Current Topics in Behavioral Neurosciences 32

Michael H. Baumann
Richard A. Glennon
Jenny L. Wiley *Editors*

Neuropharmacology of New Psychoactive Substances (NPS)

The Science Behind the Headlines

Springer

Current Topics in Behavioral Neurosciences

Volume 32

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The Science Behind the Headlines

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ISSN 1866-3370 ISSN 1866-3389 (electronic)
Current Topics in Behavioral Neurosciences
ISBN 978-3-319-52442-9 ISBN 978-3-319-52444-3 (eBook)
DOI 10.1007/978-3-319-52444-3

Library of Congress Control Number: 2017937529

Printed on acid-free paper

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

Preface

Drug abuse and addiction are persistent problems in modern society, and an alarming new trend is the nonmedical use of so-called "designer drugs" or "legal highs," more formally known as "new psychoactive substances" (NPS). By definition, NPS are drugs of abuse that are not controlled by the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which might pose a public health threat [1]. The chemical structures of many NPS are based on compounds extracted from the biomedical or patent literature, whereas others are analogs of illicit drugs or prescribed medications. In all cases, the substances are engineered to evade existing drug control laws. At the present time, there are NPS designed to mimic most major types of abused drugs – stimulants (e.g., bath salts), cannabinoids (e.g., spice), and hallucinogens (e.g., NBOMes). NPS produce subjective effects resembling those of their progenitors, but life-threatening adverse effects are well established and include tachycardia, hyperthermia, agitation, psychosis, violent behavior, coma, and even death. Most NPS are synthesized by Asian companies and are marketed for worldwide distribution via the Internet. The United Nations Office of Drugs and Crime (UNODC) reported that between 2008 and 2015, more than 600 NPS were identified by 102 countries and territories, and this number is expected to rise [2]. NPS represent a serious global public health threat, since there is no quality control in their manufacturing or packaging, and their biological effects are unknown when they first emerge into the recreational drug marketplace.

The purpose of this book is to provide the most up-to-date knowledge about the neuropharmacology, structure-activity relationships, and toxicology of NPS. The initial idea for the volume was based on a symposium entitled, "Bath salts, spice and related designer drugs: the science behind the headlines," held at the 2014 annual meeting of the Society for Neuroscience, in Washington DC [3]. The number of contributors for the book grew from the original symposium participants to include an international panel of experts in the field of NPS. Eighteen peer-reviewed chapters provide a rich source of information about the neurobiological effects of synthetic cathinones, cannabinoids, and hallucinogens. The topics

presented range from molecular mechanisms of action to behavioral effects and include preclinical and clinical findings. The collective data demonstrate that NPS can produce effects that are similar to the drugs they intend to mimic. However, higher potency, enhanced efficacy, and idiosyncratic metabolism can render certain NPS much more dangerous than traditional drugs of abuse. The editors are indebted to each of the principal authors, and their coauthors, who committed time and expertise to craft seminal chapters for the book; we are also grateful to Springer publishing for guidance and support throughout the publication process. Our understanding of NPS is only just beginning, yet we hope this volume provides useful information to scientists, clinicians, law enforcement agencies, and policymakers who are engaged in responding to the growing phenomenon of NPS. We believe that disseminating unbiased scientific information about NPS is a key first step for increasing public awareness about the risks associated with these substances, thereby decreasing demand and avoiding potential harms.

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Contents

The Growing Problem of New Psychoactive Substances (NPS) 1
Bertha K. Madras

Structure-Activity Relationships of Synthetic Cathinones 19
Richard A. Glennon and Małgorzata Dukat

Interactions of Cathinone NPS with Human Transporters and Receptors in Transfected Cells 49
Linda D. Simmler and Matthias E. Liechti

Electrophysiological Actions of Synthetic Cathinones on Monoamine Transporters 73
Ernesto Solis, Jr.

Neuropharmacology of 3,4-Methylenedioxypyrovalerone (MDPV), Its Metabolites, and Related Analogs 93
Michael H. Baumann, Mohammad O. Bukhari, Kurt R. Lehner, Sebastien Anizan, Kenner C. Rice, Marta Concheiro, and Marilyn A. Huestis

Decoding the Structure of Abuse Potential for New Psychoactive Substances: Structure–Activity Relationships for Abuse-Related Effects of 4-Substituted Methcathinone Analogs 119
S. Stevens Negus and Matthew L. Banks

Reinforcing Effects of Cathinone NPS in the Intravenous Drug Self-Administration Paradigm 133
Lucas R. Watterson and M. Foster Olive

Predicting the Abuse Liability of Entactogen-Class, New and Emerging Psychoactive Substances via Preclinical Models of Drug Self-administration 145
Shawn M. Aarde and Michael A. Taffe

The Affective Properties of Synthetic Cathinones: Role of Reward and Aversion in Their Abuse 165
Heather E. King and Anthony L. Riley

MDMA, Methylone, and MDPV: Drug-Induced Brain Hyperthermia and Its Modulation by Activity State and Environment 183
Eugene A. Kiyatkin and Suelynn E. Ren

Neurotoxicology of Synthetic Cathinone Analogs 209
Mariana Angoa-Pérez, John H. Anneken, and Donald M. Kuhn

Combination Chemistry: Structure–Activity Relationships of Novel Psychoactive Cannabinoids 231
Jenny L. Wiley, Julie A. Marusich, and Brian F. Thomas

Pharmacological and Toxicological Effects of Synthetic Cannabinoids and Their Metabolites 249
Sherrica Tai and William E. Fantegrossi

Tripping with Synthetic Cannabinoids ("Spice"): Anecdotal and Experimental Observations in Animals and Man 263
Torbjörn U.C. Järbe and Jimit Girish Raghav

Pharmacology and Toxicology of *N*-Benzylphenethylamine ("NBOMe") Hallucinogens 283
Adam L. Halberstadt

Clinical Pharmacology of the Synthetic Cathinone Mephedrone 313
Esther Papaseit, José Moltó, Robert Muga, Marta Torrens, Rafael de la Torre, and Magí Farré

Application of a Combined Approach to Identify New Psychoactive Street Drugs and Decipher Their Mechanisms at Monoamine Transporters 333
Felix P. Mayer, Anton Luf, Constanze Nagy, Marion Holy, Rainer Schmid, Michael Freissmuth, and Harald H. Sitte

NPS: Medical Consequences Associated with Their Intake 351
Fabrizio Schifano, Laura Orsolini, Duccio Papanti, and John Corkery

The Growing Problem of New Psychoactive Substances (NPS)

Bertha K. Madras

Abstract The term "new psychoactive substances" (NPS) can be defined as individual drugs in pure form or in complex preparations that are not scheduled under the Single Convention on Narcotic Drugs (1961) or the Convention on Psychotropic Substances (1971). NPS may be categorized by chemical structure, by psychoactive properties, by biological targets, or by source (plant, synthetic, or combined). The emergence of hundreds of NPS in the past decade is challenging for public health and drug policies globally. The novelty of NPS, their ambiguous legal status, ability to evade toxicological tests, swift adaptation to legal restrictions, global Internet marketing, and scant public knowledge of their adverse effects are among the key drivers of this twenty-first century phenomenon. Multi-disciplinary research in areas of biology, epidemiology, prevention, and web analytics are needed to develop effective responses in a domain capable of overwhelming current international conventions and national drug control policies. Ultimately, research-guided prevention education will fortify societies against this tidal wave.

Keywords Cathinones • New psychoactive substances • Synthetic cannabinoids

Contents

1 Introduction 2
2 What Drives Expanding Use of NPS? 3
2.1 Information Revolution 3
2.2 Vague Legal Status and Elusive Detection 4
2.3 Guileful Marketing 6

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Curr Topics Behav Neurosci (2017) 32: 1–18
DOI 10.1007/7854_2016_34
Published Online: 27 August 2016

3 Scope of the NPS Problem 6
3.1 Prevalence and Use 6
3.2 Medical Consequences 7
3.3 Purity and Quality 8
4 Role of the Internet 9
4.1 Drug-Related Content Exists Across Social Media Sites 9
4.2 Harnessing Social Media 10
5 Various Classes of NPS 10
5.1 Most Common Classes of NPS 10
5.2 Stimulant "Bath Salts": Cathinones and Pyrovalerone Analogs 11
5.3 Synthetic Cannabinoids 12
5.4 Other New Psychoactive Drugs 13
6 Solutions 13
6.1 Research Informed by Data-Sharing 13
6.2 Monitoring of Social Media 14
6.3 Integrating Sources of NPS Information 14
7 Gauging Biological Effects 15
7.1 Screening for and Testing NPS 15
7.2 The Unknowns 15
8 Public Education 16
8.1 Public Awareness and Research 16
9 Conclusions 16
References 16

1 Introduction

Foraging for food over millennia, humans serendipitously discovered that certain plants and fungi could produce diverse sensations distinct from satiety. A few were pleasantly arousing (tobacco, tea leaves, and coffee beans), and the liquid of fermented plants relaxed, dulled stress or melancholy, elevated mood, and intoxicated. One plant extract reduced pain, promoted euphoria, and induced sleep (opium) while others engendered euphoria and energy (coca and ephedra), or intoxicated, relaxed, heightened sensory perception and impaired thinking (marijuana). Some generated hallucinations and delusions (peyote and mushrooms). With the dawn of modern chemistry in the late 1700s, it became feasible to purify and identify the chemical structures of the psychoactive components in plants and fungi. Inspired by scientific curiosity or the drive to optimize medicinal properties of these compounds, chemists then synthesized variations of these and many other naturally occurring compounds. The unintended consequences of this inquiry and medical progress were not predictable: electronic sources of articles in medicinal chemistry, pharmacology, and biology journals, of patents, and failed candidate therapeutics became a treasure trove for entrepreneurs to craft psychoactive substances destined for furtive markets. This glut of new psychoactive substances has overwhelmed public health services, and created paroxysms in global public policy and legal systems. The spread of new psychoactive substances conceivably poses a

public health challenge greater than that of substances listed in current drug conventions.

The term "new psychoactive substances" (NPS) can be defined as individual drugs in pure form or in complex preparations that are not scheduled under the Single Convention on Narcotic Drugs (1961) or the Convention on Psychotropic Substances (1971). NPS may be categorized by chemical structure, by psychoactive properties, by biological targets, or by source (plant, synthetic, or combined). The designation "new" is not necessarily limited to newly designed compounds with no historical precedent, but may also include compounds modified from progenitors or substances previously conceived of, some many decades ago. The majority are chemical analogs of drugs in restricted categories (e.g., THC or tetrahydrocannabinol, cocaine, cathinone, amphetamine, or methamphetamine, ketamine, LSD or lysergic acid diethylamide, and methaqualone), and may elicit psychoactive effects similar to the parent drug, or a more amplified response. Others may evoke unique or complex sensations because of their hybrid structures, or because several compounds with differing pharmacological profiles are amalgamated and sold as a unit. This diverse array includes phenethylamine derivatives such as synthetic cathinones and their pyrovalerone analogs, synthetic cannabinoids, piperazines, ketamine analogs, tryptamines, benzofurans, and opioids [1, 2].

At present, synthetic cathinone analogs and synthetic cannabinoids occupy a major share of this market.

The rapid expansion of products containing NPS in the past decade is fueled by a convergence of the information revolution, vague legal status, uncertain detectability, and financial incentives combined with guileful marketing.

2 What Drives Expanding Use of NPS?

2.1 Information Revolution

The Internet is a "global neural network" that can be exploited to disseminate promotion and distribution of these drugs instantly. The venues are chat rooms, blogs, instant messaging sites, social networking, or multimedia sites. At minimal cost, descriptions of new drugs, their positive psychoactive effects, doses, synthetic routes, and purchasing sites are accessible worldwide on computers, or mobile devices such as smart phones or smart watches. A blunt snapshot of the global reach of this market can be gleaned from the European Union (EU) funded Psychonaut Web Mapping Project, tasked with real-time identification of emerging NPS (sometimes known as "legal highs") through regular monitoring of the Internet. The project detected over 200 discussion forums, social media sites, online shops, websites, and other Internet resources on YouTube, eBay, Google, and Google Insight [3]. Many of the marketing sites are impervious to legal sanctions, as it takes time to deliberate the evidence and move newly emerging drugs into a legally

restrictive zone, especially internationally. Imperfect international agreements and a gradual dissolution of international resolve to attenuate drug use confound solutions to this unique problem.

2.2 Vague Legal Status and Elusive Detection

More often than not, substances that imitate controlled drugs are unscheduled, unregulated, and not under the auspices of international law. Their nebulous legal status is an incentive for entrepreneurs to introduce new drugs quickly into the global market. The chemical structures of NPS differ from their progenitors (hallucinogens, stimulants, depressants, and euphoriants) that reside in restrictive drug schedules of the Controlled Substances Act (CSA) in the United States (USA), or in analogous schedules of other nations, and in international conventions. Reviving abandoned drugs by mining old sources (e.g., from chemical journals or patents) or creating new entities with slight or major structural variations can transform the restricted progenitor drug into an uncertain category of legal status, a "legal gray zone." The allure of NPS is magnified by current limitations in detecting them. Identifying these drugs for forensic, workplace, legal, and policy purposes is constrained by a lack of reference materials and the need for sophisticated detection methods which are not routinely available (e.g., mass spectroscopy). NPS tempt drug users who seek "legal highs" to circumvent the legal consequences of using standard drugs [4], desire drugs to be undetectable in drug screens, and attract poly-substance users seeking novelty in drug experiences. Despite the worldwide glut of marijuana, synthetic cannabinoid users report their reasons for using as curiosity or experimentation (91%), a desire to feel good or get high (89%), to relax (71%), and to get high without risking a positive drug test (71%) [5].

The chemical structures of NPS are designed to keep one step ahead of federal and international laws that restrict distribution and sale of specific chemicals. Law enforcement is in a perpetual race to outflank producers of NPS, a contest as old as the 1920s. During that era, chemists circumvented international drug laws by developing analogs of banned opioids. By the 1960s, a wave of new psychoactive drugs flooded American culture, some being absorbed into the culture to persist to this day. Other drugs lost popularity, because of safety concerns and undesirable psychoactive profiles. The incentives for producers are the same as they were 90 years ago, to evade legal sanctions and to profit before safety concerns precipitate scheduling. Nations respond differently to this challenge [4]. Some countries have introduced generic controls, controls on analogs, or imposed temporary restrictions on specific drugs until more data accumulates. Increasing surveillance of NPS has led to legislative actions taken by the Drug Enforcement Administration (DEA) of the USA, the World Health Organization (WHO), and other agencies of the United Nations. The WHO Expert Committee on Drug Dependence (ECDD) continues to review and render decisions on the scheduling of new substances [6, 7] in 2014 and 2015.

In the 1960s, the drug pandemonium in the USA catalyzed the formation of the DEA in 1973, a unified federal agency charged with regulating drugs with high abuse potential. Drugs were placed into five categories known as schedules. The most restrictive category, Schedule I, requires validation by a preponderance of evidence showing high abuse potential, no currently accepted medical use in treatment in the USA, and a lack of accepted safety for use. Schedule I controlled substances are regulated by administrative, civil, and criminal sanctions imposed on persons who handle (manufacture, distribute, import, export, engage in research, conduct instructional activities, and possess). Schedule II–V drugs have medicinal uses and their placement in each of the four categories is governed by relative abuse potential and safety profile. The DEA has emergency powers to temporarily schedule a drug for 36 months, a time frame to accumulate evidence for/against long-term drug scheduling. When poison control centers, emergency departments, or morgues become flooded with patients suffering from adverse effects of NPS, the legal "gray zone" can rapidly morph into a definitive Schedule I status. Automatic scheduling of novel drugs can be problematic without strong evidence for potential public harm, even if they are similar chemically and bind to the same receptors as do analogous scheduled drugs. These parameters frequently, but not uniformly, predict abuse liability. Examples in this regard include cannabidiol, a non-psychoactive analog of THC of marijuana, or non-amine nitrogen derivatives of the psychostimulants cocaine or CFT (WIN 35,428), which bind with high affinity to the dopamine transporter but do not penetrate the CNS [8]. In an effort to constrain the explosion of NPS, a Synthetic Drug Control Act of 2015 was introduced in the US Congress, to add more than 200 synthetic substances to Schedule I. Internationally, the WHO separately and in conjunction with other United Nations agencies conducts similar surveillance and recommends updates on scheduling.

Yet some have questioned the cost-benefit of drug scheduling and whether it effectively curtails NPS use. With curiosity and experimentation as primary motivators for NPS users of synthetic cannabinoids, despite a glut of marijuana, this contention is questionable [5]. It has been argued that an unintended consequence of drug scheduling may be the distribution of more dangerous drugs to replace the scheduled drug. An example is α-PVP (α-pyrrolidinovalerophenone, or "flakka") a demethylated derivative of pyrovalerone and analog of cathinone. α-PVP was gleaned from an early patent or perhaps from a more recent medicinal chemistry manuscript focused on medications for cocaine addiction [9]. More than 130 deaths have been associated with α-PVP, and hospitalizations were required for non-fatal acute intoxications. In cases where α-PVP use was established unambiguously by forensic verification, neurological and cardiovascular effects consistent with an extensive psychostimulant toxidrome have been observed and included cardiotoxicity, violent behavior, and display of psychotic behavior [10]. Emergency scheduling to ban methylone (3,4-methylenedioxy-*N*-methylcathinone) and MDPV (3,4-methylenedioxypyrovalerone) saw increases in methylone encounters with law enforcement, although whether prevalence of use increased in tandem is not clear [11].

On the other hand, mephedrone (4-methyl-*N*-methylcathinone) and related cathinones were controlled in the United Kingdom (UK) in 2010. Emergency department presentations of patients with acute toxicity related to mephedrone peaked prior to, and then fell significantly following, the control of mephedrone. The control of mephedrone in the UK may have been effective in reducing the acute harm associated with the drug [12].

2.3 Guileful Marketing

Wily packaging and labeling often blurs the authentic identity of NPS, reduces stigma, and attempts to evade legal sanctions with disclaimers. Packaging resembles standard quality products: "bath salts," "soap," and misleading labeling insinuates innocuous use: "air fresheners," "legal/herbal highs," "plant food," "insect repellent," "fireplace kindling," "bidet refreshers," and "humidity adsorbents." Disclaimers ("not for human consumption," "research purposes only," and "research chemicals") attract less legal attention and provide a veil of legitimacy on promotional materials. To entice consumption by young users, some synthetic cannabinoids, cathinones, and phenethylamines are sold in packages embellished with bright colors and cartoons and marketed with tasty varieties (blueberry, strawberry, mango, and bubblegum).

NSP are distributed in the USA in convenience stores, "head shops," stores catering to adult products, smoke shops, gas stations, and via the Internet. They may be displayed openly, or hidden from view to be sold only to trusted customers. Although the more common NPS are restricted, a small change in structure can transform a regulated into an unregulated chemical and nullify regulatory oversight. Legal constraints are less manageable if NPS are sold via the Internet, especially since their sources are mainly in Asia or unidentified, and may be beyond the reach of law enforcement. Financial incentives for producer and consumer are another driver of this market. The synthetic routes for producing most NPS are not challenging for competent chemists. The enterprise is lucrative, as the cost of starting materials is inconsequential compared with high markups in retail sales. Based on the cost of a dose unit, the user can purchase certain synthetic drugs at far lower cost than conventional drugs sold on street markets [1].

3 Scope of the NPS Problem

3.1 Prevalence and Use

Synthetic cathinones (mephedrone and MDPV) were among the first NPS to emerge and are frequently used interchangeably with other stimulants such as

amphetamine and MDMA. Cathinones are primarily synthesized in Asia, exported, and then packaged. In Europe, more than 70 new cathinones have been recently identified. The EU Early Warning System (EWS) recorded the appearance of 418 NPS during the period of May 2005–December 2014 [13–15], with more than 450 of them currently monitored by the European Monitoring Center for Drugs and Drug Addiction [16]. In 2014, 101 new substances were detected for the first time and reported to the EWS, including 31 designer cathinones, 30 synthetic cannabinoids, and 9 phenethylamines. Sixteen public health alerts were issued in 2014. In the same year, the United Nations Office of Drugs and Crime documented the emergence of 540 different NPS in a worldwide survey of 80 countries [17]. It is estimated that 2.9 million people 15–24 years in the EU have tried NPS.

In the USA, NPS were first encountered in 2009 and since then, more than 250 new synthetic compounds have been identified. Synthetic cannabinoid use remains the most prevalent [18]. Synthetic cannabinoids are the fourth most popular drug class among 8th graders (after marijuana, inhalants, and amphetamines), the third most popular among 10th graders (after marijuana and amphetamines), and the fourth most popular among 12th graders (after marijuana, amphetamines, and Adderall®). Current Monitoring the Future survey data shows that there were no significant increases or decreases in use of "bath salts" in 2015. Use rates of MDMA (3,4-methylenedioxymethamphetamine), or ecstasy or Molly declined among 8th, 10th, and 12th graders since 2010, and continued to show significant declines in 2015 among 10th and 12th graders [19]. Despite these promising trends, indicators of use gleaned from the American Association of Poison Control Centers (AAPCC) show that in 2014, there were 3,677 calls to poison centers regarding *synthetic marijuana exposures*, a 37.8% increase from 2,668 in 2013. This represents the first increase since the number of calls peaked in 2011 at 6,968, with 2012 and 2013 showing a decline in the number of calls.

In contrast, AAPCC statistics show a declining number of calls to poison centers for cathinone exposure. For the year 2014, there were 580 calls, a 41.7% drop from the 995 calls in 2013. In the previous reporting period from 2012 to 2013, the number of calls dropped from 2,691 to 995, a 63% decrease. Although the data suggests that synthetic cathinone abuse is declining, the rebranding of these drugs as MDMA, "molly," or "flakka," to confuse or conceal their content as a synthetic cathinone, may compromise accuracy of self-reported survey data. Users may report MDMA use, when in fact the substance is a cathinone such as methylone or ethylone, or a pyrovalerone analog. Sophisticated analytical methods are the only procedures able to clarify trends in use of psychostimulant substances.

3.2 Medical Consequences

Most chemical classes of NPS can produce adverse psychiatric and medical consequences ([20]; see Schifano et al. this volume). Patients intoxicated with NPS

present a significant burden to healthcare professionals, especially those involved with emergency medical care. The long-term neuropsychiatric consequences of NPS exposure are not known, but acute effects (e.g., agitation, hallucinations, psychosis, violent behaviors, and coma) are associated with their use. In the USA, an alarming spike in toxic exposures and fatalities associated with abuse of synthetic cannabinoids has occurred.

3.3 Purity and Quality

Quality control in manufacturing and a standard of purity do not exist for NPS. Cautious buyers may seek sellers who offer safety data or documented purity, but no regulatory bodies guarantee these claims. Each substance may harbor contaminants, or incorrectly identified compounds, to confer a potential health risk. The potent dopamine neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was a contaminant generated during clandestine synthesis of a meperidine analog in the 1980s. Had the target chemical been synthesized and purified according to procedures described in the source medicinal chemistry journal, the byproduct MPTP would not have produced severe parkinsonism in seven young heroin addicts [21]. Another repugnant example of indifference to purity, quality control, or safety in clandestine production is manganese contamination of ephedrone used in its synthesis [22]. Users can develop an "ephedrone parkinsonism" (EP) characterized by a complex, rapidly progressive, irreversible, and levodopa non-responsive parkinsonian and dystonic syndrome due to manganese toxicity.

NSP packets often include multiple substances. The chemical compositions of packets sold as "bath salts" (cathinones) vary widely, as do purity and safety. A convenience sample of 35 individual packets of "bath salt," purchased in six California cities and over the Internet, identified and quantified all substances in these products [23]. The majority of products (91%) contained either one ($n = 15$) or multiple cathinones ($n = 17$). Of the 14 different compounds identified, MDPV was the most common. Other cathinones detected were buphedrone, ethcathinone, ethylone, MDPBP (an MDPV analog), α-PBP (an α-PVP analog), other designer amines (ethylamphetamine and fluoramphetamine), and 5-IAI (5-iodo-2-aminoindane). Also detected was the antihistamine doxylamine, which had not been previously identified in the US "bath salt" products. In some cases, dramatic differences were found in either total cathinones or synthetic stimulants between products, even with the same declared weight and even between identically named and outwardly appearing products. These findings reveal not only inconsistencies in overall composition of "bath salts" from batch to batch, but significant qualitative and quantitative differences of cathinones and other drugs.

The cannabinoids in "Spice" or "K2" are also heterogeneous and contain a number of unregulated compounds [24]. In a 3-year study involving over 3,000 products described as vegetable material, powders, capsules, tablets, blotter paper,

or drug paraphernalia, forensic testing confirmed the presence of 26 synthetic cannabinoids, 12 designer stimulants, and 5 hallucinogenic-like drugs. Overall, synthetic cannabinoids were significantly more prevalent than all the other designer drugs detected, but precise compositions were unpredictable and often formulated with multiple agents. The synthetic cannabinoids JWH-018, AM2201, JWH-122, JWH-210, and XLR11 were most commonly detected in green vegetable material and powder products. But tablets, capsules, and powders also contained designer stimulants such as MDPV, methylone, and pentedrone (-α-methylaminovalerophenone). Hallucinogenic drugs were rarely detected, but generally found on blotter paper products. Without quality assurance and with deceptive labeling, compounds vary from product to product, from batch to batch and even contain "hot spots" within each packet. This array of untested poly-pharmaceuticals places users at risk of adverse health consequences, and baffles emergency department physicians and staff who are powerless to identify the most significant threat to patient health and select effective antidotes.

4 Role of the Internet

4.1 Drug-Related Content Exists Across Social Media Sites

Drug policy, public health, and substance use research are being challenged by the emergence of the Internet to promote and market NPS anonymously. NPS conventionally were sold in buildings hosting "specialty shops," gas stations, or on the street, venues that limit sales, customer base, and expose the distributors to law enforcement. The Internet has recently evolved into a primary base of operations for NPS, changing the dynamics of marketing, reducing risk to suppliers and buyers, and expanding markets globally without personal contacts. It enables sellers and buyers to directly purchase precursors or products from source countries online.

Social networking sites, drug-themed apps, video- and picture-sharing services, and drug forums are venues for discussions, advertisements, and sales. Open websites distribute non-controlled substances or NPS with nebulous legal or international controls. "Dark net markets" which exist covertly on the Internet and are inaccessible through standard web browsers provide anonymity in buying and selling NPS. In 2013, EMCDDA identified 651 websites selling "legal highs" to Europeans [13–15]. These overt or covert sites may use untraceable currencies such as bitcoin and litecoin. Online, virtual drug markets, international sources, and cryptic websites challenge drug control policies and enforcement [14]. The evidence is insufficient on the role of social media in supply and use of NPS to formulate policies addressing these sites.

4.2 Harnessing Social Media

The Internet may be the driver of NPS, but it can also be used to counter its impact. Social media has been exploited to clarify patterns of drug use, reasons for using, and to improve prevention and treatment outcomes [25]. Regular multilingual qualitative assessments of websites, fora for drugs, and other online resources have been conducted using the Google search engine in eight languages from collaborating countries [26]. An online survey of the UK youth on a website found 31.4% of the respondents reported use of mephedrone (41.4%), *Salvia divinorum* (20.0%), "Spice drugs" (10.7%), methylone (1.4%), naphyrone (NRG) (2.1%), benzylpiperazine (BZP) (2.1%), with 15.7% not knowing what they were consuming. The majority (78.9%) considered these substances to be legal, while 50.8% were aware that illegal substances were included in the product.

A Recreational Drugs European Network (RDEN) project established itself as the first Europe-wide prevention program designed for NPS using novel communication technology-based forms of intervention. Prevention messages have been developed, tested, and disseminated via technological tools such as interactive websites, SMS alert, social networking (Facebook and Twitter), multimedia (YouTube), smartphone applications (iPhone), and virtual learning environments (Second Life). More than 650 NPS products and combinations were identified and relevant information disseminated to target populations. Advice given to the EU, international agencies, and national policy makers concluded that web-monitoring activities are needed to map the spread of NPS and match these data with targeted prevention programs. International partnerships were deemed fundamental for shaping a response to this international challenge.

5 Various Classes of NPS

5.1 Most Common Classes of NPS

There are a variety of NPS which include psychostimulant cathinones and their pyrovalerone derivatives, cannabinoids, hallucinogens, dissociative anesthetics, and opioids. The two most commonly used classes of drugs in the USA are synthetic cannabinoids and cathinones. Synthetic cannabinoids (commonly known as "Spice" and "K2") are synthesized in laboratories and simulate, but are not pharmacologically identical with THC, the main psychoactive ingredient in marijuana.

5.2 *Stimulant "Bath Salts": Cathinones and Pyrovalerone Analogs*

Cathinones, also commonly known as "bath salts," can produce pharmacological effects substantially similar to cathinone, methcathinone, MDMA, amphetamine, methamphetamine, and cocaine. The trace amine phenethylamine, found in the brain, is the backbone for most stimulant-type NPS. Analogs of cathinone and pyrovalerone (a pyrrolidine derivative of cathinone) are relatively easy to prepare and can be chemically fashioned in a myriad of ways to produce stimulants, stimulant-hallucinogens, or "entactogens" or "empathogens." Variants currently available represent a small fraction of conceivable structures. Among the more common ones detected recently in the USA are ethylone > MDMA > methylone > α-PVP > MDPV [11]. Mephedrone, methylone, ethylone, and pyrovalerone analogs, including MDPV, NRG, and α-PVP ("flakka"), are among the chemicals packaged as "bath salts," with substituted cathinones (synthetic derivatives of the stimulant cathinone in the plant khat) the most commonly found. These packets are sold as plant foods, insect repellent, bath salts, stain removers, under brand names such as Bliss, Blue Silk, Cloud Nine, Ivory Wave, and others. The products have been widely available in the UK for several years, but emerged in the USA more recently. They are typically manufactured in Asia and then imported into the USA through mail services, packaged and resold in stores or via the Internet.

Synthetic cathinones are usually insufflated or swallowed in their powder or crystal forms but can also be administered by injection, smoking, gingival delivery, or injection via intramuscular or other routes. Nationwide, typical male and female abusers of these substances range from teenagers to those in their 40s. Users often have an extensive history of drug abuse. Some abusers describe the effects as similar to methamphetamine, ecstasy, and cocaine, and have referred to the substances as "complete crank" while others use the term "fake cocaine" or "fake MDMA." Synthetic cathinones produce amphetamine-, MDMA-, or cocaine-like subjective effects by activating monoamine signaling in the brain and periphery via monoamine transporters (see Glennon and Dukat, this volume). These pharmacological effects are consistent with alterations in dopamine, serotonin, and norepinephrine biology [27]. The subjective effects of synthetic cathinones have previously been reviewed [28, 29], with the current book updating the literature. Clinical symptoms reported by healthcare providers involve the majority of organ systems: psychiatric, neurological, gastrointestinal, cardiac, pulmonary, renal, eyes, ear, nose, and throat. The spectrum of psychoactive effects includes aggression, dizziness, memory loss, seizures, blurred vision, anxiety, hallucinations, depression, dysphoria, euphoria, fatigue, increased energy and decreased concentration, panic, and paranoia. Other reported effects involve palpitations, shortness of breath, chest pain, dry mouth, abdominal pain, anorexia, vomiting, erectile dysfunction, discoloration of the skin, and muscular tension. Negative effects of synthetic cathinone use can include heart attacks, kidney and liver failure, paranoia, panic

attacks, and rhabdomyolysis (breakdown of muscle tissue). They can also produce extreme agitation, which accounts for the steep rise in emergency department mentions. Not all cathinones are the same, with each eliciting a somewhat unique set of health risks and psychoactivities. Use continues, especially among youth, regardless of mounting evidence that they engender risks and adverse consequences, including emergency department mentions, slow clearance of adverse effects, addiction, psychiatric and cardiovascular effects, and even death. A paucity of information exists on the biological, physiological, and toxicological effects of many of these drugs, especially regarding their long-term effects after heavy and prolonged use.

5.3 Synthetic Cannabinoids

Synthetic cannabinoids were initially reported in the USA in December of 2008. The popularity and abuse of these substances and associated products has spread rapidly since then. Synthetic cannabinoids originally were limited to a few compounds (e.g., JWH-018 or 1-pentyl-3-(1-naphthoyl)indole), but others emerged rapidly, in parallel with the explosion of unique designer cathinones. JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol were packaged and sold individually, or dusted on plant material and marketed with misleading designations. More recently identified cannabinoids include XLR11, AB-FUBINACA, and AB-PINACA [30]. Prior to being temporarily placed in Schedule I on March 1, 2011, "K2" and "Spice" were marketed under the guise of "herbal smoking mixtures," "incense," "herbal blends," "air freshener" and designated "not for human consumption." Promoted as legal alternatives to marijuana, they became widely available over the Internet, and sold in gas stations, convenience stores, tobacco and head shops to various populations.

Synthetic cannabinoids are distinctly different from the progenitor phytocannabinoids in *Cannabis sativa* or *Cannabis indica*. They are a conglomerate of a number of compounds designed to mimic the effects of THC in marijuana, and do so by targeting the cannabinoid receptors in brain. However, "Spice" or "K2" synthetic cannabinoids differ from marijuana because of their high potency and full efficacy at CB1 receptors, active metabolites, more robust and persistent effects, and the possibility of activating other non-cannabinoid brain receptors (see Wiley et al., this volume). Each year different cannabinoids emerge in the market, the chemical composition of "Spice" changes, and physiological and toxicological effects remain unknown in this shifting marketplace.

"Spice" has been implicated in numerous medical emergencies and reports of toxicity [30–33]. Symptoms may resolve spontaneously, but range from mild to moderate intoxication, nausea, emesis, weakness, tachycardia, hypertension to psychosis. Several reports have described users in "excited delirium," agitated, and sweating profusely. Severe symptoms include cardiac arrhythmias, myocardial infarction, hyperthermia, psychosis, respiratory depression, flaccid paralysis,

rhabdomyolysis, seizures, coma, and even death. Protocols for emergency responses are "ad hoc" for each individual, with antidotes based not on a large body of pharmacological evidence, but on what is effective for the individual [34, 35]. Synthetic cannabinoids conceivably are addictive but the full spectrum of long-term consequences remains unknown.

5.4 Other New Psychoactive Drugs

The full spectrum of NPS is beyond the scope of this Introduction. Hundreds of other NPS exist, beyond the categories of synthetic cathinones and cannabinoids. These compounds can be classified by structure (e.g., piperazines, benzofurans, 2C-phenethylamines, tryptamines, NBOMe, methoxetamines, diphenidines, and synthetic opioids), or on the basis of their likely psychoactive effects (e.g., psychostimulants, hallucinogenic/psychedelics, cannabimimetics, dissociative anesthetics, and opioid-like) [36]. Each generation of NPS is not designed to improve safety but to increase markets. As these compounds change, as their doses remain unknown, and as the majority have not undergone systematic evaluation in laboratory animals or humans, their use amounts to a global human experiment without informed consent, safety standards, or safeguards [36].

6 Solutions

6.1 Research Informed by Data-Sharing

As witnessed by the opioid epidemic in the early twentieth century, the surge in NPS may overwhelm agencies and healthcare provisions globally before international and comprehensive strategies mature, or if social customs divert attention to different drugs. Synthetic drug producers rapidly adapt to shifting drug trends and legal status by modifying chemical structures to develop legions of new "legal" NPS. The advent of novel compounds is announced instantaneously on social media and other Internet sites, leading to quick adoption and significant profits before the legal gray zone evaporates. Some infrastructure exists to subdue this global challenge to public health; the US DEA, the WHO's Expert Committee on Drug Dependence, the EMCDDA, and the United Nations Office on Drugs and Crime (UNODC) monitor NPS sites. In the USA, a newly established National Drug Early Warning System (NDEWS, http://ndews.org/) uses state-of-the-art methodologies to track emerging drug trends and disseminate information. Yet exploitation of the Internet and other forms of social networks [37–40] for an effective NPS public education/prevention campaign has not materialized on an ambitious grand scale. Nor is there a research infrastructure developed to shape

effective prevention messages that counter the appeal of NPS, and that targets appropriately user demographics, advertising methods, that account for the influence of interpersonal ties, and how to shape and deliver effective messages to educate potential or actual users on NPS.

The core of a prevention campaign is scientific evidence to document the potential consequences to users. Accumulation of such research data has been thwarted by the sheer number of current NPS, the complexity of marketed packets crammed with multiple drugs, and the complex pipelines for broadcasting and marketing NPS to evade legal restraints [41]. Research costs become prohibitive, considering the labor-intensive, time-consuming systematic evaluation of a single drug, multiplied by hundreds of unique substances, the swift emergence of others, and the complexity of exploring multiple drug combinations. These limitations clearly necessitate the use of large-scale biological screening methods and concentration on the most problematic substances. Integrated *real-time* Internet monitoring of trends can streamline the process.

6.2 Monitoring of Social Media

Research on NPS has been slow to adapt to social media as a form of communication. Improved methods of monitoring online social media content, possibly through real-time, well-constructed web analytics, can rapidly identify new trends. Research needs to progress from static identifiers of drug-related social media content to assessing how it affects drug use and how to exploit web analytics to shape prevention. Some examples of media monitoring include an NIDA-sponsored NDEWS which collects data from social media and web platforms to identify illicit drug trends and a program to interrogate the role of social media in drug use, addiction, prevention, and treatment. The EMCDDA also uses sophisticated techniques for monitoring web-based drug trends. Notwithstanding these important achievements, integration at an international level may be necessary as the trends in NPS apparently spread from different focal points in different nations.

6.3 Integrating Sources of NPS Information

Clinical cases, emergency department mentions, poison control centers, forensic lab reports (pathology and toxicology), medical reportage, and drug seizures provide critical information for emergency drug scheduling by international agencies and for public health responses. Is it possible to streamline this laborious, assimilative process in real-time and develop rapid responses in a timely manner? Efficient monitoring and responses would require real-time data entry, web analytics, integration of international databases to assist in developing guidelines for

prioritizing prevention, in addressing medical emergencies, in forensics, and alerting national laboratories of the need for new chemical standards.

7 Gauging Biological Effects

7.1 Screening for and Testing NPS

The majority of NPS have not been subjected to extensive testing in controlled laboratory conditions. New compounds or analogs of known drugs can affect brain function unpredictably. Yet the responses they elicit in humans are gleaned largely from single case reports. An algorithm of key screening strategies in vitro and in vivo can inform the field and provide leads for emergency department antidotes. One effective method for predicting drug mechanisms is by broad automated screening at key elements of brain communication systems, the neuro-receptorome, which includes transporters, receptors, and ion channels [42]. Current neuroscience research has identified the biological substrates of "classical" drugs of abuse, which generally affect these three target categories [27]. With new or hybrid structures, it is important to be receptive to unpredictable targets. For example, the plant-based hallucinogen salvinorin A was presumed to function at the classic hallucinogenic receptor, the serotonin 5-HT_{2A} subtype, until broad receptor screening identified its agonist actions at the kappa opioid receptor [43]. Deciphering the subtleties of target actions require further excavation of receptor agonist/antagonist, transporter substrate/inhibitor, or channel facilitator/blocker properties. Broad screening may also identify molecular targets contributing to side effects [44]. Preclinical behavioral, pharmacological, and physiological screening can offer limited but valuable information on the abuse liability of new compounds and potentially hazardous neurotoxic, cardiovascular, pulmonary, or temperature dysregulating effects, as well as pharmacokinetic properties, rates of metabolism, and pharmacology of metabolites. Psychiatric symptoms, which cannot be modeled adequately in animals, require clinical case reportage.

7.2 The Unknowns

The long-term consequences of continued use of NPS (brain and organ damage, cognitive impairment, addiction, psychosis, and psychiatric symptoms) remain essentially unknown for most drugs and require intense scrutiny, with defined tests that efficiently address this void. Other unknowns include the unpredictable responses elicited by a mixture of three or five compounds sold in the same packet, or in "hot spots" generated by spraying plant material, whether the pharmacological effects of a drug mixture will be additive, synergistic, antagonistic, or whether NPS

synergistically or antagonistically interact with other drugs (e.g., alcohol or medications).

8 Public Education

8.1 Public Awareness and Research

Public awareness of the risks posed by NPS is scant and coordinated; international efforts to exploit social media are embryonic in nature. Public unawareness of specific hazards posed by NPS, of how drugs are approved as prescription medications, and of NPS misinformation proliferated via the Internet is not balanced by compelling counter-evidence. Factual online prevention videos inspire few views in comparison with videos and chat rooms that portray NPS in a positive light. Research on how to develop effective messages and increase traffic to Internet prevention sites is essential to drive scientifically based information towards Internet users at risk. Targeted messages may also offer NPS users opportunities to engage in bidirectional communication, that can tailor, if necessary, information on treatment and recovery support services.

9 Conclusions

The emergence of NPS is challenging for public health and drug policies globally. The novelty of NPS, their ambiguous legal status, ability to evade toxicological tests, swift adaptation to legal restrictions, global Internet marketing, and lack of public awareness are among the key drivers of this twenty-first century phenomenon. Multi-disciplinary research in areas of biology, epidemiology, prevention, and web analytics are needed to develop effective responses in a domain capable of overwhelming current international conventions and national drug control policies. Ultimately, research-guided prevention education will fortify societies against this tidal wave.

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Structure-Activity Relationships of Synthetic Cathinones

Richard A. Glennon and Małgorzata Dukat

Abstract Until recently, there was rather little interest in the structure-activity relationships (SARs) of cathinone analogs because so few agents were available and because they represented a relatively minor drug abuse problem. Most of the early SAR was formulated on the basis of behavioral (e.g., locomotor and drug discrimination) studies using rodents. With the emergence on the clandestine market in the last few years of a large number of new cathinone analogs, termed "synthetic cathinones", and the realization that they likely act at dopamine, norepinephrine, and/or serotonin transporters as releasing agents (i.e., as substrates) or reuptake inhibitors (i.e., as transport blockers), it has now become possible to better examine their SAR and even their quantitative SAR (QSAR), in a more effective and systematic manner. An SAR picture is beginning to emerge, and key structural features, such as the nature of the terminal amine, the size of the α-substituent, stereochemistry, and the presence and position of aromatic substituents, are being found to impact action (i.e., as releasing agents or reuptake inhibitors) and transporter selectivity.

Keywords DAT • Methcathinone • Monoamine transporters • NET • QSAR • SAR • SERT

Contents

1 Introduction 20
2 Early SAR of Cathinone 23
3 The Methcathinone Years 28

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Curr Topics Behav Neurosci (2017) 32: 19–48
DOI 10.1007/7854_2016_41
Published Online: 20 November 2016

4 Current SAR Studies 30
5 Overall Conclusions 41
References 44

1 Introduction

Structure-activity relationship (SAR) studies aim to define the qualitative influence of chemical structure on a given biological action and are focused on identifying *what*, and to what extent, substituents and – where applicable – the stereochemistry of substituents alters activity (i.e., action, potency). Recognized, but not widely acknowledged, is that more than a single SAR might be formulated for a given series of agents [1]. Consider that the behavioral actions of a series of agents might be related to their ability to activate a specific neurotransmitter receptor in the brain. An SAR might be formulated for these agents to bind at the target receptor using an in vitro radioligand binding assay (often referred to as a *structure-affinity relationship* or *SAFIR* study), whereas a different SAR might be formulated for their ability to act as agonists in an in vitro functional assay (e.g., some of the agents that display affinity for the receptor might function as weak partial agonists or antagonists rather than as agonists at the receptor of interest). Additionally, compounds that fail to bind at the receptor might act in an *allosteric* manner. Furthermore, the SARs for these actions might differ from SAR derived from their behavioral actions because some of the agents might be rapidly metabolized in vivo, or might be unable to penetrate the blood-brain barrier to reach their intended target. SAR is essentially linked to the assay from which the biological data were obtained, and the formulated SAR is not always conveniently extrapolated to different pharmacological actions/assays.

Quantitative structure-activity relationship (QSAR) studies attempt to explain *why*/*how* certain structural features influence the actions of a given series of agents. Once SAR studies have been conducted, a QSAR study can be performed using correlational analysis (often referred to as a *Hansch analysis*) to identify whether action/potency within a series of agents might be related to a specific physicochemical property of the substituent being altered. Measures include, but are not limited to, electronic character (as measured by the Taft steric parameter E_s or Hammett σ value), steric size (e.g., volume), overall or specific shape (e.g., Verloop parameters), and lipophilicity (π values). Other parameters consider the molecule as a whole.

Typically, SAR and QSAR studies are not an end unto themselves; rather, they are a means to an end. For example, the results of such studies can be employed (1) in drug design, to enhance the potency or selectivity of an agent; to reduce side (or off-target) effects; to reduce toxicity, or to alter metabolism; and (2) to investigate mechanisms of drug action.

As a general caveat, SAR and QSAR studies should focus on data derived from a common assay – ideally, data generated from the same laboratory and obtained

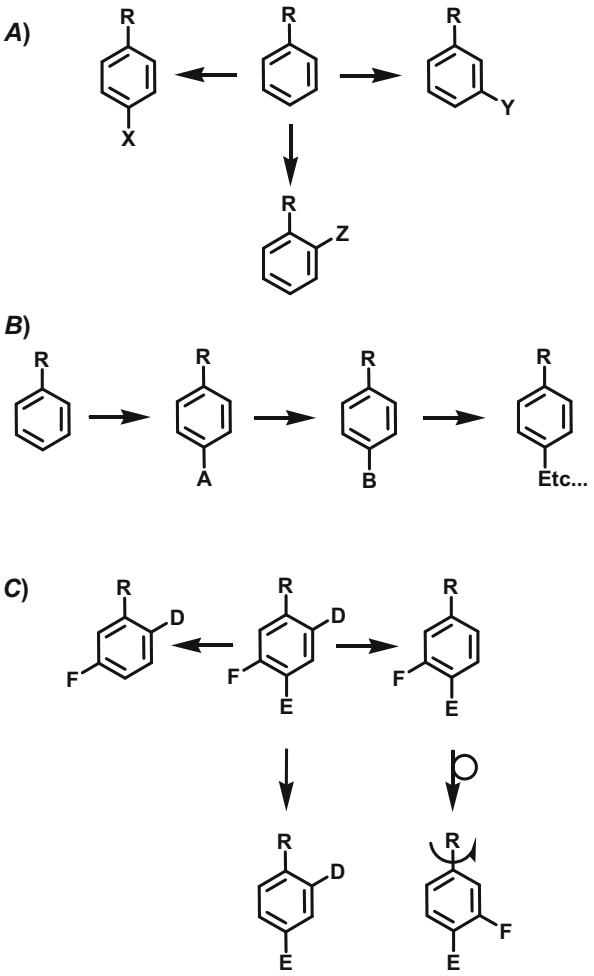

Fig. 1 Examples of three types of SAR studies that can be pursued. Panel (**A**) depicts a nonlinear SAR study where the structure of a molecule is modified one substituent at a time; results can be related back to a common molecule in a systematic manner. Panel (**B**) exemplifies how structures can be related to one another by a single and, usually, position-consistent, structural alteration. Panel (**C**) is a combination of these two approaches and depicts the concept of "deconstruction"

under similar conditions. Employing biological data for one compound from one study with data from (an)other compound(s) from different laboratories or from unrelated studies does not provide reliable SAR results other than from, perhaps, a simple qualitative perspective. The latter approach is not uncommon when a new agent has been identified and attempts are being made to learn something of interest. Certainly, such data are not amenable to QSAR studies. Better yet are data generated where the structure of a molecule is modified one substituent at a time whereby results can be related back to a common molecule in a systematic manner (i.e., nonlinear SAR; see Fig. 1A), or where structures can be related to one another by a single structural alteration (linear SAR; see Fig. 1B). Another approach to SAR is to "deconstruct" a molecule by removing one substituent at a time to identify its influence on a particular action (see Fig. 1C); the latter is actually a combination of the above two approaches.