Handbook of Experimental Pharmacology 252

Hans H. Maurer
Simon D. Brandt *Editors*

# New Psychoactive Substances

## Pharmacology, Clinical, Forensic and Analytical Toxicology

Springer

# Handbook of Experimental Pharmacology

Volume 252

More information about this series at http://www.springer.com/series/164

Hans H. Maurer • Simon D. Brandt
Editors

# New Psychoactive Substances

## Pharmacology, Clinical, Forensic and Analytical Toxicology

Springer

*Editors*
Hans H. Maurer
Department of Experimental and Clinical Toxicology
Institute of Experimental and Clinical Pharmacology and Toxicology
Saarland University
Homburg (Saar), Germany

Simon D. Brandt
School of Pharmacy & Biomolecular Sciences
Liverpool John Moores University
Liverpool, United Kingdom

ISSN 0171-2004 ISSN 1865-0325 (electronic)
Handbook of Experimental Pharmacology
ISBN 978-3-030-10560-0 ISBN 978-3-030-10561-7 (eBook)
https://doi.org/10.1007/978-3-030-10561-7

Library of Congress Control Number: 2018966537



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Preface

Historically, the legislative control of substances with perceived desired psychoactive effects has always triggered a search for non-controlled alternatives, and the appearance of psychoactive substances of predominantly synthetic origin can be traced back to these efforts. In the last decade, so-called new psychoactive substances (NPS) exploded into the consciousness of policy makers, researchers, practitioners, as well as the general public. NPS are typically viewed as substances not listed in the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, or the United Nations Convention on Psychotropic Substances, 1971, that may pose public health or social risks similar to the substances listed therein. Driven by globalization, easy access to NPS, the striking number of substances, their chemical diversity, and the realization that ideas for large-scale production originated from the – sometimes forgotten or otherwise unexplored – scientific literature, along with the growing numbers of life-threatening poisonings and other harms, have moved the NPS phenomenon firmly onto the policy agenda. Consequently, a variety of legislative and other policy responses have been formulated throughout the globe in an effort to protect public health.

As the dust is beginning to settle, it is now clear that the use of NPS has graduated somewhat from psychonautic explorations of substances obtainable from Internet retailers to a more complex phenomenon. For example, involvement of crime groups has led to NPS being increasingly sold, sometimes surreptitiously, on the "illicit" market, including as falsified (fake) medicines – which can have disastrous consequences. Psychoactive drugs have to be seen as commodities, which means that an overlap exists between "traditional" substance users and markets normally attracting the attention of user groups interested in health and image and performance enhancement. In this respect, globalized trade, electronic forms of communication, effective and cheap shipping, and contract manufacturing organizations available across the globe have placed the NPS phenomenon neatly within a larger phenomenon that encapsulates the areas associated with "designer" medicines, pharmaceuticals, and dietary supplements whereby novel analogs, also frequently originating from older scientific literature, are available for purchase by the sometimes unsuspecting public. New ways of masking detection and identification of NPS and the development of new dosage forms are also being devised. In the latter case, the sale of nasal sprays and e-liquids containing fentanyl derivatives raises

concerns about the spread of such substances to new user groups. Recent years have also witnessed increasing numbers of outbreaks of severe poisonings associated, for example, with synthetic cannabinoid receptor agonists (SCRAs) and synthetic opioids.

However, reflecting the highly dynamic nature of the market, detailed information about the epidemiology of NPS use, including prevalence, is still limited. It is also unclear whether the rate at which new appearances appear on the market will be sustained. What does emerge is that there is a greater need for protecting both people who use these substances and the broader public health.

The content of this book has been assembled to serve scientists, scholars, healthcare providers, law enforcement, policy makers, and people who use drugs and who are fascinated by and exposed to the multilayered facets of the NPS phenomenon. Its highly dynamic nature means that this can only be a snapshot, but it is hoped that readers will get a taste of diverse perspectives provided by the contributing authors and how this information helps to complement the knowledge available on "traditional" psychoactive substances that still dominate the market.

In Part I, Evans-Brown and Sedefov set the stage by describing the origins of NPS and giving an overview of the situation in Europe from the perspective of the early warning and risk assessment activities conducted by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) that allows the European Union to rapidly detect, assess, and respond to public health and social threats caused by these substances. Then Tettey et al. from the United Nations Office on Drugs and Crime (UNODC) introduce the reader to the important activities being coordinated at the global level. On an individual level, people interested in the effects of NPS typically turn to electronic forms of communication for information, such as online discussion boards. At the same time, Passie and Brandt review the rich tradition of self-experiments with psychoactive substances carried forward by scientists and therapists for over a century, which shows that systematic approaches have been available that explored the nature of drugs and drug experience. In most cases, data from self-experiments are the only source on the clinical effects, as controlled human studies in this context are normally not carried out.

Part II is dedicated to providing an overview of the pharmacology of representative examples of commonly encountered NPS. This section begins with synthetic cathinones (Baumann and coworkers) where it is shown that some of the structural features are associated with monoamine transporter-mediated release of neurotransmitters, whereas others direct their activity toward uptake inhibition. Simmler and Liechti follow on with the coverage of amphetamine- and 3,4-methylenedioxymethamphetamine (MDMA)-like NPS. SCRAs are possibly the most diverse and perplexing class of substances that have attracted significant attention, not least from a public health perspective because of the large number of outbreaks of mass poisoning they have caused. The challenge of digesting this complex topic has been taken on by Banister and Connor, who provide two chapters on the origins and evolution of these substances from the viewpoint of molecular pharmacology. At the same time, the emergence of new synthetic opioids on the streets has caused particular concerns regarding their association with significant

numbers of life-threatening poisonings and fatalities. The overview presented by Beardsley and Zhang examines three synthetic opioids (U-47,700, MT-45, and acetylfentanyl) as representative examples belonging to three chemical classes. An increasing number of benzodiazepine-based NPS that predominantly originated from early scientific explorations carried out decades ago have resurfaced in recent years. While sold as substances in their own right, they have also been seen as fake diazepam and alprazolam. Moosmann and Auwärter provide insights into the number and types of substances that have been encountered. Classic serotonergic psychedelics, including psilocybin and lysergic acid diethylamide, are progressively explored in a range of clinical investigations. Clinton Canal offers a detailed discussion on preclinical experimental approaches for studying mechanisms of action of these substances, classic and new. The second part of this book finishes with two contributions provided by Wallach and Brandt who tackle the topic related to dissociative drugs represented by phencyclidine (PCP), 1,2-diarylethylamine-, and ketamine-based NPS.

In Part III, the attention is turned toward the clinical, forensic, and analytical toxicology of NPS. This area of work is especially important since the experiences gained in this field can not only increase the understanding of NPS effects on humans but also play a central role in the detection of harms for early warning systems. This section of the book commences with an overview of recent developments in the field of bioanalysis presented by Wagmann and Maurer who include topics related to sample preparation, methods of analysis and detection, data evaluation, and pitfalls. This is then supplemented by a contribution of Markus Meyer who offers an update on the toxicokinetics of NPS that considers the period between May 2016 and November 2017. From a European perspective, an important contribution to early warning was made by the STRIDA project that monitored the occurrence of poisonings linked to NPS in Sweden. Here, Helander and Bäckberg offer an overview of their experience with analytically confirmed poisonings presenting in hospital emergency departments and intensive care units that occurred during a ~6-year period from 2010 to early 2016 and which also included about 2,600 cases of suspected NPS intoxication. A common challenge experienced by healthcare professionals when dealing with adverse effects associated with NPS use is that information about drug identity is typically not available when it comes to a clinically meaningful time frame. Hill and Dargan inform the reader that clinicians aim for identifying the clinical toxidrome based on the clinical features observed at presentation. The authors provide an overview of the different sources that may inform the understanding of patterns of acute toxicity with NPS and review the existing literature. The most tragic outcome associated with NPS toxicity is death. Kronstrand et al. review the circumstances, antemortem symptoms, and toxicological findings that have led to death following use of NPS, thus offering a forensic toxicology perspective. The authors conclude that deaths attributed to NPS significantly increased during the last 2 years and that this might have been a reflection of a shift from SCRAs and cathinones to the more toxic and dangerously potent fentanyl derivatives, which adds to the general debate about the perceived shift from illicit opioids/diverted opioids to some of these new analogs. In the final contribution,

Ort et al. demonstrate how the chemical analysis of wastewater adds an important piece of the epidemiological puzzle in the effort to understand community-wide drug use.

The editors are grateful to the HEP editors Veit Flockerzi and Jim Barret for providing us with the opportunity to compile this book and the team at Springer especially Susanne Dathe and Anand Venkatachalam for their support and constructive collaboration. Finally, the editors would like to express their gratitude to all the authors who contributed to this book, which would have not been possible without their willingness to spend their valuable time on writing the chapters.

Homburg (Saar), Germany — Hans H. Maurer
Liverpool, UK — Simon D. Brandt

# Contents

**Part I Introduction**

**Responding to New Psychoactive Substances in the European Union: Early Warning, Risk Assessment, and Control Measures** . . . . . 3
Michael Evans-Brown and Roumen Sedefov

**Emergence, Diversity, and Control of New Psychoactive Substances: A Global Perspective** . . . . . 51
Justice N. A. Tettey, Conor Crean, Susan C. Ifeagwu, and Martin Raithelhuber

**Self-Experiments with Psychoactive Substances: A Historical Perspective** . . . . . 69
Torsten Passie and Simon D. Brandt

**Part II Pharmacology**

**Neuropharmacology of Synthetic Cathinones** . . . . . 113
Michael H. Baumann, Hailey M. Walters, Marco Niello, and Harald H. Sitte

**Pharmacology of MDMA- and Amphetamine-Like New Psychoactive Substances** . . . . . 143
Linda D. Simmler and Matthias E. Liechti

**The Chemistry and Pharmacology of Synthetic Cannabinoid Receptor Agonists as New Psychoactive Substances: Origins** . . . . . 165
Samuel D. Banister and Mark Connor

**The Chemistry and Pharmacology of Synthetic Cannabinoid Receptor Agonist New Psychoactive Substances: Evolution** . . . . . 191
Samuel D. Banister and Mark Connor

**Serotonergic Psychedelics: Experimental Approaches for Assessing Mechanisms of Action** . . . . . 227
Clinton E. Canal

**Phencyclidine-Based New Psychoactive Substances** . . . . . 261
Jason Wallach and Simon D. Brandt

**1,2-Diarylethylamine- and Ketamine-Based New Psychoactive Substances** . . . . . 305
Jason Wallach and Simon D. Brandt

**Synthetic Opioids** . . . . . 353
Patrick M. Beardsley and Yan Zhang

**Designer Benzodiazepines: Another Class of New Psychoactive Substances** . . . . . 383
Bjoern Moosmann and Volker Auwärter

**Part III Clinical, Forensic, and Analytical Toxicology**

**Bioanalytical Methods for New Psychoactive Substances** . . . . . 413
Lea Wagmann and Hans H. Maurer

**Toxicokinetics of NPS: Update 2017** . . . . . 441
Markus R. Meyer

**Epidemiology of NPS Based Confirmed Overdose Cases: The STRIDA Project** . . . . . 461
Anders Helander and Matilda Bäckberg

**Patterns of Acute Toxicity Associated with New Psychoactive Substances** . . . . . 475
Simon L. Hill and Paul I. Dargan

**Fatal Poisonings Associated with New Psychoactive Substances** . . . . . 495
Robert Kronstrand, Davide Guerrieri, Svante Vikingsson, Ariane Wohlfarth, and Henrik Gréen

**Wastewater Analysis for Community-Wide Drugs Use Assessment** . . . . 543
Christoph Ort, Lubertus Bijlsma, Sara Castiglioni, Adrian Covaci, Pim de Voogt, Erik Emke, Félix Hernández, Malcolm Reid, Alexander L. N. van Nuijs, Kevin V. Thomas, and Barbara Kasprzyk-Hordern

# Responding to New Psychoactive Substances in the European Union: Early Warning, Risk Assessment, and Control Measures

Michael Evans-Brown and Roumen Sedefov

## Contents

1 Introduction ..... 5
2 The Origins of New Psychoactive Substances (NPS) ..... 7
3 The Situation in Europe ..... 9
3.1 Production, Marketing, and Supply ..... 10
3.2 "Spice," Smoking Mixtures, and the Synthetic Cannabinoid Receptor Agonists ..... 14
3.3 New Synthetic Opioids and the Fentanils ..... 21
3.4 Recent Developments ..... 26
4 Responding to New Psychoactive Substances in the European Union ..... 27
4.1 Legal Framework ..... 27
4.2 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) ..... 28
4.3 Early Warning ..... 28
5 Conclusions ..... 37
5.1 What Is Next for New Psychoactive Substances? ..... 37
References ..... 39

**Abstract**

New psychoactive substances (NPS) are drugs that are not controlled by the United Nations international drug control conventions of 1961 and 1971 but that may pose similar threats to public health. Many of them are traded as "legal" replacements to controlled drugs such as cannabis, heroin, benzodiazepines, cocaine, amphetamines, and 3,4-methylenedioxymethamphetamine (MDMA). Driven by globalization, there has been a large increase in the availability and, subsequently, harms caused by these substances over the last decade in Europe. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is monitoring more than 670 NPS that have appeared on Europe's drug market in the last 20 years, of which almost 90% have appeared in the last decade. While some

M. Evans-Brown (✉) · R. Sedefov
European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal
e-mail: michael.evans-brown@emcdda.europa.eu



H. H. Maurer, S. D. Brandt (eds.), *New Psychoactive Substances*,
Handbook of Experimental Pharmacology 252, https://doi.org/10.1007/164_2018_160

recent policy responses have been successful in reducing availability and sales of these substances in some settings – such as "legal highs" and "research chemicals" sold openly in the high street and online – and there are signs that growth in the market is slowing, new challenges have emerged. This includes monitoring a growing number of highly potent substances – including 179 synthetic cannabinoid receptor agonists and 28 fentanils – that can pose a high risk of life-threatening poisoning to users and can cause explosive outbreaks. This chapter briefly traces the origins of NPS, provides an overview of the situation in Europe, and discusses the work of the EMCDDA as part of a legal framework of early warning, risk assessment, and control measures that allows the European Union to rapidly detect, assess, and respond to public health and social threats caused by these substances.

**Keywords**

Adulteration · Benzodiazepines · Designer drugs · Dietary supplements · Early warning systems · Fentanils · Globalization · Legal highs · Misbranding · New psychoactive substances · Opioids · Outbreaks · Preparedness · Public health policy · Risk assessment · Synthetic cannabinoid receptor agonists · Synthetic cathinones

## Acronyms and Names of the Discussed New Psychoactive Substances (NPS) and Controlled Drugs

| | |
|---|---|
| α-Methylfentanyl | *N*-[1-(1-Methyl-2-phenylethyl)-4-piperidinyl]-*N*-phenyl-propanamide |
| $\Delta^9$-THC | (6a*R*,10a*R*)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol ($\Delta^9$-tetrahydrocannabinol) |
| AB-CHMINACA | *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide |
| Acetylfentanyl | *N*-Phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-acetamide |
| Acryloylfentanyl | *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide (acrylfentanyl) |
| ADB-CHMINACA | *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide |
| Carfentanil | Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino] piperidine-4-carboxylate |
| CUMYL-4CN-BINACA | 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide |
| Cyclopropylfentanyl | *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] cyclopropanecarboxamide |

| | |
|---|---|
| 4F-iBF | *N*-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl) piperidin-4-yl]propanamide (4′-fluoroisobutyrylfentanyl) |
| 4-Fluorofentanyl | *N*-[4-Fluoro-1-(2-phenylethyl)piperidin-4-yl]-*N*-phenylpropanamide |
| 5F-MDMB-PINACA | Methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate (5F-ADB) |
| Fentanyl | *N*-Phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-propanamide |
| Furanylfentanyl | *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (2-furanylfentanyl) |
| HU-210 | 3-(1,1′-Dimethylheptyl)-6aR,7,10,10aR-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol |
| JWH-018 | (1-Pentyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone |
| LSD | (8β)-*N*,*N*-diethyl-6-methyl-9,10-didehydroergoline-8-carboxamide (*d*-lysergic acid diethylamide) |
| MDMA | 1-(2*H*-1,3-Benzodioxol-5-yl)-*N*-methylpropan-2-amine (3,4-methylenedioxymethamphetamine) |
| 3-Methylfentanyl | *N*-[3-Methyl-1-(2-phenylethyl)piperidin-4-yl]-*N*-phenylpropanamide |
| Methoxyacetylfentanyl | 2-Methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide |
| MDMB-CHMICA | Methyl (2*S*)-2-{[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate |
| THF-F | *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl) |

## 1 Introduction

This world is increasingly complex and interconnected. New risks are constantly emerging that can threaten public health; some are familiar, others are novel. Driven by globalization, the serious cross-border threats to health from the (re)emergence and spread of infectious diseases (such as Zika, yellow fever, and Ebola) and the growing market of unlicensed and falsified (fake) medicines are just two examples of policy areas that have required extensive changes to their regulatory systems, both at the level of legislation and implementation, in order to manage these risks more effectively (Directive 2011/62/EU 2011; WHO 2018; Decision No 1082/2013/EU 2013). Drug markets have not been immune to these global changes either, with new psychoactive substances (NPS) providing an important case study of how new threats can rapidly emerge and establish themselves in society (EMCDDA 2016a).

NPS are a broad range of drugs that are not controlled by the United Nations international drug control conventions of 1961 and 1971 but that may pose similar threats to public health (Single Convention on Narcotic Drugs 1961; Convention on Psychotropic Substances 1971; Council Decision 2005/387/JHA 2005; Regulation (EC) No 1920/2006). Many of them are traded as "legal" replacements to established controlled drugs such as cannabis, heroin, benzodiazepines, cocaine, amphetamines, and MDMA (EMCDDA 2016a, 2018a).

Over the last decade, there has been a large increase in these substances as globalization and new technologies, such as the Internet, have allowed them to be produced, sold, and supplied on an industrial scale (Griffiths et al. 2013; Evans-Brown and Sedefov 2017). This has led to a range of challenges for public health policy and practice. At least initially, national drug control laws struggled to keep up with a steady flow of new substances appearing – their open sale in shops on the high street and Internet often adding to this problem (EMCDDA and Eurojust 2016; EMCDDA 2018a). The consumer base has also grown in parallel with the range of substances and products that were offered. It includes people who use them recreationally; those with problematic drug use, who self-medicate; as well as people wanting to look better, get fitter, or enhance their performance at school or work (Griffiths et al. 2013). Reports of severe and fatal poisonings involving these substances have also grown substantially (EMCDDA 2018b).

Nonetheless, the picture across Europe (which has more than 500 million inhabitants) is complex as the situation differs widely both geographically and over time. In addition, the capability and capacity to detect and report events that are important for early warning activities (such as poisonings that are confirmed by laboratory testing) can also differ, meaning that there is both under-detection and under-reporting in some areas and settings. More generally, understanding the epidemiology of NPS remains weak. This includes problems with estimating the prevalence of use of new substances, which can be a complex and frustrating task because of the large number of substances and products that are available but also because of the highly dynamic nature of the market. In many cases, individuals do not actually know what new substance they are using, while in other cases they may not even realize that they are using a new substance; for a discussion of these issues as well as review of prevalence data, the reader is referred to Sumnall (2016).

While some of the recent policy responses have been successful in reducing the availability of NPS in some settings – such as measures aimed at reducing the open sale of "legal high"-type products in high-street shops – the overall continued availability of new substances is driving greater complexity into the drug situation. This includes major new challenges, such as an increase in the number of highly potent substances appearing on the market. These pose a high risk of life-threatening poisoning to users, can cause explosive outbreaks, and, in some circumstances, may pose a risk of occupational exposure to personnel (EMCDDA 2018b).

In Europe, a three-step legal framework of early warning, risk assessment, and control measures allows the European Union to rapidly detect, assess, and respond to public health and social threats caused by these substances. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is responsible for the first two

steps in this system, namely, operating the EU Early Warning System with Europol (the European Union Agency for law enforcement cooperation) and conducting risk assessments, whereas the European Commission, the Council of the European Union, and the European Parliament are responsible for control measures (Council Decision 2005/387/JHA 2005; Regulation (EC) No 1920/2006).

This chapter briefly traces the origins of new psychoactive substances, provides an overview of the situation in Europe, highlights some of the recent major concerns and challenges using the synthetic cannabinoid receptor agonists and the fentanils as case studies, and discusses how the European Union (EU) is responding to this threat. In doing so, information is drawn from material and approaches developed by the EMCDDA's early warning and risk assessment activities that aim to support and strengthen national- and EU-level preparedness and responses to these substances.

## 2 The Origins of New Psychoactive Substances (NPS)

Humans have used psychoactive substances (drugs) for thousands of years. Throughout this time, they have been used for medicinal and spiritual purposes, for relaxation, pleasure, and curiosity, as well as to enhance creativity and performance. Initially, most of these substances were from the use of plants, such as the opium poppy, ephedra, coca, peyote, and cannabis (Berridge and Edwards 1981; Schivelbusch 1993; Courtwright 2002; Sneader 2005; Miller 2014; Richards 2016).

As the field of organic chemistry developed during the nineteenth and twentieth centuries, scientists were able to isolate the active substances from such plants. It also allowed them to determine their chemical structures, manipulate them, and develop a range of new substances (Sneader 2005). Crude opium from the poppy was purified to give morphine, whose structure was tweaked to give diacetylmorphine – a more potent opioid that was sold from the 1890s onward under the trade name heroin and marketed, incorrectly as it turned out, as a "nonaddictive" replacement to morphine (Courtwright 2002). Ephedra led to the isolation of ephedrine, which was subsequently used to make amphetamine – a potent stimulant that was extensively overprescribed in the 1950s in America for weight loss and mood disorders (Rasmussen 2008a, b). Other developments in the field of chemistry led to the discovery of additional sources that could be used as the building blocks for new chemicals, leading, overall, to the invention of a large range of psychoactive substances (Sneader 2005).

The goal of much of this work was to develop new and better medicines. While a relatively small number were successfully commercialized as such, many others fed into the research cycle, being used as pharmacological and clinical tools to study the body, provide insights into disease states, and as chemical templates for developing new types of substances. The results of this ongoing work are cataloged in the scientific and patent literature that provides the blueprints and recipes for making thousands of psychoactive substances (Sneader 2005).

Of the substances that were used as medicines, many spread beyond the sphere of medicine – driven by consumer demand, weak regulation, and wider social and

cultural changes (Tone 2008; Herzberg 2010, 2012; Rasmussen 2012; Berridge 2013). As concerns grew during the twentieth century over the health and social harms caused by these medicines, control measures were increasingly introduced or tightened in an attempt to reduce their availability and limit their harms (Brunn 1975; Musto 1973; McAllister 1999). In many cases illicit markets sprang up, some of which were supplied by diverted medicines or from illicit laboratories. In addition, attempts were made to get round these controls. For example, after morphine became a controlled drug in the 1920s, pharmaceutical companies produced vast quantities of the non-controlled morphine esters benzylmorphine and acetylpropionylmorphine to sell on the illicit opioid market (Anonymous 1953); in the 1960s, following the discovery and synthesis of THC, which is the main psychoactive constituent of cannabis, raids on illicit laboratories found the ingredients and recipes to make "synthetic marijuana" (New York Times 1968), while from the late 1970s onward, the fentanils (highly potent derivatives of the opioid analgesic fentanyl) were made in illicit laboratories and sold as heroin or "synthetic heroin" to unsuspecting users (Baum 1985; Henderson 1988, 1991).

Until the 1960s, most of the substances that did appear on the illicit drug market were medicines. After that, a handful of the other substances also began to appear as word of their effects escaped research laboratories and spread to small groups of people who were keen to experiment with them. Some failed to catch on further and remained "chemical curiosities," usually because the pharmacological effects were of interest only to a small number of people or because of the unpleasant or harmful effects that they produced (Meyers et al. 1968; Shulgin 1975; Cooper 1988). Others, such as LSD and MDMA (or "ecstasy" as it is better known), spread widely, being produced in hobbyist and illicit laboratories and eventually became important substances for the drug market. Many of these substances have fascinating and sometimes long and complex stories that tell of how they came to be discovered and used within society (Beck and Rosenbaum 1994; Collin 1997; Reynolds 1999; Dyck 2008; Morris and Wallach 2014; Passie and Benzenhofer 2016, 2018).

So, the appearance and use of "new" substances is not a new chapter in the history of drug use (Sumnall et al. 2011; Brandt et al. 2014). While diverted medicines, such as pregabalin (Baird et al. 2014; Häkkinen et al. 2014; McNamara et al. 2015), and substances produced in illicit laboratories, such as 4-methylamphetamine (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2014a), continue to be important sources of new substances, what is new is the dramatic increase in the speed and quantity in which new substances have appeared on the drug market over the last decade or so. The handful of substances has turned into hundreds, as entrepreneurs and crime groups have systematically exploited the literature (Fig. 1) and mass produced a large range of new substances and branded products, leading to huge growth in the market (Griffiths et al. 2013; EMCDDA 2016a, 2018a, b).

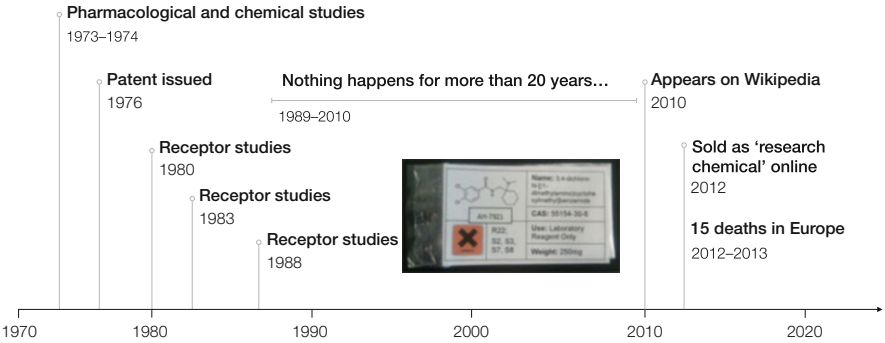


**Fig. 1** AH-7921 is just one of the hundreds of substances from the scientific and patent literature that entrepreneurs have exploited in the last decade. The substance is a structurally unique synthetic opioid analgesic that was invented during the mid-1970s as part of the search for a "better morphine" by the pharmaceutical company Allen and Hanburys Limited (that eventually became part of GlaxoSmithKline). Known by its company code name, AH-7921 was researched in nonclinical studies but was not commercialized as a medicine. Twenty years after the last research paper on it was published, a Wikipedia page for the substance was created that highlighted its opioid pharmacology including its similarities to morphine. Analysis of a sample purchased from an online vendor made in July 2012 confirmed that AH-7921 was being sold openly in Europe under the guise of being a "research chemical." Users were also discussing it online as a "legal opioid." By the end of 2013, the substance had been detected on the drug market in 9 countries in Europe and involved in at least 15 deaths. Vendors based in Europe and China were offering up to multi-kilogram quantities of the substance. Similar to other opioids, AH-7921 can pose a risk of life-threatening poisoning from respiratory depression. Following a risk assessment by the EMCDDA in 2014, AH-7921 was subject to control measures in Europe (EMCDDA 2014b). In 2015, it was also controlled by the international drug control system. A total of 38 new synthetic opioids have been detected in Europe since 2009. © European Monitoring Centre for Drugs and Drug Addiction, 2018. Reproduction of the timeline is authorized provided the source is acknowledged. Image of AH-7921 kindly provided by Dr. Roland Archer, States Analyst, States of Guernsey. © Dr. Roland Archer

## 3 The Situation in Europe

By the end of 2017, the EMCDDA was monitoring more than 670 new psychoactive substances that have appeared on Europe's drug market over the past 20 years. Almost 600 (90%) of these have appeared in the last decade, including 51 substances that were reported for the first time during 2017 (Fig. 2). They include a broad range of substances, including synthetic cannabinoid receptor agonists (SCRAs), synthetic cathinones, opioids, benzodiazepines, phenethylamines, and tryptamines (Fig. 2). While the situation differs widely across Europe, this dramatic growth is also reflected in large increases in seizures made by law enforcement over this period as well as substantial increases in reports involving severe and fatal poisonings (EMCDDA 2018a, b).

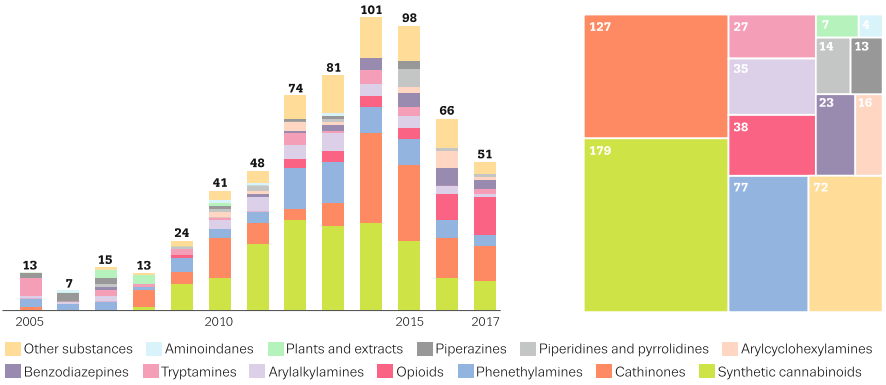


**Fig. 2** New psychoactive substances notified to the EU Early Warning System for the first time 2005–2017: number per year (left) and total number per category (right). European Monitoring Centre for Drugs and Drug Addiction, 2018. Reproduction is authorized provided the source is acknowledged

During 2016, more than 70,000 seizures of new substances that weighed 4.1 tons were reported to the EU Early Warning System by law enforcement agencies from across Europe (Fig. 3). Similar to recent years, the seizures were dominated by SCRAs and synthetic cathinones, which, together, accounted for around 80% of the total number and quantity of new substances reported during the year (Figs. 4 and 5). The larger number of seizures reported for SCRAs reflects their use as "legal" replacements to cannabis, which is the mostly commonly used drug in Europe. The larger number of seizures reported for the synthetic cathinones reflects their use as "legal" replacements for large markets in cocaine, amphetamines, MDMA, and other controlled stimulants (EMCDDA 2018a, b).

Seizures of new psychoactive substances reported to the EU Early Warning System must be understood as minimum values, as data are drawn from case reports rather than monitoring systems. Reports are influenced by a range of factors such as increasing awareness of new substances, their changing legal status, law enforcement capacities and priorities, and the reporting practices of law enforcement agencies. The data are not directly comparable to the data on established controlled drugs. The data also include a small number of new psychoactive substances that have been recently controlled internationally under the UN drug control conventions.

## 3.1 Production, Marketing, and Supply

The growth in the market observed in recent years has only been possible because of a shift in production from small-scale illicit laboratories in Europe to chemical and pharmaceutical companies operating predominantly in China that are capable of making these substances on an industrial scale. This has been driven by globalization and new technologies, with increasing expertise and capacity in the Chinese science

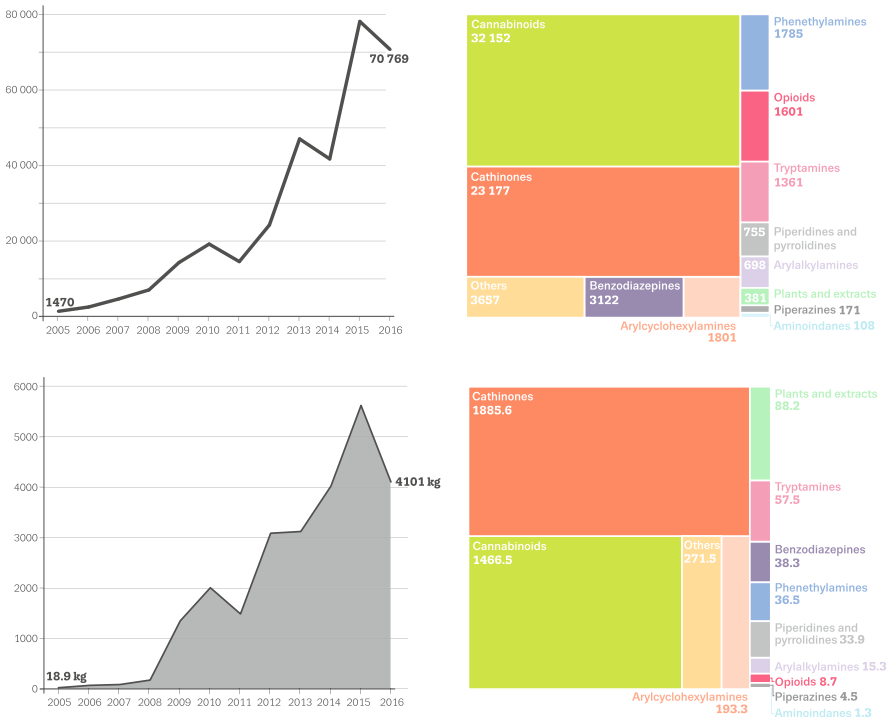


**Fig. 3** Number and quantity of new psychoactive substance seized by law enforcement reported to the EU Early Warning System: trends and distribution by category in 2016. © European Monitoring Centre for Drugs and Drug Addiction, 2018. Reproduction is authorized provided the source is acknowledged

and technology economy, low labor costs, the Internet, and cheap and efficient shipping (Smil 2010; Stearns 2011; Morris 2012; Levinson 2016). Using online marketplaces to advertise their catalog, the companies offer a diverse range of highly pure products in quantities that range from a few milligrams to tens or even hundreds of kilograms (Halford 2015; Deprez et al. 2018). Furthermore, some offer a custom chemical synthesis service. Other ingredients, equipment (such as tableting and packaging machines), and packaging materials that are needed to make products (see below) may also be sourced from companies based in China. Companies based in India can also be an important source of NPS, particularly those substances that are also classed as medicines (such as modafinil and tramadol).

From China, the substances are shipped to wholesalers, retailers, and dealers in Europe by express mail and courier services (Fig. 6), whereas larger quantities ship by air and sea cargo (Fig. 7) (EMCDDA 2016a). Consignments are often misdeclared as common goods of low value, including foodstuffs and other chemical products, in order to conceal their true nature and avoid suspicion by customs and border forces (EMCDDA 2016a). This includes the case of the opioid acetylfentanyl – an analog of fentanyl that was linked to 29 deaths in Europe during 2015 – where consignments

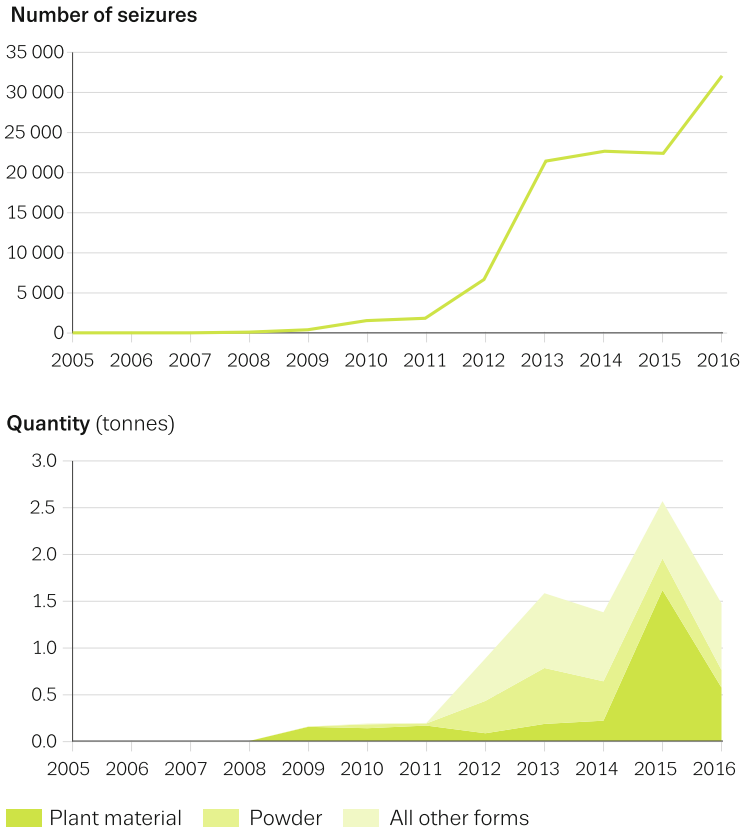


**Fig. 4** Seizures by law enforcement of SCRAs reported to the EU Early Warning System: trends in number of seizures and quantity seized, 2005–2016. © European Monitoring Centre for Drugs and Drug Addiction, 2018. Reproduction is authorized provided the source is acknowledged

were misdeclared as a commonly used adhesive called "hot melt powder" (EMCDDA 2016b). Suppliers and importers may also deliberately route NPS to specific air and seaports in Europe where the substances are not controlled in order to reduce the chance of seizure (EMCDDA 2016a).

In Europe, some NPS are then processed into branded products that are sold openly or under the counter in shops as well as online (Griffiths et al. 2013; EMCDDA 2016b; Södertörns Tingsrätt 2018). At least initially, it was these products that characterized the growth in the market, with the three main categories being marketed as "legal highs," "research chemicals," and "dietary supplements." The products were designed to be attractive to consumers, avoid the attention of regulators, and sidestep consumer protection laws. "Legal highs" were packaged in colorful packaging often suggestive of controlled drugs or psychoactive effects and were usually labeled as "not for human consumption" and as advertised as "incense," "plant food," or "novelty items," while "research chemicals" were labeled

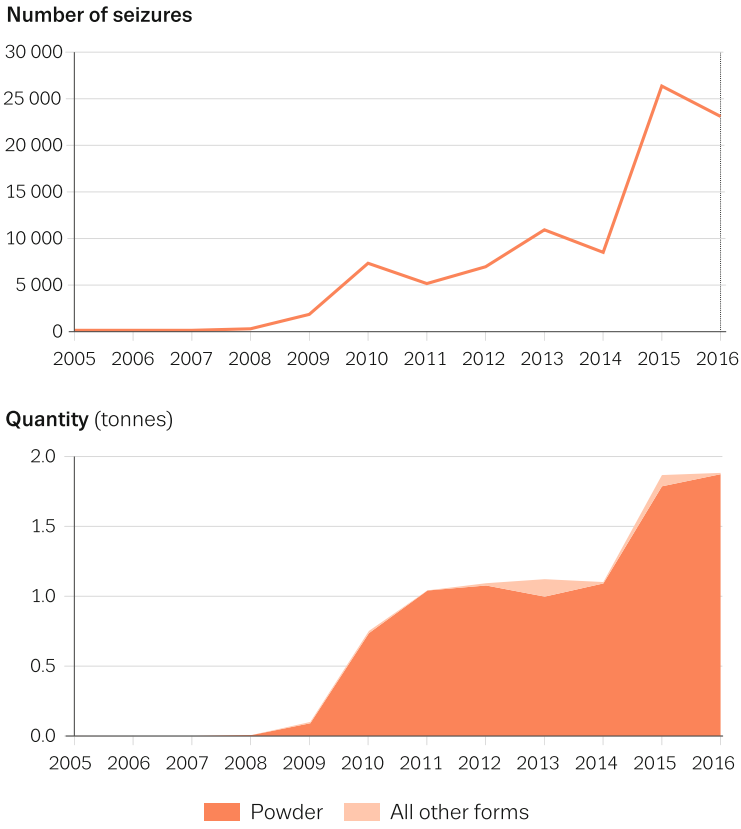


**Fig. 5** Seizures by law enforcement of synthetic cathinones reported to the EU Early Warning System: trends in number of seizures and quantity seized, 2005–2016. © European Monitoring Centre for Drugs and Drug Addiction, 2018. Reproduction is authorized provided the source is acknowledged

as "not for human consumption" as well as "laboratory reagents." Some of the "dietary supplements" are advertised as "natural" products in order to avoid regulatory scrutiny as well as to dupe consumers into thinking that such products are safe and healthy options – a trick that is also widely used to sell unlicensed and fake medicines, particularly those for weight loss, sexual enhancement, and performance enhancement ("doping") (Evans-Brown et al. 2014; Abbate et al. 2015; Cohen et al. 2016). More recently, with vaping on the rise, e-liquids containing SCRAs and fentanils have appeared on the market, while the sale of ready-to-use nasal sprays containing fentanils has also increased in some areas (EMCDDA 2017a, 2018b; Peace et al. 2017; Helander et al. 2017; Ujváry et al. 2017; Södertörns Tingsrätt 2018) (Fig. 8).

Increasingly, NPS are also repackaged into smaller quantities or made into tablets and other dosage forms which are then sold on the illicit drug market either under

**Fig. 6** A seizure of two packages each containing approximately 500 g of cyclopropylfentanyl. The seizure was made by the Polish Customs Service in September 2017. The packages were shipped from China and had transited through Belgium before being seized in Poland. Cyclopropylfentanyl is a derivative of fentanyl and was involved in more than 80 deaths in Europe during 2017. Images kindly provided by Central Customs and Tax Laboratory, Poland. © Central Customs and Tax Laboratory

their own name or passed off as established controlled drugs to unsuspecting users. New benzodiazepines and new synthetic opioids are also used to make fake tablets of commonly prescribed benzodiazepine and opioid analgesic medicines, these too are also sold on the illicit market (Fig. 9) (EMCDDA 2016a, 2018a, b). Sales are through existing street-level drug markets as well as online markets, including on the darknet (EMCDDA 2016b; National Crime Agency 2018).

## 3.2 "Spice," Smoking Mixtures, and the Synthetic Cannabinoid Receptor Agonists

One of the most popular types of "legal high" products over the last decade has been those sold as "legal" replacements to cannabis. They first began to appear in Europe around the mid-2000s as products called "Spice" but are known by many other names including "smoking mixtures," "herbal incense," "K2," "black mamba," and "fake weed" (EMCDDA 2009, 2017b; Jack 2009). Initially, Spice appeared to be a relatively harmless blend of plant material. It was advertised as a "exotic herbal blend" that "released a rich fragrance when burned" (Fig. 10). People who smoked

**Fig. 7** Seizure of 40 kg of highly pure MDMB-CHMICA powder that was intercepted by Luxembourg Customs in December 2014. The powder was contained in forty 1 kg packages and was seized at Luxembourg Airport where it was in transit from China to Spain. The quantity seized would have been sufficient to make millions of doses as smoking mixtures. Images kindly provided by Luxembourg Customs. © Luxembourg Customs

**Fig. 8** Unlabeled nasal sprays containing acryloylfentanyl that were sold online in Sweden in 2016. In the past few years, nasal sprays containing fentanils have become increasingly common in parts of Europe. Compared to injecting, nasal sprays make it easier for people to use fentanils while still giving them a similar psychoactive effect. Their use can pose a high risk of accidental poisoning. With their ease of use, nasal sprays could make the use of fentanils more attractive and socially acceptable, helping the use of these substances spread more widely. Image kindly provided by Prof. Anders Helander, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden. © Prof. Anders Helander

Spice claimed that it had "strong" cannabis-like effects, but it was not until 2008 that researchers discovered that in fact the plant material was laced with synthetic cannabinoid receptor agonists (SCRAs) such as JWH-018 and HU-210 (Auwärter et al. 2009; Griffiths et al. 2013; EMCDDA 2017b) – substances that mimic the effects of THC, which is the main psychoactive constituent of cannabis (Gaoni and Mechoulam 1964; Huestis et al. 2001). THC's effects on the central nervous system are believed to predominately involve activation of the $CB_1$ cannabinoid receptor that mediates the psychopharmacological effects (Gaoni and Mechoulam 1964; Huestis et al. 2001; Pertwee and Cascio 2014). Similar to THC, SCRAs also activate these receptors that form part of the endocannabinoid system – a system that helps regulate a large number of physiological functions in the body such as behavior, mood, pain, and appetite (Pertwee 2015). Many SCRAs were first developed to study this system and in the hope of developing new medicines (Pertwee 2005, 2015; Reggio 2009). Since 2008, 179 SCRAs have been detected on the drug market in hundreds of different products, making them the largest group of substances monitored by the EMCDDA. Alongside being sold as "legal" replacements to cannabis, some people also use them to avoid positive drug screens performed in the criminal justice system, in drug treatment programs, as well as in the workplace. Most smoking mixtures are made in Europe, sometimes on an industrial scale. The SCRAs are typically imported as powders from China (Fig. 7), dissolved using solvents such as acetone or methanol, and then mixed with or sprayed onto plant