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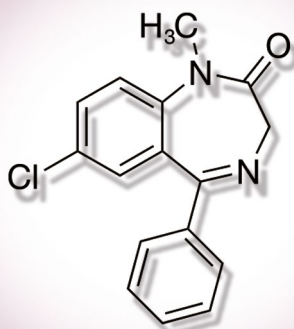
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Non-medical use of benzodiazepines: a growing threat to public health?

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About the SMART Update

Synthetic drugs constitute one of the most significant drug problems worldwide. After cannabis, amphetamine-type stimulants (ATS) are the second most widely used drugs across the globe, with use levels often exceeding those of heroin and/or cocaine. Along with ATS, the continued growth 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 drugs and traditional illicit drug markets is being observed. By August 2017, the emergence of NPS had been reported from 110 countries and territories. Trends on the synthetic drug market evolve quickly each year.

The UNODC Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) Programme enhances the capacity of Member States in priority regions to generate, manage, analyse, report and use synthetic drug information to design effective policy and programme interventions. Launched in September 2008, the Global SMART Programme provides capacity building to laboratory personnel, law enforcement and research officers in the Pacific, East and South-East Asia, South Asia, the Near and Middle East, Africa and Latin America; and regularly reviews the global amphetamine-type stimulants and new psychoactive substances situation. Its main products include online drug data collection, situation reports, regional assessments and the UNODC Early Warning Advisory (EWA) on new psychoactive substances. The EWA is a webportal that offers regular updates on new psychoactive substances, including trend data on emergence and persistence, chemical data, supporting documentation on laboratory analysis and national legislative responses (available at: www.unodc.org/NPS).

The Global SMART Update (GSU) series is published twice a year in English, Spanish and Russian and provides information on emerging patterns and trends of the global synthetic drug situation in a concise format. Each issue of the Global SMART Update contains a special segment and short segments on the topic of interest.* This issue is fully dedicated to the topic of the concomitant use of benzodiazepines and opioids, and does not contain country-specific segments. Past issues have covered topics such as the fentanyl group of synthetic opioids, UNGASS 2016 recommendations, injecting use of synthetic drugs, legal responses to NPS, and key facts about synthetic cannabinoids. Electronic copies of the Global SMART Updates and other publications are available at: www.unodc.org/unodc/en/scientists/publications-smart.html.

* The information and data contained within this report are from 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: UNODC, Global SMART Update Volume 18, September 2017.

Non-medical use of benzodiazepines: a growing threat to public health?

ABSTRACT

Non-medical use of prescription benzodiazepines, has been a long-established problem that has been associated with a large number of overdose deaths worldwide. Most recently, the concomitant use of benzodiazepines and opioids has been linked to a number of deaths that occurred in the recent opioid crisis, featuring in a rising number of fatalities and adverse events in North America and in Europe. In recent years, several new psychoactive substances (NPS) belonging to the benzodiazepine class have also emerged on the market and are being sold under street names such as “legal benzodiazepines”, “designer benzodiazepines”, and “research chemicals”. The use of such NPS belonging to the benzodiazepine class and the non-medical use of pharmaceutical benzodiazepines pose a great threat to public health.

Introduction

The previous Global SMART Update Volume 17 provided an overview of the rapidly unfolding public health threat posed by extremely potent synthetic opioids, fentanyl and its analogues in light of the sharp rise in opioid-related deaths (mainly in North America and, to a lesser extent, in Europe). Recently, increasing evidence has emerged that polydrug use particularly involving sedatives/hypnotics such as benzodiazepines, might be linked to some of these fatalities.

The current Global SMART Update focusses on the concomitant use of benzodiazepines and opioids in the context of the recent opioid crisis in certain parts of the world. Non-medical use of benzodiazepines in combination with the misuse of prescription opioids has been implicated in a growing number of deaths in the United States. Benzodiazepines are also the most common prescription medicines associated with acute intoxication cases in Europe. Whereas benzodiazepines are a class of medicines widely used to treat various medical conditions, both opioids and benzodiazepines are central nervous system depressants in which concomitant use may lead to pronounced drowsiness, respiratory depression, coma or death. The non-medical use of benzodiazepines with opioids has been, and continues to be, a factor of concern for control and preventive measures. Since 1984, certain

benzodiazepines have been placed under international control to prevent their abuse whilst ensuring the availability of some of these benzodiazepines as essential medicines.¹

In recent years, the documented risks entailed in the concomitant non-medical use of opioids and sedatives/hypnotics have been further exacerbated by the ready availability of counterfeited benzodiazepines and the increasing emergence of “designer benzodiazepines”, a common street name for new psychoactive substances (NPS) belonging to the benzodiazepine class. Many NPS belonging to the benzodiazepine class are substances that have not been approved as medicines in the pharmaceutical industry on the basis of safety and/or efficacy. Such substances are potentially more harmful than pharmaceutical benzodiazepines with unknown pharmacological/toxicological profiles and have added to the complexity and dangers of the illicit market for benzodiazepines.

The threat of benzodiazepines: deaths and intoxications associated with opioid and polydrug use

Opioids represent a class of powerful substances used in medicine for the treatment of severe pain. The

non-medical use of opioids however presents serious risks including the potential for abuse, dependence, overdose and fatalities. Benzodiazepines are a class of medicines widely used to treat conditions such as anxiety, insomnia and seizures. In terms of non-medical use, benzodiazepines have been used to produce effects such as relief of mental stress and anxiety, improved coping with situational pressures or psychological problems, or relief of side-effects associated with over-stimulation or withdrawal of other drugs. Chronic use of benzodiazepines may result in the development of tolerance and dependence. Both opioids and benzodiazepines are central nervous system depressants and concomitant use may lead to pronounced drowsiness, respiratory depression, coma or death.

Non-medical use of benzodiazepines in combination with prescription opioids has been implicated in a number of overdose deaths. In the United States, the use of prescription benzodiazepines and opioids coupled with the use of additional drugs, such as heroin, have culminated in several fatalities. From 1999 to 2013, data from the United States has shown that drug-related deaths involving opioid medications have accounted for around 175,000 fatalities.² Over this period, the rate of deaths involving benzodiazepines increased by 514 per cent and the rate of deaths encompassing both prescription benzodiazepines and opioids rose by 819 per cent.³ Over a five-year period, between 2010 and 2014, alprazolam and diazepam were among the 10 drugs most frequently involved in drug overdose deaths. Among the deaths involving alprazolam and diazepam, more than 95 per cent also involved more than two other additional drugs. Based on 47,055 drug overdose deaths

1 World Health Organization (WHO) 20th WHO Model List of Essential Medicines: 20th List. March 2017.

2 Office of National Drug Control Policy (2015) *National Drug Control Strategy 2015*.

3 Centers for Disease Control and Prevention (CDC); National Center for Health Statistics. “Underlying Cause of Death on CDC Wide-ranging Online data for Epidemiology for Research.” 2015.

Table 1: Most frequent concomitantly used drugs in cases of drug overdose deaths involving alprazolam and diazepam – United States, 2014

BENZODIAZEPINES	Most frequent concomitantly used drug in cases of drug overdose deaths				
	First	Second	Third	Fourth	Fifth
Alprazolam	Oxycodone	Heroin	Hydrocodone	Methadone	Morphine
Diazepam	Oxycodone	Hydrocodone	Alprazolam	Heroin	Morphine

Source: Warner, M. et al. (December 2016) "Drugs most frequently involved in drug overdose deaths: United States, 2010-2014." *National Vital Statistics Reports* 65 (10): 1-5.

examined in the report, the most frequent drug used concomitantly with alprazolam and diazepam was the opioid, oxycodone.⁴

Moreover, according to the European Drug Emergencies Network (Euro-DEN), the most common substances associated with acute intoxication cases related to prescription medicines in Europe included benzodiazepines and opioids.⁵ National Statistics of Scotland also reported that of the 706 drug-related deaths in 2015, the use of benzodiazepines (e.g. diazepam) was implicated in, or potentially contributed to, 27 per cent of drug-related deaths in Scotland. Also, among the total number of drug-related deaths in 2015 in Scotland, 57 deaths involved the use of benzodiazepine NPS (such as etizolam, diclazepam or phenazepam).⁶

Although benzodiazepines are rarely identified in post-mortem toxicology as the only drug involved in a case of death, evidence suggests that benzodiazepines are present in a large proportion of opioid overdose cases recorded in recent years in North America and Europe.⁷



Source: UNODC

Australia: Benzodiazepines associated with more than half of non-fatal overdoses of PWID

QUEENSLAND, Australia – February 2017. A drug use study conducted during September and October 2013, among 50 people who inject drugs (PWID) and who reported to have had a non-fatal overdose in the past 12 months, found that the non-medical use of benzodiazepines were associated with 52 per cent of the overdoses. In this regard, these substances have been associated with more than half of non-fatal overdoses of people who inject drugs. In these cases of non-fatal overdose, benzodiazepines (mostly under the brand name of either "Xanax®" or "Valium") had been used by participants within 24 hours before the overdose occurred. Polydrug use was also commonly reported among participants. After benzodiazepines, 44 per cent of participants reported to have used heroin, followed by 42 per cent reporting the use of other prescription drugs, and 36 per cent reporting the use of fentanyl and its analogues. In the presence of other drugs is it difficult to establish a direct link between the benzodiazepines either on their own or in synergy with other substances as a cause of the non-fatal intoxication.

Najman, J. M., et al. (March 2017) "When Knowledge and Experience Do Not Help: A Study of Nonfatal Drug Overdoses." *Journal of Addiction Medicine*: 1-6. Abstract available at: www.ncbi.nlm.nih.gov/pubmed/28368905

4 Warner, M. et al. (December 2016) "Drugs most frequently involved in drug overdose deaths: United States, 2010-2014." *National Vital Statistics Reports* 65 (10): 1-5.

5 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) "Addiction Hospital emergency presentations and acute drug toxicity in Europe: update from the Euro-DEN Plus research group and the EMCDDA." Lisbon, August 2016.

6 National Records of Scotland. *Drug-related deaths in Scotland in 2015*, August 2016.

7 Sun, E.C. et al. (March 2017) "Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis." *The BMJ*: 356; Abrahamsson, T. et al. (May 2017) "Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—A nation-wide register-based open cohort study." *Drug and Alcohol Dependence* 174: 58-64.

Pharmaceutical benzodiazepines have also often been misused by polydrug users in concomitance with other drugs, such as opioids and cannabis. For high-risk opioid users in Europe, the most commonly reported pharmaceutical benzodiazepines associated in drug-related deaths are alprazolam, clonazepam, diazepam, flunitrazepam and oxazepam.⁸ Between October 2013 to March 2014, data collected from

hospital emergency departments in 10 European countries (constituting the European Drug Emergencies Network, Euro-DEN) showed that, after alcohol at 59.4 per cent, benzodiazepines at 22.8 per cent were most commonly used in combination with cannabis among the 320 hospital cases involving cannabis use.⁹

8 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) "Perspectives on Drugs: The misuse of benzodiazepines among high-risk opioid users in Europe." Lisbon, June 2015.

9 Dines, A. M. et al. and Euro-DEN Research Group (December 2015) "Presentations to the emergency department following cannabis use—a multi-centre case series from ten European countries." *Journal of Medical Toxicology* 11(4): 415-421.

Table 2: International control of benzodiazepines under the United Nations Convention on Psychotropic Substances of 1971

YEAR OF SCHEDULING DECISION	SCHEDULE	SUBSTANCE NAME	
1984	IV	Alprazolam	Haloxazolam
		Bromazepam	Ketazolam
		Camazepam	Loprazolam
		Chlordiazepoxide	Lorazepam
		Clobazam	Lormetazepam
		Clonazepam	Medazepam
		Clorazepate	Nimetazepam
		Clotiazepam	Nitrazepam
		Cloxazolam	Nordazepam
		Delorazepam	Oxazepam
		Diazepam	Oxazolam
		Estazolam	Pinazepam
		Ethyl loflazepate	Prazepam
		Fludiazepam	Temazepam
		Flurazepam	Tetrazepam
Halazepam	Triazolam		
1990	IV	Midazolam	
1995	III	Flunitrazepam	
	IV	Brotizolam	
2016	IV	Phenazepam	

Source: UNODC Early Warning Advisory (EWA) on NPS. "April 2017 – UNODC: Several countries place benzodiazepine derivatives under national control." April 2017. Available at: www.unodc.org/LSS/Announcement/Details/065118d5-b238-48d8-9d7f-b95fb5d11411

Various forms of polydrug use involving benzodiazepines have been associated with a number of health consequences, which has been of public concern for some years (see Box for case of benzodiazepines associated with non-fatal overdoses of people who inject drugs and frequent polydrug users). Generally, the combined use of benzodiazepines and other CNS depressant drugs is associated with an overall greater risk of overdose and HIV transmission that can impede treatment for opioid addiction and exacerbate respiratory depression, leading to potential fatalities.¹⁰

Benzodiazepines – Ensuring access for treatment while countering abuse

Benzodiazepines are extensively used in the treatment of conditions including anxiety, insomnia and seizures. However, their non-medical/recreational use has been a long-established problem that has been associated with abuse, dependence and a large number of overdose deaths worldwide. More recently, in North America and in Europe, the non-medical use of benzodiazepines has featured in a rising number of fatalities and adverse events.

Since 1984, a total of 36 benzodiazepines have been placed under international control under the United Nations Convention on Psychotropic Substances of 1971, designed to ensure access to these useful medicines whilst countering their liability for abuse and dependence. Benzodiazepines, diazepam, lorazepam and midazolam, are currently listed in the 20th WHO Model List of Essential Medicines and are

thus considered effective and safe medicines that should be accessible in healthcare systems.

Over time, some pharmaceutical benzodiazepine products have been discontinued. For instance, **nimetazepam** (frequently sold under the brand name "Erimin") is a pharmaceutical benzodiazepine for which licensed production was discontinued in 2015.¹¹ Despite this measure, unlicensed preparations of nimetazepam are available and, in recent years, it has become available online and is reportedly used in a club-drug context in the United Kingdom.¹² Nimetazepam also continues to be illicitly sold in some regions.

Some benzodiazepines not under international control, were approved

10 Horsfall, J.T. and Sprague, J.E. (February 2017) "The Pharmacology and Toxicology of the 'Holy Trinity'." *Basic and Clinical Pharmacology and Toxicology* 120 (2): 115-9; Jones, J.D., Mogali, S., and Comer, S.D. (September 2012) "Polydrug abuse: a review of opioid and benzodiazepine combination use." *Drug and Alcohol Dependence* 125 (1-2): 8-18; Ickowicz, S. et. al. (October 2015) "Benzodiazepine use as an independent risk factor for HIV infection in a Canadian setting." *Drug and Alcohol Dependence* 155: 190-4.

11 Lim, W. J. L. et al. (February 2017) "Detection of phenazepam in illicitly manufactured Erimin 5 tablets." *Drug Testing and Analysis* 9 (2): 293-305.

12 NEPTUNE (Novel Psychoactive Treatment UK Network) "Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances." London, 2015.

Table 3: List of effects of benzodiazepines

DESIRED EFFECTS	UNDESIRED ACUTE EFFECTS	EFFECTS OF CHRONIC USE
<ul style="list-style-type: none"> • Relief of tension, mental stress and anxiety • Positive feelings of calmness, relaxation and well-being in anxious individuals • Improved coping with situational pressures or psychological problems • Relief of side effects associated with over-stimulation or withdrawal of other drugs (i.e. as part of a pattern of multiple drug use) 	<ul style="list-style-type: none"> • Reduced mental activity and alertness, drowsiness, lethargy and impairment of clarity of thought and judgement may occur • Potential impairment of muscle coordination, dizziness, low blood pressure, or fainting • Diminished emotional responses to external stimuli, e.g. pain 	<ul style="list-style-type: none"> • Development of tolerance, psychological and physical dependence • Headache, irritability, confusion, memory impairment, depression, insomnia and tremor • Abrupt cessation may lead to withdrawal syndrome which can include insomnia, anxiety, perceptual hypersensitivity, tremors, irritability, nausea and vomiting, mental confusion and life-threatening convulsions

Source: United Nations (2016) *Terminology and Information on Drugs*.

as pharmaceuticals only in a restricted number of countries and remained largely unknown in most countries. For example, **phenazepam**, a benzodiazepine developed in the former Soviet Union in the 1970s, was only licensed in the Russian Federation and some parts of the Commonwealth of Independent States (CIS) as a pharmaceutical product prescribed to treat anxiety and withdrawal symptoms.¹³

Over time, there have been increasing reports of non-medical use of phenazepam, which has been associated with a rising number of fatalities, particularly in Europe.¹⁴ In some cases, phenazepam has been found to remain in the human body for a long period of time after ingestion, with some reports of severe adverse effects lasting up to five days or to three weeks following ingestion.¹⁵ As a result, phenazepam was

placed under international control in 2016.¹⁶

Etizolam, a pharmaceutical product licensed in Japan, Italy and India, was first reported in 2011 in the United Kingdom on the internet.¹⁷ Particularly, the recreational use of etizolam has been widespread in Scotland and has been associated with drug-related deaths in various parts of the United Kingdom.¹⁸ However, there is limited information on the dependence potential or the number of fatalities associated with etizolam.¹⁹ For this reason, etizolam is currently under surveillance by the World Health Organization (WHO).²⁰

Several countries in East and South-East Asia, including Brunei Darussalam, Hong Kong (China), Indonesia, Malaysia, the Philippines,

Singapore and the Taiwan Province of China, have reported non-medical use of benzodiazepines.²¹ In Malaysia, **nimetazepam** is a commonly abused sedative and is used as a substitute of heroin. It is also increasingly used by methamphetamine users to facilitate a come-down after excessive use.²²

In recent years, several new psychoactive substances (NPS) belonging to the benzodiazepine class have also emerged on the market and are being sold under street names such as “legal benzodiazepines”, “designer benzodiazepines”, and “research chemicals”. The use of such NPS belonging to the benzodiazepine class pose a great threat to public health, particularly in view of the absence of information on their pharmacological and toxicological profiles.

The complex nature of the illicit market for benzodiazepines

Benzodiazepines encountered on the illicit drug market are primarily diverted from the legitimate trade of medicines rather than synthesized in clandestine laboratories.²³ The risk

¹³ World Health Organization (WHO) Expert Committee on Drug Dependence. “Phenazepam: Pre-Review Report. Agenda item 5.8.” Thirty-seventh Meeting, Geneva, 16-20 November 2015; Drug Enforcement Administration (DEA) “Phenazepam.” April 2014.

¹⁴ Corkery, J.M., Schifano F., and Ghodse, A.H. (May 2012) “Phenazepam abuse in the UK: an emerging problem causing serious adverse health problems, including death.” *Human Psychopharmacology* 27 (3): 254-61; Kriikku P., et. al. (July 2012) “Phenazepam abuse in Finland: findings from apprehended drivers, post-mortem cases and police confiscations.” *Forensic science international* 220 (1-3): 111-7.

¹⁵ World Health Organization (WHO) Expert Committee on Drug Dependence. “Phenazepam: Pre-Review Report. Agenda item 5.8.” Thirty-seventh Meeting, Geneva, 16-20 November 2015.

¹⁶ Phenazepam is currently under international control under Schedule IV of the United Nations Convention on Psychotropic Substances of 1971.

¹⁷ O’Connor, L.C., Torrance, H.J., and McKeown, D.A. (March 2016) “ELISA detection of phenazepam, etizolam, pyrazolam, flubromazepam, diclazepam and delorazepam in blood using Immunalysis® Benzodiazepine Kit.” *Journal of Analytical Toxicology* 40 (2): 159-161.

¹⁸ Advisory Council on the Misuse of Drugs (ACMD) “Advice on U-47,700, etizolam and other designer benzodiazepines.” United Kingdom, 2 December 2016.

¹⁹ World Health Organization (WHO) Expert Committee on Drug Dependence. “Etizolam (INN): Pre-Review Report. Agenda item 5.7.” Thirty-seventh Meeting, Geneva, 16-20 November 2015.

²⁰ World Health Organization (WHO) “Substances under Surveillance.” Available at: www.who.int/medicines/access/controlled-substances/substancesundersurveillance.pdf?ua=1

²¹ UNODC, Annual Report Questionnaire; Drug Abuse Information Network for Asia and the Pacific (DAINAP).

²² Abdullah, A. F. L. et. al. (January 2012) “Forensic drug profiling of Erimin-5 using TLC and GC-MS.” *Malaysian Journal of Forensic Sciences* 3(1): 11-15.

²³ United Nations Office on Drugs and Crime (UNODC) *Terminology and Information on Drugs*, 3rd edition. March 2016.

of diversion of medicines from their intended use in medical treatment to non-medical use and sale on illicit drug markets can occur at all points of the pharmaceutical trade. Diversion can occur at pharmaceutical manufacturing sites, at wholesale distribution of medicines, at the physician's office, at retail pharmacies, or when patients receive treatment.²⁴ Methods of diversion are also wide-ranging and can include: the illegal sale and repeated use of prescriptions by physicians and pharmacists; patients obtaining prescriptions from several doctors (also known as the "doctor shopping" phenomenon); theft of medicines; and forgery and/or alteration of prescriptions by patients.²⁵

Over the years, benzodiazepines have been diverted from legitimate trade on a large scale in various regions worldwide for onward sale at illegal drug markets. For instance, in the United States, the leader of an online pharmacy that illegally distributed benzodiazepines including other prescription drugs and illegal tablets was sentenced to prison in January 2017.²⁶ Under the names of "Discount Pharmacy" and "A-1 Pharmacy", this internet operation had shipped hundreds of thousands of tablets, including the opioid hydrocodone and the benzodiazepine alprazolam (under the brand name "Xanax®"), across the United States to thousands of people who did not have valid prescriptions for these substances. Over a three-year period, the operation generated a revenue of more than USD 9 million.

In the United States, alprazolam is considered to be among the top three prescription medicines that are diverted from the licit market. According to the Drug Enforcement Administration (DEA), there were



Source: UNODC

United States: Leader of an online pharmacy that illegally distributed prescription drugs was sentenced to prison

SEATTLE, United States – 27 January 2017. In early 2017, a man pleaded guilty at the United States District Court for the Western District of Virginia in Harrisonburg for purchasing tablets containing flubromazolam between June 2015 and September 2015 and distributing these with the false claim that they contained alprazolam (often sold under the brand name of "Xanax®").²⁷ According to the defendant, the tablets he distributed did not contain any labeling to inform users of their flubromazolam content. Under the names of "Discount Pharmacy" and "A-1 Pharmacy", this internet operation had shipped hundreds of thousands of alprazolam ("Xanax®"), as well as hydrocodone, phentermine, and codeine (sold under various brand names such as "Tylenol 4") tablets to thousands of people across the country who did not have valid prescriptions for these substances. The investigation of this case revealed that the defendant employed this approach to misbrand 100-300 tablets purchased from the "dark web".

United States Attorney's Office Western District of Virginia. "Cross Junction Man Pleads Guilty to Misbranding Charge." 3 February 2017. Available at: www.justice.gov/usao-wdva/pr/cross-junction-man-pleads-guilty-misbranding-charge

almost 40,000 alprazolam reports from federal, state and local forensic laboratories in 2011 and another 18,068 reports between January and June 2012.²⁸

Large scale diversion of benzodiazepines has also been reported in the United Kingdom, where the Medicines and Healthcare products Regulatory Agency (MHRA) conducted a large scale investigation into the diversion of prescription medicines to the illegal drug market in December 2016.²⁹ Two pharmacists based in the Yorkshire region of the country were arrested after having purchased more than 200,000 packs of benzodiazepines and other drugs.

In the course of the investigation, authorities discovered an extensive network engaging in the diversion of prescription medicines that involved wholesale dealers and other businesses as well as some registered pharmacies in the United Kingdom.

The diversion of benzodiazepines and other medicines from licit trade is a problem in a number of regions. However, quantifying the magnitude of such diversion remains difficult given that there is a lack of data and information on this subject and few available systematic monitoring and data collection mechanisms.

Counterfeiting and substitution of pharmaceuticals involving benzodiazepines

Over the years, benzodiazepines have also been employed in the large scale manufacture of counterfeit medicines, also referred to as "fraudulent medicines" or "falsified medicines".³⁰ Such counterfeit medicines are usually made to

²⁴ European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) "Perspectives on Drugs: Strategies to prevent diversion of opioid substitution treatment medications." May 2016.

²⁵ European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) "Perspectives on Drugs: Strategies to prevent diversion of opioid substitution treatment medications." May 2016.

²⁶ United States Drug Enforcement Administration. "Leader of Illegal Online Pharmacy Sentenced to 8 Years in Prison." 27 January 2017. Available at: www.dea.gov/divisions/sea/2017/sea012717.shtml

²⁷ United States Attorney's Office Western District of Virginia. "Cross Junction Man Pleads Guilty to Misbranding Charge." 3 February 2017. Available at: www.justice.gov/usao-wdva/pr/cross-junction-man-pleads-guilty-misbranding-charge

²⁸ Drug Enforcement Administration (DEA) "Benzodiazepines." January 2013.

²⁹ Medicines and Healthcare products Regulatory Agency (MHRA) "Press Release: Regulator investigating the diversion of prescription only medicines." 16 December 2016. Available at: www.gov.uk/government/news/regulator-investigating-the-diversion-of-prescription-only-medicines

³⁰ United Nations "Countering fraudulent medicines, in particular their trafficking." Resolution 20/6.

resemble pharmaceutical products that instead contain different substances that may be harmful. Thus, the content of counterfeit medicines can vary significantly, ranging from products that contain the wrong ingredients, or that are without active ingredients, or that have an insufficient or excessive quantity of the active ingredients.³¹ Cases of counterfeit medicine use involving benzodiazepines discussed in this report are a global phenomenon that can potentially result in unexpected adverse effects and/or a deterioration of medical conditions.

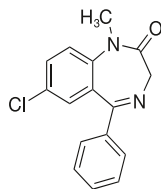
Given that the counterfeiting of medicines is difficult to detect and quantify, the extent of the problem and the size of the market for counterfeit medicines involving benzodiazepines is unknown. However, reports show that benzodiazepines feature in cases concerning counterfeit products worldwide.

In Europe, there have been various reports in recent years of counterfeit medicines that had been intercepted and found to contain benzodiazepine NPS. For instance, in 2016, Police Scotland reported that seized tablets sold as diazepam on the illicit drug market have instead been found to contain various other benzodiazepines such as etizolam, diclazepam, flubromazepam and the synthetic opioid U-47700.³² Moreover, according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), tablets sold in Europe as alprazolam were found to contain flubromazolam in 2015 whereas tablets sold as diazepam tablets in that same year were discovered to have contained phenazepam.³³ In Finland, between 1st July 2010 and 30th June 2011, the Finnish police also

...
31 World Health Organization (WHO) "Substandard, spurious, falsely labelled, falsified and counterfeit (SSFCC) medical products." January 2016. Available at: <http://www.who.int/mediacentre/factsheets/fs275/en/>; World Health Organization (WHO) "Counterfeit Drugs." WHO/IFPMA Workshop, Geneva, 1-3 April 1992.

32 Police Scotland, "The illicit benzodiazepine market in Scotland." Drug Trend Bulletin – Issue 13, September 2016; Police Scotland, "The illicit benzodiazepine market in Scotland", Drug Trend Bulletin – Issue 8, April 2016.

33 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) *European Drug Report 2016: Trends and Developments*. Luxembourg, 2016.



The Democratic Republic of Congo: 400 patients suffer acute intoxication after use of counterfeit diazepam

NONO, Democratic Republic of Congo – July 2015. On 2nd July 2015, the WHO issued an alert when over 400 patients in the area of Nono to the north-east of the Democratic Republic of Congo suffered acute intoxications after having used diazepam for their health treatment. Laboratory analysis of the tablets labeled as diazepam showed that the tablets did not contain any diazepam but instead had a content of 10-20 milligrams of haloperidol per tablet. Although most acute intoxications occurred in the area of Nono, large quantities of such tablets were also reported to have been observed in other parts of the Democratic Republic of Congo such as the Ituri Health District.

World Health Organization (WHO), "Medical Product Alert No. 4/2015: Adverse reactions caused by Falsified Diazepam in Central Africa", Geneva, 2 July 2015.

reported to have seized 26 batches of phenazepam of which some consisted of a mixture of phenazepam and other stimulant drugs.³⁴

In South-East Asia, there have also been reports of nimetazepam being substituted with phenazepam in the content of "Erimin 5" tablets in recent years. According to the Illicit Drugs Laboratory of the Health Sciences Authority in Singapore, phenazepam has been discovered in the content of "Erimin 5" tablet seizures in Singapore and in Malaysia since 2012.³⁵ Previously, "Erimin 5"

...
34 Kriikku P, et. al. (July 2012) "Phenazepam abuse in Finland: findings from apprehended drivers, post-mortem cases and police confiscations." *Forensic science international* 220 (1-3): 111-7.

35 Lim, W. J. L. et al. (February 2017) "Detection of phenazepam in illicitly manufactured Erimin 5 tablets." *Drug Testing and Analysis* 9 (2): 293-305.

India: Authorities dismantle a clandestine laboratory manufacturing alprazolam

ANDHRA PRADESH, India – October 2016. On 5th October 2016, officers of the Vishakhapatnam Directorate of Revenue Intelligence dismantled a clandestine laboratory in Jawaharlal Nehru Pharma City in the Andhra Pradesh State of India. In addition, a total of 101 kg of alprazolam were seized at the site and authorities also arrested 5 people in connection with this case. A day earlier, on 4th October 2016, the Central Bureau of Narcotics seized 700 grams of alprazolam in Indore in Madhya Pradesh State and arrested 3 people in connection with the case.

Narcotics Control Bureau. Drug Situation Report/Significant Events Report for India for the Month of October 2016. October 2016.

tablets seized in both countries usually solely contained nimetazepam or nimetazepam together with a relatively small quantity of nitrazepam.

In North America, cases of counterfeit medicines involving benzodiazepines have featured in the United States for a number of years.³⁶ Recently, in January 2017, the leader of an online pharmacy that illegally distributed tablets containing flubromazolam with the false claim that they contained alprazolam, in addition to illegally distributing various other prescription drugs and narcotic tablets, was sentenced to 8 years in prison (see Box for more information on this online pharmacy in the United States).

In some regions there have also been reports of products sold as benzodiazepine medicines, that were found to contain other substances. For instance, in July 2015, the World Health Organization (WHO) issued an alert concerning tablets labeled as diazepam that were

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36 For more information, see: Drug Enforcement Administration (DEA) "Microgram Bulletin." August 2009; United States Food and Drug Administration, "Counterfeit Drugs – An FDA Perspective." Available at: <http://indy.afdo.org/uploads/1/5/9/4/15948626/ddc-1035-fluror-pharma-counterfeiting.pdf>



Source: UNODC

Malaysia: 2.5 million nimetazepam tablets seized in a container from Taiwan Province of China

PORT KLANG, Malaysia – March 2017. At Port Klang in the state of Selangor, the Special Tactical Intelligence Narcotics Group (STING) and the Royal Malaysian Customs seized 2.5 million nimetazepam tablets, at a value of around 50 million Malaysian Ringgit, concealed in a container from Taiwan Province of China in March 2017. According to the Malaysian Narcotics Criminal Investigation Department, these tablets were intended to be sold on drug markets in Malaysia, as well as in Indonesia, Singapore, and Thailand. Malaysian police arrested 10 men in connection with the case.

Free Malaysia Today. "Cops seize Ermin 5 pills worth RM50 million." 11 March 2017. Available at: www.freemalaysiatoday.com/category/nation/2017/03/11/cops-seize-erimin-5-pills-worth-rm50-million/



Source: UNODC

Ireland: Two cases of "Xanax®" tablet seizures in Kildare and Limerick City

KILDARE AND LIMERICK CITY, Ireland – February 2017. On 13th February 2017, the Irish National Police Service, the Gardaí, seized a large quantity of "Xanax®" tablets (presumed to contain alprazolam) with an estimated value of EUR 19,000 and 6.5 kg of "ecstasy" (presumed to contain MDMA). These substances were seized when the Gardaí from Naas Traffic Corps stopped and searched a car at a checkpoint in Kildare Town after which a man and a woman were arrested in connection with the case. Previously, on 24th June 2016, the Gardaí seized "Xanax®" tablets with a street value of EUR 9,000 together with a quantity of cannabis herb during a search operation at a house in Limerick City.

An Garda Síochána – Ireland's National Police Service. "Press Release: Drug seizure and arrests in Kildare on the 13/2/17." 14 February 2017. Available at: www.garda.ie/Controller.aspx?Page=19911&Lang=1

An Garda Síochána – Ireland's National Police Service. "Press Release: Drug seizure and arrest in Limerick on the 24/6/16." 25 June 2016. Available at: www.garda.ie/Controller.aspx?Page=18494&Lang=1

found to contain haloperidol in the north-eastern parts of the Democratic Republic of Congo (for more information see box on the acute intoxication cases in the Democratic Republic of Congo).³⁷ Previously, in 2011, the United States Food and Drug Administration (FDA) issued a warning on placing orders for alprazolam (often sold under various brand names such as "Xanax®") and certain other pharmaceutical products over the internet.³⁸ According to the FDA, there had been several cases in which such tablets that had been ordered over the internet were found to contain haloperidol.

Clandestine manufacture of benzodiazepines

In addition to the diversion of benzodiazepines from medical sources, there is also some evidence of illicit manufacture. In recent years, countries in various regions have reported the dismantling of laboratories illicitly manufacturing alprazolam and nimetazepam.

With respect to alprazolam, illicit manufacture has been reported

by countries in North America and South Asia. In North America, Canada reported to have dismantled 2 medium-sized packaging operations illicitly manufacturing alprazolam in 2014, while in South Asia, the Narcotics Control Bureau in India reported to have dismantled a clandestine laboratory in 2016 (see Box for more information on the illicit laboratory in India).³⁹

In East and South-East Asia, Malaysia also reported to have dismantled an illicit laboratory manufacturing nimetazepam in 2011 and another such laboratory in 2015.⁴⁰

Seizures and trafficking of benzodiazepines

In recent years, countries worldwide have reported seizures of various benzodiazepines to UNODC.

Nimetazepam

Between 2011 and 2015, nimetazepam seizures were reported in South-East Asian countries that included Brunei Darussalam (totaling less than 1 kg) and the Taiwan Province of China (at a total of around 12

kg).⁴¹ In early 2017, it was confirmed that another 2.5 million tablets of nimetazepam were seized in a single seizure in the Taiwan Province of China (for more information, see Box on nimetazepam seizure reported in Malaysia that had been trafficked from Taiwan Province of China).

Alprazolam

Over the years, most alprazolam seizures were reported in the United States where almost 5 tons were

37 World Health Organization (WHO), "Medical Product Alert No. 4/2015: Adverse reactions caused by Falsified Diazepam in Central Africa." Geneva, 2 July 2015.

38 United States Food and Drug Administration (FDA), "The Possible Dangers of Buying Medicines over the Internet." 26 January 2011. Available at: www.fda.gov/ForConsumers/ConsumerUpdates/ucm048396.htm

39 UNODC, Annual Report Questionnaire for Canada, 2014; Narcotics Control Bureau. "Drug Situation Report/Significant Events Report for India for the Month of October 2016." October 2016.

40 UNODC, Annual Report Questionnaire for Malaysia, 2011 and 2015.

41 UNODC, Annual Report Questionnaire, 2011-2015.

Table 4: List of benzodiazepine NPS that have been reported by Member States to the UNODC Early Warning Advisory (EWA) and benzodiazepine NPS that were observed based on other sources of information

BENZODIAZEPINE NPS	
3-hydroxyphenazepam	Flubromazepam
4-chlorodiazepam	Flubromazolam
Adinazolam	Flunitrazolam
Alprazolam triazolobenzophenone derivative	Meclonazepam
Bromazolam	Metizolam
Clonazolam	Nifoxipam
Cloniprazepam	Nitrazolam
Deschloroetizolam	Norfludiazepam
Desmethylflunitrazepam	Phenazepam ⁴³
Diclazepam	Pyrazolam
Etizolam ⁴²	Zapizolam

Source: UNODC Early Warning Advisory (EWA) on NPS, 2017.

reported to have been seized in 2014 and another 0.01 tons were reported in 2015.⁴⁴ In addition, seizures of this substance, annually totaling 1-5 kg or less per country, have also been reported between 2011 and 2015 in various regions worldwide, in countries that include Bahrain, Chile, Gambia, India, Italy, Pakistan, the Russian Federation, the Taiwan Province of China and Yemen. Most recently in early 2017, two seizure cases of “Xanax®” tablets (presumed to contain alprazolam) were also reported in Ireland.

Diazepam

Since 2010, annual seizures of diazepam mostly consisting of less than 1 kg per country (sold under various brand names that include “Relanium” and “Valium”) have been reported in a number of regions such as Europe, Central Asia and Transcaucasian countries, South and Central America, South Asia, East and South-East Asia, Africa, and the Near and Middle East. Between 2010 and 2015, larger quantities of diazepam were reported to have been seized in India (totaling 24 kg), Myanmar (totaling 7 kg), and the Russian Federation (again totaling 7 kg).⁴⁵

Other benzodiazepines

Other seizures of benzodiazepines (such as clonazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, phenazepam, and temazepam) have also been reported in recent years from various countries worldwide that mostly consisted of annual seizures totaling around 1 kg or less. Larger quantities were reported in the Russian Federation in 2014, where more than 28 kg of clonazepam were reported to have been seized.

The emergence of NPS belonging to the benzodiazepine class

As a relatively new phenomenon, NPS belonging to the benzodiazepine class have emerged on the market and are being sold under street names such as “legal benzodiazepines”, “designer benzodiazepines” or “research chemicals”. This group of substances includes substances that were tested but not approved as medicines in the pharmaceutical industry or that have been manufactured by modifying the core structure of existing pharmaceutical benzodiazepines.⁴⁶ Some of the first NPS belonging to the benzodiazepine class that were available online included substances such as diclazepam, flubromazepam and pyrazolam.⁴⁷ While certain NPS

belonging to the benzodiazepine class have pharmacological profiles similar to controlled pharmaceutical benzodiazepines,⁴⁸ profiles of most of the emerging substances are not well-described.

The risk of polydrug use involving benzodiazepines and opioids are further intensified by NPS belonging to the benzodiazepine class. Given the limited information on the pharmacology and toxicity of these substances, variations in the dosage, onset of effects, combination of substances, potency, and general patient or individual variability, the concomitant use of these substances with other drugs entails a number of risks.

So far, 18 NPS belonging to the benzodiazepine class have been reported by Member States to the UNODC Early Warning Advisory (EWA) and the emergence of an additional 4 NPS belonging to the benzodiazepine class were observed based on other sources of information (for more information see Box on the list of benzodiazepine NPS). In 2011, Germany, Norway and the United Kingdom were the first

⁴² Etizolam is currently in the ‘Substances under Surveillance’ list of the World Health Organization.

⁴³ Phenazepam is currently in Schedule II of the Convention on Psychotropic Substances of 1971.

⁴⁴ UNODC, Annual Report Questionnaire, 2014-2015.

⁴⁵ UNODC, Annual Report Questionnaire, 2010-2015.

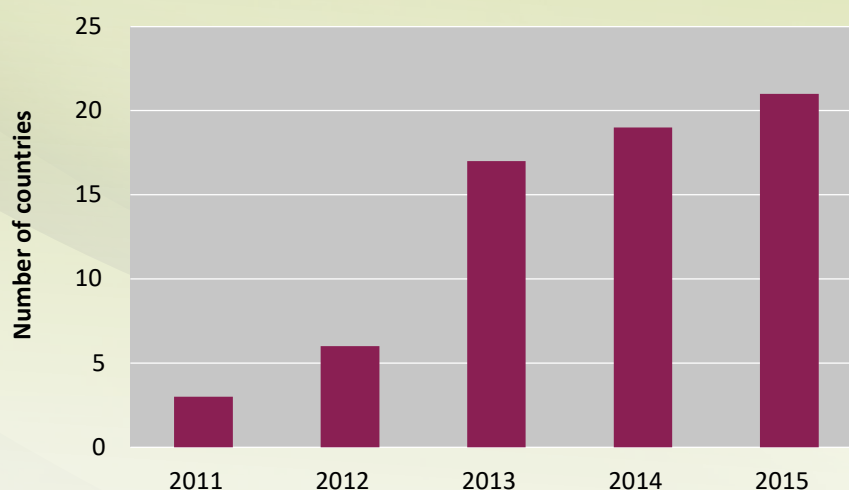
⁴⁶ Moosmann, B., King, L. A., and Auwärter, V. (June 2015) “Designer benzodiazepines: a new challenge.” *World Psychiatry* 14 (2): 248.

⁴⁷ Moosmann, B., Bisel, P., and Auwärter, V. (January 2014) “Characterization of the designer benzodiazepine diclazepam and pre-

liminary data on its metabolism and pharmacokinetics.” *Drug Testing and Analysis* 6 (7-8): 757-763.

⁴⁸ World Health Organization (WHO) Expert Committee on Drug Dependence. “Phenazepam: Pre-Review Report. Agenda item 5.8.” Thirty-seventh Meeting, Geneva, 16-20 November 2015; World Health Organization (WHO) Expert Committee on Drug Dependence. “Etizolam (INN): Pre-Review Report. Agenda item 5.7.” Thirty-seventh Meeting, Geneva, 16-20 November 2015.

Figure 1: Number of countries reporting NPS belonging to the benzodiazepine class to UNODC EWA, 2011-2015



Source: UNODC Early Warning Advisory (EWA) on NPS, 2017.

countries to report the emergence of NPS belonging to the benzodiazepine class, which included etizolam and phenazepam.

Over the years, there was an increase in the number of NPS belonging to the benzodiazepine class reported by countries to UNODC EWA. Between 2011 and 2016, there were a total of 209 reports of such substances and etizolam, phenazepam, diclazepam, flubromazepam and pyrazolam, were among the most commonly reported substances of this group. More than 72 per cent of these reports were received from European countries. Overall, the number of countries reporting the emergence of NPS belonging to the benzodiazepine class has annually increased from 3 countries in 2011 to 21 countries in 2015 (see Figure 1).

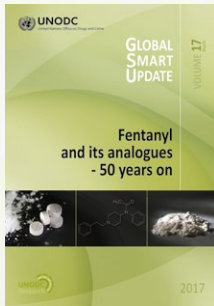
As an increasing number of benzodiazepine derivatives have appeared on NPS markets, several countries worldwide have placed some of these substances under national control. For example, in Europe, NPS belonging to the benzodiazepine class are reported to have been placed under national control in countries such as the Denmark, Finland, Sweden, Switzerland, Turkey and the United Kingdom. In East and South-East Asia, the Republic of Korea is also reported to have placed diclazepam under national control and in the Middle East, the United Arab Emirates have placed diclazepam, etizolam, flubromazepam and pyrazolam under national control.

Ongoing challenges

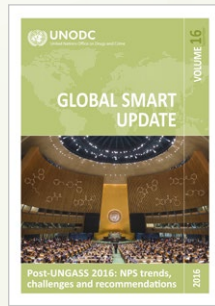
The market for benzodiazepines is highly complex and presents a variety of challenges. In the context of the opioid crisis, the concomitant use of opioids and benzodiazepines poses a significant risk to public health and their use has been involved in a rising number of fatalities in North America and in Europe. Moreover, there are a large variety of benzodiazepines available on the market, ranging from counterfeit products to NPS belonging to the benzodiazepine class, which vary significantly in terms of their duration of action, pharmacology and toxicology.

In particular, there continues to be a lack of data and information on counterfeit benzodiazepines and NPS belonging to the benzodiazepine class. The chemical and pharmacological profile of many NPS belonging to the benzodiazepine class is unknown and the content of counterfeit medicines can also differ. Thus, there is a need for further research to understand the content and nature of these products on market so as to develop effective policy responses. It is also essential to raise awareness of potential severe adverse effects surrounding polydrug use in combination with benzodiazepines and the dangers in acquiring counterfeit medicines.

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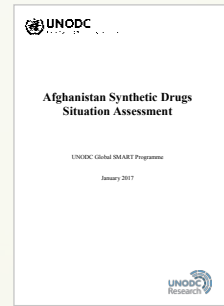
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