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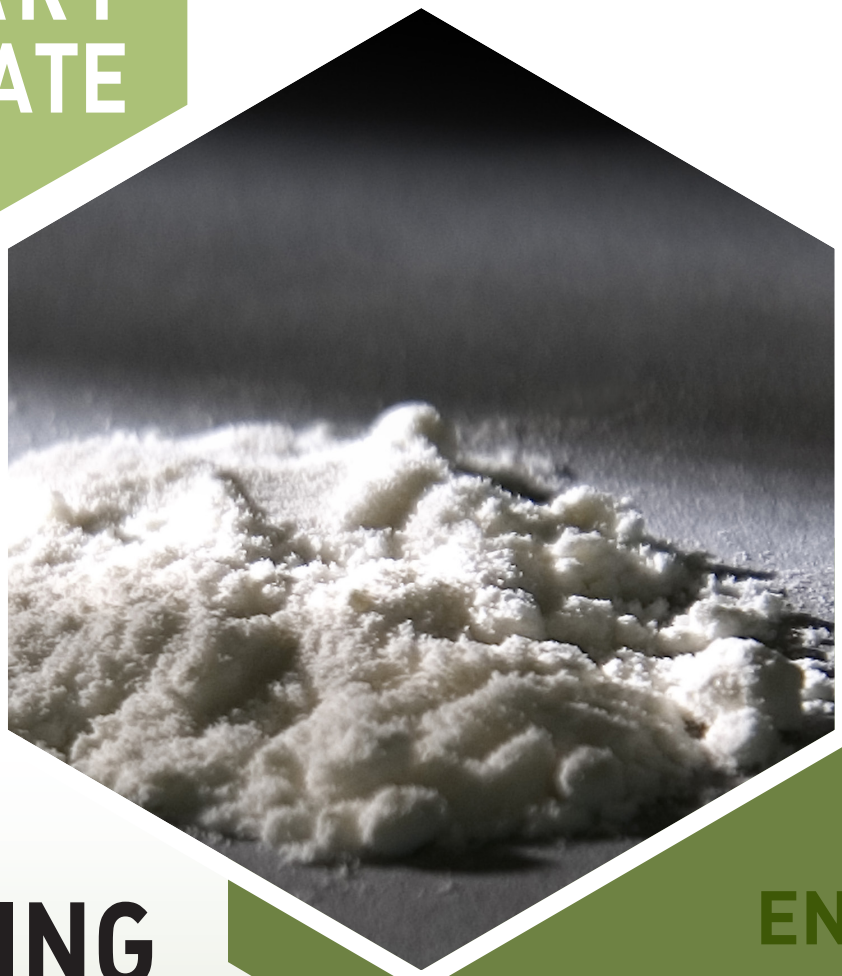
GLOBAL SMART UPDATE



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THE GROWING COMPLEXITY OF THE OPIOID CRISIS

UNODC OPIOID STRATEGY

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About the SMART Update

Synthetic drugs constitute one of the most significant drug problems worldwide. Along with synthetic drugs, the emergence of the new psychoactive substances (NPS) market over the last years has become a policy challenge and a major international concern. A growing interplay between these new substances and traditional illicit drug markets is being observed, and the synthetic drugs market continues to evolve rapidly.

The Global SMART Updates (GSU)* are biannual publications of the UNODC Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) Programme, implemented by the UNODC Laboratory and Scientific Section. The GSU is published in English, Spanish and Russian. The Global SMART Programme enhances the capacity of Member States in priority regions to generate, manage, analyse, report and use synthetic drugs information to design effective policy and programme interventions.

The main products and services of the Global SMART Programme include capacity building workshops, online drug data collection, national, regional and global assessment reports, and the UNODC Early Warning Advisory (EWA) on NPS. The EWA is a web portal that provides access to information on NPS, including on latest developments, emergence of NPS, global trends, chemical analysis, toxicology, pharmacology and legislative response. (available at: www.unodc.org/nps and www.unodc.org/tox).

Previous issues

- An expanding synthetic drugs market – Implications for precursor control (GSU 23, March 2020)
- The ATS market – 10 years after the 2009 Plan of Action (GSU 22, October 2019)
- Understanding the global opioid crisis (GSU 21, March 2019)
- Methamphetamine continues to dominate synthetic drug markets (GSU 20, September 2018)

* The information and data contained within this report are from the Annual Report Questionnaire (ARQ) submitted by Member States to UNODC, the UNODC Early Warning Advisory (EWA) on NPS, official Government reports, press releases, scientific journals or incidents confirmed by UNODC Field Offices. This report has not been formally edited. The contents of this publication do not necessarily reflect the views or policies of UNODC or contributory organizations and neither do they imply any endorsement. Suggested citation: United Nations Office on Drugs and Crime, 2019. *The growing complexity of the opioid crisis. Global SMART Update, Volume 24* (Vienna, September 2020).

Content

THE GROWING COMPLEXITY OF THE OPIOID CRISIS

A. INTRODUCTION

The current opioid crisis is a far-reaching drug and public health policy issue affecting several geographical regions. Since its appearance, endeavours have been undertaken both at the national and international level to develop integrated policy responses to address the crisis. Yet, despite some progress, the crisis continues both to expand geographically and to deepen in complexity with the emergence of a new generation of new psychoactive substances (NPS) with opioid effects, including substances belonging to chemical structural classes which were not significantly present on illicit drug markets previously. This evolution in chemical structural groups signals the potential development of similar new substances which may exacerbate the already significant challenges faced by public health and drug control systems. Additionally, the onset of the COVID-19 pandemic in late 2019 and early 2020 may further complicate and reshape existing trends in the crisis.

This issue of the Global SMART Update provides an overview of the multi-faceted opioid crisis and highlights major international and domestic policy responses to date. The Update also presents key developments related to NPS with opioid effects and examines how these developments are influenced by existing control measures. It also outlines possible policy responses and assesses how the COVID-19 pandemic may affect the ongoing opioid crisis.

"...despite some progress, the crisis continues both to expand geographically and to deepen in complexity with the emergence of a new generation of new psychoactive substances (NPS) with opioid effects,..."

The multi-faceted opioid crisis – What, why and how?

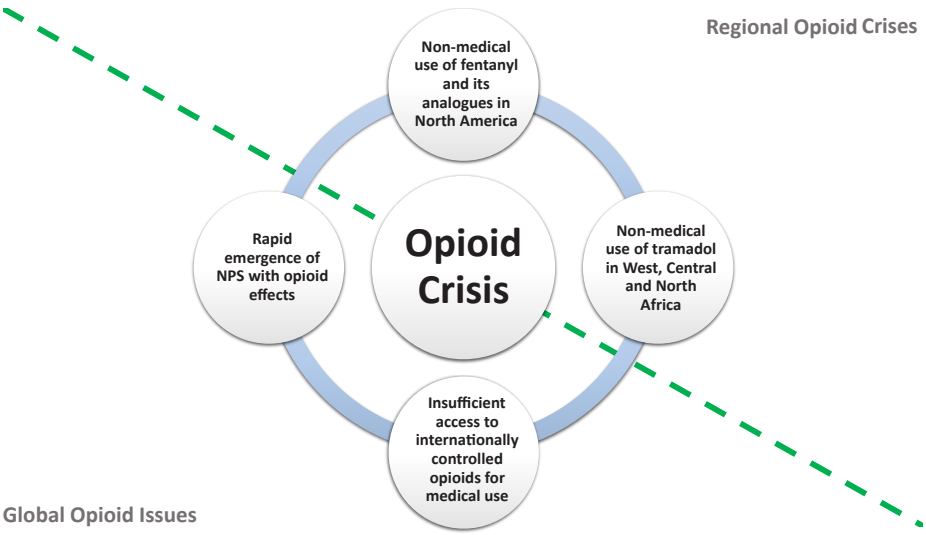
The current phase of the opioid crisis is principally defined by significant global increases in the non-medical use of opioids and opioid-related overdoses in recent years.[1] However, despite the central commonality of opioids, the crisis is actually multi-faceted in nature and its characteristics diverge sharply in different geographical regions.

The opioid crisis in North America is characterised by a highly prevalent non-medical use of opioids and high rates of mortality driven by pharmaceutical opioids, heroin and synthetic opioids[2] over the last two decades.[3,4] The present, and probably most deadly, wave of opioid use began around 2013 in the United States and is associated with fentanyl, fentanyl analogues and other synthetic opioids in the illicit drug supply[5]. The United States Centers for Disease Control and Prevention reported that although overdose deaths involving all opioids, prescription opioids and heroin decreased from 2017 to 2018, deaths involving synthetic opioids (most likely illicitly manufactured fentanyl and its analogues) increased by 10 per cent during the same period and accounted for two thirds (or 31,335) of opioid-related deaths in 2018.[6] Similarly, in Canada, increased levels of opioid-related deaths were recorded from 2016 to 2019.[7] Between January and December 2019, there were a total of 3,823 apparent opioid-related deaths in the country, of which 94 per cent were accidental and 77 per cent involved fentanyl or fentanyl analogues.[8] The region also experienced a twenty-six times increase in seizures of fentanyl from about 96 kilograms in 2015 to more than 2.9 tonnes in 2018.[9] The nature of the opioid crisis in this region seems to be largely supply-driven through a combination of factors including high prevailing rates of non-medical opioid use and the adulteration or substitution of illicit heroin and diverted pharmaceutical opioid supplies with fentanyl, fentanyl analogues and other synthetic opioids by organized crime groups in order to lower costs.[10,11,12]

"...despite the central commonality of opioids, the crisis is actually multi-faceted in nature and its characteristics diverge sharply in different geographical regions."

In West and Central Africa and North Africa however, the opioid crisis is characterised by a high prevalence of the non-medical use of pharmaceutical opioids, in particular tramadol. While national-level estimates of prevalence are not available for most countries in these sub-regions, studies and surveys in some countries indicate the widespread non-medical use of tramadol.[13] In Nigeria, a comprehensive drug survey in 2017 estimated that 4.7 per cent of its population (4.6 million people) aged between 15 and 64 had used pharmaceutical opioids for non-medical purposes, mainly tramadol and to a lesser extent codeine or morphine.[14] Likewise, Egypt has experienced an increase in the non-medical use of tramadol among drug disorder treatment admissions since 2000.[15] A national survey in 2016 estimated that 3 per cent of the adult population had used tramadol for non-medical purposes in the previous year, and nearly 68 per cent of those

FIG. 1: Global and regional characteristics of the dual opioid crisis

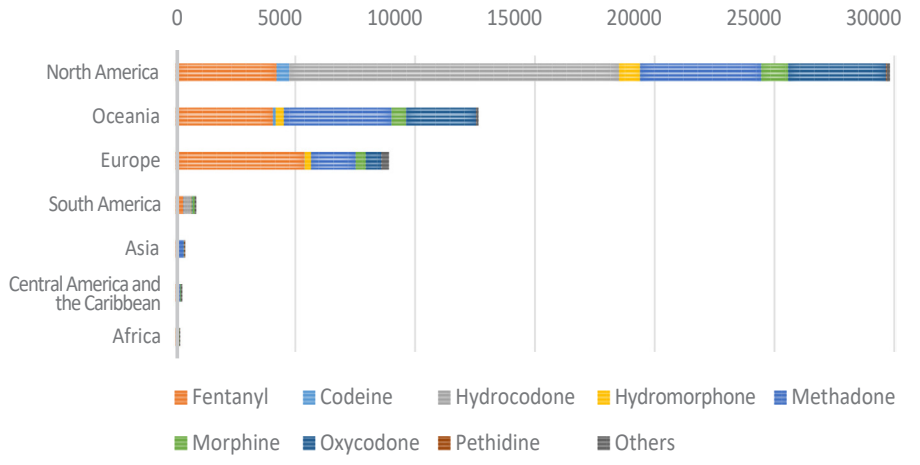


Source: UNODC elaboration

The global tragedy of unnecessary pain and suffering – insufficient access to internationally controlled opioids for medical use

In the face of the need for international control of the trafficking and non-medical use of opioids, there is a global divide regarding access to internationally controlled opioid analgesics for pain management and palliative care. Whilst an estimated 1.2 per cent of the global population used opioids for non-medical purposes in the past year, an estimated 80 per cent of the global population has limited or no access to controlled medicines, especially for the treatment of pain.[24,25] Despite a global increase in the availability of controlled pharmaceutical opioids for medical use in the last 20 years, the growth is imbalanced and skewed towards higher-income (sub)regions especially in North America, Oceania and Western and Central Europe (see Figure 2).[26] Furthermore, the increase is largely driven by the greater availability of expensive synthetic analgesics (e.g. fentanyl and oxycodone) concentrated in high-income countries, which is not matched by an increase in the availability of more affordable opiate analgesics such as morphine.[27] The Lancet Commission on Palliative Care and Pain Relief found that of the average amount of 298.5 tonnes of morphine-equivalent opioids distributed in the world annually between 2010 and 2013, 287.7 tonnes were distributed to high-income countries, representing an excess of 233 per cent of their projected need for 86.4 tonnes, whilst only 0.1 tonnes was distributed to low-income countries, which is 99.7 per cent short of their projected need for 37.2 tonnes. Similarly, the distribution of morphine-equivalent opioids to upper-middle- and low-middle-income countries fell short of their projected needs by 96.7 per cent and 99.3 per cent respectively.[28] Another significant issue identified is that on average 88 per cent of the morphine manufactured between 1997 and 2016 was converted by pharmaceutical companies to codeine or other related substances instead of being used in morphine preparations for palliative care. This is in part a result of the marketing and supply of more expensive opioids by pharmaceutical companies which has lowered the availability of opiates among all opioid analgesics over the years and ultimately the capacity of health services to treat pain, especially in low- and middle-income countries.[29] The imbalance in access to opioid analgesics for medical use and the rising non-medical use of synthetic opioids demonstrates the duality of the opioid crisis and the conflicting objectives, i.e. access versus control, faced by international and national drug control systems.

FIG. 2: Average consumption of selected opioids, by region, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, 2016-2018



Source: International Narcotics Control Board, Narcotic Drugs: Estimated World Requirements for 2020 – Statistics for 2018 (E/INCB/2019/2), pp. 264.
Note: The statistics include the eight most consumed opioids and others (including tilidine), and excludes buprenorphine and preparations listed in Schedule III of the 1961 Convention.

undergoing treatment for drug use disorders were treated for tramadol use.[16,17] The Forensic Medicine Sector of Egypt's Ministry of Justice also reported 43 deaths directly related to tramadol misuse in 2017.[18] Between 2014 and 2018, the sub-regions of West and Central Africa and North Africa together accounted for around 89 per cent of the total quantities of tramadol seized worldwide.[19] There are also indications of an expansion of the tramadol market in the Near and Middle East and South-West Asia with countries such as Lebanon, Qatar and the United Arab Emirates[20] reporting tramadol as one of their most misused substances in recent years, and the region accounting for the third largest proportion (6 per cent) of tramadol seizures between 2014 and 2018 after West and Central Africa (81 per cent) and North Africa (8 per cent).[21] The nature of the opioid crisis in these sub-regions is likely to be a result of challenges in medicines regulation and a high availability of diverted or illicitly manufactured pharmaceutical opioids on the informal market to meet demand.[22,23]

"...there is a strong need to balance drug control and public health responses with adequate access to opioid analgesics for scientific research and medical uses..."

These essential differences make the current opioid crisis multi-faceted in nature and, as a result, particularly challenging for national authorities and international bodies alike. Moreover, there is a strong need to balance drug control and public health responses with adequate access to opioid analgesics for scientific research and medical uses including pain management and palliative care.

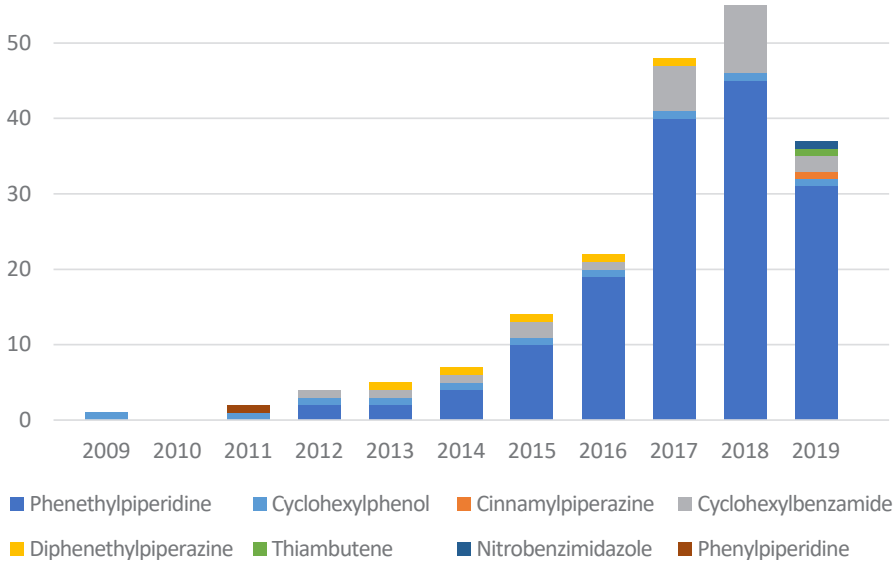
Substances with opioid effects are one of the fastest growing groups of NPS

The rapidly growing number of NPS with opioid effects on the illicit drug market represents a further serious challenge faced by the international community. Over the last decade, the number of such substances reported annually to the UNODC Early Warning Advisory (EWA) on NPS increased significantly from just one

in 2009 to 55 in 2018 (see Figure 3). Additionally, between 2015 and 2019, the number of synthetic opioids as a proportion of all synthetic NPS reported quadrupled from 2 per cent to 8 per cent.

As a result of the rapid emergence and increasing prevalence of opioid NPS, coupled with substantial public health risks, the number of such substances placed under international control has also increased. Despite representing only a small fraction of the total synthetic NPS reported to the UNODC EWA (8 per cent), almost a third, or 17 out of 60, of the NPS scheduled from 2015 to 2020 into either the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol ("1961 Convention") or the Convention on Psychotropic Substances of 1971 ("1971 Convention") were substances with opioid effects. In comparison, only 18 synthetic cannabinoids and 17 stimulant NPS were put under international control during the same period despite these pharmacological effect groups accounting for around 30 per cent of synthetic NPS reported to the UNODC EWA.

FIG. 3: Number of different synthetic NPS with opioid effects reported each year, by chemical structural class, 2009 – 2019



Source: UNODC Early Warning Advisory on NPS, 2020

Note: A total of 77 different synthetic NPS with opioid effects were reported to UNODC between 2009 and 2019 (but not all of them were reported each year). Plant-based substances were excluded from the analysis as they usually contain a large number of different substances some of which may not be known and their effects and interactions not fully understood. Data for 2019 are preliminary.

B. INTERNATIONAL AND NATIONAL POLICY RESPONSES TO THE OPIOID CRISIS

Despite these challenges, the international community has taken major steps towards developing a set of balanced international and domestic responses to address various aspects of the growing opioid crisis (see Figure 4). In 2018, the 61st Session of the Commission on Narcotic Drugs (CND) for the first time adopted a resolution with direct reference to enhancing and strengthening international and regional cooperation to address the threats posed by the non-medical use of synthetic opioids. In the same year, UNODC launched an integrated strategy based on an overarching set of complementary principles to support Member States and coordinate the international response to the opioid crisis. Furthermore, between 2018 and 2020, the CND scheduled 12 fentanyl analogues under the 1961 Convention.

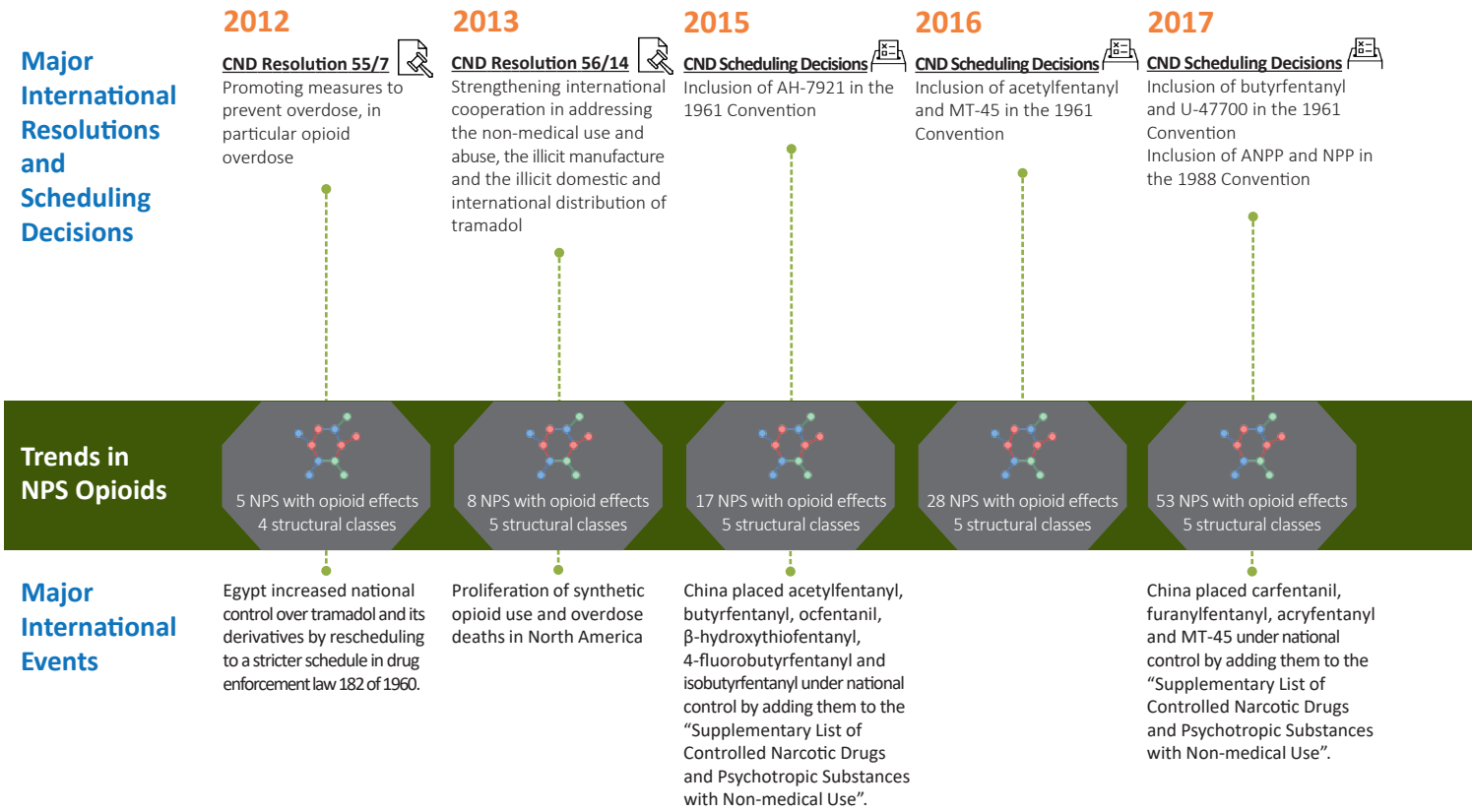
There have also been responses to the crisis at the national level. In April 2018, India scheduled tramadol in its Narcotics Drug and Psychotropic Substances Act to regulate and increase law enforcement of the manufacturing, import, export and sale of tramadol, and to impose criminal penalties for breaches of these regulations, effectively increasing controls over tramadol beyond existing prescription controls contained in its Drugs and Cosmetics Act of 1940

"...the international community has taken major steps towards developing a set of balanced international and domestic responses to address various aspects of the growing opioid crisis..."

and the Drugs and Cosmetics Rules of 1945.[30,31,32] This change appears to have had an impact on the supply of tramadol in West Africa with reports from Ghana and Nigeria indicating a significant decrease in border seizures of the drug as well as reduced availability and increases in prices of tramadol on illicit markets in those countries.[33] This impact has not been felt consistently across West Africa however with countries such as Benin still reporting large seizures of tramadol in the first half of 2019, suggesting that large-scale tramadol trafficking remains active in the region.[34,35] Likewise, despite the substance being under stricter national control since 2012, Egypt continues to seize large quantities of diverted, falsified and sub-standard tramadol (more than 231 million tablets in 2017), some of which contains a wide range of impurities.[36]

Countries including Canada,[37] China[38] and the United States[39,40] have extended their national controls over fentanyl analogues and/or fentanyl precursors, and have increased cooperation with international and domestic partners to tackle illicit activities relating to these substances. Early signs following China's 2019 extension of national control to include all fentanyl analogues suggest that less of this class of substances is being smuggled from China to North America, although attempts to manufacture these substances inside the region, especially in Mexico, using precursor chemicals from East and South Asia, are increasing.[41] Countries such as the United States have also stepped up their public health responses to promote the rational prescribing of opioids and to widen access to prevention and treatment services.[42,43]

FIG. 4: Major international and national policy events in relation to the opioid crisis, 2012-2020



Source: UNODC elaboration based on various CND resolutions and decisions, and the UNODC Early Warning Advisory on NPS.
Note: The "1961 Convention" refers to the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol and the "1988 Convention" refers to the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988. "CND" refers to The Commission on Narcotic Drugs.

C. THE GROWING COMPLEXITY OF THE OPIOID CRISIS – EMERGENCE OF A NEW GENERATION OF SYNTHETIC OPIOIDS

In addition to developments related to tramadol and fentanyl and its analogues, a new generation of non-fentanyl-related synthetic opioids has surfaced and gained traction in the illicit market, adding greater complexity to the opioid crisis. Opioids, or opioid receptor agonists, interact with the body's opioid receptors, including the mu (μ) opioid receptor which is responsible for triggering the brain reward system and producing analgesia (pain relief) by decreasing pain transmission. This results in a variety of physiological and psychological effects including respiratory depression, constipation, euphoria, sedation, a sensation of warmth and dependence.[44,45] The magnitude of these effects depends on the specific synthetic opioid used and the type of receptor(s) activated or inhibited.[46,47]
Despite having similar pharmacological effects, opioids occur in a variety of chemical structural classes ranging from morphinans to phenethylpiperidines. About 83 per cent of opioids in the Schedules of the 1961 Convention fall into four main structural classes: **morphinans** (including heroin, hydrocodone and oxycodone); **phenethylpiperidines** (including fentanyl and fentanyl analogues); **phenylpiperidines** (including pethidine and ketobemidone); and **diphenylheptanes** (including methadone and acetylmethadol). The remaining 17 per cent belong to a variety of smaller structural classes including diphenylmorpholines, thiambutenes and diphenylheptanones (see Figure 5). For the purpose of this publication, non-fentanyl-related synthetic opioids are defined as opioids belonging to dissimilar chemical structural classes to fentanyl and fentanyl analogues (i.e. phenethylpiperidines).

Trends in non-fentanyl related synthetic opioids

The number of non-fentanyl-related synthetic opioids reported has increased steadily over the last decade from an average of two substances per year between 2009 and 2014, to ten substances in 2018 alone.[48] An analysis of NPS with opioid effects according to their chemical structural class reveals trends in the structural diversity and popularity of certain chemical classes in the NPS opioid market. In 2009, only one chemical class of NPS with opioid effects was reported to the UNODC EWA. This number had grown to five by 2015 and eight by 2019, indicating a proliferation in the diversity of chemical classes of NPS with opioid effects in the global market (see Figure 6). Interestingly, substances belonging to four of the eight chemical classes including cyclohexylbenzamides (e.g. U-47700, AH-7921), diphenethylpiperazines (e.g. MT-45), cinnamylpiperazines (e.g. 2-methyl-AP-237) and cyclohexylphenols (e.g. *O*-desmethyltramadol) were not included in the schedules of the 1961 Convention prior to 2015. In addition, substances in three chemical classes of opioids, cinnamylpiperazines, thiambutenes

2018

CND Resolution 61/8
Enhancing and strengthening international and regional cooperation and domestic efforts to address international threats posed by the non-medical use of synthetic opioids

CND Scheduling Decisions
Inclusion of acrylfentanyl, carfentanil, ocfentanil, 4-Fluoroisobutyrfentanyl, furanylfentanyl and tetrahydrofuranylfentanyl in the 1961 Convention

73 NPS with opioid effects
5 structural classes

India introduced more restrictive control measures for the manufacturing, import, export and sale of tramadol by scheduling it into its Narcotics Drug and Psychotropic Substance Act.

China listed NPP and 4-ANPP as controlled precursors in the Schedule to the "Regulation on the Administration of Precursor Chemicals".

Launch of the integrated UNODC Opioid Strategy

UNODC OPIOID STRATEGY — PREDICT PREVENT PROTECT — RESPONSE TO THE OPIOID CRISIS

2019

CND Resolution 62/4
Advancing effective and innovative approaches, through national, regional and international action, to address the multifaceted challenges posed by the non-medical use of synthetic drugs, particularly synthetic opioids

CND Resolution 62/5
Enhancing the capacity of Member States to adequately estimate and assess the need for internationally controlled substances for medical and scientific purposes

CND Scheduling Decisions
Inclusion of cyclopropylfentanyl, methoxyacetylfentanyl, *ortho*-flurofentanyl and *para*-flurofentanyl in the 1961 Convention

77 NPS with opioid effects
8 structural classes

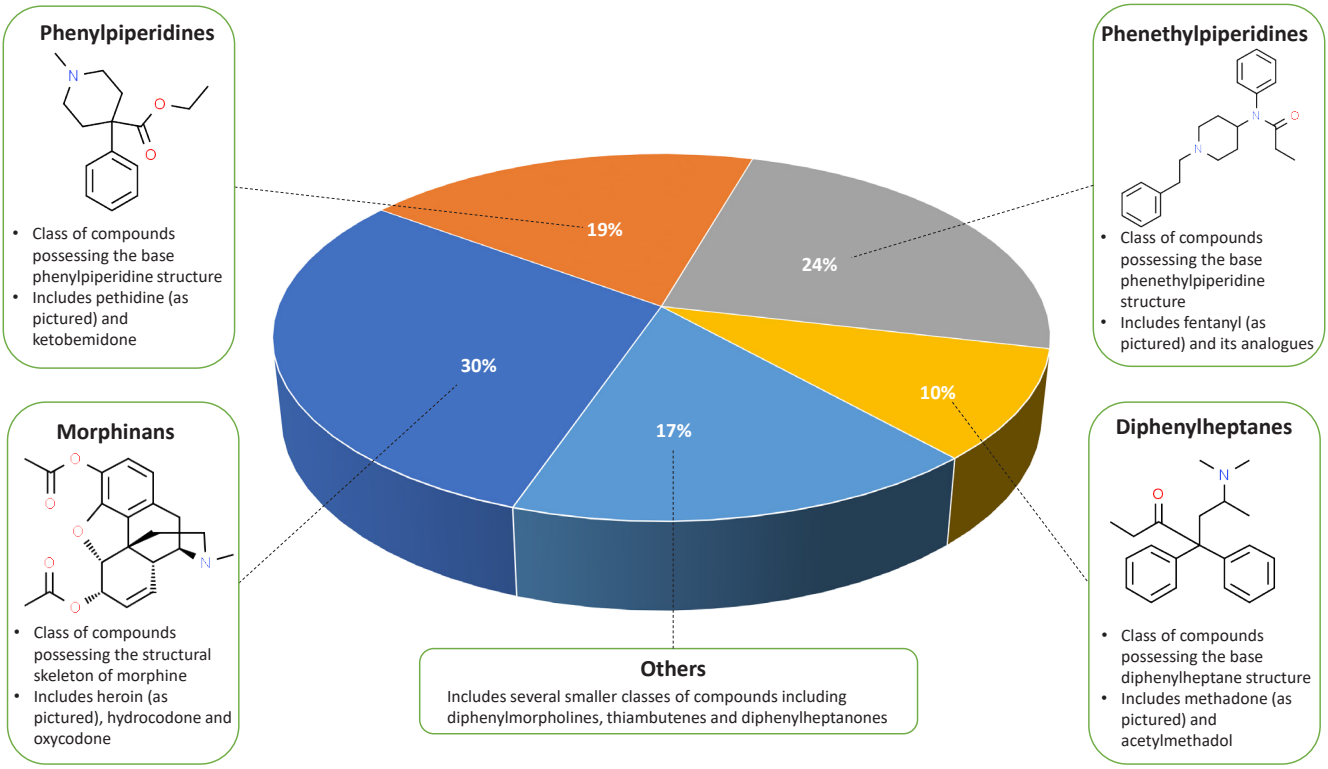
China introduced drug controls based on generic legislation with regards to fentanyl, which effectively placed more than 1,400 known fentanyl analogues in the "Supplementary List of Controlled Narcotic Drugs and Psychotropic Substances with Non-medical Use".

2020

CND Resolution 63/3
Promoting awareness-raising, education and training as part of a comprehensive approach to ensuring access to and the availability of internationally controlled substances for medical and scientific purposes and improving their rational use

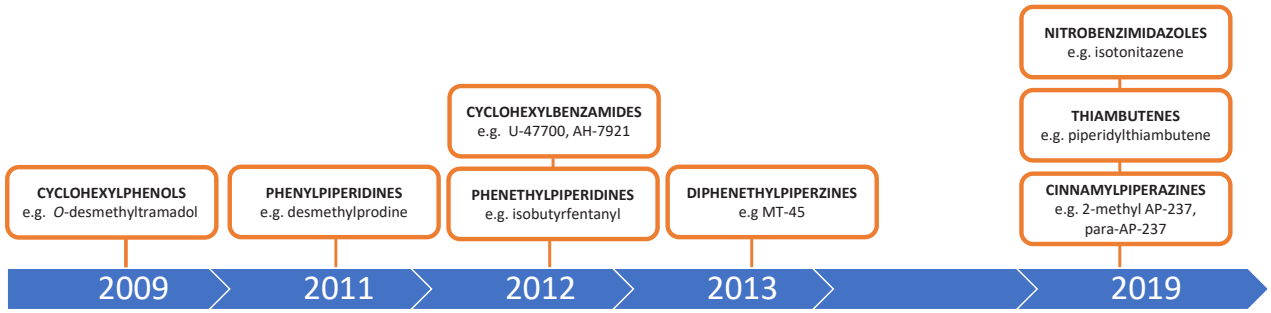
CND Scheduling Decisions
Inclusion of cyclopropylfentanyl and valerylfentanyl in the 1961 Convention

FIG. 5: Distribution of opioids in the 1961 Convention, 1961-2020



Source: UNODC elaboration based on the Schedules of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol ("1961 Convention"), as at 7 May 2020.
Note: Based on analysis of 124 opioids in the Schedules of the 1961 Convention, excluding opiates.

FIG. 6: Chemical structural classes of NPS with opioid effects reported to UNODC EWA, 2009-2019



Source: UNODC, Early Warning Advisory on NPS, 2020.
Note: Based on an analysis of 77 different synthetic NPS with opioid effects reported to UNODC. Plant-based substances were excluded from the analysis as they usually contain many different substances some of which may not be known and whose effects and interactions are not fully understood. Data for 2019 are preliminary.

(e.g. piperidylthiambutene) and nitrobenzimidazoles (e.g. isotonitazene) only surfaced in the global NPS market in 2019. Phenethylpiperidines (or fentanyl analogues in general) remain the dominant and fastest growing chemical class of opioids among NPS with opioid effects, followed by cyclohexylbenzamides (see Figure 3).

Brorphine (1-{1-[1-(4-bromophenyl)ethyl] piperidin-4-yl}-1,3-dihydro-2*H*-benzimidazol-2-one) is an instance of a recently emerging non-fentanyl-related synthetic opioid that has been increasingly detected in seized drug samples and forensic casework since 2019, especially after the temporary scheduling of isotonitazene by the United States Drug Enforcement Administration in June 2020.[49] Despite having structural similarities to fentanyl, brorphine differs in key aspects with the additional presence of the 4-bromo and 1,3-dihydro-2*H*-benzoimidzole-2-one groups (or the phenethylpiperidine-benzimidazolone sub-class), therefore falling outside the typical scope of generic legislation for fentanyl analogues.[50]

These trends in NPS with opioid effects indicate a shift in the synthetic opioid market towards newer and more varied chemical classes of opioids to quickly replace "older generations" of substances once they are under control and become subject to rigorous scrutiny by law enforcement officials. Many of these non-fentanyl-related synthetic opioids are neither new nor recent inventions however, but rather, their appearance in the illicit market is recent. The majority of these "new" opioids fall into categories of either pharmaceuticals that were originally developed as therapeutic agents but were never commercialized (also known as "failed pharmaceuticals"), or are falsified or unregistered/unlicensed pharmaceuticals that are sold in countries where they are not approved for medical use. Other "new" opioids are typically analogues of opioids from either of these two categories developed through successive modifications

"...a shift in the synthetic opioid market towards newer and more varied chemical classes of opioids..."

to their chemical structures to circumvent existing legislation. Although the potency and pharmacological effects of these non-fentanyl-related synthetic opioids may differ significant from fentanyl, they can still be highly dependence producing and dangerous, as opioids in general have a narrow therapeutic index, wide interindividual response variability and potentially life-threatening toxicity. For these reasons, a very small variability in dosage can lead to serious therapeutic failures and/or adverse drug reactions resulting in significant incapacity or even death.[51] In common with fentanyl and its analogues, non-fentanyl-related opioids may be sold as stand-alone products or used as adulterants or constituents of drugs such as heroin or falsified pain medication, and can be bought from a variety of sources including both the Internet and the Dark Web.[52,53]

Failed pharmaceutical opioids: from potential medicines to public health threats

Many "new" non-fentanyl-related opioids were originally developed by the pharmaceutical industry over the past five decades in attempts to search for alternative therapeutic drugs to morphine without dependency-related adverse effects, but were not further developed or were considered "not suitable for human consumption". They have subsequently been "re-discovered" in the past few years with information about them taken from scientific literature or patent filings in order to clandestinely manufacture and sell them on the illicit market.[54] The following paragraphs describe examples of failed pharmaceutical opioids that are prevalent or emergent in illicit markets.

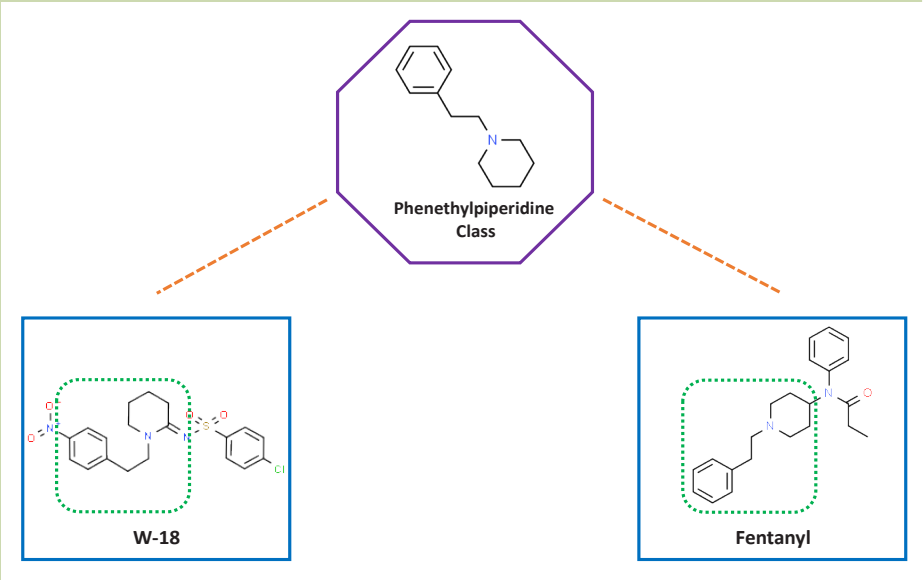
Isotonitazene is an emergent highly potent synthetic opioid which has been encountered in seized drug samples and forensic casework since 2019. It was first developed in the mid-1950s as part of a series of nitrobenzimidazole class of opioids, which includes etonitazene, metonitazene and clonitazene, in a search for better and safer opioid analgesics.[55,56,57] Two isotonitazene analogues, etonitazene and clonitzene, are included in Schedule I of the 1961 Convention because of their ability to produce morphine-like effects and sustain and suppress abstinence phenomena from morphine dependence.[58] In vitro and in vivo studies have found that isotonitazene is a highly potent mu opioid receptor agonist which may potentially be as potent as fentanyl and is 500 times more potent in mice relative to morphine.[59,60] Although there is presently no information about the side effects of consuming isotonitazene, its pharmacological characteristics indicate that the risks would be similar to other opioids, including dependence, respiratory depression, and potentially life-threatening overdose.[61] Reports of isotonitazene in seized drug samples and toxicology cases in North America and Europe have been submitted to the UNODC EWA since 2019.[62] Significantly, a study found 18 deaths in the Midwestern United States where isotonitazene was identified in biological samples. Other opioids (fentanyl, morphine, tramadol, piperidylthiambutene and U-47700), as well as designer benzodiazepines (flualprazolam and etizolam), were also identified in most of these cases.[63] In February 2020, authorities in Canada seized 1,900 falsified hydromorphone tablets that were found to contain isotonitazene.[64]

Compounds in the phenethylpiperidine-benzimidazolone opioid sub-class including brorphine were first developed by Janssen Pharmaceuticals as central nervous system depressants with morphine-like analgesic activity. While structural analogues of

Structural similarity does not equate to pharmacological activity – the cases of W-18 and benzylfentanyl

An emergent synthetic opioid gaining popularity, W-18 (or 4-chloro-*N*-{(2*E*)-1-[2-(4-nitrophenyl)ethyl]piperidin-2-ylidene} benzene-1-sulfonamide) was developed in 1981 at the University of Alberta and belongs to a class of compounds referred to as the "W" series.[65] Despite being structurally related to fentanyl (see Figure 7), W-18 differs in key chemical aspects with the presence of an aryl sulfonamide group which could potentially lead to differences in pharmacological effects between the substances. Although the original patent indicated that W-18 had an analgesic potency 10,000 times greater than morphine, recent animal and in vitro studies reveal no activity for W-18 or any of its metabolites at the opioid receptors.[66,67] Another fentanyl analogue, benzylfentanyl, has been found to be "essentially inactive" when assessed for morphine-like activity, dependence liability and analgesic effect.[68,69] It is likely that its presence in seized drug samples is due to it being used as a precursor in the fentanyl manufacturing process, resulting in a residual amount of the unreacted substance after synthesis.[70] These examples demonstrate that substances sharing structural similarities with known opioids do not necessarily equate to having similar pharmacological activity. Therefore, additional structure-activity relationship studies are always required for new emerging substances to predict or determine if there is a pharmacological activity that warrants control.

FIG. 7: Comparison between chemical structures of W-18 and fentanyl



Source: UNODC elaboration.

brorphine have been previously reported in the literature,[71] there is little information on when the substance was first synthesized.[72] Recent in vitro studies on brorphine found that it has a potency greater than morphine and acts as a full mu opioid receptor agonist which would likely result in opioid-like pharmacological effects.[73,74] Brorphine users have reported similar effects including euphoria and dependence, and the substance has been actively discussed and compared to other synthetic opioids in online forums.[75,76] The grey granular powder bears similarities to isotonitazene and has been detected in seized drug samples and toxicology cases in Belgium, Canada, Sweden and the United States since 2019.[77,78,79] Most recently, between June and July 2020, brophine was detected in seven post-mortem cases in the United States alongside fentanyl, flualprazolam and heroin.[80]

One of the most prevalent non-fentanyl-related synthetic opioids around the world in recent years is U-47700, which belongs to the cyclohexylbenzamide class of opioids. This substance, originally developed by the Upjohn Company in 1978, has one tenth of the potency of fentanyl and about 7.5 times the potency of morphine in mice studies.[81,82,83] Its popularity in the illicit market is presumably due to its reportedly desirable short-lived euphoric and mood-lifting effects, which are experienced in waves and create an intense urge among users to continue re-dosing.[84] Negative effects have also been reported by users including anxiety, nausea, respiratory depression and abdominal pain, which are all typical side effects of classic opioids.[85] Between 2015 and 2019, U-47700 was reported to the UNODC EWA in seized materials by 30 countries across the Americas, Asia and Europe, far exceeding any other non-fentanyl-related synthetic opioid in terms of reach. The same substance was also reportedly detected in a total of 48 toxicology cases submitted to the UNODC EWA by five countries in North America, Europe and Oceania between 2016 and 2019.[86] After being placed under international control in 2017, the number of reports of U-47700 to the UNODC EWA declined globally.[87,88] This most likely led to a search for non-scheduled substances which mimic the effects of U-47700, resulting in recent appearances in the illicit market of U-47700 analogues (e.g. isopropyl-U-47700, 3,4-methylenedioxy-U-47700, U-48800 and U-49900) and other U-series synthetic opioids previously developed by the Upjohn Company (e.g. U-47931E, U-50488 and U-51754).[89] Two new analogues of U-47700, 3,4-difluoro-U-47700 and N-ethyl-U-47700, were also discovered in the United States in the first quarter of 2020.[90]

AH-7921 is another popular substance belonging to the cyclohexylbenzamide class of opioids, which shares structural similarities with U-47700. It was developed by Allen & Hanburys Limited in 1974 but was never made available for medical use, possibly due to its highly addictive properties observed in animal studies.[91,92] Limited animal studies also indicate that AH-7921 has a similar potency and risk of respiratory depression to morphine. Users of this substance have reported opioid side effects including euphoria, mental relaxation, pleasant mood lifts, analgesia, nausea and dependence.[93] Though less prevalent than U-47700, AH-7921 has been reported to the UNODC EWA by 16 countries[94] and has been detected in seized samples and cases of acute non-fatal intoxications and deaths in Europe,[95] East Asia[96] and North America.[97] It was placed under international control in 2015.[98]

Availability of falsified and unlicensed pharmaceutical opioids

In addition to failed pharmaceutical opioids, falsified and/or unregistered/unlicensed pharmaceutical opioids have also surfaced in markets where they are not approved for medical use. One such substance is tianeptine, a tricyclic antidepressant and anxiolytic that is also a full mu opioid and delta opioid receptor agonist.[99] Tianeptine does not have the common side effects of most antidepressants, such as sedation, and is prescribed in Europe, Asia and Latin America.[100] There are multiple documented cases of recreational use and dependence related to tianeptine, presumably as a result of its atypical pharmacological profile, ability to induce euphoria at high doses and relatively mild side effects.[101] Case studies and reports of tianeptine dependence found opiate-like euphoria and withdrawal symptoms including myalgia, nausea, vomiting and agitation.[102,103] Though tianeptine is not approved for medical use in the United States of America, it has recently been encountered by law enforcement in the country in various forms including bulk powder, falsified hydrocodone and oxycodone tablets, and in individual stamp bags commonly used to distribute heroin.[104] The United States Centers for Disease Control and Prevention reported a marked increase in tianeptine exposure calls to the National Poison Data Systems, from 11 cases between 2000 and 2013 to five in 2014 and 81 in 2017, suggesting an increase in the non-medical use of the substance which the United States Drug Enforcement Administration termed an "extreme public health concern" in the context of the country's current opioid crisis.[105,106] A 2018 study also identified two fatalities in the United States associated with the use of tianeptine purchased on the Internet.[107] More recently, tianeptine was identified in eight seized materials and toxicology cases in the United States from the fourth quarter of 2019 to the first quarter of 2020, including three toxicology cases in 2020.[108,109]

AP-237 (or bucinnazine) and its structural analogues (2-methyl AP-237 and *para*-methyl AP-237) are further examples of illicitly manufactured pharmaceutical opioids appearing in seized materials in several countries.[110] The parent compound, AP-237, was originally developed in Japan in the late 1960s as an opioid analgesic belonging to the cinnamylpiperazines class and is prescribed to cancer patients in China for pain management.[111,112] In 2012 it was included as an essential analgesic drug in China's National Essential Medicine List, but it was removed without official explanation in 2018.[113,114] Studies in mice indicate that AP-237 has both lower potency and likelihood of dependence compared to morphine, but there are no known clinical studies for human dependence related to AP-237.[115,116] Its structural analogue, 2-methyl AP-237, developed in the 1980s in Italy,[117] appeared on the synthetic drug market in 2019.[118] According to its patent, 2-methyl AP-237 possesses analgesic activity and is less toxic than AP-237 in mice.[119] Although there are no formal studies of its side effects, it is likely to share the typical physiological and psychological effects of classic opioids. In 2019, Canada and Sweden reported the detection of this substance in seized materials to the UNODC EWA[120] and in the first quarter of 2020, it was positively identified in one seized drug and two forensic toxicology cases in the United States.[121] Another structural analogue, para-methyl AP-237, was first reported in late 2019 in the United States, however there is no scientific literature to date on its pharmacological effects.[122]

D. RESPONDING TO AN INCREASINGLY COMPLEX OPIOID CRISIS

The emergence of new non-fentanyl-related synthetic opioids can be seen as an unintended consequence of the efficacy of existing control measures in reducing product life cycles and minimising the adverse public health effects of existing synthetic opioids. The displacement/replacement effect is a by-product of a complex cyclic interaction between the imposition and circumvention of novel control measures amid changing market dynamics. As governments introduce new regulatory responses and enhanced forensic tools to detect, identify and interdict existing substances, so organized crime groups respond by identifying, manipulating, manufacturing and distributing new synthetic substances to exploit the limitations of current forensic technologies as well as chemical analogue/generic loopholes in the law. This interaction is further driven by the preferences and behaviours of users being influenced by factors such as the substitution and adulteration of new substances in existing drug supplies.[123]

Without existing control measures however, extremely potent opioids such as fentanyl and its analogues would become entrenched on illicit drug markets with potentially devastating effects. There is some limited evidence to date indicating some degree of success of existing control responses in reducing the availability,[124] use and rate of accidental overdose deaths[125,126,127] associated with the existing generation of synthetic opioids. It is therefore essential to continue engaging in this cyclic interaction to prevent synthetic opioids from gaining the firm foothold in illicit markets that certain established drugs already have. The question is how policy-makers can address the growing complexity of the opioid crisis and further shorten the product life cycles of emergent synthetic substances of abuse by influencing this complex cycle.

"The displacement/replacement effect is a by-product of a complex cyclic interaction between the imposition and circumvention of novel control measures amid changing market dynamics."

Improving access to opioids for medical use

The dual nature of the opioid crisis calls for an informed approach that balances stemming the non-medical use of internationally controlled opioids with improving access to them for pain management and palliative care. Competent national authorities may wish to refer to guidelines on estimating national requirements of controlled substances[128] and adopt the use of online and electronic systems developed by various international organisations to reassess their current estimates and simplify the import and export process of controlled medicines.[129] Nationally, governments may wish to introduce changes to their health systems in order to improve access and the availability of controlled medicines for both pain management and palliative care whilst maintaining proper oversight such as allowing electronic prescribing, especially in remote areas, permitting a larger base of trained health-care professionals to prescribe opioid analgesics and instituting national health insurance and price-setting systems for essential medicines. In addition, international organisations and national authorities alike may wish to promote ethical approaches among pharmaceutical companies and physicians, rational prescribing practices and overcoming stigma associated with opioid use as well as to extend training in pain management and palliative care to more health-care professionals.

The importance of early warning systems

The growing complexity of the opioid crisis

highlights the key role of national, regional and global early warning systems in the monitoring and early detection of new substances. Given their accelerating replacement rates, access to timely information on the emergence, prevalence and harm of new substances of abuse is critical for stakeholders to develop policy responses. However, the effectiveness of early warning systems ultimately depends on unfettered and prompt information-sharing among international, regional, country and local partners, which remains an on-going concern in several parts of the world. Breaking down barriers to information-sharing requires joint efforts from international and regional organisations and Member States alike and technical assistance with setting up national systems should be provided wherever there is a lack of capacity to identify new synthetic opioids.

Improving forensic capacities

The ability to identify new substances goes hand in hand with a continuous need to update forensic capacities with advanced, and sometimes prohibitively costly, analytical technologies. In circumstances where access to chemical reference materials, screening tools or forensic data is insufficient, the cross-border sharing of investments in powerful, advanced analytical technologies could be considered, such as nuclear magnetic resonance spectroscopy for determining the molecular structures and purity of new substances. At the same time, investments and efforts to update the software and spectral libraries of existing laboratory and field-based forensic analytical technologies are encouraged, along with the development and validation of analytical methodologies, to ensure the ability to identify and/or verify the presence of new synthetic opioids.

Expanding public-private partnerships

The emergence of new synthetic opioids has created a compelling need for testing equipment, toxicology screens, reference materials and forensic and chemical expertise to assist forensic laboratories and law enforcement with the identification of these substances and to verify their analysis. This presents opportunities for collaboration between public and private entities to share information and jointly develop forensic and chemical expertise, materials and technologies to reduce the time lag between the initial appearance of a new substance and the capacity to detect it in samples. There are also opportunities for governments to support research by the scientific community related to the forensic identification, pharmacology and epidemiology of new substances of abuse which is essential for expanding knowledge and enhancing control responses related to these substances.

Enhancing legislative responses

The enhancement or extension of existing legislation to control the sale and/or use of emergent psychoactive substances, especially synthetic opioids, represents a further option for response. Governments which have adopted analogue or generic legislation, or a combination, may wish to consider expediting the process of legislating against new structural classes of synthetic opioids not yet covered by existing laws. Alternatively, the adoption of a broader neurochemical approach could be considered to control any new substances with opioid-like effects. The United States, for instance, introduced such an approach for the control of cannabimimetic agents through the Synthetic Drug Abuse Prevention Act of 2012. These agents are defined as "any substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays" within five defined structural classes.[130] The same approach could be extended to opioid analgesic agents demonstrated by scientific tests to bind to the body's opioid receptors within a set of prescribed structural classes.

A broader approach would be the adoption of specific NPS-related legislation that controls the manufacture, supply, personal possession and/or use of any substance capable of producing a psychoactive effect. This would potentially address the general supply and/or use of all NPS without needing to list all substances individually in the legislation. Similar legislation has been enacted in Australia,[131] Austria[132] and the United Kingdom[133] to varying degrees. Despite its success in eliminating the open sale of NPS and to some extent reducing their availability, use and toxicity, such legislation is not without its challenges and limitations.[134] One significant challenge relates to the enforceability of this type of legislation given the ambiguity of defining "psychoactive effect", as well as the limited information available on the pharmacological activity of some of these substances.[135] Proving psychoactive effect may also require forensic capacities to conduct both in vivo and in vitro testing, along with expert witnesses to adduce and interpret available evidence in court.[136] In addition, such a broad legal approach could inadvertently inhibit the meaningful research, development, testing and use of new psychoactive substances with legitimate pharmaceutical uses and therefore exceptions need to be built into the legislation to prevent this.

E. CONCLUSION

The multifaceted opioid crisis continues to grow in complexity with marked variations in different parts of the world presenting significant challenges to the international community. These challenges are compounded by the emergence in illicit markets of a greater variety of synthetic opioids in chemical structural classes distinct from fentanyl and fentanyl analogues. Despite their recent appearances, many such "new" non-fentanyl related opioids are derived from past failed, falsified or unregistered/unlicensed pharmaceutical opioids introduced into the illicit market in a bid to circumvent existing controls. The emergence of these substances underscores the importance of strengthening early warning systems, expanding public-private partnerships and enhancing existing legal approaches to respond to the growing complexity of the opioid crisis thereby further shortening the life cycles of emergent synthetic substances of abuse. Despite the formidable challenges, experience shows that the international community is capable of pulling together and making strides at both national and international levels to curb the supply and demand for synthetic opioids. Current increased awareness levels, as well as reduced availability, use, harms and product life cycles, associated with some synthetic opioids are all testament to efforts undertaken in recent years. Beyond interdiction measures, the international community should consider renewed efforts to improve access to controlled opioids for pain management and palliative care to alleviate unnecessary suffering and achieve a holistic and balanced approach to addressing the opioid crisis.

"...emergence of these substances underscores the importance of strengthening early warning systems, expanding public-private partnerships and enhancing existing legal approaches to respond to the growing complexity of the opioid crisis..."

Impact of the COVID-19 pandemic on the evolving opioid crisis

The onset of the COVID-19 pandemic has brought wide-ranging and profound effects to the world, leading to unprecedented closures of non-essential parts of the economy accompanied by border and movement restrictions on a scale unmatched by past market crises. As was the case in previous major crises, it is likely that the pandemic has affected many aspects of the illicit drug market, in particular the evolving opioid crisis.[137]

Effects on the trafficking and manufacture of synthetic opioids

Despite early indications of disruption to illicit synthetic opioid manufacture and trafficking in some regions, recent evidence months into the pandemic suggests that these activities have resumed to normal levels and possibly intensified.[138] For instance, a year-on-year comparison of fentanyl seizure trends at the borders of the United States indicates that the earlier perceived disruption to the fentanyl trade was extremely short-lived,[139,140] with seizures resuming to previous levels as of February 2020, despite temporary restrictions on non-essential travel.[141] Similarly, the pandemic seems to have had little impact on tramadol trafficking with large-scale seizures of the drug being reported in Kuwait and India from February to July 2020.[142,143] Taken together, these preliminary trends in seizures indicate minimal disruption to illicit synthetic opioid manufacturing and trafficking activities in the wake of the pandemic.

However, the impact of the COVID-19 pandemic on the production and trafficking of opiates remains unclear, affecting in turn the wider market for opioids. At present, there is insufficient or inconclusive information available on the current state of Afghanistan's opium harvest, which has accounted for approximately 84 per cent of global opium production over the past five years.[144,145] In any event, if illicit opiate activities are indeed affected, it would be prudent for governments to closely monitor illicit drug markets for developments such as the adulteration or substitution of opiate supplies with cheaper and potentially more harmful synthetic opioids such as fentanyl and its analogues from illicit sources.[146]

Effects on the use of synthetic opioids

The COVID-19 pandemic may further expose opioid users to increased vulnerability to problematic drug use and overdose if the economic fallout drives a switch to more efficient methods of administering drugs, such as injecting, in order to compensate for lower purchasing power and maximize the psychoactive effects.[147,148] However, this heightens the transmission risks of blood-borne diseases such as HIV/AIDS and hepatitis C, while the sharing of drug paraphernalia e.g. inhalation devices may also increase the spread of COVID-19 itself, further burdening already-strained healthcare systems.[149] User behaviour may also shift through abstaining or moving to lower potency or purity opioids, resulting in lower adjusted tolerance and increased risk of opioid overdose as supply and quality improve.[150] Possible reductions or suspensions of public health resources and capacities for harm reduction and drug treatment services as a result of the pandemic, especially opioid substitution treatment, may further exacerbate these vulnerabilities.[151] The American Medical Association recently cited concerns over increases in opioid-related mortality in more than 35 states during the pandemic and urged flexibility in the provision of harm reduction services.[152]

The rapidly evolving drug scenario amid the COVID-19 pandemic highlights the need for policymakers and other stakeholders to actively monitor emerging trends and enact suitable policies to respond to changes in drug manufacturing, trafficking and user behaviour. These changes may have a long-term impact on opioid markets and drug use patterns with corresponding implications for future public health and drug control requirements.

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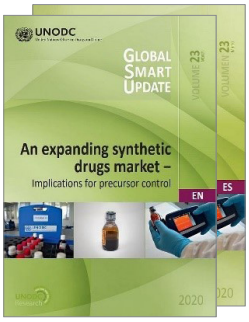

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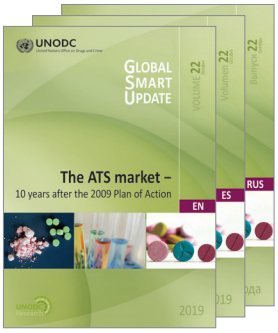

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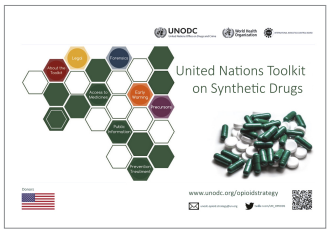

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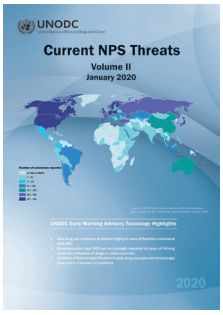

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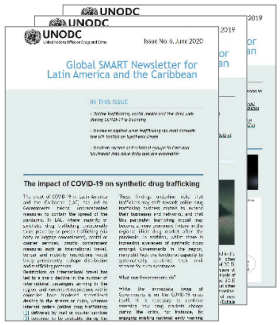

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