SO-PREP

Toolkit on key responses to synthetic opioids

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Acronyms and Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
APA	American Psychological Association
API	Application Programme Interface
ASAM	American Society of Addiction Medicine
Benzos	Benzodiazepines
C-EHRN	Correlation - European Harm Reduction Network
CNS	Central Nervous System
COVID	Coronavirus Disease
CRA	Community Reinforcement Approach
CRISM	Canadian Research Initiative in Substance Misuse
CSO	Civil Society Organisation
csv	Comma Separated Value
DCR	Drug Consumption Room
DIMS	Drug Information and Monitoring System [Netherlands]
DORS	Digital Overdose Response System
DPIC	Dutch Poisons Information Centre
DULF	Drug User Liberation Front
EC	European Commission
EHRC	European Harm Reduction Conference
EMA	European Medicines Agency
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMD	Electronic Medicine Dispenser
EMS	Emergency Medical Service
ESCAPE	European Syringe Collection and Analysis Enterprise
EU	European Union
EuroNPUD	European Network of People who Use Drugs
Europol	European Union Agency for Law Enforcement Cooperation
EWA	Early Warning Advisory
EWN	Early Warning Network
EWS	Early Warning System
FTIR	Fourier Transform Infrared spectroscopy
GC-MS	Gas Chromatography coupled to Mass Spectrometry
GDPR	General Data Protection Regulation
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
html	Hypertext Markup Language
HPLC	High Performance Liquid Chromatography
ICER	Institute for Clinical and Economic Review
IDPC	International Drug Policy Consortium
INDCR	International Network of Drug Consumption Rooms
IP	Internet Protocol
IRC	Internet Relay Chat
IS	Information System
JITAI	Just-In-Time Adaptive Interventions
Lab	Laboratory
LDIS	Local Drug Information System
MID	Major Infectious Disease
MDI	Monitor of Drug-related Incidents [Netherlands]
mg	Milligramme
MOR	μ-opioid receptor
NDEWS	National Drug Early Warning Systems [USA]
NFI	National Forensic Institute [Netherlands]
NGO	Non-Governmental Organisation
NIDA	National Institute on Drug Abuse [USA]
NORS	National Overdose Response Service
NPS	New Psychoactive Substance
NSO	Novel Synthetic Opioid
OAT	Opioid Agonist Treatment; also referred to as Opioid Agonist Therapy and Opioid Substitution Treatment, or Therapy (OST), and Medication-Assisted Treatment (MAT)
OFDT	Observatoire Français des Drogues et des Toxicomanies (French Monitoring Centre for Drugs and Drug Addiction)
OPS	Overdose Prevention Site
OWS	Opioid Withdrawal Syndrome

P2PN	Peer-to-Peer Naloxone
PIN	Professional Information Network
PPE	Personal Protective Equipment
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Controlled Trial
Reitox	Réseau Européen d'Information sur les Drogues et les Toxicomanies
SAMSHA	Substance Abuse and Mental Health Services Administration [USA]
SINTES	Système d'Identification National des Toxiques et Substances (French National Identification System for Drugs and Other Substances)
SO	Synthetic Opioid
SO-PREP	Strengthening Synthetic Opioids health systems' preparedness to respond to the potential increases in prevalence and use of Synthetic Opioids
SSTI	Skin and Soft Tissue Infection
THN	Take-Home Naloxone
TLC	Thin-Layer Chromatography
TTP	Time-Triggered Protocol
TTPS	Secure Time-Triggered Protocol
UNODC	United Nations Office on Drugs and Crime
URL	Uniform Resource Locator
WHO	World Health Organization

Glossary of terms

Algorithm: A process or set of rules to be followed in calculations or other problem-solving operations, especially by a computer.

Analogue: A person or thing seen as comparable to another.

Antidote: A substance that can remedy or counteract a form of poisoning.

Application Programme Interface (API): A type of software interface that connects computers or computer programmes.

Assertive community treatment: An intensive and highly integrated approach for community mental health service delivery.

Bag-mask ventilation: Sometimes known by the proprietary name Ambu bag or generically as a manual resuscitator or "self-inflating bag", is a hand-held device commonly used to provide positive pressure ventilation to patients who are not breathing or not breathing adequately.

Benzodiazepines: A class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. As depressants - drugs which lower brain activity - they are prescribed to treat conditions such as anxiety, insomnia, and seizures.

Blood-Born Infections (BBIs): Viruses that are carried in the blood, specifically hepatitis B, hepatitis C and human immunodeficiency virus (HIV).

Captcha: A type of challenge–response test used in computing to determine whether the user is human; typically a way of thwarting spam and automated extraction of data from websites.

Carfentanyl: A form of synthetic opioid that is up to 100 times more potent that fentanyl.

Chatbot: A software application used to conduct an on-line chat conversation via text or text-to-speech, in lieu of providing direct contact with a live human agent.

Clearnet: The visible part of the internet indexed by search engines.

Cognitive Behavioural Therapy (CBT): A talking therapy that can help to manage problems by changing the way an individual thinks and behaves; most commonly used to treat anxiety and depression but can be useful for other mental and physical health problems.

Community Reinforcement Approach (CRA): Encompasses cognitive-behavioural therapy (CBT) and network therapy approaches, including building drug refusal skills and improving vocational, social, family and recreational aspects of the lives of clients.

Contingency management: A behaviour modification intervention which reinforces desired behaviours through incentives.

Crawler bot: A crawler downloads a series of webpages and then extracts hyperlinks from which other web pages can be downloaded based on previously established parameters; also called a spider or spiderbot.

Cryptomarkets: Also known as darknet markets; a platform for the exchange of goods and services, both legal and illegal, on the dark web that remain hidden from the world due to the use of anonymising browsers - such as TOR - based on encryption techniques.

Darknet: Internet services only accessible through anonymising software, configurations, or authorisation to access. Through the dark web, private computer networks can communicate and conduct business anonymously without divulging identifying information, such as a user's location.

Data anonymization: The process of removing personally identifiable information from data sets, so that the people whom the data describe remain anonymous.

Deep web: Part of the world wide web that is unindexed and includes paywalled websites and password-protected websites; the dark web is part of the deep web.

Digital inequality: The economic, educational, and social inequalities between those who have computers and online access and those who do not.

Drug checking: Allows people who use drugs to anonymously submit a drug sample that has been purchased on the illicit drug market for chemical analysis.

Drug Consumption Rooms (DCRs): Legally sanctioned and professionally supervised health care facilities that provide

safer and more hygienic conditions for people who use drugs to consume pre-obtained drugs in a non-judgmental environment that reduces the health and public order issues associated with such activities in public spaces and facilitates voluntary access to social, health, economic, legal and drug treatment services. Also known by many other terms including safe injection facility.

e-health: The overarching term for digital (computer-based) information and communication technologies that provide tools and services to enhance prevention, diagnosis, treatment, monitoring and management of health.

Early Warning System (EWS): A multidisciplinary network of key stakeholders that enables information exchange among key actors directly or indirectly involved in the field of drugs to identify early events of emerging drugs that pose a potential threat to public health.

European Medicines Agency (EMA): An agency of the EU that seeks to foster scientific excellence in the evaluation and supervision of medicines for the benefit of public and animal health.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA): The leading authority on illicit drugs in the EU that provides independent scientific evidence and analysis on all aspects of the changing threat to individual lives and wider society, with its work contributing to EU and national policies to protect Europe's citizens from drug-related harms.

Fentanyl (and its analogues): A form of synthetic opioid that readily penetrates into the brain, resulting in overdose levels being reached rapidly, with death occurring within 5 minutes; estimated to be around 100 times stronger than morphine.

First responder: Someone who is one of the first people to arrive to deal with an emergency, especially those trained in the required response, such as a paramedic, police officer, or firefighter.

Gender diversity: An umbrella term to describe gender identities that demonstrate a diversity of expression beyond the binary framework of male and female.

General Data Protection Regulation (GDPR): A regulation in EU law on data protection and privacy in the European Union and the European Economic Area.

Geotagging: The process of adding geographical identification metadata to various media such as a geotagged photograph or video, websites, SMS messages, QR Codes or RSS feeds.

Google Trends: An online tool created by Google that analyses user inquiries made to Google that reflects the search interest in a specific topic and provides both real-time data concerning the past seven days and non-real-time data between 2004 and up to 36 hours before the Google Trends inquiry.

Harm reduction: Refers to policies, programmes and practices that aim to minimise negative health, social and legal impacts associated with drug use, drug policies and drug laws.

Informed consent: A principle in medical ethics and medical law that a patient should have sufficient information before making their own free decisions about their medical care.

Internet Relay Chat (IRC) bot: A set of scripts or an independent programme that connects to Internet Relay Chat (IRC) as a client, and so appears to other IRC users as another user. An IRC bot differs from a regular client in that instead of providing interactive access to IRC for a human user, it performs automated functions. Intramuscular : Situated or taking place within, or administered into, a muscle.

Intravenous: Existing or taking place within, or administered into, a vein or veins.

Just-In-Time Adaptive Interventions (JITAI): An intervention design aiming to provide the right type/amount of support, at the right time, by adapting to an individual's changing internal and contextual state.

Layperson: A person without professional or specialised knowledge in a particular subject.

Lipid-soluble: The maximum concentration of a chemical that will dissolve in fatty substances, and that can disperse through the environment via uptake in living tissue.

Low-threshold services: Services that have minimum criteria to restrict who can access them.
m-health: e-health programmes that are supported by mobile devices.

Meta-analysis: The examination of data from a number of independent studies of the same subject, in order to determine overall trends.

Methadone: A synthetic opioid agonist used for chronic pain and also for opioid dependence.

Morbidity: Refers to having a disease or a symptom of disease, or to the amount of disease within a population; also refers to medical problems caused by a treatment.

Mortality: A term used for death rate, or the number of deaths in a certain group of people in a certain period of time.

Motivational Interviewing: A directive, client-centred counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence.

Mu (μ) Opioid Receptors (MORs): A class of opioid receptors with a high affinity for enkephalins and beta-endorphin, but a low affinity for dynorphins; also referred to as μ-opioid peptide receptors.

Naloxone: A medication used to reverse the effects of opioids; commonly used to counter decreased breathing in opioid overdose. Naloxone may also be combined with an opioid to decrease the risk of misuse through injection.

Network therapy: Individual psychotherapy or family therapy in which an attempt is made to involve not only immediate family members but also other relatives, friends, and neighbours as sources of emotional support and possible vocational opportunity.

New Psychoactive Substances (NPS): A new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in such conventions.

Novel Synthetic Opioids (NSOs): These comprise synthetic opioids, such as fentanyl and its analogues, that share the analgesic and CNS depressant properties similar to other opioids; a sub-group of NPS.

Off-patent: Medicine on which there are no exclusive marketing rights; the patent has expired.

Opioid agonist treatment (OAT): The main and most-researched approach to the treatment of opioid dependence usually using methadone or buprenorphine – morphine-like substances with the same effects as natural opium extracts which, depending on the needs of a client, can be prescribed for short or long treatment periods - and is associated with considerable reductions in overdose mortality risk among people who use opioids; also known as opioid substitution therapy (OST) and medication-assisted treatment (MAT).

Opioid use disorder (OUD): The chronic use of opioids that includes a desire to obtain and take opioids despite social and professional consequences that causes clinically significant distress or impairment with major health, social, and economic impact that can be treated using evidence-based treatment methods, such as OAT.

Opioid Withdrawal Syndrome (OWS): A set of symptoms arising from the sudden withdrawal or reduction of opioids where previous usage has been heavy and prolonged; signs and symptoms can include drug craving, anxiety, restless legs, nausea, vomiting, diarrhea, sweating, and an increased heart rate.

Outreach: The activity of providing services to any population that might not otherwise have access to those services. A key component of outreach is that the group providing it is not stationary, but mobile and involves meeting someone in need of an outreach service at the location where they are located.

Overdose: An excessive and dangerous dose of a drug.

Oxygenation: The addition of oxygen to any system, including the human body; also refers to the process of treating a patient with oxygen, or of combining a medication or other substance with oxygen.

Party drugs: A loosely defined category of recreational drugs which are associated with discothèques in the 1970s and nightclubs, dance clubs, electronic dance music parties, and raves in the 1980s to today; also referred to as club or rave drugs.

Peers: A person who is equal to another in abilities, qualifications, age, background, and social status; a person who has equal standing with another or others.

Pharmacopoeia: An official publication containing a list of medicinal drugs with their effects and directions for their use.

Pharmacotherapy: Therapy or treatment of a disease or disorder using pharmaceutical drugs, as distinguished from therapy using surgery, radiation, movement, or other modes.

Post-Traumatic Stress Disorder (PTSD): A mental health condition caused by a traumatic experience resulting in flashbacks, nightmares, feeling very anxious and difficulty sleeping, etc.

Potency: A measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug evokes a given response at low concentrations, while a drug of lower potency evokes the same response only at higher concentrations.

Prescription opioids: Used mostly to treat moderate to severe pain, though some opioids can be used to treat coughing and diarrhoea. Opioids can also make people feel very relaxed and "high" - which is why they are sometimes used for non-medical reasons.

Psychosocial treatment: Psychosocial refers to an individual's psychological development in, and interaction with, their social environment; psychosocial treatments, or interventions, include structured counselling, motivational enhancement, case management, care-coordination, psychotherapy and relapse prevention.

Psychosis, Psychotic experiences: When someone perceives or interprets reality differently to the people around them; subthreshold forms of hallucinations and delusions.

Punitive: Used to describe costs that are so high that they are difficult to pay, and that are often used to punish someone or limit their activities.

Randomised Controlled Trial (RCT): A form of scientific experiment used to control factors not under direct experimental control. Examples of RCTs are clinical trials that compare the effects of drugs, surgical techniques, medical devices, diagnostic procedures or other medical treatments.

Recidivism: The tendency of a convicted criminal to reoffend.

Recreational drug use: The use of a psychoactive drug to induce an altered state of consciousness either for pleasure or for some other casual purpose or pastime by modifying the perceptions, feelings, and emotions of the user.

Reddit: An American social news aggregation, content rating, and discussion website. Registered users submit content to the site such as links, text posts, images, and videos, which are then voted up or down by other members.

Reitox (Réseau Européen d'Information sur les Drogues et les Toxicomanies): The European information network on drugs and drug dependence with members drawn from designated national institutions or agencies responsible for data collection and reporting on drugs and drug dependence.

Relapse: A deterioration in someone's state of health after a temporary improvement; part of the recovery process and should not be interpreted as failure.

Respiratory depression: Also known as hypoventilation or hypoventilatory syndrome, meaning that ventilation of the lungs is inadequate to perform needed gas exchange, leading to the abnormal retention of carbon dioxide in the blood; sometimes a respiratory rate of fewer than 12 breaths per minute is used as a definition of respiratory depression.

Safe supply: The provision of pharmaceutical-grade substances of known composition built on the premise that providing an alternative – such as non-adulterated drugs of known quality/quantity with user agency in consumption methods - to the street drug supply will limit the use of adulterated drugs, such as fentanyl, and reduce overdose events.

Scheduling: The designation of substances into categories in accordance with national and/or international drug control treaties.

Scraper bot: Looks for the relevant information based on the criteria decided by the developer of the scraper and stores it in a database.

Sedation: The action of administering a sedative drug to produce a state of calm or sleep.

Stimulants: An overarching term that covers many drugs including those that increase activity of the central nervous system and the body, drugs that are pleasurable and invigorating, or drugs that have sympathomimetic effects, i.e. any drug that causes an effect similar to that produced by stimulation of the sympathetic nervous system.

Synthetic Opioids: Substances that are wholly synthesised from chemicals with analgesic effects that are similar to those of heroin and morphine, but that are much stronger and more potent and thereby associated with a higher risk of overdose. SOs are often used in medicine for the treatment of severe pain and in palliative care.

Take-Home Naloxone (THN): Overdose education and naloxone distribution to people who use opioids and their social networks to shorten the time to the administration of the antidote while awaiting emergency medical services for professional management and post-overdose follow-up.

Telegram: A freeware, cross-platform, cloud-based instant messaging service that also provides end-to-end encrypted video calling, VoIP, file sharing and several other features.

Telemedicine: Enables communication - using telecommunication technologies - between a patient and health care provider without having to meet in person to provide a diagnosis, treatment, education, or intervention; it also allows for monitoring of the patient and the provision of medicine.

Titration: A common laboratory method of quantitative chemical analysis to determine the concentration of an identified analyte. A reagent, termed the titrant or titrator, is prepared as a standard solution of known concentration and volume. Also known as titrimetry and volumetric analysis.

Trauma: A deeply distressing or disturbing experience.

United Nations Office on Drugs and Crime (UNODC): Its mission is to contribute to global peace and security, human rights and development by making the world safer from drugs, transnational organised crime, corruption and terrorism.

Vulnerability: The quality or state of being exposed to the possibility of being attacked or harmed, either physically or emotionally.

World Health Organization (WHO): A specialised agency of the United Nations responsible for international public health.

Introduction

Introduction to So-PREP

There has been a drastic increase in the use and associated harms of synthetic opioids (SOs) in the past two decades worldwide. This issue highlights the importance in paying attention to different interventions to mitigate the burden of SO use. The European research project, 'Strengthening Synthetic Opioids health systems' preparedness to respond to the potential increases in prevalence and use of Synthetic Opioids (SO-PREP)', aims to reach this goal by developing a set of guidelines focusing on a set of interventions for people who use SOs.

1. Framework of the Toolkit

In general, there is considerable agreement on how to respond to opioids. However, the emergence of synthetic opioids on drug markets brings along new challenges where the simple expansion of traditional measures proves to be an insufficient response. The highly potent and pharmacologically diverse synthetic opioids create a complex and unpredictable market whereby people who use drugs often lack information and other means of keeping themselves safe. This calls for a concerted set of innovative approaches to reduce this threat to public health.

The aim of this Toolkit is to provide information and practical support to service developers and providers on the challenges presented by synthetic opioids, with recommendations and guidance on the implementation of seven selected key responses:

- Early warning systems
- Internet monitoring
- e-Health
- Drug checking
- Drug consumption rooms
- Naloxone
- Opioid agonist treatment

In addition, this Toolkit discusses the possibility of a novel response called safe supply. The key approach of the Toolkit is to transfer the specificity of SOs to the beforementioned set of key responses while also providing practical recommendations to overcome operational and policy level challenges.

The Toolkit is based on existing scientific evidence, documented good practices and experience from countries across Europe and North America as well as expert opinions. The lack of sufficient evidence on appropriate responses to problems related to the use of synthetic opioids can lead to numerous preventable deaths and adverse health outcomes. To overcome the lack of practical guidelines, countries with experiences with SOs should share their experience so that others can be better prepared and equipped.

The key question asked by this Toolkit is: What aspects of the selected key responses need to be adapted/ changed to work for synthetic opioids?

2. Problem definition

2.1. What are synthetic opioids?

Opioids comprise a wide range of substances, including opiates and their synthetic and semi-synthetic analogues[1]. Unlike morphine (an opiate derived from the poppy plant) or heroin (a semi-synthetic opioid synthesised from morphine), fentanyl and other synthetic opioids (SOs), such as tramadol and methadone, are wholly synthesised from other chemicals. SOs are substances with analgesic effects that are similar to those of heroin and morphine, but that are much stronger and more potent and thereby associated with a higher risk of overdose. SOs are often used in medicine for the treatment of severe pain and in palliative care. Therefore, two separate supply chains exist for SOs: diversion and misuse from the licit supply chain (medical and veterinary health care) and the illicit supply chain in which they are synthesised in clandestine laboratories. Both scenarios have been seen on different drug markets. The first fentanyl analogues began to appear in illicit drug markets in the United States as early as 1979 and the diversion of pharmaceutical fentanyl was documented as early as the 1980s. From the 1980s through to the early 2000s, there have been many documented instances of clandestine fentanyl production in the United States that have resulted in a significant number of overdose deaths[2].

In the US from 1999 to 2018, more than 750,000 persons have died from a drug overdose, the majority of which involved an opioid. The rising tide of these overdose deaths has been described as a triple wave phenomenon: deaths due to prescription opioids, both natural and semi-synthetic, rose from 1999 and peaked in 2017; heroin-related overdose started rising significantly after 2010 and also peaked in 2017; synthetic opioid-related (predominately illicit fentanyl and fentanyl analogs) overdoses rose dramatically from 2014 to the present[3].

In the EU, heroin remains the most commonly identified opioid on the illicit drug market. Starting from the 1980s, Europe has witnessed overdose epidemics mainly due to heroin and opioids are implicated in approximately three-quarters of fatal drug overdoses (an exception is Estonia where SOs have dominated the drug market since the early 2000s). Although Europe as a whole is currently not facing a SO crisis of the size and nature as seen in North America (if comparing mortality rates due to overdoses in 2018, the figure in the US is nine times that of the EU), the use of SO has been growing in some EU countries[4], implicating the need to strengthen preparedness in this area.

2.2. Main challenges posed by synthetic opioids

Adverse health effects

The main health effects of SOs are similar to regular opioids and may include stupor, changes in pupillary size, cold and clammy skin, cyanosis, coma, dependence and respiratory failure leading to death. Opioids depress respiration by acting on μ-opioid receptors (MORs) and reducing the drive to breathe. The very high potency of SOs mean that only small amounts of the drug are required to produce respiratory depression and, thus, even a minor error can result in too much being taken. The highly lipid soluble molecules of some SO (e.g. fentanils) also means that they readily penetrate into the brain, resulting in overdose levels being reached rapidly. In comparison, a heroin overdose may take more than 30 minutes to occur after injection, while a fentanyl overdose death can occur within 5 minutes, substantially reducing the time window for potential intervention. In addition, fentanils are able to 'break through' heroin-induced tolerance and produce respiratory depression even in heroin-tolerant individuals. Coingestion of opioids, especially highly potent SO, with benzodiazepines or other central nervous system (CNS) depressants greatly increases the risk of overdose[5].

In addition, the different pharmacokinetic profiles of SOs may also affect drug use practices with implications for infectious disease transmission. For example, the rapid onset of action and comparatively short duration of effect of fentanyl, as compared to heroin, can lead to more frequent use and injections. Higher injection frequency is linked to a higher risk of syringe and needle sharing, which can increase viral (e.g. HIV and Hepatitis C Virus (HCV)) exposure events[6]. In addition, skin and soft tissue infections (SSTI) are very common, harmful and costly among people who inject drugs[7].

Scarce scientific evidence

Although the pharmacological properties of fentanyls have been described in scientific literature for over 60 years, important misconceptions and anomalies still exist as to how these drugs act, requiring further studies[8]. Data regarding the effects of fentanyl analogues in humans is scarce and exists in animal models but, as they share a similar mechanism of action their clinical features, are considered indistinguishable. Scientific literature regarding the toxicity and harm potential of novel synthetic opioids (NSO) is very limited, but they share analgesic and CNS depressant properties similar to other opioids[9]. As the life cycle of most NSO is very short, it is difficult to carry out detailed research on them and the long term effects of SOs are mostly unclear. All these factors greatly challenge the development of effective evidence-based interventions for people who use synthetic opioids.

Complexity of the synthetic opioid market

As of today, SO markets have been largely dominated by fentanyl and its analogues that number over 1,400 in total. They also vary largely in their potency, with carfentanyl being up to 100 times more potent that fentanyl. Over recent years, however, there has been a rapidly growing number of new psychoactive substances (NPS), among which the number of SOs reported between 2015 and 2019 has quadrupled from 2 per cent to 8 per cent[10]. With fentanyl analogues being increasingly controlled via class-wide scheduling, many non-fentanyl-related opioids are now emerging on the recreational opioid market, rendering the landscape highly complex and dynamic[11]. For example, of the ten new non-controlled SOs detected for the first time in 2020, only one was a fentanyl[12].

Most of the various non-fentanyl opioids that have emerged over recent years have very short lifecycles and do not become popular among people who use drugs (an example of a more prominent NSO group would be 'nitezenes'). Forensic toxicology laboratories are burdened with the detection of these highly diverse, often very potent, drugs for which standard reference material may be lacking, delaying testing capabilities[13]. This leads to a concern that deaths associated with SOs may be a growing problem in Europe but are underreported[14]. This makes the entire SO market situation very volatile and unpredictable, especially for users.

Potency and unpredictability

The use of new SO is not always intentional as people who use drugs might not be aware of the actual contents of the drugs used. As SOs are highly potent, dosage may be difficult to measure and their effects may be unknown or little understood by users. For example, long-term opioid users may be at increased risk of experiencing an overdose if they lack familiarity with the effects and appropriate dosage of these new substances. In addition, where new opioids are sold as heroin, or found mixed with or as a contaminant in other drugs, the risk of accidental overdose is also increased as users are not opioid-tolerant. It is unclear whether people who sell drugs purposefully adulterate stimulants with SOs or if it is a result of unintentional cross-contamination. In addition to the adulteration of drugs with SO, the SOs themselves are often mixed with adulterants (some of which may be pharmacologically active) that can have unexpected or life-threatening effects that users and drug services might be unprepared to address.

SOs also pose an increasing challenge for law enforcement. The high potency of SOs makes them more efficient for drug smugglers and dealers – smaller packages are easier to conceal or transport. In addition, they are more profitable; for example, by dose-equivalency, fentanyl is orders of magnitude cheaper to produce than heroin. As they are fully synthetic, it makes SOs also resistant to the effects of climate and plant diseases. These factors make SOs preferable for drug suppliers[15].

Scheduling

Over recent decades, the increase in NPS (including NSOs) has put pressure on existing national and international drug control mechanisms. As the international control system only allows individual substances to be scheduled rather than broad classes of substances, and with such decisions needing to be evidence-based, constantly emerging

NPS cause considerable difficulties. Greater flexibility in legislative approaches exist at the regional and the national levels where some countries have responded by adopting more proactive policies that control classes of substances (analogue, generic, and neurochemical legislation) or by imposing blanket bans on all psychoactive substances. However, this also elicits concerns about the appropriateness of these measures as they might have a negative effect on research or add stigmatisation to people who use drugs[16]. It should also be clear that while legislation may be effective in reducing the availability of one (or several) opioid(s), even generic legislation (aiming to cover a wide range of analogues, such as the Chinese ban on fentanyl analogues) may spark the creativity of illicit drug manufacturers towards other (known or unknown) compounds, some of which have greater potential for public harm and deadly outcomes[17].

Early Warning Systems

Executive summary

An Early Warning System (EWS) on drugs is a multidisciplinary network comprised of key stakeholders that enables information exchange among key actors directly or indirectly involved in the field of drugs. An EWS aims to identify early events of emerging drugs that pose a potential threat to public health. It assesses the risks and provides information to enable the planning of effective responses. For example, an EWS can help identify the emergence of new drug threats and changes in the drug market, such as new use patterns, unusual concentrations, or contents such as toxic adulterants. Such events provide valuable information to an EWS network.

Although national, European, and even global EWS exist for drugs, these systems would benefit from further improvements. It is essential that these systems are agile, responsive to new trends and threats, and not hindered by bureaucracy. Moreover, the right stakeholders who have first-hand information (such as forensic toxicology labs, law enforcement, research centres, institutions for dependency care, harm reduction initiatives) about emerging drugs and trends need to contribute to the EWS and exchange the information with each other and with the policy-makers. Furthermore, EWS should be designed to respond to localised outbreaks of harmful or adulterated drugs. Local EWS need to detect dangerous trends as they emerge.

As part of EWS, there is also a need to develop and strengthen real-time alert protocols within European countries to issue alerts from dangerous SOs as soon as they are found in circulation. Depending on the severity and scope of the situation, the alerts may be local, regional, or national. Their target audiences may include people who use drugs, health workers, outreach workers, harm reduction services, law enforcement, and other relevant populations. Enhancing the rapid flow and exchange of information is key to national and international SO-preparedness. Rapid local alert systems are excellent ways to inform and warn the public of potentially harmful substances.

Given that SOs are not yet causing significant problems in Europe, it is important to be well-prepared. Once the new potent SOs enter the drug market, momentum will be gone. Therefore, it is essential to respond rapidly to a crisis in its early stages. If the use of SO increases in Europe, rapid communication, EWSs, and the rapid exchange of information are crucial parts of preparedness planning.

1. General description of EWS

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Union Agency for Law Enforcement Cooperation (Europol), with the support of EU Member States, the European Medicines Agency (EMA), and the European Commission (EC), have been working together since 1997 to monitor and assess the risks of new emerging drugs on the European drugs market and provide for the establishment of an 'early warning system'[18]. The general objective of EWS is to maintain a surveillance system that includes information from multiple sources such as epidemiology, public health, security, as well as data on NPS and other emerging drug phenomena to support the development of rapid interventions[19]. In 2013, the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) was launched to monitor, analyse and report emerging NPS trends at the global level[20].

1.1. The EU EWS

The European EWS is a mechanism for the rapid detection and exchange of information on NPS, preceding and informing risk assessments and responses to the health and social threats of these drugs[21]. The EWS aims to ensure that timely, accurate, and sufficiently detailed information on NPS reaches the public on time to allow them to take action to prevent or reduce the risk of harm[22]. Operated by the EMCDDA, in close cooperation with Europol, the European EWS is the first step in a three-step legal framework designed to allow the EU to rapidly detect, assess, and respond to health and social threats caused by NPS.

The EWS aims to build, maintain, and strengthen situational awareness, preparedness, and response activities at the national and EU level. The EWS is composed of a multiagency and multidisciplinary network that includes the EMCDDA, 29 national early warning systems (in 27 EU Member States, Turkey, and Norway), Europol, and its law enforcement networks, the EMA, the EC, and other partners. At the end of 2020, the EMCDDA was monitoring around 830 NPS, 46 of which were first reported in Europe in 2020. In addition, 67 NSOs were detected between 2009 and 2020, including ten reported in 2020[23].

When a NPS is detected for the first time in a Member State, it reports the observation to the EWS, which again informs its network through a formal notification through the EMCDDA and its Reitox (Réseau Européen d'Information sur les Drogues et les Toxicomanies) network and Europol and its national units. Based on this assessment, if the EMCDDA determines that the substance meets the definition of a NPS, then a formal notification is issued to the Network on behalf of the reporting Member State. If Europol and the EMCDDA find that the information they are given requires the collection and analysis of more information, they will publish a joint report delivered to the European Council, the EC, and the EMA. Importantly, the information provided in the formal notification allows forensic and toxicology laboratories to include the substance in their analytical screening, allowing it to be identified and therefore monitored.

EWS are established in order to be able to address the rapidly changing availability and use of emerging drug threats. An EWS supports the early detection of new

substances and helps disseminate information on new drugs, new drug use patterns, and availability or market trends. Scientific, evidence-based information on the changing drug market is essential in making informed policy decisions to address any changes and to protect public health from possible health and social threats and drug-related criminality[24].

The significant impacts of an EWS in protecting health include the following[25]:

Awareness ↑ Preparedness ↑ Responses ↑ Harm ↓

EWS can play a central role in situational awareness, preparedness, and responses to health threats caused by NPS. Yet, like all public health interventions, strengthening these systems is a continuous process, and work remains to be done. The recent developments in the NPS market highlight the importance of continued investment in strong EWSs at both the national and EU level and a more rapid risk assessment process at the EU level to help protect the health and security of people living in Europe[26].

1.2. National EWS

Many governments have started establishing EWS at a national level. National EWS are commonly hosted by an institution, such as the national drug observatory or equivalent, which collects and analyses the collected information among various stakeholders. In Europe, EMCDDA coordinates a network of 30 national focal points (the Reitox Network). However, the EMCDDA does not control or advise the focal points on how to construct national EWS networks. Thus, in Europe, member states show quite different approaches. In some countries, the national EWS network only includes authorities such as representatives of the police, customs, forensic services, etc. In other countries, the network may consist of hundreds of people that have some connection to drug issues. In the latter approach, it may not be easy to control the sensitivity of the information delivered in the formal notifications. Therefore, EMCDDA EWS alerts always note that the information is restricted and may not be made publicly available.

LABORATORIES	OTHER FORENSIC EXPERTS	LAW ENFORCEMENT OFFICERS (POLICE AND CUSTOMS)
• detect and identify nps from analysis of seized material • provide confirmatory data on medical events occurring from use of substances and harms from toxicological analysis	• monitor, discuss and investigate the situation observed	• reduce the supply of substances • tackle possible criminal activities • are aware of the possible occupational exposure related risks
HEALTH CARE PROFESSIONALS	**OTHER INSTITUTIONS OR STAKEHOLDERS**	**POLICY MAKERS**
• assist in addressing potential harms for protection of public health	• contribute expertise to assess risks and advise on possible responses	• understand dynamics of the nps market • make evidence-based policies

FIGURE 1: UN Toolkit on synthetic Drugs: communication and knowledge-sharing between various experts[27].

Another example from The National Drug Early Warning Systems (NDEWS) from the United States:

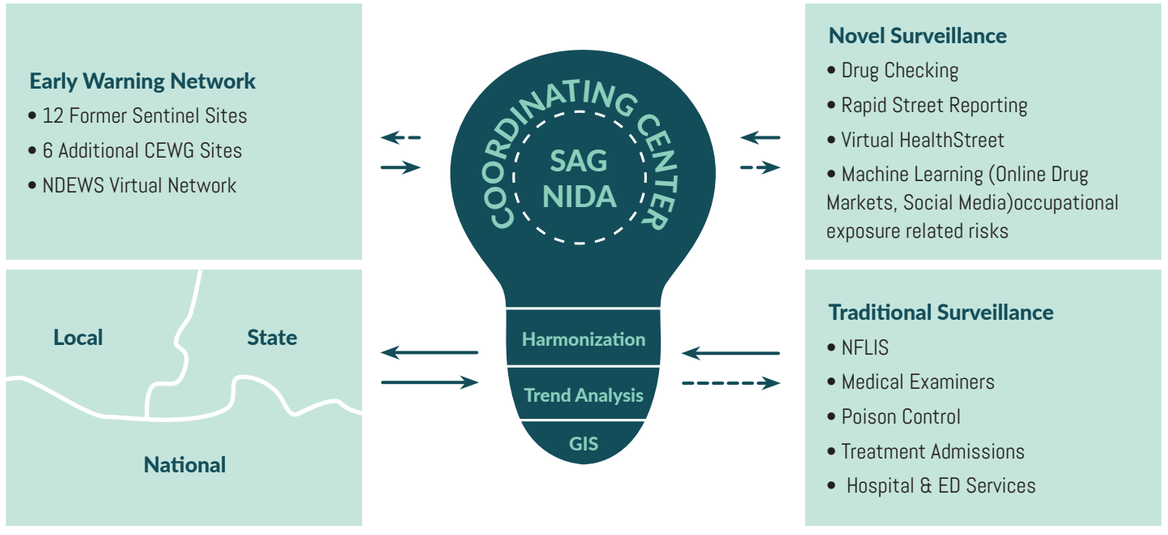


FIGURE 2: The National Drug Early Warning System, NDEWS[28].

At a national level, it is important to have the capacity to collect credible and reliable data to develop a national EWS. This allows countries to detect problems earlier, and any false or misleading information can be corrected quickly and countries can be better prepared to identify threats and put evidence-based solutions in place. In addition, there are cross-national EWS, including the previously mentioned EMCDDA EWS at the European level and the UNODC EWS at a global level. As a result, both national systems and the European/global systems benefit from each other through enhanced information exchange.

NDEWS includes surveillance to detect early signals of potential drug epidemics. In addition, the system implements an expanded Early Warning Network (EWN) that utilises novel surveillance methods and harmonises and disseminates data in a rapid and timely manner. The resulting system is more responsive than reactive. As a result, the national EWS can play a central role in situational awareness, preparedness, and responses to health threats caused by new and emerging drug trends.

Possible information sources at the national level include[29]:

» Law enforcement agencies and their laboratory networks responsible for the forensic analysis of drug seizures; these include police, specialised drug units, customs, border guards, prosecutor offices, prisons, etc.;

» Analytical toxicology laboratories that are responsible for clinical casework that involves the analysis of biological samples, particularly those related to serious adverse events such as cases of poisoning presented at hospital emergency departments;

» Forensic toxicology laboratories that are responsible for casework that involves the analysis of biological samples, particularly those related to medico-legal death investigations (such as post-mortem toxicology);

» Poison centres and related toxic surveillance systems;

» Health and care systems, including: hospital emergency departments; psychiatric departments; specialised and non-specialised treatment centres; outreach and street work agencies; drug prevention and harm reduction establishments; low-threshold services; drug helplines; and general practitioners, etc.;

» Drug checking programmes;

» National medicines regulatory authorities and the national pharmacovigilance systems;

» Universities and research establishments;

» Key informants, including: service users; organisers of mass gathering events (festivals, concerts, raves, etc.); owners and staff of clubs, etc.;

» Online fora where people who use NPS share experiences; and,

» Scientific publications and grey literature; printed and electronic media.

The structures of EWS can vary across different countries as they should meet the needs of local institutions and drug use patterns. Most EWS operate within a formal framework that defines its role, network of stakeholders and the legal basis for information sharing. Although some systems are also based on informal means of communication, dealing with sensitive and confidential information requires the establishment of standardised protocols. In addition, providing real-time information exchange requires close collaboration and trust among stakeholders in order to prevent or reduce the risk of harm, increase awareness and improve safety[30].

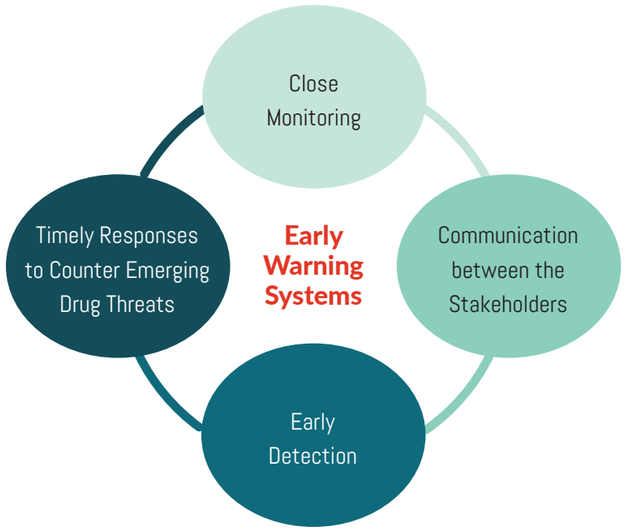


FIGURE 3: What does a functioning early warning system require?[31]

1.3. Local EWS

Although national and European-wide EWS exist, there is a need to identify, risk assess and respond to localised outbreaks of NPS and adulterated drugs. A well-organised and comprehensive local drug information system (LDIS) that uses consistent and efficient processes for sharing and assessing information, and issues rapid alerts where needed, can help ensure that high-quality, adequate information rapidly reaches the right people. As part of National EWS, there is also a need to develop and strengthen real-time alert protocols and local EWS within European countries to communicate risks from dangerous SOs as soon as they are found in circulation.

Depending on the severity and scope of the situation, the alerts may be local, regional, or national. Their target audiences may include the right stakeholders who have first-hand information about new drugs, such as people who use drugs, health workers, outreach workers, harm reduction services, law enforcement, and other relevant populations. Enhancing the rapid flow and exchange of information is key to national and international SO-preparedness. Rapid alert systems are excellent ways to inform and warn the public of potentially harmful substances. Rapid information sharing is particularly crucial among at-risk groups.

Digital interventions, such as mobile applications, could be used for alerting people who use drugs about highly potent or potentially harmful substances or adulterants. There is also a need for national databases and digital platforms for rapid data exchange. Moreover, the coordination,

implementation, evaluation, and reporting of data should be enhanced. In addition, information from people who use drugs and low-threshold services, such as drug consumption rooms, should be used in EWS. This can provide rapid on-site information about new or harmful SOs or especially harmful batches of drugs. Digital platforms for the collection of user-level information may be considered. Information should be disseminated to the public and all relevant stakeholders, such as health care professionals, first responders, and law enforcement officers. Educating individuals who may get into contact with people who use SOs is essential to enhance response capacity at the individual level.

Rapid communication and information sharing between various actors in the network, such as forensic laboratories, law enforcement officers, first responders, and health care professionals (such as low threshold health service centres and housing units) is also essential in reducing opioid-involved deaths.

2. Transferability of EWS to SOs

Over recent years, there has been a sharp increase in the production and distribution of new SOs, such as fentanyl and its derivatives, in Europe. At the end of 2020, the EMCDDA was monitoring around 830 NPS, of which 67 were SOs[32]. While SOs are not the largest group of NPS, they are generally associated with the highest risk of an overdose of all NPS.

In addition to the sale of illicitly manufactured fentanyl mixed with drugs such as heroin, cocaine, methamphetamine, and falsified (fake) medicines, there are also new products and new modes of administration such as nasal sprays and e-liquids, so the importance of robust monitoring and EWS that can detect and monitor both new and controlled SOs cannot be overstated. In addition, new testing-based surveillance methods, such as syringe residue and wastewater analysis, may become increasingly valuable in the future[33].

Many European countries have shortcomings in the rapid exchange of timely information. Therefore, the main challenge is to strengthen cooperation and systematic data collection and information exchange across all relevant partners. There is a need for national databases and digital platforms for rapid data exchange. Moreover, the coordination, implementation, evaluation, and reporting of data should be enhanced.

The recent developments in the NPS market serve to highlight the importance of continued investment in strong EWS at both national and EU level, as well as a more rapid risk assessment process at EU levels to help protect the health and security of people living in Europe[34].

Advantages and challenges of developing a national/local EWS

Developing a well-functioning local EWS that can provide real-time alerts to prevent and reduce drug-related harms, overdose and deaths needs to involve all relevant partners: people who use drugs, services, non-governmental organisations (NGOs), law enforcement agencies, hospitals, and emergency units. Such a system requires a well-organised flow of information and a clear understanding of everybody's role (including which information is relevant for whom to avoid information overload). In addition, it needs separate management to ensure that the provided information is competent and consistent.

Implementation models

» Good practice from France:

In France, the French Monitoring Centre for Drugs and Drug Addiction (Observatoire Français des Drogues et des Toxicomanies, OFDT) publishes information if there is a national threat. The National Public Health Agency and the Public Health Ministry can also post about such national threats. Often, as drug signals vanish quickly, this is done in the frame of the "drug signal process" to display alerts at the local level (city or region) through specialised services and notably with the support of NGOs using social networks to inform users quickly. NGOs can also take responsibility and lead such publications.

The French National Identification System for Drugs and Other Substances (Système d'Identification National des Toxiques et Substances, SINTES) combines surveillance and EWS through the efforts of law enforcement laboratories and social workers to provide relevant and timely information regarding the follow-up of drug trends and the identification of new or potentially dangerous substances to professionals, the public and European partners[35].

» Good practice from the UK and Ireland:

UK and Ireland DrugWatch[36] is an informal online Professional Information Network (PIN). The group aims to raise and establish standards for drug information, alerts and warnings.

» Good practice from the Netherlands (DIMS and RED ALERT):

In the Netherlands, the monitoring system is a well-developed, elaborate, and comprehensive system to monitor the use and incidents of illegal drugs with input from various sources, such as law enforcement agencies, the health care system, and consumers. In particular, consumer input nationwide through the Drug Information and Monitoring System (DIMS) is a special asset for monitoring and understanding trends and patterns of drug availability. DIMS is funded by the Ministry of Health and coordinated by the Trimbos Institute. It is one of the oldest drug-testing systems worldwide. In 2018, a total of 13,540 visitors supplied 12,634 samples for testing. The staff of DIMS also monitors online markets (in both the clearnet and the darknet) on the sale of substances and other consumer trends. One weakness of the drug checking service is that it is not fully known what groups use these services. In general, it seems that mostly recreational users make use of the services, while marginalised drug users do not[37].

Part of the monitoring and EWS in the Netherlands includes the possibility to announce a public warning, the so-called "Red Alert". Red Alert is a national or regional warning if there are signs of unusual harms

or risks caused by specific drugs. The warning starts a procedure of rapidly performed identification and warnings, including an app-based consumer notification. The Red Alert system operates under the responsibility of the Ministry of Health and the procedures follow a protocol.
There are three situations in the Netherlands that can initiate a Red Alert:

1. When drugs with a serious health risk have been offered and identified at one of the drug checking facilities;

2. When the police or National Forensic Institute (NFI) finds hazardous drugs;

3. When local medical authorities report serious incidents with drugs.

Other types of response: Twitter

Another example of an instrument that could be used for both monitoring the web for emerging SOs[38] and also as a communication channel to issue alerts, is Twitter, an effective platform for fast and reliable information sharing and early warnings (local EWS) when there are laboratory-verified exceptional findings that could pose a risk to people who use drugs.

The benefits of Twitter include:

» The information is immediately available to everyone;

» Any false, inaccurate, or misleading information can be corrected quickly;

» Journalists take advantage of Twitter messages, so information spreads widely and rapidly;

» There are also social, health, and substance use organisations and employees active on Twitter, with information flowing in real-time.
Twitter can give a lot of added value to information sharing and rapid alerts with "little effort", especially between experts, practitioners, and policy-makers. However, consideration should be given as to whether this channel is suitable for specific groups of people who use SOs. Aspects to consider when setting up a Twitter account include: who would be a relevant actor for administration (Governmental authorities, Reitox National Focal Points, or laboratories)? What are their duties and responsibilities?

Examples of Twitter accounts in Europe:

MANDRAKE:
https://twitter.com/MANDRAKE_LAB

WEDINOS Project:
https://twitter.com/WEDINOSProject

THE LOOP:
https://twitter.com/WeAreTheLoopUK

Drogvarningar:
https://twitter.com/drogvarningar

Outside of Europe:

NDEWS:
https://twitter.com/NDEWSnews

The Loop Australia:
https://twitter.com/WeAreTheLoopAU

Know Your Stuff:
https://twitter.com/KnowYourStuffNZ

3. Operational challenges for the successful implementation of a National EWS

Data collection

Timely data collection poses a series of challenges for an EWS. Firstly, the right stakeholders who have first-hand information about a new drug trend might not be able to contribute to the EWS. It is a challenge to get more relevant agencies and professionals involved in the network to provide necessary data. Forensic laboratories are an essential source of credible information but detecting highly diverse NSOs that may be present in very low concentrations is a challenge for many laboratories. Another shortcoming is the long waiting time for forensic expertise to provide results with some forensic analysis, for example, taking more than a month. Slow information flows means that police, public health officials, researchers, and people who use drugs do not know the risks until it is too late. Data collection from people who use drugs and substance use services is also vital for an EWS, but it is limited without anonymous drug checking services.

Issuing warnings

One of the challenges that an EWS might face is that it does not provide alerts on new trends in drug use because this action is not included in its objectives. For example, there is an awareness that SOs may become a bigger problem in many European countries, but there has not yet been the need for new methods of information exchange. Reaching potential SO users with the right information through appropriate channels is a further challenge as certain user communities might be difficult to reach. This is especially relevant when considering the use of digital interventions. Establishing the appropriate channels, such as in low-threshold services or 'housing first' units, should be undertaken before SOs emerge on the drug market.

Rapid information exchange

It is important that an EWS is agile and responsive to threats and unhindered by bureaucracy and to rapidly disseminate information on NSOs and other emerging drug phenomena among relevant stakeholders. One of the challenges is how to arrange the rapid flow of information through a network: exchanging information and a rapid flow of information are important, and the network with a fast flow of information should be comprehensive. Many European countries have shortcomings and room for improvement in the rapid

flow of information. Rapid information sharing is particularly key among at-risk groups who might be threatened by highly potent NSOs.

Lack of coordination and established protocols

An EWS relies upon many diverse sources of information and requires established protocols for data validation and assessment. Coordination of these processes between relevant stakeholders can often be enhanced. In addition, the way locally relevant information is made public should also be planned. Currently, in some countries, these networks only comprise authorities but not civil society organisations (CSOs) or people who use drugs. In other countries, the network may consist of hundreds of people that have some connection to drug issues. In the latter approach, it may not be easy to control the sensitivity of the information delivered in formal notifications. Media reports and other warnings regarding novel, potent, adulterated or contaminated drugs have also increased over the last decade. However, these reports are often inaccurate, rarely confirmed by toxicology tests and may sometimes be counterproductive to public health messages intended to reduce drug-related harms and deaths.

4. Policy considerations for service providers

Include all relevant sources of information

Platforms for the collection of user-level information, such as drug consumption rooms and drug checking services, should be considered in an EWS. This can provide rapid on-site information about new or harmful SOs or bad batches of drugs. Data from emergency services and hospitals can help detect the emergence of harmful substances on the drug market and increases in the use of harmful substances. Following and monitoring drug trends, changes in drug consumption patterns, including online drug markets, both on the dark web and clearnet (including social media platforms) and drug fora could provide additional useful information. In addition, the use of innovative research methods such as wastewater and syringe residue analysis should be considered.

Disseminate information to all affected populations

Information should be disseminated to the public, relevant stakeholders, and populations at-risk, depending on the specific case. The network should include members from the law enforcement sector (police, customs, and border forces); relevant laboratories (forensic science and toxicology laboratories); poison centres; hospitals; government departments responsible for implementing drugs policy; national medicines regulatory authorities; and specialised services for people who use drugs including low-threshold services, outreach work, housing units, and peers. In addition, educating individuals who may come into contact with people who use SOs is important to enhance response capacity at the individual level. It can also be useful to utilise Internet message boards, for example, as sources and in the dissemination of information. It is very important to be present on all channels.

Maintain network functioning

It is important to keep the network members motivated and active by ensuring that information and innovations are routinely shared throughout the system. In addition, the network should meet regularly to ensure that the system works satisfactorily. The capacity of members should be stimulated and strengthened via ongoing education. It is strongly advised that stakeholders be supported to stimulate growth in their respective fields on EWS-related topics [39]. Finally, maintaining EWS functioning depends on the stability and sustainability of funding. In many countries, the EWS clearly requires more resources.

Internet monitoring

Executive summary

Communication channels on the clearnet and the dark web can be used as marketplaces to discuss or trade SOs. As such, online monitoring of these channels can be used to gain insight in, and the evolution of, the demand and supply of SOs. Unlike the communication channels accessible through the clearnet, darknet markets are more hidden for internet users. Darknet markets are only accessible using anonymisation software such as Tor[40]. Consequently, the monitoring of darknet content generally requires more (technological) skills than the monitoring of clearnet content.

In this Toolkit we describe the difference between manual and automatic drug monitoring and the different channels that can be monitored. We also discuss basic principles to start SO monitoring as well as existing practices in online SO monitoring, focusing on both the demand and supply side of SO. Furthermore, we present some obstacles in the monitoring of these channels and how to overcome them. We conclude by stating some recommendations for policy and practice when implementing online SO monitoring.

Online SO monitoring provides unique information that is not available through more traditional research methods, such as surveys. It is hoped that this Toolkit can inspire and support you along the way.

1.General description of online (drug) monitoring

Internet surveillance entails the monitoring of digital data exchanged on the internet, such as the clearnet and deep web[41]. The clearnet is generally described as the visible part of the internet indexed by search engines as opposed to the deep web which is unindexed and includes paywalled websites and password-protected websites. A part of the deep web is the darknet which consists of internet services only accessible through anonymising software[42, 43]. Consequently, the monitoring of darknet content generally requires more (technological) skills than the monitoring of clearnet content.

Various online communication channels on the clearnet and the darknet can be used as underground marketplaces to discuss or trade legal but also illegal goods and services[44]. These channels include Google Trends, Instagram, Twitter, Facebook, chat rooms, cryptomarkets, clearnet and the darknet online discussion board (see below). As such, online monitoring of these channels can be used for gaining (new) insight into these (il)legal phenomena and the inner workings of these underground places, as well as allowing predictions related to the (evolution of these) phenomena[45].

One of these illegal phenomena that could be perfectly monitored online are (evolutions in) the demand and supply of illegal drugs. Online drug monitoring refers to the "systematic monitoring of trends and developments concerning substance use via the internet"[46]. Amongst others, this involves the monitoring and systematic data gathering on search behaviour, discussions, user experiences, drug markets and the supply of drugs[47].

Online drug monitoring of these channels provides unique information that is not available through more traditional research methods, such as surveys, making it a great addition to other, more regular, systems.

1.1. Manual or automatic online data collection

Online data can be collected manually or automatically. Manual collection involves copying and pasting data from online spaces. One could opt for manual collection when lacking technical skills. However, this is a very time-consuming task[48]. Automatic data collection can be divided into indirect (leaks) and direct monitoring (active monitoring and mirroring/ web crawling)[49].

Indirect monitoring

Indirect monitoring is the monitoring of leaked information on the internet, such as the publication of databases of online forums and customer lists. Due to their sensitive nature, leaks do not remain online for long, so continuous monitoring is needed to stay up-to-date. Leaks can be gathered by building software that looks for certain keywords on forums, blogs and social media sites, and through security podcasts[50]. Indirect monitoring also refers to gathering information collected by third parties, such as search engines and the Internet Archive[51]. Google Trends has already been proven to provide information on consumer interests and popularity of substances [52] and has been used in studies focusing on NPS[53]. For example, through Google Trends it is possible to determine how often a word is searched, which can be an indication of the popularity of substances[54].

Active monitoring

An example of direct monitoring[55] is active monitoring which includes the active monitoring by researchers themselves of short-term communications on platforms such as online chat rooms and social networks[56]. Various efforts have already been undertaken in this regard. More specifically, Fallmann, et al.[57], present a system to automatically monitor various information channels such as Internet Relay Chat (IRC) and web forum marketplaces. Décary-Hétu, et al.[58], developed an automated framework to monitor hacker chat rooms for which the data can also be used for content analysis, providing information on needs, techniques and behaviour. The Psychonaut Web Mapping Project manually searched the internet, such as websites, online shops, newsgroups, and

Facebook, for two years to regularly monitor relevant websites and collected and archived data with the goal to identify emerging NPS trends [59, 60] .

Mirroring

Another technique of direct monitoring is mirroring. Using a crawler and scraper robot, web pages can be downloaded and then specific information extracted which can be stored in a structured database [61]. Crawling and scraping bots have already been used to monitor drugs online [62, 63, 64]. In the context of drugs, the Trimbos Institute has already developed a scraping tool to monitor online discussions on NPS which gathered information such as the number of newly started discussions topics and the date they started, the number of messages and how much topics were viewed [65, 66, 67]. This allows for the early detection of new drugs and changes in drug markets, such as the rising popularity of emerging NPS [68, 69]. The I-TREND project, coordinated by OFDT, developed a partially automated crawler to first identify surface web e-shops offering NPS and to monitor these shops as well as user forums [70, 71]. The EMCDDA also crawled various markets on the darknet to analyse the darknet drug supply [72, 73]. Both crawled data from clearnet and darknet drug forums and data from Google Trends provide almost real-time insights as opposed to official data sources [74].

For social media networks, such as Facebook, Twitter, and Instagram, application programme interfaces (APIs) can be used to gain access into the collected information of networks [75, 76].

2. Online monitoring as a key response to (the emergence of) SO

In this chapter we discuss how existing methods in the context of online (drug) monitoring can be adapted to the emergence of SOs on the internet. We present the different kinds of online channels that can be monitored, as well as some preparatory steps that need to be taken before starting online drug monitoring. Furthermore, we discuss existing practices in online monitoring with a focus on 1) the demand side; and, 2) the supply side of SOs.

In this Toolkit we do not focus on the distinction between clearnet and darknet. We rather want to address some basic preparation principles relating to (preparing) the monitoring process, regardless of whether the monitoring relates to clearnet or darknet content.

2.1. Online SO monitoring on the clearnet versus the darknet: preparation is key

SOs are found on both the clearnet and darknet [77, 78]. Ideally, to fully monitor trends in SOs, both the clearnet and the darknet should be monitored. Using only traditional search engines, such as Google, results in solely accessing websites and forums on the clearnet. As such, for a full view on the topic, the darknet and its cryptomarkets should also be included. Locating darknet content can be undertaken manually or by using a scoped crawler (see below) [79]. However, discovering darknet websites to be crawled can be difficult[80]. For manual identification, online directories, such as Hidden Wiki, and specialised darknet search engines, such as DuckDuckGo, TORCH, and Recon, can be used, although these search engines may be unreliable. Hence, researchers can also make their own list of websites using posts on clearnet forums, blogs and social media networks referring to darknet content [81].

Firstly, determining the most relevant search strategy and keyword selection to ensure every relevant source that may be useful can be identified. Secondly, automatic monitoring happens by using web crawlers and scrapers, hence they need to be developed in such a way that everything can be scraped and stored.

Keyword selection and search strategy

A search strategy focusing on the problem at-hand is needed to identify the relevant online spaces and messages that can provide the necessary information. This implies the usage of appropriate keywords[82]. Internet users may also use jargon, synonyms or (deliberately) misspelled words, so many (misspelled) variations of words should be included in your keyword selection as well as such terms as “U47700”, “u44770” or “pinky” for U-47700 or “carfentanyl” for carfentanil [83].

With regards to SO-related keywords, it is important to stress that the keyword selection should be adapted to the specifics of the online space you are monitoring such as Telegram or discussion forums (see below). Thus, a screening strategy might be developed to identify keywords specific to different online spaces. After identifying various forums and websites, the content of these sites can be analysed to extract new keywords[84]. Generic search terms, such as ‘drugs forum’, ‘research chemicals forum’, ‘designer drugs forum’, ‘legal highs forum’, and ‘new psychoactive drugs forum’, result in identifying forums related to drugs (including NPS) in general, but can also be scanned for information on SOs using SO-related keywords when scanning forum discussions[85]. Already existing lists of SO-related keywords can also be used and expanded. For example, the EMCDDA list of SOs[86] or van der Gouwe, et al.[87] that identified almost 60 terms of new SOs that were used to crawl (sub)forums. Scientific studies on the availability of SOs on the clearnet and darknet, such as by Lamy, et al.[88], can also be used to determine what kind of SO exists and thus can be used as keywords.

As the number of different SOs is growing exponentially in Europe and worldwide, this process of identifying new keywords should be periodically repeated to stay up-to-date and to identify new types of SOs. Translations of the various keywords should also be used to identify forums and discussion posts only available in languages other than English.

Various search engines differ in the search algorithm they use and the way they scan and index websites. This can result in different results for each search engine used and even when the same keywords are used [89]. Thus, when you aim to monitor hidden phenomena such as illegal drugs on both the clearnet and the darknet, you not only use Google as a search engine but also other search engines such as Bing or DuckDuckGo. Google may choose not to show certain search results and other search engines may show

search results higher on the list of found results (and thus faster to find) in comparison to Google. In addition, Google does not index content on the darknet [90]. In order to find content on the darknet (as opposed to DuckDuckGo and others (see supra)), other search engines residing on the darknet can be used, such as Torch.

Web crawling and scraping

The basics concerning crawling and scraping are generally simple, although as previously stated, finding the websites can be more challenging on the darknet. When the websites and the keyword selection have been identified, relevant data can be extracted using crawlers and scrapers.

A crawler downloads a series of webpages and then extracts hyperlinks from which other web pages can be downloaded based on previously established parameters. The scraper then looks for the relevant information based on the criteria decided by the developer of the scraper and stores it in a database[91, 92]. As the goal is to mine data related to SOs, a scoped crawler can be implemented which limits the crawler's activity to web pages that fall within the scope of the crawler[93]. There are different types of scoped crawlers. With regards to online drug monitoring, a topical crawler that focuses on webpages relevant to the defined topic is likely to be the most useful[94].

Decisions need to be made on the specifications and level of automation. Specifications include the type of data to be gathered, the method of storage and the type of connection protocol that the crawler can use. Scrapers need to be taught what information they should look for and extract. Previously conducted research can provide guidance here[95, 96]. In mirroring prior successful attempts at monitoring NPS on forums, such as by Guarita, et al.[97]; Rhumorbarbe, et al.[98], the same kind of data should be scraped: the link to the post; the title of each thread; the number of newly started discussion topics since the previous measurement; the date of creation; the number of views and replies; the number of posts in a thread; and the number of users involved in the discussions. The data should be stored in a uniform way by comma separated value (csv) file type as that should allow most software to read the data no matter the source of the information or time of gathering. Crawlers usually connect to regular connections (Time-Triggered Protocol (TTP)), though it may be wise to ensure a crawler connects through secured connections (Secure Time-Triggered Protocol (TTPS)) as some websites are only accessible this way[99]. Automation refers to the time intervals that the crawler should crawl, feeding the crawler files to ensure it only spends time on the sections of a webpage that are relevant to the researchers. Access to websites is sometimes restricted by forcing people to login or enter a captcha, which not every scraper or crawler can bypass[100].

2.2. Examples of online monitoring channels for the prevalence of SO

Indirect monitoring channels

» Google Trends

One example of an indirect monitoring tool is Google Trends, an online tool created by Google that analyses user inquiries made to Google that reflects the search interest in a specific topic. Google Trends provides both real-time data concerning the past seven days and non-real-time data between 2004 and up to 36 hours before the Google Trends inquiry. The tool allows people to compare different search terms or topics across different regions and time on a normalised scale ranging from a search interest of 0 to 100[101], and to collect weekly or monthly reports[102].

For example, search terms like 'etazene' and 'U-47700' (both SOs) can be compared to illustrate the difference in search interest over the past twelve months worldwide[103]. Researchers should, however, be mindful of using the correct search strategy (see supra) as Google Trends sees each (mis) spelling of a word as a different search[104]. Using the aforementioned example, entering 'etazone' or 'etazen' (both synonyms) or 'U-47.700' (different spelling) ends in different results, but using an operator such as '+' (for example, 'etazene + etazone + etazen') should resolve this issue[105].

» Leaked databases

Using leaked data from forums and other websites is also one way to indirectly monitor a phenomenon. As opposed to using forums as a source of data in itself, forums can also be a place to access leaked databases containing information such as messages, email addresses, internet protocol (IP) addresses and passwords[106], and revenues (such as McCoy, et al.[107]). Leaks may be less useful in monitoring. As leaks are fleeting in nature, the existence of leaks needs to be monitored closely and frequently whilst not necessarily containing useful information. Their existence also depends on third-party activity and it is not guaranteed that leaks of websites and forums with a focus on drugs and SO will appear. Thus, the costs may outweigh the benefits.

Direct monitoring channels

» Online discussion boards

Online discussion boards or forums play a major role in the online monitoring of SOs as they are places where promoting, selling and discussion takes place[108]. These discussion boards are available on both the clearnet and darknet. Monitoring discussion boards is mostly useful for monitoring changes in substances and substance use, less for estimating the prevalence of drug use[109]. Many forums and discussion boards that discuss drugs and/or their use can be found using traditional search engines on the clearnet. The Psychonaut Project[110] provides a list of drug discussion boards, some of which also include SOs that are still active today (though sometimes using a new Uniform Resource Locator

(URL)). PsychonautWiki[111] also has an overview of various discussion boards, some which also focus on NPS (including SOs). Drug discussion boards on the darknet are sometimes connected to cryptomarkets and, in this way, the identifying cryptomarkets can lead to the identification of darknet drug discussion boards. As indicated earlier, darknet content is not as easily found as clearnet content. For this purpose, various websites exist that are also available on the clearnet that provide links to cryptomarkets and forums. Information on discussion boards can be manually gathered or through the use of a webscraper. Some forums and discussion boards are not immediately accessible as they may require a registered account or the filling out of a captcha. In the case of manual data gathering, this should not be an issue. However, in the case of automatic data collection using scrapers, the scraper may need to be altered so that it can bypass these restrictions, or manual intervention is needed.

» Social media

Demant and Bakken[112] have noted that social media markets generally offer the more common type of drugs, such as cannabis and cocaine, as opposed to darknet markets which have a wider variety, though NPS might also be found there[113]. Given the nature (i.e. short texts) of most of the mentioned social media channels, these channels could be more relevant for monitoring the supply of SOs on the clearnet.

Social media sites are more difficult to crawl as they actively block crawlers, but gathering their data is still possible through their APIs[114]. Through APIs, it is possible to make requests to social media servers to retrieve posts and information on, and connections between, users[115, 116], although APIs often restrict how much and how often data can be gathered[117]. As for Instagram, posts are identified by using drug-related hashtags. For this, existing datasets on drug-related posts can be used (for example, the New York State Attorney General's office dataset in Zhou, et al.[118] . In case these are not available or accessible, the list of SO-related keywords (see supra) can be used. It is advised to only gather posts with two or more relevant hashtags to increase accuracy and to keep the list up-to-date by using an algorithm that mines frequently used hashtag sets[119].

An Instagram crawler also exists that collects URLs, post metadata and profile metadata[120]. Whilst advertised as a tool for marketing, the gathered data could also be used to determine sentiments.

Twitter can also be used as a tool to monitor the emergence of SOs. As with Instagram, tweets can be collected using the platform's API filtering for specific keywords. By using the machine learning model Biterm Topic Model, it is possible to detect themes in short texts like tweets. This has made it possible to identify tweets about the online marketing and sale of prescription opioids[121], which could easily be applied to SOs when using the appropriate keywords. Besides giving insight into the amount of people using Twitter to advertise sales (and how this evolves over time when actively monitored), it is also a tool to identify online shops[122].

Facebook and Telegram are also places where SO sales occur[123, 124, 125]. Though given the existence of public, private and secret groups and the lack of post limitations, as opposed to the character limit of Twitter, and different post formats, such as photos on Instagram, a greater emphasis is placed on discussion. Thus, Facebook and Telegram groups should also be looked into and monitored for discussions about usage and effects.

Facebook also does not allow automatic data collection[126]. Hence, manual data collection is needed but given the private nature of the posts, this may also be difficult legally and/or ethically (see below). Identifying these groups should work in the same way as with the previously mentioned channels by entering SO-related keywords in the search bar. However, these groups are often closed, meaning only members can see the content[127], or are secret, meaning only those who have been invited can search for and access the group.

Telegram messages are cloud-based and encrypted end-to-end and can be set to self-destruct. A same way of working, as explained above, should occur, meaning manual data collection rather than automatic data collection. Following the work of Blankers, et al.[128], the Telegram search engine and keywords related to SO could be used to find specific groups or markets. Once subscribed, all posts placed in this group could be read starting from the subscription date. Messages could also be downloaded and stored as hypertext markup language files (html-files).

» IRC chat rooms

Décary-Hétu, et al.[129], developed a framework to monitor information on IRC chat rooms. Despite it being applied to online hackerspaces, it could also be used in other instances. IRC search engines, such as Netsplit, can perform searches using specific keywords to identify relevant IRC networks and channels. In the case of drug monitoring, it may be more useful to perform general searches, such as "drugs", as opposed to immediately focusing on SOs, as the search query merely identifies spaces, not messages; this, however, does not identify more exclusive chat rooms. Befriending users is often needed to access more hidden spaces. Existing drug forums can also include links to relevant IRC chat rooms[130].

Messages on IRC chat rooms are not saved but an IRC bot can be developed to monitor and store certain information, such as people entering and leaving, messages, usernames, and IP addresses. There are also many freely available IRC bots, such as Eggdrop, that can be adapted and expanded in accordance with research needs. Just like web scraper data, this data is usually saved as comma-separated value file type. The collected messages can then be subjected to content analysis to identify needs or behaviours[131].

2.3. Case studies of online monitoring of SOs

Examples of online monitoring related to the demand for SOs

» The I-TREND project

The I-TREND project[132] developed an automated tool to monitor general trends in NPS. It consisted of several workstreams, including the monitoring of user forums and a survey of users. Results showed that forums were an efficient way to reach a large

and invisible portion of NPS users and were capable of highlighting trends in the interest of users and identifying demand-related factors, such as lower availability and quality of traditional drugs on the regular market that may push users towards NPS alternatives[133, 134]. The intention was to summarise information on intake methods, dosage and adverse effects, though the available data was too limited[135].

» The Trimbos Institute: Scraping tool

The Trimbos Institute developed a scraping tool to monitor discussions related to NPS on drug forums and discussion boards based upon the pioneering work of the I-TREND project. Though it focuses on NPS in general, it should also be applicable specifically to SOs. The tool allowed the determination of the number of posts on NPS and their contents. The quantity of new topics can be used as a proxy for estimating the popularity of new NPS, including SOs[136, 137]. A sentiment analysis was used to monitor (changing) opinions of users on NPS (see below).

» The sentiment analysis of Blankers, et al.

Blankers, et al.[138], scraped two drug discussion forums and subjected the posts on drugs, such as 4-fluoroamphetamine, to a sentiment analysis. This type of analysis allows the determination of view on drugs in positive or negative terms. Changes in sentiment coincided (or preceded) with reports on health incidents. The authors do note that in order to use forum sentiment trend monitoring for drug monitoring, more research is needed on "the predictive validity of automated forum sentiment monitoring to discover emerging trends in (attitudes towards) substance use behaviour"[139].

However, the use of online discussion board data has several benefits. Researchers do not need to intervene in these discussions to scrape the data and the data is usually of higher-level validity because the lack of involvement reduces the risk of contamination. There is also less of a risk of disclosing information that was not meant to be disclosed because the posts are written by the users themselves[140, 141]. A limitation of using online discussion board data to monitor the demand side is the usage of more closed-off channels, limiting the amount of observable channels. Also, more research is needed that establishes the representativeness of data from drug forum users, which is why this type of data should be triangulated with other data sources[142].

Examples of online monitoring relating to the supply of SOs

» I-TREND's SASF

The I-TREND project, mentioned above, also included the monitoring of the supply side through online shops. This led to SASF, a semi-automated e-shop finder that gathers data such as type of shop, location and products[143]. At the time, the tool still required manual intervention[144], which led to the development of its successor.

» PsyIT's SASF2

The I-TREND project led to a new and fully automated machine learning crawler to monitor webshops selling NPS. A user-friendly interface showed the shops that were identified after a Google inquiry using a combination of NPS names from the EMCDDA's database and the words 'buy' and 'online'. This has led to the identification of 62 e-shops offering SOs by December 2018 and 27 e-shops by September 2019[145, 146, 147].

SASF2[148] provides insight into the dynamic nature of these kinds of shops by monitoring the status of shops (active or terminated), showing that most only remain active for a few months. Its machine learning based nature allowed the tool to continually improve its recognition of e-shops, minimising human input[149]. SASF2 can also be expanded to include multiple countries and languages[150]. The downsides are that the tool is limited by the restrictions related to the amount of free Google searches and server capacity and that the machine learning algorithms need to be adapted in accordance with the different countries and languages. SASF2 also limits itself to the first 20 outcomes, which may result in the fact that many shops and SOs are not included and remain invisible, though this cut-off point could be set higher to include a larger scope. The tool also does not include contextual information, such as prices, quantities and availability, only showing the range of products[151].

» Monitoring Telegram by Blankers, et al.

The monitoring activity conducted by Blankers, et al.[152], is different from the other examples provided above as it is not a tool but rather a method. They analysed Telegram groups to evaluate whether changes in psychoactive substance trade on Telegram markets in the Netherlands could be observed during the COVID-19 pandemic. They used the keyword "drugs" in Telegram search engines to find three Telegram market groups. After subscription to these groups, they were able to read all posts placed in each group. They used the Telegram desktop client to export the chat corpus of the groups that they were following. The chat corpora were stored as html files and later imported in R. In R, the authors extracted relevant data of the html-based chat corpora and stored these data in a dataset.

At the same time, they created a database containing different key words or phrases they wanted to search for in the Telegram posts, such as common names for more than 300 different substances. They used 5–19 key words for each substance and they evaluated whether any of the key words or phrases were present in a post stored in their dataset. If so, the presence of the key word or phrase in the post was recorded in the dataset. After the pattern-matching procedure was completed, they had a final dataset that was used for further analysis, containing all posts, associated dates, the Telegram channel where the post was published, and information on the presence of any of the key words or phrases in each post[153].

Reporting on SO online monitoring

Monitoring data from the demand for, and/or supply of, SOs could be used in several ways, such as writing an annual report on the situation regarding SOs being present in a particular country. Visualisations, based on these data, could be made to fuel (policy) reports concerning the demand and/or supply of SOs.

An example of such practice is the annual report of the Reporting Desk for New Drugs[154]. The Reporting Desk for New Drugs analyses and reports on data collected on demand and supply of NSP collected by diverse organisations in the Netherlands.

On its webpage, it states that, "The Customs Laboratory of the Netherlands and the Netherlands Forensic Institute provide data about seized new psychoactive substances that have been sent to their laboratories for analysis. The Drugs Information and Monitoring System (DIMS) provides data about new psychoactive substances that have been detected after laboratory analysis of consumer samples submitted to a drug checking service. The Monitor Drug-related Incidents (MDI) and the Dutch Poisons Information Centre (DPIC) share data about adverse health-related events related to the use of new psychoactive substances. Additional information about new psychoactive substances being used in the Netherlands is also collected from pre-selected online consumer discussion boards about drugs"[155].

Figure 4: Reporting Desk for New Drugs in the Netherlands[156]

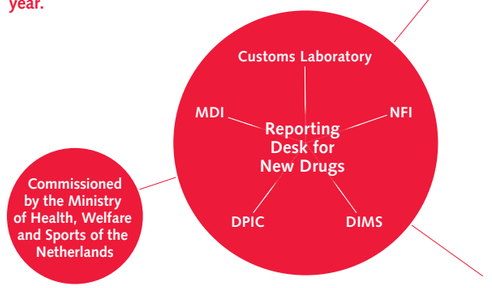
Annual Report 2020

Reporting Desk for New Drugs

Trimbos instituut
Netherlands Institute of Mental Health and Addiction

What is the Reporting Desk for New Drugs?

The Reporting Desk for New Drugs is a large-scale national surveillance study in the Netherlands, which is coordinated by the Trimbos Institute. Through this surveillance study, data are collected about new psychoactive substances in the Netherlands. The Reporting Desk for New Drugs reports on which new psychoactive substances had been discovered to be present in the Netherlands, and if available, in which quantities these new psychoactive substances have been detected on the illicit drug market during the last year.



Organization: The Reporting Desk for New Drugs assembles, analyzes, and reports on data collected by a variety of organizations in the Netherlands about the production, trade, and consumption of new psychoactive substances. The Customs Laboratory of the Netherlands and the Netherlands Forensic Institute provide data about seized new psychoactive substances that have been sent to their laboratories for analysis. The Drugs Information and Monitoring System (DIMS) provides data about new psychoactive substances that have been detected after laboratory analysis of consumer samples submitted to a drug checking service[1]. The Monitor Drug-related Incidents (MDI) and the Dutch Poisons Information Centre (DPIC) share data about adverse health-related events related to the use of new psychoactive substances. Additional information about new psychoactive substances being used in the Netherlands is also collected from pre-selected online consumer discussion boards about drugs.

Application: The annual report from the Reporting Desk for New Drugs is used by the Ministry of Health, Welfare and Sports in the Netherlands and the Coordination point for Assessment and Monitoring new drugs (CAM[2]) to assess the distribution and possible risks associated with the sale, transport, and use of new psychoactive substances.

What are new psychoactive substances?

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines new psychoactive substances as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat"[3]. The Reporting Desk for New Drugs focuses on substances that have been produced in and introduced to the illicit drug market for their psychoactive properties since the early 2000s.

A few substances, such as 2C-B, GHB/GBL, DMT, and ketamine, have also been included in the Reporting Desk for New Drugs, as these substances are being monitored by the European Monitoring Centre for Drugs and Drug Addiction as well monitored under the framework of the European Joint Action on new synthetic drugs. In this Annual Report 2020 of the Reporting Desk for New Drugs, these substances are referred to as 'classic' psychoactive substances.

New psychoactive substances classified into substance groups

New psychoactive substances are usually classified according to their chemical structure or pharmacological properties. These classifications include:

- Synthetic cannabinoids
- Cathinones
- Phenethylamines
- Tryptamines
- Piperazines
- Other new psychoactive substances:
  - arylcyclohexylamines
  - synthetic opioids (i.e. fentanyl derivatives)
  - new benzodiazepines

Currently, there is no nationwide surveillance system for new psychoactive substances in the Netherlands, which means that underreporting of all new psychoactive substances is likely. However, the information from the Reporting Desk for New Drugs gives an indication of the situation regarding new psychoactive substances being present in the Netherlands on the illicit drug market.

3. Operational challenges

Lack of expertise

The most important factor that can inhibit the implementation of an online monitoring system is a lack of technical expertise. This might be especially possible when monitoring channels on the darknet because access to the darknet requires more technical involvement than clearnet monitoring. Therefore, a thorough preparation is important before entering and monitoring the darknet.

Furthermore, manual monitoring may be easier than automated monitoring and, as such, is more accessible for people with limited (technological) knowledge and skills. However, manual monitoring might be less useful when monitoring a large number of websites because it results in a large amount of data that needs to be managed and analysed correctly.

Automated monitoring usually involves web crawlers and scrapers. Designing and configuring such tools correctly requires sufficient programming skills in coding languages not held by every researcher. Either computer scientists need to be involved (as part of a research team or by outsourcing this task) who can build a customised crawler and scraper. Other possibilities involve the usage of existing frameworks that can be adapted, or the involvement of commercial services (such as import.io; zyte.com; webscraper.io)[157]. An example of a paid crawler and scraper specialized in identifying sales and services on the darknet is Datacrypto[158]. A free tool for mining data both on the clear- and dark-net is D-miner[159].

Another free alternative is contacting those who have already developed tools for monitoring drugs such as NPS. The people behind SASF2 already noted that their tool could be used to mine similar markets and expanded to include different languages[160]. Automated tools will, however, always need a manual touch, as new SOs appear on the markets quite fast. Therefore, the crawling method needs to be adapted, such as through follow-up with a manual search.

A further challenge is that the administrator or moderator of the market place or online discussion board that you are scraping might blocked such activities. When scraping on a large scale is begun, it may overload the server's resources, generate huge traffic and, as a of result, such actions might get blocked. Risk of getting blocked quite quickly occurs when such rules are not known, or actions are not adapted quickly.

As indicated earlier, not every scraper or crawler is able to enter a website and start the scraping for information due to the existence of captchas or they require registration and logging in to the website. Using a scraper or crawler not adapted to these blockages limits the number of websites that can be monitored. This might, however, be easily solved. A crawler can be adjusted to ensure it stores the login information so the website can be entered without manual intervention (assuming the project has the necessary people with the skills to do this)[161]. Crawlers are sometimes able to solve simple captchas (i.e. character recognition of text-based captchas), but for more complex captchas manual intervention may be needed[162]. In particular, darknet websites make extensive use of complex captchas. For this, commercial services can be used, such as Death By Captcha, that solve captchas and send it automatically to the crawler in exchange for a small fee[163, 164, 165].

Representativeness of data

There are issues with regards to the generalisability of the data. More research is needed to understand to which populations that generalised information can be attributed and to which degree online users are representative of the general population of drug users[166, 167].

Focusing on Google Trends, its results only form an indication of the search interest of a term. It is not possible to figure out the intention behind the search, i.e. if it was in fact related to a specific drug and not another similar word[168], or with what intention the person searched the term (i.e. just looking up what it means or with the intention to buy it). Queries also need to cross an unspecified threshold before being reported by Google Trends[169], meaning that lesser known or searched for SOs remain unreported.

Ethical issues

One ethical issue related to online research is that of informed consent. Opinions are divided on whether informed consent is needed with regards to using data from online public platforms. And if so, whose informed consent is needed (individuals or administrators/moderators).

Relying on the consent of individual users by posting a public message informing users of a discussion forum for their permission can greatly limit the scope of the research and not every member will see this. Permissions can also be given by the administrator and/or moderators, though this does not necessarily reflect the opinions of all members. One can also rely on the terms of the website to see if its data can be used[170].

Given the illegal nature or grey zone surrounding SOs, it is not unlikely that some individuals may not be open to this monitoring. With forums restricted to purely discussions on usage methods, effects of drugs and harm reduction, this may be less of an issue. Other places with a focus on sales, such as vendor websites, may prove to be more difficult to retrieve consent[171]. However, websites accessible without needing a registered account or invitation can be considered to be public and, thus, is public data for which no consent is needed[172]. It is more difficult with some (parts of) websites that are only accessible after registration or invitation by members as they may expect a higher level of discretion due to their own efforts in limiting access. These issues concerning consent may be solved by getting consent from the appropriate ethics committee so that individual consent is no longer necessary[173].

Another related issue is that of participation. Invitations to closed-off websites stem from previous interactions which establish trust between all parties involved. Chat room members may become suspicious of others who do not actively participate and ban those people. Ethics committees often disallow active participation[174]. Hence, either the committee needs to be convinced of the necessity in accessing invitation-only websites, or these channels need to be excluded which could thereby exclude a part of a population which, in turn, may be problematic if this

subset differs significantly from those active on more accessible websites.

4. Policy considerations when implementing SO online monitoring

Develop a legal framework for the online monitoring of SOs

Currently, a (legal) framework for the online monitoring of SOs does not exist. However, it does exist for the monitoring of NPS via the operation of the EWS[175]. These EMCDDA guidelines aim to provide a common understanding for operating the EWS on NPS by defining the rationale, procedures, roles and responsibilities and, as such, supporting a timely monitoring of NPS. The guidelines aim to provide a framework allowing countries to implement or strengthen their national EWS.

This Toolkit can serve as an inspiration or starting point for the development of a (legal) framework specifically adapted to the online monitoring of SOs. This should include a common definition of SOs and an overview of the involved institutions and their roles with regards to collecting, analysing and disseminating information.

Stimulate the need for clear privacy and data management

One of the biggest challenges with regards to online monitoring is obtaining the informed consent of those who are monitored, as explained above (see supra, III Operational challenges). Related to this is the privacy of those whose data is used and, subsequently, the management and protection of this data.

In particular, automatic monitoring tools can result in a huge amount of big data that needs to be managed effectively[176]. Data collection and storage needs to occur in accordance with existing privacy legislation, such as the General Data Protection Regulation (GDPR). A data management plan should be implemented that describes what data is collected and how as well as how data is analysed, stored and shared. Collecting and disseminating personal data that can be used to track individual users of the studied platforms should be avoided, such a pseudonyms, real names, email and IP addresses, if unnecessary[177, 178], to manage the potential harm that can be caused; or data should be anonymised/ pseudonymised.

As adequate online monitoring requires the monitoring of various websites in different languages and, thus, the involvement of different countries, certain agreements on data sharing need to be considered. By extension, an electronic information system may need to be developed[179] to ensure every involved party has access to the relevant information.

Discuss what kind of data is needed and include feedback on SO monitoring

Firstly, to ensure that there is no overload of information, discussion is needed as to which kind of data (and how detailed) the online monitoring tool aims to collect and whether this information is already (partially) available through other organisations or tools. This data can also help in the triangulation of the gathered data. Secondly, in order to (keep) engage(d) those responsible for SO monitoring, ensure that everyone is up-to-date on the process and receives feedback on their input. An annual (or other) timeframe should be organised with all involved parties where preliminary results, but also new monitoring challenges, can be discussed.

Organise workshops and training to stimulate the use of SO monitoring

To stimulate SO monitoring, ensure that everyone is up-to-date on the specifics of online monitoring or to strengthen existing SO monitoring; training and workshops could be organised to exchange expertise. This should cover all knowledge and skills needed for both indirect and direct monitoring, and for all of the different types of channels that can be used for monitoring. This training should address all who might be interested in monitoring SOs or who are already involved in it, referring to all relevant parties that have a role to fulfill in this task, from those responsible for the actual monitoring to those responsible for analysis and reporting; those with former experience in online monitoring can be a substantial source of knowledge.

Include a budget for (systematic) online SO monitoring

Large-scale data collection, especially in the case of automatic monitoring tools, requires an adequate and sufficient budget to cover all costs. These costs are related to the training of personnel, all the person-hours needed, costs related to building a customised crawler and scraper that covers all research needs, or the hiring of external people to cover this, and costs related to data management.

E-health

Executive summary

E-health is a relatively novel health care practice that utilises electronic information and communication technologies. It has great potential for improving access to, and the quality of, care and by increasing the efficiency of health care practices. In the field of substance use disorders, eHealth is still a relatively limited field, although research interest has been growing rapidly in recent years.

E-health interventions are available for all three main pillars of drug policy: prevention, treatment and harm reduction. Innovative and novel interventions, tools, and devices have been developed in recent years. Particularly with regard to opioid overdose interventions, research initiatives are growing and show great potential. However, many of the interventions are still in their pilot phase and effectiveness has not yet always been demonstrated. Further research and investments are urgently needed to develop and test these interventions and to facilitate the possibility of widespread implementation.

There are many considerations to take into account when developing eHealth interventions. The functioning of applications needs to be accurate and flawless, especially when used to prevent opioid overdoses, as someone's life depends upon it. It is also important to consider the needs of the users. Digital literacy, privacy concerns, and ease of use are key factors that may influence whether users are able, and willing, to make use of e-Health interventions.

1. General description of e-health

Basics of e-health

E-health is the overarching term for digital (computer-based) information and communication technologies that provide tools and services to enhance prevention, diagnosis, treatment, monitoring and management of health. It includes the sub-category m-health which refers to e-health programmes that are supported by mobile devices. Digital health care has the potential to improve access to care and to provide more client-centered care, while also increasing the efficiency of health care[180]. Furthermore, digital health care facilitates the tailored implementation of interventions among new target populations and among populations with specific needs[181].

Prevention

E-Health drug prevention is a relatively small field and mostly includes online self-help interventions and information services. Most online self-help interventions target cannabis users and, to a lesser extent, cocaine users. Information services, such as informative websites, provide information about a wide range of drugs. Psycho-educative e-health applications are widely applied in lifestyle interventions but research is scarce concerning drug interventions[182]. Some research indicates the need for interventions that target specific types of people who use drugs such as party drug users, chemsex drug users, and veterans[183, 184, 185]. However, this selective prevention is still in its early stages and research is limited.

Treatment

Telemedicine enables communication between a patient and health care provider without having to meet in person. Using telecommunication technologies, a health care provider can provide a diagnosis, treatment, education, or intervention. It also allows for monitoring of the patient and the provision of medicine. Behavioural interventions are one aspect of telemedicine which is also being explored for substance use disorders.

Harm reduction

Harm reduction aims at reducing negative consequences associated with drug use. It includes well-known 'physical' interventions such as drug consumption rooms. Many online harm reduction interventions aim to create digital alternatives to these interventions or to facilitate the delivery of potentially life-saving information to users.

Overall effectiveness of using e-health in drug interventions

The majority of empirical evidence on the effectiveness of e-health interventions for drug use disorders focuses on cannabis use[186], and, to a lesser extent, on stimulant and opioid use[187, 188]. A meta-analysis of 21 studies examined the effectiveness of digital prevention and treatment interventions for reducing cannabis use. Although cannabis use was significantly reduced directly after finishing the interventions, the effect did not last in the long-term.[189] Preventive interventions were more promising with sustained effects up to 12 months. Another meta-analysis of 17 studies was carried out to determine the effectiveness of e-health interventions in reducing the use of opioids, cocaine and amphetamines[190]. E-health interventions yielded a significant decrease in opioid use (four studies) and any illicit drug use (nine studies) after treatment. E-health interventions for stimulants only yielded small and non-significant decreases in use. While most of these studies are not tailored to opioid users, it is worth noting the apparent difficulty in developing e-health interventions that are effective.

2. Transferability of e-health to SOs

In this section, the transferability of e-health interventions to SOs is described based on the three main pillars of drug policy: prevention, treatment, and harm reduction. Each pillar is divided into relevant topics. For each topic, key examples of e-health interventions are presented. This is not an exhaustive list of all available literature and interventions but is intended to provide a selection of the most promising interventions available to-date.

2.1. Preventive e-health

Research on the effectiveness of digital prevention interventions for (synthetic) opioid users is very limited to-date. Research on other digital drug prevention interventions show the tentative potential of e-health interventions in this field.

Information services

Päihdelinkki is an online web portal and information service on drug use and cessation of drug use (https://paihdelinkki.fi/). The website offers information and self-tests on drug and alcohol problems, depressive symptom and behavioural dependence. A pilot on the web-based self-assessment service for Finnish drinkers showed that the service could be a useful tool to reduce excessive drinking[191]. Furthermore, it is worth noting that most questions received by the Päihdelinkki counseling service during 2012-2016 concerned opioids, benzodiazepines and rehabilitation[192]. As there are concerns that e-health might exclude opioid users due to digital literacy issues, it is encouraging to see that the online counseling service was well-utilised by people who use opioids or who knows someone who uses opioids. Although this information service lacks an evidence-base, the availability of accurate and easily accessible information about drugs is of great importance for the self-empowerment of users. Specifying such websites for SOs and particular target groups can be a vital tool to educate users about the effects, health risks and potential threats of SOs.

Monitoring patient risk

PainCoach is a mobile e-health application which monitors patient risk, guides patients in pain management and potentially reduces use of opioids after a total knee replacement[193]. The app provides information and advice on pain medication use, when to exercise and rest, and when to call the hospital. Participants in the PainCoach intervention used 44.3% less opiates than the care-as-usual control group. Given the increasing number of problematic prescription opioid users in Europe, and that prescription opioid use was at the start of the opioid epidemic in the U.S., it is important to also target this area of prescription opioid use. Interventions that reduce the use of prescription opioids should be used as that may also prevent the development of opioid use disorders in the long-term.

Indicated prevention

Indicated prevention is a third branch of drug prevention, after universal and selective prevention. It does not necessarily aim to prevent drug use, but rather to prevent the development of dependence, diminish frequency of use, and prevent risky patterns of substance use. 'Keep it Real' (Version 2) is a web-based indicated prevention intervention for young people to reduce drug use and psychotic experiences induced by cannabis, alcohol, methamphetamine, and heroin[194]. This intervention uses Cognitive Behavioral Therapy and Motivational Interviewing techniques. So far, the programme has only been pilot-tested in people who use cannabis regularly. The pilot demonstrated preliminary evidence for the effectiveness and acceptability of the programme. At 3- and 6-months, a significant reduction in cannabis use and psychotic experiences with moderate effect was shown. Indicated prevention interventions such as 'Keep it Real' could help users of (synthetic) opioids to regulate or reduce their use. Regulating use could be particularly helpful to prevent overdoses. More research on indicated prevention is needed to develop effective e-health interventions for people who use opioids.

2.2. Treatment e-health

SOs challenge the traditional provision of treatment and there is a need to pursue strategies that attract and retain high-risk individuals to OAT[195]. A key component will be the provision of stronger-acting OAT medication, such as fentanyl patches. In addition, e-health intervention apps may have a potential role as alternative approaches to better attract and retain clients in treatment. They may be used as additional tools to lower the threshold to treatment. This can be especially useful in areas where it may be difficult to receive treatment due to geographic limitations. Apps can also provide a low-threshold setting for additional or intensified support that SO users may need. Moreover, when clients receive stronger-acting OAT medication, additional supervision and guidance may be needed to avoid misuse or diversion. E-health apps can provide a feasible and practical mode for enhanced treatment supervision. More research is needed to assess the effectiveness of various interventions.

Behavioural drug use treatment

ReSET-O is a mobile self-help intervention for clients with an opioid use disorder that uses behavioural treatment as a complementary treatment to buprenorphine[196, 197, 198]. The intervention applies a Community Reinforcement Approach (CRA) and uses rewards and reinforcement to encourage positive and constructive behaviours, such as contingency management. CRA encompasses cognitive-behavioural therapy and network therapy approaches, including building drug refusal skills and improving vocational, social, family and recreational aspects of the lives of clients. The intervention was tested in a randomised controlled trial (RCT) and found to be effective as an adjunct to buprenorphine therapy compared to treatment-as-usual; it also had higher retention rates. Moreover, the intervention was found to be cost-effective[199].

Another behavioural intervention is the Marigold mobile platform which is a tailored chat support group for people who are in treatment for opioid use disorder[200]. The app enables text-based group therapy and peer support; a group moderator is used to support conversations in the group chat. The app uses artificial intelligence techniques to identify expressed intentions to harm oneself or others and malicious behaviour. The app is yet to be analysed in a feasibility and acceptability study. However,

the Marigold mobile platform has potential in supporting (synthetic) opioid users by engaging them in treatment through peer support[201] and providing useful information in a low-threshold setting[202].

Telemedicine

MySafeRx is a mobile technology platform that combines electronic drug delivery, text messaging, and video conferencing. It allows patients to use a drug under supervision and receive motivational instruction (see http://mysaferx.org/). MySafeRx consists of four components that are interconnected through a website and a mobile application: a medicine box (Medicasafe 3000) with an electronic locking system; text messaging (programmed notifications and private messages); daily videoconference meetings with a short motivational intervention; and verification of medication intake by videoconference. A pilot study evaluated the feasibility, utility, and acceptability of the MySafeRx model in opioid-dependent clients[203]. The participants received buprenorphine-naloxone treatment for four weeks, supplemented by mobile guidance and compliance monitoring. The pilot showed that the MySafeRx platform can be used in outpatient care to strengthen compliance during periods of treatment instability. MySafeRx also provides reliable confirmation that clients have taken their medication.

CBT4CBT is computer-based training for cognitive behavioural therapy which is combined with OAT. This intervention combines a telemedicine intervention (OAT) with a behavioral intervention (CBT4CBT). The programme makes use of Connections, a 7-module web-based system for teaching cognitive and behavioural skills, such as decision-making and problem-solving. A study assessed the effectiveness of CBT4CBT among opioid-dependent clients who were randomised either to buprenorphine treatment (the control group) or buprenorphine treatment with the CBT4CBT programme (the intervention group). The results show a positive effect of the intervention on urine toxicology screens (91% negative for opioids versus 64% in the control group) and good treatment retention rates (82.6 days of treatment versus 68.6 days in the control group). The results suggest that validated web-based solutions tailored to the target group can be used to enhance opioid agonist treatment[204].

Another example of telemedicine is a virtual clinic set up for clients receiving OAT[205]. Clients could make a virtual appointment by filling in an online form. During the appointment, a health care provider would interview the participant and checked if they were eligible for OAT. All participants that received OAT were guided through 2- to 4-weekly appointments. In a pilot study, the intervention was evaluated as feasible and successful in providing low-barrier access to OAT medication.

A review of telemedicine[206] demonstrates that such interventions for clients with opioid use disorder are promising in terms of treatment satisfaction and reduction in health care costs. In terms of actual effectiveness, however, more research is needed. Hybrid telemedicine and in-person counseling models could be used to improve treatment retention and outcomes for people who use (synthetic) opioids[207].

2.3. Harm reduction e-health

Harm reduction is arguably the most important pillar with regard to the prevention of (synthetic) opioid overdoses. The interventions presented above provide a multitude of different approaches by which users can reduce the risk of overdose and engage in safer drug use. Not only can E-health facilitate access to existing interventions, such as drug checking and DCRs, but it also opens the door to innovative new methods of harm reduction. App-based monitoring of users, whether through phone operators or biofeedback, are digital versions of a DCR that can be particularly useful for people who do not have a DCR nearby or who do not want to use drugs in a DCR. Also, the injectable naloxone device stands out as a potentially very effective tool for saving lives. These interventions require careful and impeccable design to ensure the effectiveness of the app. The interface must be well executed and location tracking must be accurate. Finally, a study has shown that people who use opioids are supportive of, and willing to use, a range of wearable devices that are able to detect and reverse overdoses[208]. Privacy and comfort were listed as two important factors that would influence their willingness to use a device.

Online overdose prevention

Most opioid overdose-related deaths take place when individuals use opioids alone. Numerous applications have been developed to empower users to prevent or reduce the risk of overdose when using drugs.

The Digital Overdose Response System (DORS) is a mobile application that people can use while consuming drugs. They have to press a button on a timer once per minute to indicate that they are conscious. If the user does not press the button, an egg timer goes off and connects the user to a human operator. If the user does not respond to the operator, an ambulance is sent to the location of the user. DORS is only available in Alberta, Canada; a very similar mobile application called the Lifeguard app was developed in British Columbia, Canada[209]. A further (similar) application is a phoneline service called the National Overdose Response Service (NORS), also developed in Canada. People who use drugs call a phone number and stay connected to a human operator for 15-30 minutes while they use a substance. If the user is not responsive, an ambulance is sent to the location of the user. Within the first year of the implementation of these apps, operators initiated emergency responses to more than 30 incidents, meaning potential overdoses[210, 211].

Another application to prevent overdoses works by monitoring human respiratory changes via an algorithm[212]. The algorithm utilises the speaker and microphone of a smartphone to turn it into a short-range active sonar system. This system is able to measure chest motion and respiration by means of inaudible acoustic signals. The algorithm was tested in the operating room, as a patient under anesthesia undergoes the same physiological changes as a person with an overdose. In 19 cases out of 20, the application recognised the symptoms of an overdose. Other researchers built on this idea and developed an automated wearable naloxone injector system. The individual wears the device and when the sensor detects a change in breathing which is life-threatening, it triggers the injection of a shot of naloxone[213]. This device can also be helpful when overdoses occur several hours after taking an

opioid, as can be the case when combining opioids with benzodiazepines and alcohol. A less invasive alternative could be to link the respiratory sensor to an alarm system to notify emergency services and/or individuals who carry naloxone.

ORION aims to raise awareness of the risk of overdose. The ORION application can be used by physicians and clients to identify and support individuals who are most at risk of overdose. ORION consists of a risk-assessment and the programme is performed in cooperation with a doctor who is able to provide explanations and counsel. The idea behind the app is that learning about personal risk will help influence people who use drugs to make lifestyle changes. However, a pilot study demonstrated no significant effect of the programme; there was no difference in the self-efficacy scores measured before and after the intervention[214].

Warning system

Red Alert is a digital drug warning app developed by the Trimbos Institute in the Netherlands (see https://www.drugsredalert.nl/). It warns users about potentially dangerous substances identified in the country, such as substances that are highly-dosed, contaminated, or that contain unknown substances. Furthermore, it provides information about drug testing locations, how drug testing works, and harm reduction tips for safer drug use. Currently, the Red Alert app (and the drug checking service which is linked to the app) mostly serves people who use MDMA/ecstasy. However, it could also benefit users of SOs. On the one hand, it could warn users of party drugs and/or Psychonauts about samples of drugs, such as ecstasy and cocaine, that are laced or contaminated with SOs. On the other hand, the app could also be adapted for the population of people who use opioids. Opioid samples may not have the distinguishable characteristics as ecstasy tablets, such as form and colour, so warnings about dangerous samples might have to be described in terms of other features, such as the location in which they were purchased. It might also be necessary to develop a separate app for people who use opioids to better serve the population. Such an app could include a peer-review section for people to directly share information on the platform themselves. The app could have the option of putting pins on a map indicating where dangerous substances were purchased.

Needle and syringe programme finder

The Populi Needle Exchange Point Finder is an app to reduce harm associated with injection drug use. The app provides information about nearby needle and syringe programmes and lets people share their opinion about these places. People commenting on different sites could help others choose the safest place and could provide useful information to help improve these services. The effectiveness of the app has not been evaluated, but it was highly rated for its user experience and feasibility[215]. This app could also be useful for users of SOs and could be expanded with information about DCRs. SOs are associated with a higher risk of overdose and DCRs are important tools in preventing opioid overdose deaths (see the Chapter above on DCRs).

Chatbot

Robo is the first chatbot for people who use opioids that provides drug-related information[216]. It was developed by means of deep learning techniques that analysed drug-related conversations on Reddit. The goal of the chatbot is to provide an alternative to extensive social media research when people with opioid use disorder have questions about their dependence or rehabilitation process. The chatbot is still in its early stages but the researchers are planning to add drug-related information from medical experts in addition to the social media-based responses. Although Reddit is not a reliable platform for giving accurate advice on using opioids, the way people communicate on the platform may be valuable to incorporate into the chatbot. For SOs specifically, which are highly potent, correct and reliable information is essential.

3. Operational challenges

Treatment retention

Treatment retention is a big challenge in digital health interventions in general[217]. In addition, treatment retention is a problem for opioid use disorders, with nearly half of participants quitting interventions prematurely within three months,[218, 219, 220]. Given the high drop-out rate, it is questionable to what extent results on the effectiveness of interventions are generalisable, including the users that dropped out[221]. Yet there are also some e-health interventions that demonstrate retention rates that are higher than treatment-as-usual[222, 223]. The challenge for future research will be to understand what components of interventions are effective and what contributes to participants dropping out.

Providing evidence-based e-health programmes

A recent review emphasised the importance of using digital health technologies in providing medication-assisted treatment for opioid use disorder.[224] However, it was also pointed out that there was a lack of empirical evidence for the long-term effectiveness of the currently available interventions. Furthermore, a scoping review of nine mobile health interventions for opioid-related harm showed that none of the included studies reported on the effectiveness of their interventions, meaning that it is unclear whether, in fact, the interventions reduce opioid use[225]. However, the reviewers pointed out the high acceptability of m-health applications for telemedicine and behavioural intervention purposes. M-health applications with geo-location features were less accepted and might face challenges in implementation[226, 227, 228, 229].

Digital inequality

An ongoing challenge is that treatments do not always reach the right target groups. Digital inequality can exacerbate this problem due to factors such as limited access to the internet or technology and lacking digital skills. People with opioid use disorders in vulnerable living situations can be disproportionately affected by this issue. Since online counseling and telemedicine have increased due to the COVID-19

pandemic, digital inequalities have presumably had a more significant influence on the uptake and retention of opioid use disorder treatment, although research is lacking on this topic[230].

4. Policy considerations for service providers

Ensure the safety of service users

When using technology for prevention, treatment or harm reduction, it is important to ensure the safety of the user. This does not only refer to data privacy, but also translates to the way the technology functions and delivers its service[231]. The greater the user is dependent on the technology, the more important it is to ensure it always works. People with opioid use disorders are a vulnerable group, especially while using such drugs. Automated alarm systems for overdoses need to function with very high accuracy for them to not cause unnecessary deaths. Therefore, quality criteria for digital (synthetic) opioid interventions should be developed[232]. Another consideration for ensuring the safety of users is the practical context of drug use. For example, the context in which drugs are used can be complicated, such as using in public, and stigma and discrimination can also play a role[233]. These contextual circumstances can play a role when research does not translate well from the clinical setting to the practical field.

Ensure data privacy and safety

Ensuring data privacy can be a convoluted process. With the rise of new technologies and new capabilities for data processing, relatively simple concepts such as anonymisation and informed consent become more and more complex[234, 235]. Challenges for future apps include safe storage and anonymisation of data, and prevention of cyber-crime. In addition, influential companies, such as Google and Apple, have a growing commercial interest in health data[236]; their influence should be avoided when dealing with vulnerable populations such as people with substance use disorders. The General Data Protection Regulation focuses on creating a consistent legal framework in the European Union for policy on personal data, including personal health data[237]. The framework emphasises explicit consent for data processing, although this might not always be feasible in scientific research since data are often used by multiple researchers in different projects. When consent for data processing is not explicitly stated, data privacy and safety may be at risk which makes it a crucial aspect of e-health data privacy and safety[238].

Mitigate digital health inequalities

There are two evident ways of mitigating digital health inequalities: to equip people with digital health skills and to develop interventions for people with low digital health literacy. Although these pathways seem obvious, they come with challenges. To teach digital health skills, researchers can work together with clinicians, educational institutes and community organisations to identify people who would benefit the most from improving their digital health skills[239].

A study by Li[240] pointed out that digital privacy skills play a significant role in influencing digital health skills. Therefore, digital privacy education should be incorporated in digital health literacy programmes in order to achieve better outcomes with particular focus on disadvantaged communities. Research also shows that inequalities in digital health literacy are explained by age, gender, education, and health status[241, 242, 243]. The development of tailored e-health interventions for people with low digital health literacy may be needed. It is also important to offer the intervention in different languages and to (pilot) test the acceptability of apps in different cultures or sub-populations to see if and why uptake or retention may be low.

Invest and innovate

Innovative or novel technologies are needed to develop more effective e-health interventions. For example, investing in digital interventions[244] with chatbots and more interactivity and flexibility can result in more accessible e-health interventions. Chatbots can also provide low-barrier support for people who use drugs[245]. Furthermore, interventions which include geotagging, for use in overdose prevention, or just-in-time adaptive support can address problems of people who use drugs in a timely manner which is especially important for users of SOs. Just-in-time adaptive interventions (JITAI) can intervene when a person is vulnerable or most susceptible to change[246].

These interventions often use (artificial intelligent) techniques to monitor the user of the technology, including mobile applications, sensors, etc. Although the effectiveness of JITAI for harm reduction has not been tested with substance users[247], JITAI are generally found to be effective, with moderate to high effect sizes[248]. Further research on JITAI for substance users and especially (synthetic) opioid users is warranted. Finally, wearable technology that monitors body functions and acts on life-threatening bodily changes could be a very effective tool in preventing opioid overdoses. There is a clear need for further development of novel, low-cost innovations and wearable devices for preventing overdoses[249].

Drug checking

Executive summary

In a growing number of countries, drug checking is considered a well-established and effective tool to monitor drug markets and provide consultation to reduce harm associated with drug use at both an individual and population level. Drug checking services exist in many shapes and sizes ranging from office-based to mobile and using testing methods ranging from very basic, but fast, to state-of-the-art technology, but time consuming.

In recent years, drug checking has been tailored to meet the needs of different target audiences, including people who use opioids. In particular, in countries where the opioid crisis is causing devastation due to increasing rates of overdose deaths, drug checking has been implemented to deal with the increasing presence of fake medicines or illicit drugs adulterated with fentanyl or its analogues.

Since drug checking is based on the chemical analysis of mainly illicit drugs purchased by people who use drugs, it is still a delicate subject in many countries. These complexities impede service providers in finding sufficient funding necessary to operationalise a drug checking service.

What needs to be considered when establishing a drug checking service in general and specifically for people who use opioids is described in this Toolkit. In addition, the most relevant operational barriers, and how to overcome them, have been assessed.

Overall, the most important lesson that can be learned from existing drug checking services in making the initiative a success is to gain trust and support from policymakers and national or local authorities as well as prospective service users who may initially be suspicious and not easily persuaded to visit a drug checking service for several reasons. Only when users are 'on board' and submit their drug samples for chemical analysis can a drug checking initiative be a valuable asset to the wider community.

1. General description of drug checking

A drug checking service allows people who use drugs to anonymously submit a drug sample that has been purchased on the illicit drug market for chemical analysis. Once results of the analysis are available, information on the content and purity of the drug sample is usually combined with harm reduction advice, consultations, and brief interventions. The gathered data can be used to monitor drug markets and to issue alerts when potentially highly dangerous substances are detected, but also for education, prevention and policy interventions.

While drug checking services have demonstrated their capacity for monitoring drug markets (and identifying novel threats), there is still little evidence for drug checking as a harm reduction tool in terms of behaviour change, although multiple studies do show the positive impact of drug checking on the intention to dispose of a drug once an adulterant has been detected[250].

A short history of drug checking

The first consumer drug checking initiatives started in the mid-1960s in the United States when drug samples bought on the illicit drug market could occasionally be submitted for chemical analysis. After being absent for a few decades, drug checking services re-emerged in Europe when, during the late 1980s and early 1990s, electronic dance music and raves were becoming increasingly popular, including the use of ecstasy and other related stimulant drugs that were used for recreational purposes.

In 1992, the Drugs Information and Monitoring System (DIMS) was established in the Netherlands to coordinate already existing but semi-legal drug checking initiatives both at events and at offices situated in institutions of dependency care. In the years that followed, more drug checking services were established across Europe, mostly designated for people who use drugs for recreational purposes. With the emergence of NPS during the mid-2000s, the type of drugs submitted to these services and type of attendants was expanding.

In a review conducted in 2017, a total of 31 drug checking services operating in 20 countries were identified, not only in Europe but also in Australasia and the Americas[251]. This number is still increasing with new initiatives that are currently being set-up in multiple countries, such as in Norway and Scotland.

Office-based versus mobile drug checking

Drug checking services vary in multiple ways depending on the objective of the service and for which target population these services operate. Most drug checking services are either office-based (also known as stationary) and open for consultation at specific hours during the week; or mobile (also known as on-site) at festivals/music events. Some drug checking initiatives also offer a postal service or accept drug samples submitted from abroad.

In the Netherlands, drug checking services are all office-based and, in most cases, are housed in drug prevention departments of centres for dependency care. In other countries, office-based drug checking services can be part of multi-purpose harm reduction services, such as drug consumption rooms. Notably, at a global level most drug checking services are mobile and operate at festivals or large events and specifically target partygoers.

In recent years, a growing number of drug checking services have emerged in the United States and Canada as part of their strategy to prevent overdose

due to the adulteration of drugs, in particular fentanyl or its analogues. Most of them, however, do not offer a full chemical analysis, but rather provide mainly fentanyl strips. Nevertheless, a few drug checking services, such as in Toronto[252], also started to offer a full chemical analysis of the submitted drug sample and tailored feedback as soon as the test results are available.

Different analysis techniques used for drug checking

The extent to which a drug checking service can prevent harm associated with drug use or the monitoring of drug markets ranges from simply demonstrating the presence of a certain substance to analysing the full composition of a submitted drug sample. This largely depends on the available resources that are needed to get access to equipment that allows a full chemical analysis of a drug.

The simplest way to test a drug sample is through the use of colorimetric agents or, as in the United States and Canada, the use of fentanyl strips. Other commonly used techniques include Thin-layer chromatography (TLC), Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, High performance liquid chromatography (HPLC) and Gas chromatography coupled to mass spectrometry (GC-MS).

The most elaborate way is to use more state-of-the-art lab-based analysis techniques based on mass spectrometry which will give the most accurate and reliable results that can be used for monitoring drug markets and for issuing public health alerts. However, apart from the high costs and technical skills that are required, most of these techniques are not suitable for mobile applications. Drug checking services that operate on-site mostly make use of other techniques with high accuracy, such as FTIR, or Raman spectroscopy. To detect substances under the limit of detection, reagent tests are often used in drug dependence.

Which type of technique is the most suitable also depends on the need for a fast test result within minutes, such as on-site at a festival, but also at a harm reduction service. Test results using more state-of-the-art analysis techniques are usually not available until several days after submission of the drug sample.

The following section will focus on how to implement drug checking for SO detection as a key response in overdose prevention with special attention paid to the different types of challenges associated with drug checking for this specific purpose and how these can be overcome.

2. Transferability of drug checking to SOs

In the United States and Canada, the opioid crisis – and, in particular, the rise in fake medicines or illicit drugs adulterated with fentanyl and its analogues on the drug market - has played a pivotal role in the recent emergence of drug checking initiatives in these countries. In Europe, SOs, such as fentanyl analogues, are rarely detected in drug samples submitted to drug checking services. This is not entirely surprising since drug checking services in Europe mostly operate at festivals and other music events visited by people who use drugs for recreational purposes.

The illicit drug market is highly dynamic and new threats, such as the recent emergence of novel classes of SOs or designer benzodiazepines, demand that drug checking service continue to develop to step-up to these challenges.

Important considerations prior to establishing a drug checking service

Before setting-up a drug checking service, the purpose of the service should be considered. This can vary from harm reduction, or more specifically overdose prevention on an individual or community level, to market monitoring and risk surveillance, or a combination of these. Since most drug checking services in the past have been developed for people who use drugs recreationally, special attention should be paid to adapting the service to people who use opioids, who are mostly dependent users. What do they need to benefit from the service and what is needed to persuade them to attend a drug checking service and to submit a drug sample?[253]

It is obvious that most people who use drugs do not visit a drug checking service at all. This is particularly the case for people who use opioids, although studies on this subject are limited. One specific study conducted in Canada found that although most drugs submitted to a drug checking service in the area were found to be adulterated with fentanyl, this finding alone did not persuade people to submit their drug sample for analysis[254]. Another recent study confirms that the potential success of a drug checking service for this population lies beyond showing the benefits at an individual level[255]. Either way, how you reach out to the target audience strongly impacts upon the success of the service.

Building trust

An important lesson learned from existing drug checking services is that to attract people to your service the threshold to attend must be low. It is key that the anonymity of a visitor is guaranteed. Ideally, the service is free to people who want to submit their sample for analysis. Another important reason why people who use opioids in particular are reluctant to submit a sample for analysis is the fact that most of them use opioids on a regular (if not daily) basis and have limited resources[256]. Taking this into consideration, the service should aim for the intake of as little as possible of the substance and test results should be available to the person who provided the sample as fast as possible. In this way, tailored harm reduction advice can be provided and risks associated with use can be mitigated.

When available, the test result needs to be communicated in a clear and comprehensive way, in line with the level of understanding of the person that submitted the sample. More importantly, information about the test results should always be reliable and discussed in a non-judgmental way without any message that might strengthen the stigma towards drug use. Only then will people come back to the service or promote the drug checking service to others.

Especially in countries that have a more repressive drug policy, people might be suspicious or even afraid to use a drug checking service due to being arrested. It would, therefore, make sense to collaborate with other harm reduction initiatives that have already gained the trust of the target audience and also to have experience in dealing with the stigma that surrounds opioid use.

Accessibility of a drug checking facility

As mentioned above, when setting-up a drug checking service for people who use opioids, an office-based drug checking service in a location that users already visit for other purposes is highly recommended. An important aspect when choosing the location is the accessibility of the service. Do people need to travel long distances to attend the drug checking service or is the service part of other harm reduction services for people who use opioids?

Preferably, people should attend the service without having to make an appointment, but it might be necessary to have specific weekly or daily opening hours when the service is available. Although it should be clear where and when the drug checking service can be accessed, it is recommended to draw as little attention as possible, especially at the location itself, to secure the anonymity of attendants.

The pros and cons of different analysis techniques for testing drugs

Depending on the objective of the service, location of the service, type of drugs that can be expected at the service and available resources, choices can be made between different drug analysis techniques. Ideally, a drug checking service should have access to a state-of-the-art analysis technique that enables a full and reliable analysis of the content and purity of the submitted drug samples. With a full understanding of the composition of the sample, overdose or intoxication caused by adulterations can be avoided or reduced. This is of particular importance when drug checking is being implemented to monitor the SO market. Not only is this market highly unpredictable and volatile, the majority of substances belonging to the class of SOs can pose extremely acute health risks at very low concentrations[257].

In forensic science, mass spectrometry technologies (such as GC-MS or other similar techniques) are considered the gold standard for drug analysis. In some countries, drug checking services have established collaborations with laboratories in hospitals or in academic settings to reduce costs and to avoid the deployment of trained staff who are technically skilled to run these techniques. However, one major disadvantage of these state-of-the-art analysis techniques is that it usually takes several days before test results become available and can be communicated to the person who submitted the sample, while the pattern of use associated with opioids might require fast test results. To overcome such barriers, existing state-of-the-art analysis techniques are constantly adjusted to meet the needs associated with rapid on-site SO detection. For example, by making use of a portable GC-MS[258] or paper spray MS[259].

Certain other analysis techniques can be used on-site and are able to provide test results within minutes. One example of an analysis technique that is frequently used by drug checking services operating both on-site and stationary at offices is Fourier Transform Infrared (FTIR). The major advantage of this particular analysis technique is that in most cases it can give reliable test results on the composition of a sample within minutes. It is also relatively affordable and easy to handle. In Canada, several drug checking initiatives have successfully used FTIR in combination with test strips in order to detect drug samples adulterated with fentanyl[260].

One disadvantage, however, is that FTIR poorly discriminates between mixtures containing more than one substance at low concentrations. Hence, test results should always be cross-checked with another analysis technique, such as a reagent test. Moreover, to interpret the results in a correct way, and to determine whether a test result is reliable or inconclusive, the operator should have a functional understanding of the technique.

If no other analysis techniques are available, even colorimetric tests alone - or the use of fentanyl test strips - can be of added value as they at least give an indication of the presence of a certain substance. Costs are low and by providing them for free via a drug checking service it is the simplest way to get in contact with people who use opioids. However, a major concern with these kind of simple analysis techniques is that the full content of the sample remains unknown and, more importantly, the presence of any adulterants cannot be identified. Therefore, colorimetric tests are usually only used in addition to another analysis technique for cross-checking.

Protocols and safety measures

To ensure the quality of the drug checking service, it is highly recommended to develop protocols that describe responsibilities of the staff, quality requirements of working with drug samples and, most importantly, standard operating procedures for protection and safety when handling drug samples, especially with highly potent substances such as fentanyl and its analogues. The latter encompasses the availability and use of disposable examination gloves, but also of protective clothing, face masks and safety glasses. Sufficient ventilation in the room, access to tap water and an eye shower are other examples of safety measures that should be in place to increase safety of the staff operating the service.

In some countries where take-home naloxone (THN) programmes have been implemented, naloxone in different forms might also be available for staff operating a drug checking service once they have received training. However, the safety measures described above should be sufficient to protect staff from exposure to highly potent substances.

Legal arrangements

Since the possession of drugs in most countries is a legal offence, service providers who want to implement drug checking need to make specific

arrangements with either national or local authorities to allow people who use drugs to submit samples and to allow staff operating a drug checking service to handle these drugs without being prosecuted. This makes establishing a drug checking service quite challenging, but lessons can be learned from existing drug checking services that have already dealt with these legal challenges.

The type of arrangements, and whether these are officially documented, varies considerably between countries or even regions. One strategy to mitigate legal risks for people who use drugs or staff operating a drug checking service might be to house them at already legally protected (harm reduction) services. Another strategy is to imbed drug checking within a scientific research programme to issue an exemption to handle and analyse illicit drugs, including SOs. In countries where the opioid crisis is causing high mortality rates, policy-makers might be convinced to legally protect drug checking services that operate either temporarily or under specific conditions.

Ideally, drug checking services should be able to obtain a license to legally possess illicit drugs for testing purposes, but - except for New Zealand - this is still a utopia in many countries. Nevertheless, several governments have already acknowledged drug checking as part of their drug policy. However, financial support is still lacking in most countries.

3. Operational challenges

Legal barriers

In most countries, the possession of certain classifications of drugs is illegal and this makes it more difficult to establish a drug checking service in agreement with all national and local stakeholders. Most, if not all, drug checking services that are currently operational have had to overcome several legal hurdles. Every country has its own drug policy which can have a major impact on the degree to which authorities are open to making specific arrangements to allow the handling of drugs for testing purposes. It is advisable to find out what is possible within the legal boundaries of a country and be transparent as to what is to be achieved and how.

The costs of establishing and operating a drug checking service

Without financial support from a government or funding via other sources, a drug checking service cannot be established and maintained. Establishing and operating a drug checking service can be very costly depending on the analysis technique that will be used. In addition, access to an annual budget is needed for additional expenses such as gloves, test strips and other equipment needed to maintain the service. Only a few drug checking services in the world receive full financial support from governments. Most drug checking services are NGOs that fully rely on donations from multiple sources which requires structural investment in the visibility of the drug checking service. This can be achieved in multiple ways, including communicating public warnings once potentially dangerous drugs have been detected, although this should be undertaken with care to guarantee the impact of such warnings. Alternatively, by collaborating with other harm reduction services or scientific research programmes, additional costs might be limited.

Uncertainty of behavioural outcomes

To what extend drug checking impacts the behaviour of people who use drugs is still under investigation. While evidence is growing that a brief intervention alongside personalised feedback about the content of a drug sample has a positive impact on the behavioural intention, to dispose of the drug sample in the case it contains an adulterant, it remains to be determined what the effects are on the enacted behaviour. Although people who use drugs for recreational purposes are more likely to dispose of their drugs when an adulterant is detected compared to people who use opioids, at least being in contact with this population might already have an effect on reducing the risk of overdose.

Finding a suitable location

It will be difficult to find a suitable location that is easy to access. To overcome this challenge, it is again recommended to collaborate with other harm reduction services because they are usually centrally located and open on a daily basis. By collaborating with another harm reduction service, people who already make use of the service can more easily submit a sample for analysis while visiting the location for another purpose.

Safety measures

The use of protective clothing, safety glasses and other materials that protect staff from exposure to highly potent substances might discourage people from visiting a drug checking service. However, sufficient low-threshold safety measures can be taken, such as wearing disposable examination gloves. Other materials should be present at the drug checking service as well but can be stored until needed. A protocol that describes all safety procedures is strongly recommended and should be evaluated on a regular basis.

4. Policy considerations for service providers

In many countries, drug checking remains a controversial subject irrespective of the legal status of illicit drugs. Nevertheless, an increasing number of studies have shown the added value of drug checking for monitoring purposes and for risk surveillance. In some parts of the world, governments or agencies such as the EMCDDA already embrace drug checking as a strategy to prevent drug-related harm.

Collaborate with laboratories and harm reduction services

The most important condition for successful implementation of drug checking is that the service in question has access to analysis techniques that enable the reliable detection of a wide range of (newly emerging) substances already at low concentrations and that other analysis techniques that provide reliable test results within minutes are available on-site as well.
For market monitoring purposes and risk surveillance, it makes sense to collaborate with a hospital or university to gain access to more state-of-the-art analysis techniques that allow analysis of both the content and purity of the submitted drug sample. By doing so, maintenance costs and regular training of skilled staff can be circumvented. Nevertheless, it is highly recommended that staff with sufficient expertise on different domains, including pharmacology and/or chemistry and harm reduction, be included.

By imbedding a drug checking service within other harm reduction programs several barriers can be overcome increasing the potential success of the drug checking service also on the longer term. It is necessary to overcome legal hurdles through making arrangements with national or local authorities to allow the handling of drugs by staff operating a drug checking service.

Communicate and disseminate your results

There is an ongoing debate in some countries as to whether drug checking encourages drug use. However, drug use is never safe even when the drug contains just the anticipated substance as purchased. This message should always be communicated when results are provided to the person who submitted the sample(s). In this way, drug checking services can never be held liable for any health issues arising from drug use or become accused of promoting drug use.

Make clear to policy-makers as to how drug checking can contribute to the identification of emerging novel threats and in risk surveillance when potentially highly dangerous substances are detected as well as how it can minimise harm at an individual and community level. Evaluate activities on a regular basis and be transparent about activities. Disseminate the results of activities to increase the amount of evidence showing the added value of drug checking for different purposes and for different populations. The growing number of studies highlighting the added value of drug checking as a key response to tackle the opioid crisis can be used to receive funding, to raise awareness and to encourage policy-makers to enable drug checking for this specific purpose.

Meet the needs of people who use SOs

Service providers that want to implement a drug checking service for people who use SOs should be aware that drug checking was initially set-up for people who use drugs for recreational purposes. Most recommendations apply for drug checking in general, but service providers should always bear in mind that to meet the needs of people who use SOs, certain adaptations can make this key response a success.

It will be a major challenge to attract people who use opioids to a drug checking service and to persuade them to submit a drug sample for analysis, let alone to make them come back or promote the service to others. To overcome this challenge, ensure that the threshold to attend a drug checking service is as low as possible and that results are fast, reliable and communicated in a neutral way. As mentioned above, it is key to ensure that the drug checking service is fully anonymous. Trust from people who use drugs is essential and can be gained by collaborating with other harm reduction services that are already being visited by people who use opioids. They know how to deal with stigma and how to provide information in a neutral way. In addition, they can reach out to people that are not yet aware of the service and demonstrate to them the added value of a drug checking service. It is recommended to make to service free for users and to provide the test results as fast as possible since most people who use opioids use on a regular basis and have limited resources.

Drug Consumption Rooms (DCRs)

Executive summary

Since 1986, and with 143 sites open in 87 cities in 16 countries as of early 2022, Drug Consumption Rooms (DCRs) have been a key response in implementing preventative and interventional overdose strategies for people who use drugs and contribute to better health outcomes and their quality of life. DCRs are legally sanctioned and professionally supervised health care facilities that provide safer and more hygienic conditions for people who use drugs to consume pre-obtained drugs in a non-judgmental environment that reduces the health and public order issues associated with such activities in public spaces and facilitates voluntary access to social, health, economic, legal and drug treatment services.

DCRs are currently equipped to respond to the use SOs by providing a supervised, hygienic, and safe space for drug use; by promoting education and information about substances and safer use practices; establishing and implementing overdose strategies; and enhancing self-care and self-regulation practices among their users. However, when there is a steep increase in SO use, DCRs may need to adapt their activities, resources and regulations, and staff may need to develop new knowledge and skills.

SOs, particularly fentanyl and its analogues, are very potent substances and, as such, they are playing an increasing role in both non-fatal and fatal drug overdoses. Experiences and literature from countries currently facing a crisis of SO overdose-related deaths suggest the need for DCRS to adapt their current overdose prevention and intervention strategies in the case of sharp increase in their use in Europe. Other adaptations include increased alertness for the appearance of new substances and combinations; increased awareness, information and harm reduction strategies among staff and service users; increased access to naloxone and to adapt its training and administration protocols; the increased involvement of people who use drugs in developing, implementing, monitoring and evaluating the services; and further implementation of intersectional and integrated models of service, including drug checking, mental health support, gender-specific activities, or HIV/HCV community-based testing, among others.

1. General description of DCRs

Drug Consumption Rooms (DCRs) are legally sanctioned and professionally supervised health care facilities that provide safer and more hygienic conditions for people who use drugs to consume pre-obtained drugs in a non-judgmental environment that reduces the health and public order issues associated with such activities in public spaces and facilitates voluntary access to social, health, economic, legal and drug treatment services[261]. The first officially operational DCR opened in Bern, Switzerland, in June 1986[262], with an increasing number year-on-year, with 143 sites open in 87 cities in 16 countries as of early 2022[263].

Benefits of establishing a DCR

There is substantial evidence to demonstrate a wide range of benefits to individuals, communities and broader public health from operational DCRs. Among others, evidence shows that DCRs have a substantial impact in reducing the number of deaths due to a drug overdose, both within a facility and in the areas surrounding a DCR; DCRs contribute to the reduction in the transmission of blood-borne infections; DCRs do not increase drug use, nor do they encourage people to initiate drug use; promote safer approaches to drug use ('safer-use'); crime and public nuisance decreases in areas around DCRs, contributing substantially to the effective management of open drug scenes; DCRs reduce noise complaints and public safety concerns; DCRs provide primary physical and mental health care while also increasing access to other health and support services for the most marginalised people who use drugs, including OAT and drug treatment; offer vaccination, such as for COVID-19; DCRs result in substantial savings in health care costs in the medium-to-long term; and provide 'real-time' drug market monitoring data to alert people who use drugs and public health professionals of dangerous substances circulating in the community[264, 265, 266, 267, 268, 269, 270, 271].

There are various criteria for establishing and operating DCRs based on the policies of local authorities and national legislation, as well as the specific setting and access to target groups. To abide by relevant national legislation, drugs used in a DCR must be obtained prior to entry, and direct drug dealing or sharing is not allowed within the DCR[272]. Although variations may exist in some specific legal jurisdictions, standard criteria for the use of a DCR include a minimum age of 18 years or parental/guardian written permission; the individual must be a registered service user; no admittance if the individual is drunk or intoxicated; visitors and staff are not allowed to assist users in administering their drugs; and no violence.

Models of service provision

Overall, three models of DCRs are operational in Europe, namely integrated, specialised and mobile, each model usually being part of a broader, interlinked network of services[273]. Most teams include nurses and social workers among its units, medical doctors form part of nearly every second team, and security staff form part of one-third of DCR teams[274].

The most common type of DCRs are integrated into low-threshold facilities or socio-medical centres, such as drop-in centres. Access is regulated by staff and limited to a specific group of service users in a dedicated area. Less common, specialised DCRs operate as a stand-alone service, forming partnerships with other socio-medical services.

Often, specialised DCRs are set up in close vicinity to other drug services and located near an open drug scene, knowing that there is a high need for safe and hygienic use environments in these locations. Mobile DCRs are comprised of a specially designed van with injection or smoking booths. This model is chosen on occasions as it offers a more socially acceptable option to a fixed site. Furthermore, mobile DCRs can cover large regional areas and reach drug users in different locations in a city, such as suburbs and outskirts.

Less common DCR models include housing/shelter facilities with a DCR, allowing drugs to be consumed in designated parts of the facility; and overdose prevention sites that are temporary supervised facilities that operate as 'lifeguard' stations for people who use drugs[275].

2. Transferability of DCRs to SOs

2.1. What is already in place and can be useful for a response to SOs?

To a certain extent, in the event of a SO crisis, DCRs in Europe may continue responding in the way that they always have, by providing a supervised, hygienic, safe space for drug use; promoting education and information about substances and safer use practices; establishing and implementing preventative and interventional overdose strategies; and enhancing self-care and self-regulation practices.

Provision of safer and hygienic drug use conditions

All studies have converged to find that DCRs were efficacious in attracting the most marginalised people who inject drugs, promoting safer injection conditions, enhancing access to primary health care and reducing overdose frequency[276]. The main DCR target groups are long-term, marginalised drug users, particularly those experiencing homelessness and using drugs in public spaces. DCRs also contribute to reducing the risks of violence for marginalised women and gender-diverse people who use drugs, providing a refuge from the various forms of violence experienced on the street[277]. DCRs have also been found to disrupt drug scene dynamics, such as gender power relations, enabling women and gender-diverse people to assert agency over drug use practices[278].

An essential element that determines the good functioning of DCRs are safety (feeling safe, being safe), hygiene (access to clean materials) and that there is no stress. The space where drug consumption occurs is physically separated from other parts of the facility and access to it is controlled, offering a space for drug use protected from public view. Before entering, staff assess what substance the individual is planning to use and offers hygienic equipment, material and advice on safer use. Thanks to supervised consumption, lower-risk and more hygienic drug consumption is ensured.

Promotion of safer drug use practices

DCRs employ a twofold strategy comprising an informational and an interventional-preventative component. The first element of the preventative strategy consists of being apprised as to which drugs are available; their potency and potential adulteration; the different routes and techniques of administration; and disseminating this information to individuals using the facilities. Fentanyl and other SOs, when used to cut substances, can also be found in stimulant drugs, not only opioids. Furthermore, providing insights into the risks of various combinations of substances is also crucial. The second element of the preventative strategy consists of actual interventions in case of overdose and health-related emergencies; more information in this regard is provided below.

Overdose prevention

Evidence shows that DCRs have a substantial effect on reducing mortality from drug overdose by intervening to prevent overdoses that may happen within the facilities and, additionally, by reducing mortality in the vicinity of the facility[279]. In fact, no death due to overdose has ever been reported at a DCR where research has been conducted[280, 281]. In addition to saving lives, DCRs have also proven to be effective in reducing the frequency of drug overdose[282].

Existing DCRs develop and implement safer organisation policies, including site-specific overdose prevention procedures, adequate equipment, and ensure that a complementary type of overdose prevention service – such as overdose prevention lines and emergency services - remain available. DCR staff are also provided with tools, methods and strategies to develop a clear understanding of the substance use habits of the individuals with whom they work, including substances used; patterns and methods of consumption; current use of drug-using paraphernalia; and having an updated overview of overdose cases and their circumstances, among others.

As a supervised facility, DCR staff monitor the behaviour of individuals, identify and understand potential risks and harms and respond accordingly. As mentioned above, DCR teams include nursing staff, doctors, or adequately trained social workers. For instance, within the facility, staff pay attention to symptoms of opiate overdose, such as movement or language difficulties, blue lips or nails, tiny pupils, cold skin, dizziness and confusion, slow or lack of breath, or inability to wake up. However, as explained later in this chapter, signs of overdose for SOs may vary. Lastly, the provision of timely and relevant information remains an essential element in the generic and emergency responses to SO use and overdose.

Naloxone provision

Complementing their safer organisation policies and site-specific overdose procedures and equipment, some DCRs have naloxone to be administered in severe cases where individuals experience respiratory problems or become unconscious[283, 284]. On these occasions, naloxone is administered to reverse the effects of opioids.

However, naloxone may not always be readily administered. This poses DCR staff with a complex dilemma due to two considerations when the team must determine whether to administer naloxone. Administering this medication may save the life of

an individual who may have otherwise overdosed. However, on the one hand, doing so will inevitably lessen the individuals 'hard-earned' high. Although norms as to the circumstances under which naloxone should be administered may vary across DCRs, the experiences of staff in Denmark highlight their caution in its administration as obstructing a client's 'rush' is a highly delicate situation and may also be detrimental to the trust-based relationship established if an actual case of overdose is not really taking place. On the other hand, the staff is aware that the half-life of naloxone is shorter than that of opioids, which means that the effect of the opioid may return after the individual has left the DCR. The person could potentially be at risk of an overdose once out of reach of the facility or when again consuming opioids[285].

Being aware of this, staff may on occasions offer oxygen under the nose instead if they saturate under 90% as long as the vital signs are adequate and wait with the naloxone administration until the client becomes unconscious and stops breathing. In the case of naloxone administration, close monitoring of the individual is enacted.

2.2. Adaptations that may be needed for a response to SOs

To cope with SOs, especially due to the steep increase in SO use, DCRs may need to adapt their activities, resources and regulations, and staff may need to develop new skills. Most of the following recommendations are derived from interviews with staff of DCRs, researchers and policymakers from Canada, and related literature. DCR staff from European countries who were approached for the development of this toolkit reported to not have enough experience with people using SOs in DCRs. However, specific interviews with staff of DCRs in the Netherlands offered entry points into understanding how these services are considering their potential responses. Likewise, there is a lack of European-based literature on this topic, despite the great number of DCRs in Europe and their longer existence when compared to DCRs in Canada[286, 287].

Several of the suggestions below reflect the need to adapt the response to SO overdose, especially when many visitors may use SOs. Other adaptations involve reducing harms and the risk of having an overdose. Interviews and literature emphasise the importance of SO preparedness at DCRs to continue the further development in the integration and intersectionality of their services, such as drug checking, mental health services or HIV/HCV community testing[288, 289].

Despite focusing on SOs, several suggested adaptations can be helpful to handle other drugs and risks and thereby improving DCR services as a whole.

Alertness for the appearance of new substances and combinations

DCRs provide 'real-time' drug market monitoring data to alert individuals, harm reduction service providers, public health professionals, academic researchers and law enforcement of highly potent or adulterated batches of drugs circulating in the community that have unintended effects when taken. Its advantage lies in its capacity to provide more direct and timely information that does not rely on the longer lag in reporting of traditional public health data surveillance.

Being aware of early changes can help develop faster responses to an ever-changing environment of drug use. According to DCR staff from Canada, they could see a small handful of people using diverted prescribed fentanyl at the facilities before the overdose crisis arrived. As numbers were minimal, and staff were accustomed to clients bringing a variety of substances to a DCR, they did not pay enough attention at first. The substance was new; people using it were the experts in its use. With a new substance, the need for specific responses arrived.

More recently, according to Canadian interviewees, SOs are being complicated through contamination of the drugs with benzodiazepines. The addition of 'benzos' again leads to different symptoms of an overdose and greater difficulty in responding to it. Since naloxone only counteracts opioids, people using SOs with benzos do not regain consciousness after naloxone is administered and must be monitored for more extended periods. There are also different symptoms of withdrawal associated with benzos. Finally, DCR staff in Canada also saw the combination of SOs with stimulants more often. The 'down' from fentanyl is so strong that people feel the need to smoke stimulants to get awake and to protect themselves from theft or from others in the streets as they are not alert enough.

Syringe residue analysis

Complementing these self-reports and direct observation monitoring strategies, a new approach has been developed in Europe to monitor substances injected through analytically confirmed data at the local level: the analysis of residual content of used syringes[290]. Used syringes collected at DCRs, NSP programmes and other low-threshold facilities contain traces of drugs that can be analysed to inform public health professionals and contribute to identifying the frequency and percentage that SOs occur.

This method was first implemented by research teams and low-threshold services in Paris[291], Budapest[292], and Lausanne[293]. In 2017, the EMCDDA supported its French focal point in developing a partnership with European peers to set up a European multi-city study – the European Syringe Collection and Analysis Enterprise (ESCAPE)[294]. The recently published report based on the 2018 and 2019 data-collection campaigns in eight sentinel European cities highlights three injecting patterns associated with specific health risks deserving of particular attention.

First, the high prevalence of stimulants (cocaine, crack, amphetamines and synthetic cathinones) in most cities across all campaigns is an alert as to the increased risk of acquiring blood-borne and sexually transmitted infections among users. This risk has already materialised in Glasgow (a participating city in 2017) and Cologne, where recent HIV outbreaks among people who inject drugs have been documented. Second, carfentanil, a potent opioid, was detected in a large proportion of the syringes

from Vilnius. While the detection of fentanyl and its derivative remains rare in other participating cities, the exceptionally high overdose risk associated with these substances and the dynamic nature of the EU drug market, and the US opioid crisis, calls for vigilance. Lastly, around one-third of all syringes contained residue of two or more drugs, highlighting the fact that people who inject drugs often inject more than one psychoactive substance (or are re-using or sharing injecting material)[295].

Although findings from this data collection campaign must be interpreted with caution due to the limitations of the study, the analysis of residual content of used syringes shows the potential for DCRs to contribute with information on more stable patterns and regional specificities and to provide information with which to support an increased provision of harm reduction interventions, or an adaptation of DCR services to deal with current poly drug use, increased injecting of stimulants, or the appearance of SOs.

Drug checking services

Drug checking services enable individuals to have their drugs analysed, providing information on the content of the samples, advice and, in some cases, counselling or brief interventions. Education and awareness may be needed to ensure the uptake of drug checking services inside DCRs until clients create the habit of checking their substances before using. According to staff experience in Canadian DCRs, some clients rush to use their substances once they are inside the facility and are not willing to check their drugs beforehand. It can also happen that clients are looking for more potent drugs, even though they are more harmful. Therefore, in these situations of high potency substances, harm reduction approaches to drug use and drug checking inside a DCR can prove lifesaving.

Aware of the barriers that more specialised drug checking might entail, staff experiences in Dutch DCRs highlights alternatives and procedures that provide the linkage of such facilities with drug testing services. In case of suspicion of a highly potent or adulterated batch, a staff member may voluntarily collect and deliver a small sample of an individual for analysis at a local drug checking service. However, it is worth noting that such an exceptional and informal approach would only be possible in those countries where drug possession is not penalised and requires flexibility in the regulations and protocols of a DCR.

Awareness, information and new harm reduction strategies on SOs

According to DCR staff interviewed, the most significant change related to the SO crisis has been the frequency and type of overdoses occurring inside facilities, requiring different knowledge and responses from staff[296]. Fentanyl and analogues brought a shorter duration of the injection pattern, similar to the injecting of stimulants. The frequent injections caused higher chances of abscesses, risks for HCV and HIV, and more publicly discarded syringes. The faster cycle between injections with SOs also meant that clients became less available for conversation than when injecting only heroin, as they are more willing to move to find and use the next shot more quickly. This changes the type of information needed for prevention and the style of communication inside a DCR.

According to staff, the increased vigilance for overdose required also impacts upon the ability to focus on clients over a period of time:

> "I remember one of the worst days that I worked, me and my colleague had 14 ODs in an 8.5 hour period, 6 of them were simultaneous, because of the unknown supply. Folks buy off the streets, usually in the same batches, from the same dealers, and everyone comes in and uses at the same time. Within a couple of minutes span of each other, everyone was bluing up and not breathing". (Mina, DCR staff)[297]

SOs are very potent substances and a minimal change in dosage may lead to a fatal overdose. When overdoses occur, identifying the early signals is crucial to offer a proper and effective response that can be lifesaving. However, the presentation of overdose for SOs can vary from the typical opioid-type of sedation, respiratory depression, and looseness of muscles. With fentanyl, signs of an overdose may be quite the opposite: muscle rigidity in the chest, upper abdomen, and chin; open gaze; rigid jaw; and decorticate rigidity posture. Such modified signals were frequently witnessed by interviewees working in DCRs and described in literature[298, 299]. Staff need to be trained on these differences to carry out proper and timely identification of an overdose.

Moreover, different reactions of people while overdosing on SOs can require for modified responses. Nurses working in Canadian DCRs mentioned the difficulty in putting oxygen masks on clients to provide artificial respiration, given the muscle rigidity in their jaws. The usual practice was to first secure airways to ensure people were breathing and then give naloxone. In practice, however, with overdose types where people had erratic movements, there is no possibility to provide oxygen, so they switch to applying naloxone as much as possible. Using naloxone could also be challenging because some clients have erratic movements while overdosing. For the same reason of muscular rigidity, injectable naloxone was preferred to nasal: it is easier to inject naloxone in a large muscle area, like the thighs, when people are moving than trying to reach their nasal cavity.

Having precision scales available at a DCR can help people control the amount of substance they consume. It is also possible for DCR staff to get recommendations from a drug checking service on the usual or recommended amounts of intake for a particular substance, inform clients about it, and weigh the drug together with the client before it is used.

Increased dosage and availability of naloxone

Given the strength of SOs, the dosage of naloxone needed to revert SO overdoses is much higher when compared to that required for heroin (for more

information, see the Chapter on naloxone). This requires staff and the community to be (re)trained for the application of naloxone and to provide more naloxone than one would for heroin.

> "We started handling naloxone like candy. You need to be very liberal with naloxone. Everyone needs to have it, not only medical or HR personnel". (Paul, DCR staff)[300]

Staff not yet trained on naloxone application should receive training, even before a possible wave of SO use arrives. When waves come, drugs may take over the market quickly, in just a few months. Staff must be prepared to respond appropriately. Those already trained in the application of naloxone may need an update. As mentioned, the dosage of naloxone needed to revert SO overdoses is much higher when compared to the required dosage for heroin and staff need to know what to expect and how to react:

> "We had to change all protocols for OD response. The standard was to give 2 doses of naloxone and now we just give naloxone until you get a response. And you see people not reversed until they get 14 doses. It is really scary for the staff, and it takes a long time". (Wendy, DCR staff)[301]

Naloxone needs to be available at all community health services, pharmacies, and harm reduction services. It must be available to everyone, including friends and family of people who use drugs, not only medical or harm reduction staff. Even people not using opioids should have naloxone with them because of the risk of drugs being laced with SOs. In this way, DCRs represent an effective environment to support its availability through the development, implementation and upscaling of THN programmes in combination with training on overdose risk and management, as well as of peer-to-peer Naloxone (P2PN) distribution programmes.

Safer consumption services for women and gender-diverse people who use drugs

Women and gender-diverse people who use drugs face higher risks of disease and violence than men, and their increase vulnerability is linked to psychological, environmental and social factors[302]. Next to updated information and monitoring of drug use and overdose prevention strategies, gender-centred discussions remain crucial concerning safety and the reasons women and gender-diverse people access DCRs. This is especially important when gender diversity intersects with homelessness and sex work. Experiences and research in Canada have shown that fentanyl-adulterated opioids simultaneously exacerbate the vulnerabilities of women to both overdose and physical and sexual violence. In one study, women attending DCRs in Vancouver reported being targeted by predators who took advantage of their loss of consciousness to assault or rob them[303].

The development of gender specialised services or 'women-only' DCRs was identified as a need by the women who participated in such studies. However, most participants were aware of the difficulties in making this a reality. More pragmatic approaches that would enhance access among women and gender-diverse people would include a better understanding and responses to perceived threats of violence in the surrounding area of DCRs; the establishment of women-only hours accommodating drug-using practices generally not permitted, including assisted injections and injecting partnerships; or integrating supervised drug use in shelters or supportive housing for women and gender-diverse people who use drugs[304].

Meaningful participation of people who use drugs in DCRs

In past years, the necessity to involve people with lived experience in the development, implementation, monitoring and evaluation of drug services and policies has become increasingly important. Although peers have become a central figure in many health care delivery settings and numerous successful examples of participation of people who use(d) drugs in harm reduction settings exist, recent studies bring evidence to the current low level of involvement when it comes to DCRs[305].

People who use drugs possess the experience, knowledge, and understanding to support effective overdose response and prevention services, including peer-witnessing on-site, outreach services, mobile overdose response, delivery and collection of harm reduction supplies, and referrals.

A particularly important field of action in overdose response among people who use drugs to SOs is the appearance of P2PN programmes. P2PN can take several forms, from a fully comprehensive system run by a drug user organisation to P2PN being an integrated feature of DCRs or local needle and syringe programmes. A P2PN distribution model can look similar to a professionally run THN programme. After specific training, a professional dispenser, such as a doctor, authorised pharmacist, or nurse joins the course to dispense kits. Such activity might be delivered by a peer educator who will record the peers trained and the dispensing of naloxone.

Features of peer education training sessions on opioid overdose management may include information on the causes of an overdose; overdose risk factors; identification of overdose signs and symptoms (including differences between overdose for stimulants, heroin, fentanyl or other SOs); assessment and management of casualties; appropriate essential life support, including recovering position and rescue breaths; information on the effects of naloxone; administration and dosages for specific substances; side effects and monitoring following application of naloxone; occasional risks of aggression; common myths about overdose prevention strategies; and the legal context of naloxone and the management of encounters with health and law enforcement professionals, among others[306].

Providing mental health support

An increased rate of overdoses and deaths can significantly impact DCR staff. In the Canadian experience, the team faced daily grief and trauma and the effects of COVID-19 have only amplified the challenges:

> "We had a lot of staff burnout and staff relapse. A lot of our staff have lived experience and relapsed because of the trauma. A lot of us have PTSD from losing that many people and seeing that much death". (Mina, DCR staff)[307]

Providing mental health support and resources for staff, and fostering a workplace that promotes mental wellness, is therefore crucial. Many different signs and symptoms indicate the need to deal with mental health issues. Particular emphasis should be given to increased awareness and information and in supporting staff members to recognise symptoms early and to get professional help. Furthermore, services would benefit from having established linkages with specialised care.

In addition, exposure of people who use drugs to ongoing loss and trauma may be particularly stressful. The individuals most close to them are often friends of people they consider as family. The situation is similar for peer workers, as they not only work in a stressful environment, but they often live the same reality. For both, these experiences are compounded by social vulnerability due to their social positioning, creating conditions that may result in stress and trauma, with lasting social, emotional and mental health effects. In cases where staff members are experiencing similar emotional and mental health challenges due to increased engagement in overdose responses or lack the skills to do so, access to adequate support may not exist. Adequate responses to the appearance of SOs need to be recognised and addressed holistically and must meet the needs of people who use substances and their communities, including mental health support.

3. Operational challenges

Legal and political barriers to opening a DCR

Over the past 30 years, the number of DCRs has been rising in Europe. Nevertheless, many countries have not yet introduced this intervention, despite the need and mounting evidence. Advocacy efforts are necessary to increase the likelihood of implementation. In many countries, the traditional and stigma-driven view of 'not in my backyard' negatively influences their implementation[308]. Winning people over by providing a positive and evidence-informed perception of DCRs is crucial. Using evidence of the benefits of DCRs in other cities and countries is helpful. Advocacy may be undertaken with several stakeholders, from the general community to police, businesses, and government. Engaging with journalists may also be essential to gain support and to reduce the chance of moral panic through media hype that misrepresents DCRs[309].

Legal barriers to access naloxone

Although naloxone is available in most European cities and is included in the pharmacopoeia of all European countries[310], the drug remains primarily available to medical staff at hospitals, ambulances, or medical staff in harm reduction services. Despite this reported availability, several challenges remain in increasing access to naloxone, including no access to THN; the need for a medical prescription; regulations that articulate medical staff as the only personnel capable of administering the drug; a lack of insurance coverage for naloxone; and the lack of funding and support for naloxone training. Low threshold access to naloxone should be considered, including non-medical staff, peers, people who use opioids, their families, and friends.

Resources

Currently, there is a lack of funding in many countries to develop and implement DCRs. In addition, in many countries the funding models are inadequate as they contribute to a lack of stability and sustainability of existing DCRs and negatively impact the working conditions of staff and the health outcomes of people who use drugs. These models are linked to the legal framework and official endorsement of a facility as a health service. In several countries, including Belgium, France and Norway, DCRs were introduced - and still function - as pilot programmes, providing temporary operating permission based on a legal exception.

4. Policy considerations for service providers

From a broader perspective, there may be no specific policy considerations regarding DCRs when responding to SOs. For example, Canada is currently developing a national evidence-based guidance document with companion plain language resources targeting communities and service providers when considering implementation of DCRs[311]. Unlike European countries, the guidelines in Canada are born within the context of an opioid crisis and have opioid and SO responses at their centre. Nevertheless, the guidance focuses on helping service providers to navigate the legal ground in the country so as to be able to establish a DCR, and the experts interviewed did not perceive the guidance as being specific to SOs.

Involve people with lived experience

Meaningfully involving people who use drugs remains crucial yet rarely fully implemented in DCRs[312]. Hiring people with lived experience of opioid and SO use as paid DCR staff, and having a mechanism for client input to the service, has become increasingly important over recent years. Their input is necessary for the successful development, implementation, monitoring and evaluation of drug services and policies. People who use drugs possess the experience, knowledge, and understanding to support effective overdose response and prevention services, including peer-witnessing on-site, outreach services, mobile overdose responses, delivery and collection of harm reduction supplies, and referrals.

Adapt to changes in consumption patterns

The rapidly changing drug markets require DCRs to quickly adapt to the changing needs of their clients[313]. Several interviewees referred to a recent switch towards smoking SOs in the Canadian DCRs in which they work. The same growing desire to smoke substances was observed by Armbrecht, et al.[314], when evaluating DCRs in Canada, Australia and Europe. According to the review, clients felt there

should be no restrictions on the substances used in a safe injection site. Indeed, staff interviewed at Canadian DCRs referred to the need for facilities to allow for smoking. Canadian laws, nevertheless, make it very challenging and costly to build a smoking facility, which has been discouraging provincial governments from funding them.

Adjust DCR operating hours

Some studies have supported adjusting or extending the opening hours of DCRs to meet the needs of clients as there may be differences in the profiles of clients who use the service during daytime and nighttime, such as increased visits among women during the night. More frequent users might attend the DCR more often which may be relevant within the context of SOs and their short duration of action. In addition, a greater severity of overdoses has been noted during nighttime, supporting extended opening hours. However, extended hours can also lead to work overload among staff and will significantly increase the budget of services.

Naloxone

Executive summary

The use of highly potent SOs may cause very rapid and unpredictable life-threatening overdose, irreversible health effects and death. Naloxone is a simple and safe selective opioid receptor antagonist which blocks the action of an opioid at the receptor, thereby reversing intoxication. Naloxone can be administered through injection (with naloxone provided in ampoules or pre-filled syringes) or via intranasal spray. Administration of naloxone provides time for emergency services to arrive and for further treatment to be given if needed. Naloxone has no intoxicating effects or dependence forming potential.

Availability of naloxone needs to be expanded as it is a key part of the public health response to the growing threat of SOs. Many studies demonstrate that in the context of a SO crisis, countries should adopt flexible THN programmes, including community-based supply as it is easy to use also for lay persons. Naloxone should be available without a prescription, or at least should be provided without prescription by authorised drug services. Using peers and individuals in recovery to spread information about naloxone kits may have considerable impact. It is also important to identify where naloxone would make the most impact in saving lives within a community. Having the drug available may not be enough. As high costs of naloxone may contribute to limited dispensing, naloxone should be available free of charge.

Naloxone is not just for people who use opioids. Users are often not even aware of SOs in the drugs that they are using. These highly potent opioids can be mixed with other more commonly used illicit drugs, such as cannabis, cocaine, amphetamine, etc., or even pressed into counterfeit medicine to resemble commonly used prescription pain killers or sedatives. Due to this, naloxone should be available not only in harm reduction and opioid treatment centres but also in emergency departments, prisons, pharmacies or even recreational settings such as nightclubs. Expanding the awareness of naloxone and increasing its use by non-medical first responders can save lives. People who are at risk, or who know someone at risk, of an opioid overdose should be trained in how to use naloxone. Naloxone is a safe antidote to a suspected opioid overdose and, when given in time, can save a life. There is no need for complicated rules as to who receives it.

Prior to the new SO era, community programmes reported nearly 100% naloxone post-administration survival rates with currently recommended doses of naloxone. However, the currently recommended doses of naloxone may be inadequate in the case of highly potent SOs and redosing might be required. There is a lack of studies that have examined the appropriate dose of naloxone after exposure to SOs. Illicitly manufactured potent fentanyl, and its analogues, that are sometimes also mixed with other recreational drugs, have created new challenges and worries for the adequate treatment of overdose. One of the major concerns of increasing naloxone doses is acute opioid withdrawal syndrome. However, there is no published information on the incidence of opioid withdrawal in cases of new SO overdoses that sometimes require multiple doses of naloxone. Thus, the risk appears to be low by increasing the dose of naloxone to the levels proposed by recent studies.

Finally, the use of naloxone should not be marginalised. Some studies have shown that professionals, such as nurses, doctors, prison and police officers, have expressed concern that the availability of naloxone could promote substance use. People using drugs often feel that seeking naloxone from traditional first responders may result in punitive consequences. Naloxone is a lifesaving medicine and should not be discussed as a "red flag" for users and its use should be encouraged by all professionals. The growing threat of SOs in Europe needs a fast, flexible, and smartly targeted response.

It is also useful to remember to take steps to reduce the risk of COVID-19 exposure when responding to a suspected drug overdose and in administering naloxone.

1. General description of naloxone

The finding of an antidote to reverse the cardiovascular and respiratory depression associated with opioid overdose has been crucial. Naloxone has been approved in injectable form for over 40 years. Naloxone was first patented in New York in 1961 by scientists looking to treat constipation caused by chronic opioid use[316]. As such, it was a staple of emergency medicine and anesthesiology that slowly found its way into harm reduction communities in the mid-to-late 1990s[317].

Naloxone is a selective opioid receptor antagonist which blocks the action of an opioid at the receptor, thereby reversing intoxication[318]. Due to its capacity to transform overdoses into common, predictable, patterned, accessible, discernible, plot-able, and above all preventable events, naloxone has contributed to shifting drug policies, including harm reduction programmes. Administration of naloxone provides time for emergency services to arrive and for further treatment to be given if needed. Naloxone has no intoxicating effects or dependence forming potential[319].

Ways of administration

Naloxone can be administered through injection (with naloxone provided in ampoules or pre-filled syringes) or via intranasal spray. A nasal spray was approved in 2017 by the European Commission for EU-wide marketing, and this medication has been introduced in several European countries since early 2018. Nasal sprays may become the preferred alternative to injectable naloxone in take-home programmes

for laypeople[320]. They are easier to handle and can facilitate the use of the antidote by a broader range of people. At the same time, accessing this medication is difficult for many people in large part because of restrictive laws regulating its distribution. In many countries, naloxone is a prescription medicine and this limitation lowers access to this life-saving tool.

Availability of naloxone programs

The World Health Organization (WHO) added naloxone to its model list of essential medicines in 1983 and injectable naloxone formulations have been off-patent since 1985. In 2014, WHO recommended that naloxone should be made available to anyone likely to witness an opioid overdose. Ensuring that it is available to, and used appropriately by, first responders such as the police or ambulance staff and in emergency rooms is therefore essential[321, 322].

During the 1990s and early 2000s, activists, advocates, and researchers in the US moved naloxone from its relatively settled status within a medical enclave to the unsettled status of a commodity for mass distribution[323]. For example, in 2010, the Scottish government launched the world's first National Naloxone Programme. Following suitable training, THN is issued to people at risk of opioid overdose (people who use drugs, prisoners, etc.), their friends, family, and service workers to help prevent overdose deaths[324]. Today, more extensive regional or national THN programmes also exist in other countries with high rates of drug-related deaths, such as Estonia, Denmark, Sweden and Norway. In 2020, national, regional or local THN programmes were implemented in 10 EU countries, Norway and the UK[325].

One barrier to increasing the availability of naloxone programs can be the perception that they could result in increased opioid use and other risk-taking behaviours in people who use opioids by providing a „safety net". Health professionals, law enforcement officials and policy makers may hold such beliefs and object to increasing naloxone coverage. However, the studies reviewed to date do not support such claims and should provide decision makers with confidence that naloxone programs do not increase drug use.[326]

2. Naloxone as a key response to synthetic opioids

Accidental overdose is a common cause of death among opioid users with death rates and contributing factors differing across European countries. In recent years, highly potent SOs, notably fentanyl and its analogues, are also playing an increasing role in both non-fatal and fatal drug overdoses in Europe. Estonia is a particularly distinct example of a market where SOs have been more prevalent than traditional opioids. Illicitly manufactured fentanyl emerged on the Estonian drug market in 2002, and, within the following years, rapidly replaced heroin as the most common opioid. Due to fentanyl use, Estonia had the highest rate of overdose-related deaths in Europe in during 2007–2017[327].

As fentanyl is estimated to be around 100 times stronger than morphine, a dose as small as 2mg's is enough to kill an adult. Typically, multiple substances are implicated in overdose deaths. Opioid users are often unaware of the presence of fentanyl and its increased potency, leading to accidental overdose and increased risk of death[328]. Benzodiazepines, together with alcohol, are frequently found alongside opioids in drug-related deaths[329]. The number of illicitly manufactured medicines, such as benzodiazepines, mixed with SOs, has also been increasing in recent years[330, 331].

The dangers of SOs are related to the severe, toxic effects to the respiratory and cardiovascular systems. Such effects may cause very rapid and unpredictable life-threatening situations which may lead to death in a few minutes. Opioids act on μ opioid receptors (MORs), reducing the drive to breathe. Fentanyl molecules are highly lipid-soluble and penetrate readily into the brain, resulting in overdose levels being reached much more rapidly than with heroin or morphine. A tiny amount is enough to start the molecular chain of events that instigates the effects of opioids on the body.

Regardless of the type of opioid used, in case of an overdose, naloxone administration is an appropriate response. It can be an effective treatment for suspected opioid overdose if an adequate dose is administered in time. However, SOs pose new challenges in clinical practice. As respiratory depression is more rapid with fentanyl than with heroin, quicker oxygenation efforts next to naloxone delivery may be warranted with fentanyl-involved overdoses compared with heroin-only overdoses. Also, uncertainty on the appropriate dosing and a risk, or avoidance, of naloxone-precipitated opioid withdrawal is often highlighted as a matter of concern[332, 333, 334, 335, 336, 337].

2.1. Administration and dosage

Given the relative potency of many SOs, and the fact that they are becoming more prevalent on the illegal drug market and are increasingly combined with other controlled substances, it has been theorised that higher doses of naloxone – or even more potent and longer-acting opioid antagonists – may be required to effectively reverse overdoses[338, 339]. There are numerous studies suggesting that multiple sequential doses of naloxone have been needed for clinical reversal of new SOs and currently recommended doses of naloxone may be inadequate in that frequent redosing is required[340].

The specific treatment for NSO intoxication or overdose, as for other opioids, is naloxone which can be administered via nasal spray or by intravenous or intramuscular injection. Naloxone is currently available in different dosage forms. First, there is a liquid solution containing 04mg/ml. Second, there is a single dose autoinjector available in a 2.0mg dose. Third, there is a multidose nasal atomiser that delivers a 1mg in 1ml dose. Fourth, there is a single dose nasal spray available in 04 or 2.0mg doses, both contained in 0.1ml[341]. In 2021, a branded 8mg IN device was approved, and the development of a branded form of nalmefene is ongoing. Nalmefene is an opioid antagonist with substantially greater μ-opioid receptor affinity and a longer elimination half-life compared to naloxone[342].

When managing opioid overdose clients, the optimal naloxone regimen should rapidly reverse respiratory depression while avoiding opioid withdrawal. There is no single effective dose for all opioid overdoses. Published naloxone administration guidelines

have not been empirically validated and most were developed before fentanyl or other SOs were common. The reversal effects of naloxone on opioids are highly dependent on several factors including the opioid dose/formulation; administration mode; and concurrent medications taken. Also, client-related factors may impact the effectiveness of naloxone, such as underlying diseases; respiratory illnesses; opioid tolerance; genetic make-up of the client; and exogenous stimulatory factors[343, 344, 345].

A comparison of intramuscular and nasal naloxone administration is described in Table 1.

Table 1: Comparison of intramuscular and nasal naloxone administration (2,5, 6,20).

Route of administration	Duration	General considerations	Synthetic opioid (SO) specific considerations	Suggested doses of naloxone for SO intoxication
Intramuscular naloxone injection (04mg/ml). Care provider may not be comfortable with drawing up or giving an injection.	30-90 minutes. Depends on various factors such as strength and quantity of opioid causing overdose.	Less likelihood of precipitated withdrawal. More effective for reversing muscle stiffness caused by fentanyl (related to the rate of ingestion and higher doses of fentanyl).	Repeated doses are often required because opioids have longer duration of effect than naloxone. Monitor for rebound overdose as naloxone may wear off faster than the opioid. If you see illicit drugs in powder or liquid form, put on an additional PPE mask and wash your hands with soap and water for at least 20 seconds. If soap and water are not available and you had no skin contact with illicit drugs, use an alcohol-based hand sanitizer with at least 60% alcohol.	2-6mg injected intramuscular. May need to repeat at 2 to 3 min. intervals. Dose and interval based on client`s response. Goal: respiratory rate 8 to 10 breaths/min.
Nasal naloxone spray (4mg/0.1ml). Easy to administer.	125 minutes.	Higher likelihood of precipitated withdrawal. Less effective for reversing muscle stiffness caused by fentanyl. Coughing and sneezing may occur. Take COVID-19 precautions to administer: use gloves and face protection, especially if the person is suspected or confirmed to have COVID-19. If possible, position the person's head facing away from you. Effects of 1 spray are comparable to 5 naloxone injections. Nasal naloxone may not work in all individuals. In addition, encourage the carrying of kits of injectable naloxone.	Repeated doses are often required because opioids have longer duration of effect than naloxone. Monitor for rebound overdose as naloxone may wear off faster than the opioid. If you see illicit drugs in powder or liquid form, put on an additional PPE mask and wash your hands with soap and water for at least 20 seconds. If soap and water are not available and you had no skin contact with illicit drugs, use an alcohol-based hand sanitizer with at least 60% alcohol.	4-8mg intranasal. May need to repeat at 2 to 3 min. intervals. Dose and interval based on client`s response. Goal: respiratory rate 8 to 10 breaths/min.

The optimal naloxone dose to treat NSO intoxication or overdose is not yet established. It is of crucial importance to administer naloxone as soon as possible as SOs may induce life-threatening respiratory depression within seconds and minutes[346, 347]. Due to the higher potency of NSOs, experts recommend an initial dose of 2-6mg's injected or 4-8mg's intranasal rather than the 04mg intravenous dose often recommended for a heroin overdose. The naloxone dose may need to be repeated several times at two-to-three-minute intervals, especially if the client has taken NSOs orally which have a longer duration of action. Some clients have required cumulative naloxone doses of up to 10-to-20mg's. In every case, the dose and dosing interval should be titrated based on the actual response of the client, with the goal of restoring the respiratory rate to 8-to-10 breaths per minute. Tylleskar, et al.[348], found that those who were treated with an initial naloxone intravenous dose of 0.8mg were 60% less likely to receive multiple doses than clients treated with an initial dose of 04mg naloxone.

Prepacked naloxone kits are frequently used to reverse opioid intoxication and the number of naloxone doses in the prepacked kit is usually limited[349]. Based on the epidemiological data requiring sequential repeat dosing of naloxone, as well as the increased potency of fentanyl, it is reasonable to propose a range of increased doses of naloxone to 4-6mg's intramuscular or the intranasal equivalent of 8-to-12mg's. This approximates increases of 2–3 fold from the currently recommended doses[350]. It is so important to ensure that individuals have sufficient doses of naloxone to account for the potency of illicitly manufactured fentanyl and fentanyl analogues.

According to a study carried out in a safe injection facility in Oslo, clients at the facility were often treated with the lower naloxone dosage (04 mg) and were less likely to receive a second dose than clients at other locations despite presenting in deep coma and respiratory arrest. The staff at the facility do not administer naloxone but manage clients with bag-mask ventilation. The lower dose may be a consequence of clients being ventilated while waiting for the emergency medical service (EMS) and, therefore, becoming less hypoxic. The facility is also a well-organised work environment and allows the EMS to start to lower the titration of dosages and give this dose time to work. Clients treated in the safe injection facility were also more likely to be left at the premises, probably due to the facility offering post-overdose monitoring and counselling[351].

2.2. SO overdose symptoms

When overdoses occur, identifying the early signals is crucial to offer a proper and effective response that can be lifesaving. However, the presentation of overdose for SOs can vary from the typical opioid-type of sedation, respiratory depression, and looseness of muscles. With fentanyl, signs of an overdose may be quite the opposite: muscle rigidity in the chest, upper abdomen, and chin; open gaze; rigid jaw; and decorticate rigidity posture. Naloxone, however, also reverses skeletal muscle rigidity from fentanyl and its analogues[352].

Moreover, different reactions of people while overdosing on SOs can require for modified responses.

For example, it can be difficult to put oxygen masks on clients to provide artificial respiration, given the muscle rigidity in their jaws. The usual practice was to first secure airways to ensure people were breathing and then give naloxone. In practice, however, with overdose types where people had erratic movements, there is no possibility to provide oxygen, so they switch to applying naloxone as much as possible. Using naloxone could also be challenging because some clients have erratic movements while overdosing. For the same reason of muscular rigidity, injectable naloxone was preferred to nasal: it is easier to inject naloxone in a large muscle area, like the thighs, when people are moving than trying to reach their nasal cavity[353].

2.3. Opioid withdrawal syndrome after naloxone administration

Opioid withdrawal is one of the longest studied and most well-described withdrawal syndromes. Opioid withdrawal syndrome (OWS) is a known risk of naloxone for opioid-tolerant individuals, producing symptoms such as hyperalgesia, diarrhoea and vomiting, particularly at higher doses. Although naloxone-induced reversal is associated with very few serious side effects, this agent induces signs and symptoms associated with OWS. OWS is more likely to occur if there is tolerance and habitual use of opioids and when naloxone is dosed excessively, including over-antagonism[354]. People with physical dependence on opioids may have withdrawal symptoms within minutes after they are given naloxone. These signs and symptoms are unpleasant and associated with physical reactions, aggression, refusal of treatment and premature self-discharge, but mostly not life-threatening. Although OWS can be unpleasant for the individual, its benefits outweigh the harms of an overdose.

Studies on naloxone-precipitated OWS are very few, claiming a rate of acute OWS of 7.6% following naloxone provision and 045% of serious OWS symptoms. Some studies claim that intranasal naloxone might have a lower chance of triggering OWS than intramuscular[355]. Currently, there is no published information on the incidence of OWS related to new SOs, although in such cases where they require multiple doses of naloxone, the risk of OWS appears to be low by increasing the naloxone doses which should be tirated to avoid over-antagonism.

2.4. Naloxone availability for SO

The major challenge in preventing overdose deaths may not be the dose of naloxone, but whether there are bystanders present that carry naloxone. Community-based overdose prevention programmes (or take-home naloxone programmes (THN)) first emerged in the 1990s and they are now the main public health intervention for overdose. THN was never meant to replace callout to, and treatment by, emergency medical services. It is a head start at the scene to shorten the time to the administration of the antidote while awaiting emergency medical services for professional management and post-overdose follow-up[356].

Key elements of these programmes include overdose education and naloxone distribution to people who use opioids and their social networks. Currently,

the use of naloxone for self-administration may be limited due to access issues. Access to naloxone is generally limited to health professionals and, in many countries, there is limited availability of naloxone even in medical settings, including ambulances. Naloxone is a prescription medicine in almost all countries and while it is not usually prescribed to people likely to witness an opioid overdose, at least Italy has made naloxone available in pharmacies without a prescription[357, 358, 359, 360].

In addition, fentanyl and other new SOs appear to differ from other opioids as having a very rapid onset with high systemic levels found in overdose victims, it is important to ensure naloxone is flexible and easy to access[361]. Implementing post-overdose naloxone training, including in emergency departments or by ambulance workers, can also be useful. Such "on-the-scene" interventions could promote naloxone distribution and decrease repeated overdoses.

As THN programmes were first introduced almost 40 years ago, people who use harm reduction services or receive drug dependence treatment have usually already heard about naloxone. Prior to the emergence of new SOs, community programmes reported nearly 100% naloxone post-administration survival rates with currently approved doses of naloxone. Certain criteria for naloxone distribution have been settled: misusing prescription opioids; using heroin or illicit SOs; and having an opioid use disorder, amongst others. In the context of new SOs, it must be remembered that different populations may be affected. New SOs are also found mixed with recreational drugs[362, 263, 264, 265]. Therefore, increasing the availability, awareness and targeted distribution of naloxone is a critical component in efforts to reduce opioid-related overdose deaths.

2.5. Naloxone awareness for SO

It is important to highlight the need to improve health care staff awareness about new SOs. Ambulance and emergency departments usually have well-implemented guidelines on how to manage opioid toxication and overdose. Often harm reduction or treatment service providers are informed about new drugs on the street, but nurses and doctors working in public settings should also be informed about the changing illicit drug market to provide better health care services. Also, information should be provided to community groups, community leaders, school officials, parents, students and others about the changing illicit drug supply and risks for overdose and exposure to highly potent opioids, such as illicitly manufactured fentanyl or counterfeit drugs appearing to be legal prescription medications. Research shows that when naloxone and overdose education are available to community members, overdose deaths decrease in those communities[366, 367].

Experts propose that educating people who use other drugs than opioids must also be informed to combat the new era of overdose due to the more potent SOs. People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose and not be limited only to drug treatment and harm reduction services but also with other community members.

3. Operational challenges

Clinical uncertainty of naloxone dosing

There are numerous studies suggesting multiple doses of naloxone have been needed for clinical reversal in the new SO era. The current standard dose of naloxone is likely inadequate to reverse some overdoses caused by high-potency opioids such as fentanyl. However, the optimal naloxone dose to treat SO intoxication or overdose is not yet established. Furthermore, practitioners, lay responders, and policymakers should be aware of how a nasal naloxone spray compares to injectable antidotes in the field. This necessitates additional research into both the effect and the harm in the target group in order to make evidence-based decisions and fill the gap in existing evidence.

Most of the published naloxone administration guidelines have not been empirically validated and were developed before fentanyl or other SOs were common. New guidelines for naloxone use in the context of SOs are needed and they need to be frequently updated and practitioners should be regularly informed about the latest evidence-based achievements.

Barriers in gaining access to naloxone

However, the more important aspect of using naloxone to prevent overdose deaths may not be the dose of naloxone, but whether there are trained bystanders carrying naloxone. In many countries, as naloxone is prescription-only, non-medical services which may experience frequent opiate-related overdoses are unable to legally hold stocks of, or administer, naloxone in an emergency. Wider provision of naloxone could result in a reduction in overall drug-related deaths.

Despite reported availability, naloxone is mostly available to only medical staff at hospitals and ambulances, less so for harm reduction services and people who use drugs (60-70%). Only 40% reported availability for family and friends of people who use drugs[368]. The main challenges in gaining access to naloxone were reported as:

No access to THN.

- » Naloxone available only at drug services, thus, not for all people who use drugs.
- » Need for medical prescription.
- » Administration by medical staff only.
- » Lack of insurance coverage for naloxone.
- » Lack of funding for naloxone.
- » Lack of funding and support for naloxone training.

4. Policy considerations for service providers

Increase targeted distribution of naloxone

There is a need to increase the availability of naloxone and to ensure access for people who use drugs and their communities. Increasing the availability and targeted distribution of naloxone is a critical component in efforts to reduce opioid-related overdose deaths. It is important to ensure that individuals have sufficient doses of THN to account for the potency of illicitly manufactured fentanyl and fentanyl analogues. This includes not only the individuals who have access to it, but the locations through which it is made available (e.g. drug services, pharmacies, even medical services).

Naloxone should equally reach those individuals at the highest risk of overdose and bystanders. It is important to encourage individuals to get their own naloxone kits. Also, it is important to prioritise naloxone distribution to people who use drugs other than opioids, as SOs are sometimes also mixed with other recreational drugs. Peer navigator programmes, or recovery coaches, could be considered to intervene with individuals at the highest risk of overdose.

In addition, it is necessary to ensure effective coordination between different stakeholders. For example, prisons and social and community health services, as people who are released from prison have an increased mortality rate due to the significant risk of overdose. The initial period after release is a critical period for support. For this reason, the coordination and collaboration between prisons, community health and social services are important to ensure the continuity of care.

Train professionals and individuals to respond to SO overdose

It is important that staff and individuals possessing naloxone are given suitable training in how to respond to an overdose, as well as how to administer naloxone. Naloxone provision is one of several tools in a package of interventions to prevent opioid overdose. Other interventions include basic life support training, knowing SO overdose symptoms and also encouraging users not to use alone.

Training on naloxone application should be done before a possible wave of SO use arrives. When waves come, drugs may take over the market quickly and all stakeholders must be prepared to respond appropriately. Multiple doses of naloxone may be required for a single overdose event because of the potency of SOs and multiple doses of naloxone may be needed over time due to the prolonged effects of opioids in some cases. Those already trained in the Naloxone application may need an update. It is also important to remember to take steps to reduce the risk of COVID-19 exposure when responding to a suspected overdose.

Furthermore, the locations in which overdose prevention education and THN are provided should be increased. These locations may include inpatient and outpatient treatment programmes; primary care settings; retail pharmacies; counselling and support groups; and other community-based settings. It is also important to expand naloxone availability in other settings, such as emergency care and recreational settings.

Increase naloxone awareness and decrease stigmatisation

Stereotypes about people who use drugs are pervasive and often inaccurate. Stigma often prevents users from using health services and compounds psychological damage caused by drug use. Efforts to destigmatise opioid use should be accompanied by basic naloxone education as its wider use is difficult in communities where it is misunderstood. Raising awareness about naloxone is also important among health professionals, law enforcement officials and policy makers as beliefs about naloxone programs increasing drug use and risk-taking behaviours are common and impede implementation. Revise and, if necessary, adapt policies and practices that contribute to the stigmatisation of people who use opioids.

Opioid agonist treatment (OAT)

Executive summary

Opioid agonist treatment (OAT) - also known as opioid substitution treatment (OST) and/or medication-assisted treatment (MAT) - is the main and most-researched approach to the treatment of opioid dependence and one of the components of a wider range of treatment options available to people who use opioids. Evidence shows that OAT is associated with considerable reductions in overdose mortality risk among people who use opioids. Although OAT is available in all European countries, coverage of this intervention varies widely between countries and in many parts of Europe it remains insufficient.

Two of the most frequently used medications to treat opioid use disorder and manage withdrawal are methadone and buprenorphine, but the options go beyond these two medications and cover a range of other possibilities. Choosing the most suitable medication and mode of treatment for people who use SOs should be a shared decision between the patient and the health care provider. Regardless of the type of medication, the treatment programme works best if it is integrated with other interventions.

Identifying, reaching and engaging people who use SOs who are in need of treatment is the first step in the operational phase of all opioid treatment interventions. Understanding the reasons for not seeking treatment among people who use drugs is necessary to reach this goal through finding the gaps and increasing access to treatment. As involuntary discharge from treatment is also associated with elevated risks of mortality, involvement in treatment is important. To maximise the effectiveness of OAT for people who use SOs and guarantee its success, practitioners and service providers should increase the involvement of social networks of their clients as well as enhancing their social skills through evidence-based trainings. In addition, OAT programmes targeting people who use SOs are recommended to encourage their clients to actively engage in self-help groups through emphasising the importance and effectiveness of such groups. Co-occurrence of psychiatric disorders (dual diagnosis) is common among people with opioid dependence. Dual diagnosis can also affect the OAT outcomes for patients receiving treatment. Therefore, treatment success for people who use SOs with dual diagnosis disorders requires special attention. Populations with special treatment needs include pregnant women, young people, people living in prison, and older adults.

In addition to the above-mentioned principles, operational challenges – including relapse, diversion and misuse of medication, and overdose - as well as considerations while implementing OAT for people who use SOs, such as routine monitoring and evaluation, qualified clinicians, take-home doses of medications, major infectious diseases, and quality of life of people under treatment, are also discussed in detail in this Toolkit.

These principles are crucial to improve the quality and ensure the sustainability of OAT programmes, mitigate the risk of relapse, and improve the quality of life of people receiving treatment for SO use disorder. It should be considered that an efficient OAT system can play a protective role against the illegal opioid market. Furthermore, since sigma and discrimination in opioid use can prevent patients from seeking treatment, the principles discussed in the present guide should be implied in a stigma-free atmosphere without discrimination and negative attitudes towards people who use SOs seeking or under treatment. The increasing trends of opioid use and harms highlight the importance of scaling-up and expanding harm reduction interventions, including specialised drug treatment programmes to respond to this issue.

1. General description of OAT

Opioid use disorder is a chronic condition with major health, social, and economical consequences that can be treated using evidence-based treatment methods. OAT, also known as opioid substitution treatment (OST), and/or medication-assisted treatment (MAT), is the main and most-researched approach to the treatment of opioid dependence and one of the components of a wider range of treatment options available to people who use opioids[369]. Evidence shows that OAT is associated with considerable reductions in overdose mortality risk among people who use opioids[370]. Although methadone and buprenorphine are the most commonly used medications to treat opioid use and dependence, other medications including buprenorphine-naloxone combined, naltrexone, slow-release morphine, codeine, dihydrocodeine and diacetylmorphine are available in, and being used by, different European countries[371]. The above-mentioned medications are morphine-like substances with the same effects as natural opium extracts which, depending on the needs of a client, can be prescribed for short or long treatment periods. Regardless of the type of medication, the treatment programme works best if it is combined with other interventions including:

- Counseling
- Social support
- Routine substance use monitoring
- Harm reduction education and interventions, e.g. THN
- Relapse prevention and support
- Holistic primary care and prevention interventions, e.g. routine infection screening and immunisation

Although OAT is available in all European countries, coverage of this intervention varies widely between countries, regions, and settings. It is estimated that approximately 50% of opioid-dependent people in Europe are under OAT[372]. Evidence shows that in eight European countries, including Bulgaria, Croatia, Estonia, Greece, Lithuania, Malta, Slovenia, and Turkey, the proportion of people entering treatment for opioids among all treatment entrants was above 60%[373]. The EMCDDA also suggests that the number of people who entered into treatment for SOs in two European countries, namely Estonia and Finland, was above 50%; that was substantially higher than in other European countries. Despite improvements in some European countries, coverage of OAT in many parts of Europe is still insufficient[374].

The present toolkit has been prepared to assist practitioners and service providers working in the field of opioid treatment to enhance the quality of treatment for people who use SOs seeking treatment. The principles discussed in this toolkit have been derived from existing guidelines, tools and standards on OAT for people who use opioids.

2. Principles of OAT for people who use SOs

2.1. Identifying, reaching and engaging patients in need of treatment

Identifying, reaching and engaging people who use SOs and are in need of treatment is the first step in the operational phase of all opioid treatment interventions. Understanding the reasons for not seeking treatment among people who use drugs is necessary to reach this goal through finding the gaps and increasing access to treatment. As stated in the literature, some of the perceived reasons reported by people who use drugs who did not seek treatment include: not ready to stop using drugs; lack of affordability of treatment programmes; adverse effects of treatment at work; lack of knowledge as to where to receive treatment; and lack of accessibility due to various reasons, such as distance to the treatment location[375]. Stigma around opioid use is another significant barrier towards seeking treatment and access to care for people who use opioids. The evidence-based methods of behavioural change, such as motivational interviewing, can help deal with this issue and improve engagement of people who use SOs into treatment[376]. Many providers rely on rapid urine or saliva drug test to determine whether treatment should be initiated. However, it should be taken into consideration that some of the newer synthetic opioids may not detectable with the most common rapid tests, which highlights the need for more accurate testing methods.

Availability, accessibility, and coverage of treatment programmes can play a crucial role in treatment engagement. In other words, if treatment is not readily available or accessible, potential clients can be immediately lost[377]. In addition, practitioners need to consider that in early phases of treatment, clients can be emotionally fragile, ambivalent, and resistant to treatment; thus, immediate concerns including harm reduction, abstinence achievement, relapse prevention, and craving management should be at the centre of attention at this stage[378]. Since involuntary discharge from treatment is associated with elevated risks of mortality[379], keeping clients in treatment by the end of the treatment period should be one of the goals of each treatment programme targeting people who use SOs.

2.2. Availability of all types of medications, applications, and all modes of treatment

As noted above, there are two medications most frequently used to treat opioid use disorder and to manage withdrawal. These medications comprise methadone (mu-agonist) for managing withdrawal and treating opioid use disorder and buprenorphine (partial mu-agonist) with the same application as methadone. Although these medications are the most frequently used to treat opioid use disorder, the options go beyond these and cover a range of other medications: combined buprenorphine-naloxone; slow-release morphine; diacetylmorphine; naltrexone; codeine; and dihydrocodeine[380]. Choosing the most suitable medication and mode of treatment (e.g. oral pills, patches, injectable medications and implants) for people who use SOs should be a shared decision between the client and the health care provider, considering the following factors:

» Severity of SO use disorder and level of treatment need.

» Openness of the client to pharmacotherapy.

» Preferences of the client.

» Understanding by the client of the physical dependence of OAT.

» Prior experience of a client with OAT and other treatment approaches.

» Evidence of the safety and efficacy of the treatment options.

2.3. Social support as a fundamental aspect of OAT

The lack of social support is known as one of the predictors of initiation of substance use and its associated harms[381]. On the other hand, support from family members, friends, peers, community, and community-based organisations plays a crucial role in treatment participation, relapse prevention, and improving quality of life by creating a sense of inclusion, security, belongingness, and safety to people receiving treatment for substance use[382m 383, 384]. Social support for people under treatment can be either emotional or material through providing money, food, and residence. Furthermore, it has been evidenced that improving social skills of people who use drugs through specialised training programmes

can be an effective strategy to promote OAT[385]. To maximise the effectiveness of OAT for people who use SOs and guarantee its success, practitioners and service providers should increase the involvement of social networks of their clients as well as enhancing their social skills through evidence-based trainings.

2.4. Participation in self-help groups

Participation in self-help groups is recommended by the majority of drug dependence treatment programmes. These groups can serve as the main source of behavioural change, either as a supplement to specialised treatment or as continuity of care and social support following treatment[386]. The self-help groups are often grounded in 12-step principles, including admitting powerlessness over drug use; coming to believe in a higher power with the ability to restore a patient to sanity; making a decision to turn the will; taking and sharing and continuing inventory; preparedness; asking the higher power; listing and making amends; praying and meditating; and helping others[387]. A large body of evidence has shown the ability of engaging in self-help group therapy to optimise the outcomes of treatment and to prevent relapse[388, 389, 390]. In addition, evidence shows that emphasising the importance of self-help groups will steadily encourage more attendance and engagement in treatment[391]. By this account, OAT programmes targeting people who use SOs are recommended to encourage their clients to actively engage in self-help groups through emphasising the importance and effectiveness of such groups.

2.5. To address dual diagnosis

Co-occurrence of psychiatric disorders (dual diagnosis) is common among people with opioid dependence. Severe anxiety, depression, bipolar disorder, post-traumatic stress disorder (PTSD), and borderline personality disorder are among the most common co-occurring disorders among people with substance use disorders, including people who use SOs[392]. Evidence shows that dual diagnosis disorders are associated with severity and persistence of both mental and substance use disorders[393]. Dual diagnosis can also affect OAT outcomes for patients receiving treatment. Therefore, treatment success for people who use SOs with dual diagnosis disorders requires special attention. The following factors should be considered while starting treatment for people who use SOs living with co-occurring psychiatric disorders[394, 395]:

» Psychiatric disorder should be assessed at the starting phase of OAT, and reassessment should be undertaken after stabilisation with medications using a standard examination method.

» Pharmacotherapy should be in conjunction with psychosocial treatment.

» Health care providers should be aware of potential interactions between medications utilised to treat psychiatric disorders and those for SO use disorder.

» Assertive community treatment has been recommended for people who use SOs with co-occurring schizophrenia who have a history, or are at risk of, hospitalisation or homelessness.

» It is suggested that dual diagnosis is more common in young, male, single, and less educated patients, those with a history of conduct disorder, and in people with a history of substance use disorder in their family.

2.6. Populations with special treatment needs

Pregnant women

Pregnant women who use drugs are one of the vulnerable populations with special treatment needs. The increasing prevalence of opioid use disorders among pregnant women underlines the importance of scaling-up effective treatment programmes to mitigate the health consequences for mother, fetus, and child[396]. Evaluation of different models of care for pregnant women receiving treatment suggests that, 1) co-locating services for treatment and care will improve access; 2) inter-professional collaboration leads to coordination; 3) group treatment will improve quality of care and treatment; and, 4) criminalisation and stigmatisation of drug use are two major barriers to treatment and care for pregnant women[397]. Regarding the mode of OAT during pregnancy, the existing evidence suggests that:

» Methadone is a frequently used medication to treat pregnant women with opioid use disorder.

» Evidence shows that the buprenorphine-naloxone combination is as safe and effective as methadone and can be a proper alternative to methadone for women during pregnancy.

» Slow-release oral morphine may be an option for pregnant women who are not successfully retained in treatment with methadone or buprenorphine/naloxone[398, 399].

The method of OAT during pregnancy should be selected based on the needs of the client, their experiences, and individual circumstances. A stigma-free client-provider relationship built on trust is required to have an effective OAT for pregnant women seeking treatment for SOs.

Young people

As another vulnerable population, treatment for young people, namely adolescents and young adults who use SOs, requires special attention. Compared to other types of drugs, young people who use opioids are at greater risk of morbidity, mortality, developing severe polysubstance use disorder, acquiring blood-born infections, and developing social and legal problems[400]. On the one hand, youth are less likely to recognise the harms of substance use due to low-risk perception, such as by heroin inhaling/chasing the dragon, and lack of knowledge about the interactions between the OAT medications and other drugs. On the other hand, evidence shows that earlier initiation of opioid use is associated with increased risk of developing opioid use disorder and long-term health

and social consequences[401]. Therefore, scaling-up specific treatment interventions for young people who use SOs needs to be a priority for all service providers and aimed at mitigating the use and harms of SOs.

Although combination buprenorphine/naloxone has been recommended as an effective treatment for youth with moderate to severe opioid use disorder, the entire modes of treatment, including pharmacological and non-pharmacological, should be available to young people seeking treatment for SO use[402]. Furthermore, since withdrawal alone is associated with higher rates of relapse and health harms, routine psychosocial treatment interventions and support should be considered a fundamental aspect of OAT for young people receiving treatment for SOs.

People living in prison

A large proportion of people living in prisons have opioid use disorders and associated problems. Prevalence of illicit drug use among male and female prisoners was estimated at 30% and 51%, respectively[403]. Due to the specific environment, illicit drug use in prison is associated with elevated risks of drug-related harms including overdose and overdose mortality, violence, self-harm and suicide[404]. Evidence shows that engaging in OAT not only helps people in prison to deal with their opioid problems and increases their quality of life, but it also lowers the risk of recidivism and re-incarceration[405]. Yet the quality of treatment for people held in prisons has been chronically lower than those available for people who use drugs in non-prison settings, at 23% and 50% in Germany, for example[405].

Regardless of the type of offense and length of stay in prison, all people in prisons and other closed settings with (synthetic) opioid use should be offered OAT. The following factors have been suggested as the main components of OAT for people in prisons:

» Providing practitioners with specific trainings to avoid stigma and discrimination.

» Engaging people in prison in designing and implementing the OAT programme.

» Building relationships to engender respect for treatment.

» Emphasising integrity and authority of service providers.

» To ensure after-release continuity of care for clients who have received treatment while in prison.

OAT in prisons should be initiated in collaboration with civil society organisations to ensure that after release from prison there is a treatment place available for people who use SOs who were receiving treatment while in prison[407]. Although methadone is a frequently used medication for OAT in prison settings, all OAT medications should be available and delivered in adequate doses based on the individual needs of people who use SOs in prisons. People who use SOs who seek treatment in prisons should be abstinent from all types of illicit drugs and stable in terms of physical and mental health, educational and vocational needs, and family problems for at least 1-2 years prior to starting to taper-off the medication regimen[408].

Older adults

In Europe, the number of older people (40 years or above), as well as the age of mortality associated with opioids, are increasing[409]. Longer history of drug use, different cultural norms and attitudes towards substance use, and increasing availability of psychotherapeutic medications has made drug use and harms more severe for new generations of older adults compared to the previous older generations[410]. In addition, drug use among older people is associated with higher levels of stigma than young populations[411]. The above-mentioned issues highlight the importance of scaling-up special care and treatment programmes for older adults who use SOs.

Evidence shows that older people with opioid use disorders achieve better treatment outcomes than their young counterparts[412]. Therefore, the lack of specific services and guidelines to treat older people who use drugs, for specific SOs, is a cause for concern[413]. The following suggestions will help policy-makers and service providers to scale-up effective treatment programmes for this vulnerable population:

» Considering the age and needs of client, a bundle of psychosocial and pharmaceutical interventions should be offered to older people seeking treatment for SO use, although access to pharmacotherapy should not be seen as a mandatory requirement.

» Older people with mild-to-moderate opioid use disorder may be treated by experienced clinicians; however, for those with severe opioid use disorders, clinicians need assistance by teams or personnel with advanced skills.

» OAT should be offered to older people who use SOs who are admitted to a hospital or drug treatment facility at the onset of withdrawal.

» The costs of OAT for older adults should be covered by public health plans.[414]

3. Operational challenges

Relapse

Relapse is one of the most common challenges faced by service providers working with people who use drugs receiving treatment. Relapse should be considered as a part of the recovery process and if it occurs, it should not be interpreted that the treatment programme has been unsuccessful or a failure. Understanding the predictors of relapse is necessary to design and implement prevention strategies and to increase the chance of treatment success. Younger age, more severe opioid use before treatment, and a failure to receive aftercare have been suggested as the possible predictors of relapse[415]. Recognising individual signs of relapse, completing the entire treatment course, and receiving strong support during OAT are necessary to prevent relapse among people who use SOs who are receiving treatment.

Diversion and misuse of OAT medications

Diversion and misuse of OAT medications from their intended use in treatment are among the main risk

factors for overdose and deaths among clients under treatment for opioid use disorder[416]. Diversion is defined as, "the intentional transfer of a controlled drug from legitimate distribution and dispensing into illegal channels", and misuse is, "the use of a medication other than as directed or as indicated, whether willful or unintentional, and whether it results in harm or not"[417]. The following strategies are recommended to prevent diversion and misuse of OAT medications that can be applied to OAT for SO use disorder:

» Using misuse-deterrent drug formulations.

» Providing information, education, and risk communication including safe storage. Supervising medication dosing.

» Routine observation and monitoring of clients through toxicology tests, pill counts, ingestion observation, and unannounced monitoring.

» Continuous medical education for clinicians.

» Applying electronic medicine dispenser (EMD) systems.

» Limiting access to medications to people with legitimate need[418].

Overdose

As noted above, due to the high potency of SOs, more frequent use due to shorter half-time than traditional opioids, as well as high risks of medication misuse - such as the misuse of benzodiazepines and gabapentinoids to self-medicate or to increase the effects of opioids - diversion and relapse, people who seek treatment for SO use disorder are at great risk of overdose and overdose mortality. Thus, overdose is another major challenge facing clinicians who provide treatment for SO use disorder. Available in nasal spray and injectable forms, naloxone is the single most effective medication to reverse overdose involving opioids[419]. It has been suggested that naloxone should be made available to all first responders, including emergency medical staff, police officers, and firefighters, as well as prison staff in addition to practitioners providing treatment for SO use disorder and clients under treatment and their family members[420]. Evidence shows that a success in reversing overdose caused by potent SOs requires more doses of naloxone than overdose involving other opioids[421].

Gaps in scientific evidence

The lack of scientific evidence is one of the most important challenges facing the treatment of people with SO use disorder. The vast majority of existing treatment guidelines focus on general opioid use rather than SOs. In other words, evidence on different aspects of treatment of SO use disorder is scarce. This issue highlights the crucial role of international foundations to support studies on different aspects of the treatment of SO use disorder. The existing guidelines on OAT need to be frequently updated and practitioners providing treatment should be regularly informed about the latest evidence-based achievements in OAT. In addition, harm reduction researchers should consider this topic as a priority for their future research to fill the gap in existing evidence on treatment aspects of SO use disorders.

4. Policy considerations while implementing OAT for SO use disorder

The following considerations are necessary to improve the quality, and ensure sustainability, of OAT programmes to mitigate the risk of relapse and to improve the quality of life of people receiving treatment for SO use disorder. An efficient OAT system can play a protective role against the illegal opioid market. Since stigma and discrimination in opioid use can prevent clients from seeking treatment, the principles discussed in the present toolkit should be applied in a stigma-free atmosphere without discrimination and negative attitudes towards people who use SOs seeking, or under, treatment.

Monitor and evaluate the programme

Routine monitoring and evaluation are necessary components of OAT programmes for people who use SOs[422]. Monitoring and evaluation will allow policy-makers and clinicians to reveal the gaps in their programme and the opportunity to address such gaps. A strong information system (IS) should be in place to collect and analyse data from people receiving treatment on a regular basis, and to share the results with stakeholders to improve the quality of the programme.

Train clinicians on SOs

Qualified clinicians play a crucial role in the success of OAT programmes for people who use SOs. Yet evidence shows that many clinicians lack sufficient knowledge, education and experience to provide evidence-based treatment for people who use opioids[423]. In Germany, for example, physicians must attend a 60-hourse course to be able to prescribe medications. Providing continuous evidence-based education, vocational trainings on SOs, as well as sufficient internship programmes for clinicians will help deal with this issue.

Provide take-home medication based on client's needs

Advantages and risks of take-home doses of medications should be assessed in consultation with clients and their selected supporters and documented in the client's file[424]. Take-home doses should be granted based on the individual needs of clients without affecting their quality of life, work, or social activities. In Germany, for instance, in some states take-home doses of medications are prescribed weekly with a possibility to extend up to 4 weeks. Proceeding to physicians once a week will affect the social life of clients, their job, and their motivation to continue treatment. Take-home doses should be stored in a safe and secure place to avoid misuse or unintended harms, such as to children.

Test for major infectious diseases (MIDs)

People who use drugs, including those who use SOs, are at greater risk of acquiring major infectious diseases including HIV/AIDS and hepatitis C[425]. Evidence shows that OAT can mitigate the risk of infection transmission through modifying risk behaviours and improving adherence to treatment among people who

use drugs[426]. Therefore, testing clients of OAT for MIDs and linking clients to treatment at least twice per year should be a part of OAT for people who use SOs receiving treatment.

Provide a person-centred service

The quality of life of people who use SOs in receipt of treatment should be the centre of attention while providing treatment to them. Evidence suggests that attention to the mental, physical, and social quality of life can improve treatment outcomes for people who use opioids receiving treatment[427]. Assessing the predictors of quality of life among people who use SOs in treatment is a necessary step to reach this goal. Since sigma and discrimination in opioid use can prevent patients from seeking treatment, the principles discussed in the present guide should be implied in a stigma-free atmosphere without discrimination and negative attitudes towards people who use synthetic opioids seeking or under treatment.

Other interventions: safe supply

A novel intervention worth consideration according to the Canadian experience is safe supply. Safe supply, or safer opioid distribution, represents a novel public health intervention with the potential to directly address an overdose crisis. It could be used as a complementary intervention where other public health and harm reduction interventions have not been able to sufficiently decrease overdose fatalities due to the increasingly unpredictable and toxic drug supply. Safe supply programmes are built on the premise that providing an alternative – such as non-adulterated drugs of known quality/quantity with user agency in consumption methods - to the street drug supply will limit the use of adulterated drugs, such as fentanyl, and reduce overdose events[428].

A non-treatment-based provision of safer opioids may address the low uptake and engagement of people exposed to illicitly-manufactured SOs in traditional OAT. Contributing factors for this can be gaps in service provision and limitations of available options. It is important to recognise a wide range of drug use patterns, including people who use illicit drugs who are not interested in drug treatment and those for whom traditional forms of drug treatment are not suitable or desirable. Alternatively, it may be the case that even if enrolled in OAT, individuals may not be satisfied with their treatment, continuing to use unregulated opioids to meet their needs and thereby increasing their risk of SO exposure. Providing easy access to safer alternatives has the potential to reduce other drug-related harms, improve well-being and overall health, while increasing the likelyhood of future engagement in treatment[429].

The provision of pharmaceutical-grade substances of known composition has been implemented in Canada (18 projects operating at 30 sites), with a range of models being implemented from distribution locations and ATM-type distribution systems to direct physician or nurse-practitioner supply. There is also a peer-based programme operating in Vancouver in which substances are purchased from the dark web, tested for quality, and then distributed to clients[430]. The type of substance to be offered via safe supply is also an important point to consider, as the dosage for SOs needs to be adjusted when compared to the dosages used for heroin dependence. However, given the currently limited evidence of the effectiveness of opioid distribution and safe supply programmes, the implementation of these programmes and their various distribution models should be accompanied by rigorous evaluation and research.

» Example: the Molson programme

At least five of the seven experts interviewed for this Toolkit recommended consideration of safe supply beyond OAT and a medicalised approach, suggesting the distribution of low dose hydromorphone tablets or injection, without titration schedules, and clients being free to come whenever they wish. Such an approach could also be implemented with grassroots user-based dispensation and peer support groups. The outcomes of a hydromorphone distribution programme operating in Toronto since 2019 have been studied[431], showing very positive results. At this programme, participants receive up to five prescribed doses of hydromorphone daily, which can be taken orally, intranasally, or by injection and must be consumed on-site. The programme is operated by a service providing housing, health, and social support services to structurally vulnerable individuals. According to the study, the programme helped to reduce street drug use and overdose risk, brought improvements to health and well-being of clients, as well as improvements in co-management of pain, and economic improvements. The authors suggest that the programme is effective both in responding to the overdose crisis and in addressing inequities stemming from the intersection of drug use and social inequality.

General considerations

The aim of this Toolkit was to provide insights into the seven key responses to the threat of synthetic opioids and the evidence that is available to support their implementation. Although opioids have been the main contributor to drug overdose cases, SOs still play a minor role in the overall European opioid market. However, given the relative ease of their synthesis, high potency, profitability, issues with scheduling, and developments in the online markets, this may soon be subject to change.

In order to develop appropriate responses, it is essential to understand which substances people are using. However, as drug markets are growing increasingly complex and unpredictabale, this is challenging. Innovative monitoring instruments such as drug checking, syringe residue and wastewater analysis, or internet monitoring, have become essential parts of prevention and harm reduction measures. Many of the large number of highly diverse SOs emerging on the market have fairly short lifecycles, posing a great challenge even for forensic laboratories with state-of-the-art equipment. Online drug monitoring of different internet channels provides unique information, making it a great addition to other monitoring and research methods.

A well-functioning early warning system is able to collect data from a wide range of sources and exchange it rapidly between relevant stakeholders, issuing warnings of dangerous substances to user communities, professionals and to the public, when necessary. These communication channels, including those at the regional and international levels, need to be established before SOs emerge onto the drug market.

The majority of SOs can pose seriously acute health risks at very low concentrations and they are often misrepresented as heroin or counterfeit medicines to unexpecting users. In addition to drug market monitoring, accessible drug checking services can reduce these risks by providing individual-level consultations on the contents of their drugs combined with harm reduction advice and brief interventions to make informed choices.

In the case of SO intoxication or overdose, naloxone is the key response for reversing its effects. SOs can cause life-threatening symptoms in a matter of minutes. Expanding the awareness of naloxone, and increasing its availability and also use by non-medical first responders, can save lives. As SOs are sometimes also mixed into other illicit non-opioid drugs, it is also important to expand naloxone awareness and availability into non-traditional settings, such as nightclubs.

Drug consumption rooms are another key response in implementing preventative and interventional overdose strategies for people who use drugs and contributing to better health outcomes and quality of life. They offer a supervised, hygienic, safe space for drug use, promoting education and information about substances and safer use practices, establishing and implementing overdose strategies, and enhancing self-care and self-regulation practices among their clients.

The main approach to the treatment of (synthetic) opioid use disorder remains opioid agonist treatment. An efficient OAT system is associated with considerable reductions in overdose mortality risk and can play an important protective role against the volatile illicit opioid market. However, choosing the most suitable medication and mode of treatment to meet the needs of clients is the key to success.

The importance of meeting the needs of people who use SOs with person-centred service provision cannot be overestimated within the context of highly diverse SOs. In addition to the toxic drug supply, gaps in service provision and limitations of suitable options in traditional OAT can also be seen as contributing factors to the emergence of the safe supply approach.

Services that do not reach the right target groups are an ongoing challenge that e-health interventions aim to address. Although a relatively novel health care practice, e-health interventions show great potential and cover all of the main pillars of drug policy – prevention, treatment and harm reduction – by improving access to, the quality of care of, and increasing the efficiency of, health care practices. However, it is important to also address the issues of digital inequality so that novel interventions can truly improve the situation of people who use SOs, not exacerbate their problems.

Overall, it is clear that a multi-intervention approach is needed to address the complex issues emerging with SOs. Limiting the response to expanding traditional interventions has clearly shown to be insufficient. Introducing new and innovative approaches becomes crucial, and as every intervention has its shortcomings, integration becomes key.

One of the main challenges in dealing with SOs has been the lack of scientific evidence. However, when evidence is very limited or unavailable, relying on the knowledge and experiences of experts might be the best approach. This being said, monitoring and evaluations for interventions dealing with SOs are necessary as their implementation always depends on local factors. Further research to update guidelines and to fill in the evidence gap should be the top priority.

Finally, consideration must be given to other issues beyond supply that may contribute to a SO crisis, such as a housing crisis as well as selective and discriminatory police targeting, among others. Policies developed to cope with SOs and the overdose crises must consider the setting in which people who use substances are, and provide a support network as much as possible.

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