the current opioid epidemic in the USA, there is a need to be vigilant and not to repeat the same prescription strategies for pain that have fueled this epidemic.

Opioid Use Disorder Treatments in Switzerland

Health Care Context

Switzerland's 8.4 million inhabitants are universally required to purchase health insurance. Health insurance is provided by private companies that are required to accept every applicant. All private health insurance providers offering insurance plans within the mandatory system must cover the same benefits. By law, only services that are effective, useful, and cost-effective are covered. Tariffs and rates are agreed between insurers and providers (or determined by the responsible authority), and the Federal Department of the Interior is responsible for the description of services reimbursed. Various deductibles are available (300–2500 Swiss Francs [CHF]), and patients have to pay a retention fee of 10% of the invoice up to a maximum of 700 CHF per year. The 26 Swiss cantons (i.e., the member states of the Swiss Confederation) are responsible for health care planning and delivery, and thus the system is decentralized.

Epidemiology

As in other countries, the use of opioids in the Swiss population is challenging. Notably, telephone-based surveys tend to miss the more vulnerable segments of the population and the reporting of controlled substance use is problematic. In 2016, the Continuous Rolling Survey of Addictive Behaviors and Related Risks (CoRoIAR) indicates a lifetime prevalence of heroin use of 0.7%. Over the past 30 days, the prevalence of heroin use is below 0.1%. Based on data from the Canton of Zurich (using the registry of OAT), Nordt, and Stohler identified a steep increase in heroin use incidence from 1975 to 1990, followed by a substantial decline by 2002. The population of individuals who use heroin declined by 4% a year (low cessation rate and therefore slow decline in prevalence) [30]. Authors concluded that the harm-reduction programs and the medicalization of the heroin problem may have contributed to the limited attraction to heroin among young people [30]. Over the past 20 years, there has been a decrease in the number of nonmedical substance use-related deaths (any substance): 376 cases in 1995 and 137 in 2010 [31]. Since 2010, the mortality is stable (132 cases in 2015).

In terms of opioid prescription practices in Switzerland, there is evidence of an increase in prescription rates for pain medications over the past 10 years, including for strong opioids (morphine conversion factor > 0.3) [32]. The per capita opioid consumption of Switzerland is the 7th worldwide (following the USA, Canada, Germany, Denmark, Belgium, and Austria), before Australia [4, 33]. Between 1985 and 2015, the Swiss opioid consumption increased from 18 to 421 mg/person/year. There was a peak in 2009 (504 mg/person), followed by a slight decrease and a stabilization since 2012 [33]. Switzerland is therefore above the European mean, but the difference has been shrinking: in 1985, Switzerland had 2.5 times the per capita opioid consumption of Europe, while the difference was reduced to 1.4 in 2015 [33]. Opioids are not available over the counter and opioid formulations for OAT and "strong" opioids (for example fentanyl, hydromorphone, oxycodone, pethidine, and morphine) must be prescribed using a special prescription form ("prescription for narcotic substances"), issued in three copies, and including a unique identification number. One copy remains with the physician, one with the pharmacy, and one with the insurance provider. This may reduce the risk of nonmedical use but due to the way the health care system is organized (and decentralized), there is no central database of opioid prescriptions.

Use of Opioid Agonist Treatment for Opioid Use Disorder

The Swiss controlled substances policy model is based on "four pillars": prevention, treatment, harm reduction, and law enforcement. This model has been practiced since the end of the 1980s following the epidemic of HIV/AIDS and the so-called open drug scenes [34]. Adopted in 2015, the National Strategy for Addictions 2017–2024 defines four main objectives: prevention of addiction, providing treatments and support to people with addiction, reducing health and societal damages, and diminishing the negative consequences for society. Clinical guidelines from the Federal Office of Public Health (FOPH), the Swiss Association of the Medical Officers of the Cantons (VKS/AMCS), and the Swiss Society of Addiction Medicine (SSAM) support OAT as the first line of treatment for people with opioid use disorders [35]. OAT is considered part of the "treatment" pillar of the Swiss four pillars model and four opioid medicines are approved by the Swiss Agency for Therapeutic Products for the indication of OAT: methadone (including L-methadone), buprenorphine (including buprenorphine/naloxone), slow-release morphine, and pharmaceutical DAM. OAT must be prescribed by a physician (and is limited to one prescribing physician per patient). OAT is covered by the mandatory

health insurance system but is subject to registration at the canton level (the Swiss law requires registration and evaluation of OAT). Notably, the prescribing physician must announce the prescription to the cantonal public health officer before starting the treatment. OAT can be dispensed by a physician, at a clinic or at a pharmacy. Methadone, buprenorphine, and slow-release morphine are subject to the same regulation and no special training in addiction medicine is required for prescribing. DAM programs are subject to additional regulations and must take place in specialized centers. In addition, harm-reduction programs such as needle exchange, syringe distribution programs, and contact centers exist [34, 36, 37].

Anyone with a confirmed diagnosis of opioid use disorder can be considered for OAT. The guidelines present methadone and buprenorphine as "virtually equivalent in terms of efficacy and success rate" [35]. The guidelines do not suggest that one medication is preferable for specific patient groups. One exception is noted: L-methadone, buprenorphine, or slow-release morphine are recommended for patients with QTc prolongation [35, 38].

In 2016, 17,746 patients received OAT (out of an estimated number of 25,000 individuals with opioid use disorder (estimated coverage 70%) [39]) and most were men (69%). The most frequent options for OAT dispensation were pharmacies (44%) and by a physician/clinic (41.3%). The number of patients treated has been stable over the past 15 years (17,907 in 1999, 17,190 in 2006) [40]. Up until 2009, opioid use was the most frequently reported problem upon admission for substance use disorder treatment (excluding alcohol and tobacco). Since 2010, opioid-related admissions are second to cannabis use-related admissions.

A recent study assessed the attitudes and beliefs of patients and health care providers towards OAT, focusing on perceptions of quality and access to care [41]. From the database of OAT prescribing physicians ($n = 1397$), 200 completed the study; 44% were general practitioners, 33% psychiatrists, and 19% internists. The majority (79%) worked in private practices. The reported caseload was less than 10 patients for 59% of physicians (22% reported a caseload of greater than or equal to 20 patients). Participating patients ($n = 207$) were mostly male (66%) with a mean age of 40, and 51% were unemployed. Liquid methadone and methadone capsules were the most frequently prescribed OAT (60% and 20%, respectively), while buprenorphine represented 12%. Patients and physicians were generally satisfied with the treatment offered. Patients had a major influence on the choice of medication: 48% reported they were given options to choose from, and 54% reported having their medication of choice. Diversion and nonmedical use were considered a significant problem by 45% of physicians, and 66% of participating patients reported nonmedical use of controlled substances at least two times a month. This was more frequent among patients receiving liquid methadone (71%) and lowest among patients receiving buprenorphine (53%). Most commonly reported medications available on the street were benzodiazepines and methadone. A third of participating patients reported selling or giving their OAT medication without financial compensation. A third (31%) of physicians were ≥ 60 years old (mean age 54), indicating an aging population of physicians (this is the case for primary care providers in Switzerland in general). Physicians cited lack of training or information and financial barriers as deterring factors from engaging in OAT. Physicians desired less bureaucracy, less complicated obligations, and more support. Patients reported that several prerequisites to OAT were difficult to meet, such as daily supervised treatment (cited by 70% of respondents) and necessity to attend all appointments (63%).

The medical prescription of DAM is considered a second line of treatment for patients with persistent heroin use disorder (i.e., at least 2 years with at least two unsuccessful treatment attempts) in Switzerland [42]. Strang and colleagues published a systematic review of randomized trials of supervised injectable DAM programs. The main feature of these programs is that doses are taken under direct medical or nursing supervision. Six trials were included and showed reduction in nonmedical opioid use and better retention in treatment (compared to oral methadone treatment). Notably, Perneger and colleagues conducted a randomized trial of DAM in Geneva, Switzerland, in 1995–1996 [43]. Authors concluded that programs are effective but are not a first-line treatment, are high cost, and low-volume intervention. Compared to oral methadone, it represents a higher risk of medical complications. Nevertheless, serious complications, such as respiratory depression, have been reported at a rate of 1/6000 injections, below the hazard for street opioids [42, 44].

The long-term outcomes of DAM programs have not been evaluated in randomized trials. Guttinger and colleagues reassessed participants ($n = 366$) in Swiss DAM programs delivered at eight treatment centers 6 years after they entered the program [45]. By the end of 2000, 11.7% had died, and 46% of those still alive were in the DAM program. Among those still in treatment, nonmedical use of heroin, cocaine, and benzodiazepines significantly decreased (from 84.7% to 3.8%, 27.5% to 5.3%, and 18.8% to 4.5%, respectively). Illegal income for subsistence went from about half at study entry to 10% at follow-up. An increase in reliance on social benefits was observed among those still in treatment (from 19.1% at study entry to 39.7% at follow-up). A significant decrease in pending court cases was observed among those still in treatment (31.6% at treatment entry, 9.4% at follow-up). The proportion of patients in the DAM program reporting use of illegal heroin daily or almost daily was 3.8% (compared to 18.9% of those who terminated the treatment). Deaths in Swiss DAM treatment programs have been closely evaluated: from 1994 to 2000, the crude death rate of patients in DAM treatments, including 1-month post-discharge, was 1% per year, therefore

lower than what has been estimated among Swiss individuals who use opioids in the 1990s (between 2.5% and 3%) [46]. The most frequent causes of deaths were infections (AIDS or HIV related 34.7%, other infections than HIV 10.2%), accidents (18.4%), and suicide (16.3%). The standardized mortality ratio for the 7-year-period was 9.7 (7.3; 12.8), higher among females (17.2), than males (8.4). The low mortality rate is noteworthy when taking into account that only patients who do not respond to a long-acting opioid medication can access DAM programs. Oral DAM has also been tested in open-label prospective cohorts in Switzerland and appears to be safe [47]. In 2016, 1747 patients received DAM in one of the 21 ambulatory centers (and one prison center).

Discussion

The prevalence and impact of opioid use on population health vary within different countries and health care systems, as do related public policies and access to care. These differences are likely explained by differences in the regulation of prescription opioids and accessibility of OAT. The European approach of acute and chronic non-cancer pain has been different from the USA with more prescribing of non-opioid medications [22]. The treatment coverage of OAT is > 50% in Central Europe and the treatment offered is broad, as the harm reduction initiatives, which may explain the differences in morbidity and mortality. Nevertheless, nonmedical use of prescription opioids is increasing in some parts of Europe, as the nonmedical use of methadone and buprenorphine. Therefore, a better understanding on how medications can be diverted is needed in order to avoid undermining the benefits of OAT without compromising access to care. A close monitoring of the market is also important.

Based on the scientific consensus on its benefits in improving health, reducing morbidity, and mortality, OAT programs are available in all Central and Western European countries [48]. Nevertheless, there are important differences in approaches and national regulations across EU countries. The European Monitoring Center for Drugs and Drug Addiction (EMCDDA) and the Council of Europe (Pompidou Group) support the expansion of OAT, as well as low threshold services and other harm-reduction initiatives [48, 49]. Admission criteria and regulation should in general be less strict, and the introduction of DAM prescription programs as a second line of treatment should be supported. Treatment should be provided in a wide range of facilities, especially in prisons. General practitioners and community pharmacists should be more involved, and more physicians and fieldworkers need training and education in OAT [48, 50].

A major challenge in Europe is the aging of the population of people who use drugs and of providers. Aging individuals who use opioids will have an important impact on how health care is organized and will add to the challenges of the general aging of the population. There is a need to train and support new providers (notably through regional networks), including training in addiction medicine, at the pre- and post-graduate level.

In Europe, 1.3 million people are with nonmedical opioid use or opioid use disorder. It appears that the available treatment options and harm reduction initiatives have had a significant impact on population health. As such, EMCDDA and the Council of Europe recommend the expansion of OAT and harm-reduction programs. While coverage rates are high, there are areas for improvement, notably in prisons, and of concern, when it comes to the renewal of an aging population of providers [6•, 16]. This calls for initiatives in the area of education (training of medical students and providers), access, and coordination of health care and monitoring of existing programs and substance use trends. There are some indicators that patterns of substance use in Europe is changing, with some countries no longer reporting heroin as the substance of main concern. A close monitoring of nonmedical use of methadone and buprenorphine, of prescription opioids, and the evolution of the markets of highly potent opioids, such as fentanyl, is important to inform policy makers and clinicians.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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