Arch Toxicol (2016) 90:2421–2444
DOI 10.1007/s00204-016-1812-x

REVIEW ARTICLE

New psychoactive substances: an overview on recent publications on their toxicodynamics and toxicokinetics

Markus R. Meyer[1]

Received: 9 June 2016 / Accepted: 4 August 2016 / Published online: 24 September 2016
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Abstract This review article covers English-written and PubMed-listed review articles and original studies published between January 2015 and April 2016 dealing with the toxicodynamics and toxicokinetics of new psychoactive substances. Compounds covered include stimulants and entactogens, synthetic cannabinoids, tryptamines, NBOMes, phencyclidine-like drugs, benzodiazepines, and opioids. First, an overview and discussion is provided on timely review articles followed by an overview and discussion on recent original studies. Both sections are then concluded by an opinion on these latest developments. This review shows that the NPS market is still highly dynamic and that the data published on their toxicodynamics and toxicokinetics can hardly keep pace with the appearance of new entities. However, data available are very helpful to understand and predict how NPS may behave in severe intoxication. The currently best-documented parameter is the in vitro metabolism of NPS, a prerequisite to allow detection of NPS in biological matrices in cases of acute intoxications or chronic consumption. However, additional data such as their chronic toxicity are still lacking.

Keywords Toxicokinetics · Toxicodynamics · New psychoactive substances · NPS · Review

Abbreviations

2C-B	2,5-Dimethoxy-4-bromophenethylamine
2C-B-FLY	2-(4-Bromo-2,3,6,7-tetrahydrofuro[2,3-f][1]benzofuran-8-yl)ethanamine
2-MPA	2-Methiopropamine
3,5-AB-CHMFUPPYCA	*N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide
3-MeO-PCP	3-Methoxyphencyclidine
3-MMC	3-Methylmethcathinone
4-MEC	4-Methylethcathinone
5-APB	5-(2-Aminopropyl)benzofuran
5F-UR-144	1-(5-Fluoropentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
5-IT	5-(2-Aminopropyl)indole
6-APB	6-(2-Aminopropyl)benzofuran
AB-CHMINACA	*N*-[(1*S*)-1-(Aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide
AB-PINACA	*N*-[(1*S*)-1-(Aminocarbonyl)-2-methylpropyl]-1-pentyl-1*H*-indazole-3-carboxamide
AH-7921	3,4-Dichloro-*N*-[1-(dimethylamino)cyclohexyl]methylbenzamide
AM-1220	(*R*)-(1-((1-Methylpiperidin-2-yl)methyl)-1*H*-indol-3-yl)(naphthalen-1-yl)methanone
AM-2201	1-(5-Fluoropentyl)-3-(1-naphthoyl)indole
AM-2232	1-(4-Cyanobutyl)-3-(naphthalen-1-oyl)indole
AM-694	1-(5-Fluoropentyl)-3-(2-iodobenzoyl)indole

✉ Markus R. Meyer
markus.meyer@med.uni-heidelberg.de

[1] Department of Pharmacology and Pharmacoepidemiology, Heidelberg University Hospital, Heidelberg, Germany

AMB	Methyl(1-pentyl-1*H*-indazole-3-carbonyl)-L-valinate)
AMT	Alpha-methyltryptamine
APICA	*N*-(1-Adamantyl)-1-pentyl-1*H*-indole-3-carboxamide
APINACA	*N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide
CP-47,497-C8	2-[(1*S*,3*R*)-3-Hydroxycyclohexyl]-5-(2-methyloctan-2-yl) phenol)-C8-homologue
DALT	*N*,*N*-Diallyltryptamine
DMAR	4,4′-Dimethylaminorex
FUBIMINA	(1-(5-Fluoropentyl)-1*H*-benzo[d]imidazol-2-yl) (naphthalen-1-yl)methanone
HU-308	[(1*R*,2*R*,5*R*)-2-[2,6-Dimethoxy-4-(2-methyloctan-2-yl) phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]methanol
HU-433	[(1*S*,2*S*,5*S*)-2-[2,6-Dimethoxy-4-(2-methyloctan-2-yl)phenyl]-7,7-dimethyl-4-bicyclo[3.1.1] hept-3-enyl]
JWH-018	1-Pentyl-3-(1-naphthoyl)indole
JWH-133	(6aR,10aR)-3-(1,1-Dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-1*H*-dibenzo[b,d]pyran
JWH-200	1-(2-Morpholin-4-ylethyl) indol-3-yl)-naphthalen-1-yl-methanone
JWH-210	4-Ethylnaphthalen-1-yl-(1-pentylindol-3-yl)methanone
LSD	Lysergic acid diethylamide
MA	Methylphenyl-amphetamines
MAM-2201	4′-Methyl-AM-2201
MDAI	5,6-Methylenedioxy-2-aminoindane
MDMA	3,4-Methylenedioxymethamphetamine
MDMAR	3,4-Methylenedioxy-4-methylaminorex
MDPV	3,4-Methylenedioxypyrovalerone
MT-45	1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine
MXE	Methoxetamine
MXP	Methoxphenidine
PB-22	1-Pentyl-1*H*-indole-3-carboxylic acid 8-quinolinyl ester
Phenibut	Beta-phenyl-gamma-aminobutyric acid
RCS-4	1-Pentyl-3-(4-methoxybenzoyl)indole
RCS-8	1-(2-Cyclohexylethyl)-3-(2-methoxyphenylacetyl)indole
THC	Tetrahydrocannabinol
THJ-018	1-Naphthalenyl(1-pentyl-1*H*-indazol-3-yl)-methanone
WIN 55,212-2	[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-napthalenylmethanone

Introduction

New psychoactive substances (NPS) are an emerging class of compounds, which are mainly consumed as legal and easy available substitute for traditional drugs of abuse such as amphetamine, cannabis, cocaine, heroin, and lysergic acid diethylamide (LSD). More than 400 compounds appeared on the market in the last years, with an annual increase of approximately 100 since 2014 (EMCDDA 2015). The speed at which NPS appear and disappear and particularly the lack of information on their effects and harms are a big challenge.

Pharmacodynamics and pharmacokinetics of drugs have to be studied during the early phase of the drug-development process. Furthermore, since NPS should not be considered as therapeutic drugs (medicinal products for human use) based on a decision of the European Court of Justice (C-358/13 and C-181/14, 2014/07/10), the terms pharmacodynamics and pharmacokinetics should not be used for them. The terms toxicodynamics and toxicokinetics are used instead in this article. However, such studies are usually not done with drugs of abuse or NPS before entering the drug market, but they are necessary to face the above-mentioned challenge. As controlled human studies on the toxicodynamics and toxicokinetics of NPS are not possible for ethical reasons, in vitro approaches or in vivo animal experiments are the preferred way.

The aim of the current article is first to give a timely overview on review articles available on the toxicodynamics and toxicokinetics of NPS subgroups and second to provide an update on recently published research articles dealing with these topics. As the NPS market is highly dynamic, only articles published since January 2015 were considered for this review. A critical and comprehensive view on the field and opinion on selected publications to the topic is provided. Therefore, the present article will cover English-written and PubMed-listed studies published between January 2015 and April 2016 containing information about toxicodynamics and toxicokinetics of NPS. The

findings will be summarized starting with a view on recent review articles and followed by original articles on the NPS subgroups.

Methods

A first search of PubMed for English-written literature published between 01 January 2015 and 15 May 2016 was done using the search terms ((novel psychoactive substance) OR new psychoactive substance) AND ("2015/01/01"[Date - Publication]: "2016/05/15"[Date - Publication]) and ((novel psychoactive substances) OR new psychoactive substances) AND ("2015/01/01"[Date - Publication]: "2016/05/15"[Date - Publication]). A total of 203 articles were identified. For further identifying potentially topic-related review papers and original research papers, a search within the results was done using combinations of the search terms "pharmacology", "toxicology", "toxicokinetic", "toxicodynamic", "pharmacokinetic", "pharmacodynamic", "absorption", "distribution", "metabolism", and "excretion" in any field.

An additional search in PubMed using ((synthetic cannabinoid) AND metabolism) AND ("2015/01/01"[Date - Publication]: "2016/05/15"[Date - Publication]) identified further 95 publications, which were then again searched with the terms given above.

Results and discussion

The search identified 30 review articles and 80 original research papers published in the given time frame, which are topic related and relevant for this review. Some of the original articles were already discussed in former reviews and will not be considered in detail here. In the following, the content of the review articles will be briefly summarized with focus on the key findings. Afterwards, recent research papers are also summarized and discussed. Key aspects of both are given in Tables 1, 2, and 3.

Selected review articles on toxicodynamics and toxicokinetics of NPS published between January 2015 and April 2016

Reviews on single NPS or single NPS classes

Stimulants

Welter-Luedeke and Maurer (2016) briefly reviewed the chemistry, pharmacology, toxicology, metabolism, and toxicokinetics of the ring modified amphetamine derivatives camfetamine, three methylphenyl-amphetamines (2-MA, 3-MA, and 4-MA), 2-methiopropamine (2-MPA), and 5-(2-aminopropyl)benzofuran (5-APB), 6-(2-aminopropyl)benzofuran (6-APB, so-called benzofury), and their *N*-methyl derivatives 5-MAPB and 6-MAPB. They found that despite the scarce scientific data available but considering so-called grey literature (trip reports), this group of NPS should act as central nervous stimulants mainly by increasing the concentration of norepinephrine, dopamine, and serotonin (5-HT) by inducing their release and reuptake inhibition. The toxidrome should therefore include sympathomimetic effects, such as mydriasis, hyperthermia, and hypertension. A main focus of the article was on the metabolism, and authors found that with the exception of 5- and 6-APB, all ring modified amphetamines were extensively metabolized by *N*-demethylation and/or aromatic hydroxylation followed by partial glucuronidation and/or sulfation. Data on chemistry, pharmacology, toxicology, metabolism, and detectability were summarized in a comprehensive table.

The action of amphetamine and related compounds with focus on the monoamine transporter cycle was discussed by Sitte and Freissmuth (2015). The review is of general character on the transporter-dependent pharmacology of amphetamine-like compounds without detailed information on the particular NPS. However, it is one of the most comprehensive articles recently published to review the pharmacology of this kind of stimulants. Figure 1 summarizes the effects on the reverse operation of the neurotransmitter:sodium symporters.

The review by Tyrkko et al. (2016) contains data about basic pharmacology, metabolism, and human toxicology of synthetic cathinones and phenylethylamines and compiled case reports from both fatal and nonfatal poisonings. They concluded, in analogy to Welter-Luedeke and Maurer, that the pharmacodynamic profile of synthetic cathinones is similar to that of traditional stimulants. Overdosing may lead to toxidromes mainly of sympathomimetic and hallucinogenic character including excited delirium and life-threatening cardiovascular effects. They further summarized that cathinones and phenylethylamines are metabolized mainly by the cytochrome P450 (CYP) 2D6 isoenzyme, which might be important for possible drug–drug interactions or polymorphism.

The mechanism of action of various stimulants, amongst them methylenedioxypyrovalerone (MDPV) and alpha-pyrrolidinovalerophenone, was described by Glennon and Young (2016) to be based on a mechanistic dopamine/norepinephrine reuptake inhibition. The desired effects and acute toxicity of the stimulant 4,4'-dimethylaminorex (DMAR) were again found be similar to those seen with other sympathomimetic drugs such as 3,4-methylenedioxymethamphetamine (MDMA) and mephedrone, although

Table 1 Key aspects of selected review articles on the toxicodynamics and toxicokinetics of NPS published between January 2015 and April 2016

References	Time frame covered	Compounds covered	Content in brief
Baumeister et al. (2015)	Until end 2014	Stimulants Cannabinoids Benzodiazepines Dissociatives Hallucinogens	Pharmacodynamic mechanisms, physiological effects, longer-term effects, dependency, and addiction, but also pharmacotherapeutic potential of current major NPS classes
Castaneto et al. (2015)	Until 30 September 2014	Synthetic cannabinoids	In vivo and in vitro pharmacokinetics, analytical methods, and quantification in biological matrices
Cinosi et al. (2015)	Until April 2015	*Mitragyna speciosa* Korth. (Kratom)	Pharmacology, cross-cultural use, and side effects
Coppola and Mondola (2015)	No details given but suspected until end of 2014	DMAR	Minireview about chemistry, pharmacology, and toxicology
Davidson and Schifano (2016)	No details given but suspected until beginning of 2015	Cannabinoids Cathinones Entactogens Stimulants Opioids Tryptamines GABAergic drugs Dissociatives Piperazines	Summarizing known or predicted pharmacology with focus on the potential to be used to treat CNS disorders
Eisenstein and Meissler (2015)	No details given but suspected until end of 2014	THC and synthetic CB2 selective agonists	Effects of cannabinoids on immune function
Fattore (2016)	2010–2015	Synthetic cannabinoids	Psychotic symptoms induced by ingestion of synthetic cannabinoids and their pharmacology and toxicology with particular reference to their psychoactive effects
Glanville et al. (2015)	Until August 2014	DMAR	Desired effects and acute toxicity
Glennon and Young (2016)	No details given but suspected until end of 2015	MDPV Alpha-PVP	Mechanism of action, structure–activity relationships, metabolism, and preclinical behavioural actions
Ho et al. (2015)	Until June 2015	Ethylphenidate	Availability, cost, prevalence, patterns of use, and effects after reviewing both, published and "grey" literature
Katselou et al. (2015a)	No details given but suspected until mid of 2014	5-(2-Aminopropyl)indole	Chemistry, pharmacology, and toxicology, legal status, and analytical methodologies in biological samples
Katselou et al. (2015b)	No details given but suspected until mid of 2014	AH-7921	Chemistry, pharmacology, and toxicology, legal status, and analytical methodologies in biological samples
Liechti (2015)	No details given but suspected until end of 2014	Phenethylamines Amphetamines Synthetic cathinones Piperazines Pipradrols/piperidines Aminoindanes Benzofurans Tryptamines	Summary and brief pharmacological overview on compounds interacting with various monoaminergic targets

Table 1 continued

References	Time frame covered	Compounds covered	Content in brief
Nugteren-van Lonkhuyzen et al. (2015)	Until July 2015	2C-B 4-FA 5-APB 6-APB	Pharmacokinetics and pharmacodynamics
Owen et al. (2015)	Until May 2015	Phenibut	Prevalence of use, desired effects, and adverse effects
Parks et al. (2015)	July 2013 to December 2014	Ethylphenidate	Findings in post-mortem cases, including post-mortem and ante-mortem blood concentrations
Schifano et al. (2015)	No details given but suspected until mid/end of 2014	Synthetic cannabinoids Synthetic cathinones Entactogens/phenethylamines Stimulants Opioids Tryptamines Dissociatives Piperazines GABA-A/B receptor agonists Prescribed medications Psychoactive plants/herbs Performance and image enhancing drugs	Updates for psychiatrists on clinical pharmacology and psychopathological consequences
Siddiqi et al. (2015)	Until June 2014	MT-45	Availability, prevalence of use, and desired/unwanted effects
Sitte and Freissmuth (2015)	No details given but suspected until mid/end of 2014	Amphetamine-like compounds	Differences in the actions with regard to difference from physiological substrates, role of protein kinases in triggering efflux, role of oligomeric arrangement of monoamine transporters, blocking (paradoxical) action on disease-associated mutants of transporter, and influence of lipid composition of the plasma membrane
Su et al. (2015)	No details given but suspected until beginning of 2015	JWH-018 THC	Brief review discussing current research on metabolism of both compounds
Tittarelli et al. (2015)	No details given but suspected until mid/end of 2014	Tryptamines	Comprehensive overview on the chemistry, toxicodynamics, and toxicokinetics
Tyrkko et al. (2016)	Until end of 2014	Cathinones and phenethylamines	Pharmacology, metabolism, and human toxicology as well as case reports from fatal and nonfatal intoxications
van Amsterdam et al. (2015)	No details given but suspected until mid of 2014	Synthetic cannabinoids	Toxicity profile and the adverse effects with special emphasis on psychosis-inducing risk
Warner et al. (2016)	No details given but suspected until mid of 2015	*Mitragyna speciosa* Korth. (Kratom)	Use and prevalence, chemistry and pharmacology, and analysis of plant material and biological biosamples
Welter-Luedeke and Maurer (2016)	No details given but suspected until mid of 2015	Ring modified amphetamine derivatives	Chemistry, pharmacology, toxicology, metabolism, and toxicokinetics
Wood et al. (2015)	Until end of 2014	NBOMeS	Acute toxicity published in case reports
Zanda et al. (2016)	No details given but suspected until mid/end of 2015	Methoxetamine	Pharmacology based on case reports and preclinical findings

Table 1 continued

References	Time frame covered	Compounds covered	Content in brief
Zawilska (2015)	No details given but suspected until beginning of 2015	Synthetic cannabinoids Stimulants	Acute toxicity and negative health and social consequences in recreational and chronic users
Zawilska and Andrzejczak (2015)	2013-beginning of 2015	Synthetic cannabinoids Synthetic cathinones 5-APB and 6-APB DMAR and MDMAR Hallucinogens AH-7921 and MT-45	Pharmacological properties and metabolism, routes of administration, and effects in humans
Zendulka et al. (2016)	No details given but suspected until mid 2015	Endocannabinoid system ligands including synthetic cannabinoids	Interactions between endocannabinoid system ligands and CYPs

Articles are sorted by first author's name

the duration of unwanted effects and "comedown" appear to be longer (Glanville et al. 2015). Interestingly, at the time of the article, DMAR has been detected, along with other drugs, in 27 deaths in Europe.

Coppola and Mondola (2015) summarized pharmacological data about DMAR including a comprehensive table about demographic information, blood and urine concentration of 31 deaths related to its consumption. As no study has evaluated its effects in humans in the reviewed time frame, some in vitro pharmacological studies are discussed and the authors concluded that DMAR is a potent dopamine, norepinephrine, and 5-HT releaser with a low dopamine transporter/serotonin transporter (DAT/SERT) ratio.

Ho et al. (2015) summarized scientific literature and "grey literature" data of ethylphenidate and found that only limited data about the toxicology were available. Symptoms after ingestion are expected to include anxiety, palpitations, paranoia, and chest pain, and its toxidrome should be similar to that of other stimulant drugs, such as its analogue methylphenidate. The article also contains a comprehensive summary of data on dosage, route of administration, and onset of effects. Also post-mortem femoral blood concentrations were reported (110 and 23 µg/L) each after co-ingestion of other drugs (of abuse).

A further report on ethylphenidate was published by Parks et al. (2015) focusing on summarizing findings in post-mortem cases involving its use in East and West Scotland. A highlight of this article is a comprehensive table showing 19 individual cases' information including cause of death and toxicology findings such as post-mortem blood concentrations (ranging from 8 µg/L to >2000 µg/L) and other drugs detected within the individual cases. They also reported two ante-mortem hospital blood and serum sample concentrations to have been 30 and 460 µg/L, respectively.

Finally, Nugteren-van Lonkhuyzen et al. (2015) reviewed the pharmacokinetics and pharmacodynamics of the stimulants 2,5-dimethoxy-4-bromophenethylamine (2C-B), 4-fluoroamphetamine (4-FA), 5-APB, and 6-APB. Each compound was discussed with chapters dedicated to the pharmacokinetics, pharmacodynamic mechanism of action, clinical effects, and toxicology. A table summarizing the monoamine transporter inhibition (IC_{50}) values and ante-mortem and post-mortem blood concentrations was included and very helpful for a quick overview. They concluded that the clinical effects of the reviewed compounds were comparable with common stimulants/entactogens such as amphetamine and MDMA.

Synthetic cannabinoids

Fattore focused in her review on reports suggesting that synthetic cannabinoids may either exacerbate previously

Table 2 Key aspects of selected original papers on the toxicokinetics of NPS published between January 2015 and April 2016

References	Compound(s)	Key aspect(s)
Adamowicz and Lechowicz (2015)	UR-144	Whole-blood concentration 14.6 µg/L 4.5 h after suspected intake
Adamowicz et al. (2016)	3-MMC	Concentrations in 95 cases determined amongst them DUID cases 1–171 µg/L Traffic accidents <1–29 µg/L Drug possession 2–408 µg/L Intoxication <1–1600 µg/L Other <1–61 µg/L
Andersson et al. (2016)	AMB 5F-AMB	In vitro $t_{1/2}$ AMB 1.1 min In vitro $t_{1/2}$ 5F-AMB 1.0 min
Backberg et al. (2015a)	3-MeO-PCP 4-MeO-PCP	Serum concentrations 3-MeO-PCP below 110 µg/L Serum concentrations 4-MeO-PCP below 200 µg/L
Backberg et al. (2015b)	Butyrfentanyl 4-Fluorobutyrfentanyl	Serum concentrations butyrfentanyl 0.9 and 0.6 µg/L Serum concentrations 4-fluorobutyrfentanyl 15.0 µg/L
Backberg et al. (2015c)	3-MMC	Serum concentrations 2–1490 µg/L
Beck et al. (2015)	MDPV	Serum concentrations 1.0 µg/L–1509 µg/L (mean 63.6, median 20)
Caspar et al. (2015)	25I-NBOME	Mainly metabolized in humans/rats via *O*-demethylation but also as a minor step to 2C-I
Dinger et al. (2016a)	Methylenedioxy-derived designer drugs	All showed inhibition of the activity of CYP2D6 Six of CYP1A2 Three of CYP2A6 13 of CYP2B6 Two of CYP2C9 Six of CYP2C19 One of CYP2E1 Six of CYP3A
Dinger et al. (2016b)	Tryptamine-derived NPS	Studies revealed inhibition potential against CYP1A2, CYP2A6, CYP2D6, CYP2E1, and/or CYP3A
Ellefsen et al. (2016)	4-Methoxy-alpha-PVP	In vitro half-life: 79.7 min Intrinsic clearance: 8.7 µL/min/mg Human hepatic clearance: of 8.2 mL/min/kg
Helander et al. (2015)	Diphenidine Methoxphenidine	Serum concentrations diphenidine ranged between 2 and 262 µg/L Serum concentrations MXP 187 and 409 µg/L
Helander et al. (2016)	Acetylfentanyl 4-Methoxybutyrfentanyl Furanylfentanyl	Serum concentration acetylfentanyl 0.6–51.6 µg/L Serum concentration 4-methoxybutyrfentanyl 1.3 to 3.1 µg/L Serum concentrations furanylfentanyl 4.4 to 148 µg/L
Liveri et al. (2016)	MDPV Pentedron	Blood concentrations (post-mortem) MDPV 46 µg/L Blood concentrations (post-mortem) Pentedrone (post-mortem) 160 µg/L
Lukasik-Glebocka et al. (2016), Pasin et al. (2015)	Flubromazolam	Serum concentration of 59 µg/L about 19 h after oral intake of 3 mg

Table 2 continued

References	Compound(s)	Key aspect(s)
Mardal et al. (2016)	WIN 55,212-2	Plasma protein binding 95 % In vitro $t_{1/2}$ 8.3 min $CL_{int,app}$ 75 mL/min/kg CL_{blood} 16 mL/min/kg (well-stirred model) CL_{blood} 20 mL/min/kg (parallel tube model)
Maskell et al. (2016)	Ethylphenidate	Femoral blood concentrations 26 µg/L to 2180 µg/L
Meyer et al. (2015b)	Nine structurally different NPS	Glaucine, JWH-200, mitragynine, and WIN-55,212-2 identified as inhibitors of P-gp activity
Meyer et al. (2016)	Clonazolam Meclonazepam Nifoxipam	Mainly metabolized in humans to amino and acetamino metabolites
Obafemi et al. (2015)	AM-2201	Report on 11 patients who unknowingly ingested brownies laced with AM-2201 Symptoms onset after eating brownie 25-60 min Symptoms duration 2–10 h
Schaefer et al. (2016)	JWH-210 RCS-4	Central volumes of distribution in pig: 0.20 L/kg, and 0.67 L/kg for JWH-210, and RCS-4, respectively Clearances in pig: 0.048 L/min/kg, and 0.093 L/min/kg for JWH-210, and RCS-4, respectively
Schep et al. (2015)	BB-22 AM2233 PB-22 5F-PB-22 JWH-122 (*N*-methylcyclohexyl)	Concentrations (µg/L) at 5.5 and 8.3 h after smoking BB-22: 0.097, 0.094 AM2233: 148, 125 PB-22: 75, 84 5F-PB-22: 85, 91 JWH-122 (*N*-methylcyclohexyl): 9, 13
Thornton et al. (2015)	AB-PINACA	Serum concentrations in a 10-month-old child after chewing a cigarette AB-PINACA at 42 µg/L AB-PINACA *N*-pentanoic acid at 345 µg/L
Zaitsu et al. (2015)	MAM-2201 AM-1220 AM-2232 3-Naphthoylindole 3-(4-Methyl-1-naphthoyl)indole 5-hydroxypentyl metabolite of MAM-2201 COOH metabolite of MAM-2201	Left ventricle, right ventricle, and femoral blood concentrations as well as human metabolic pathways of MAM-2201, AM-1220, AM-2232 after analysing corresponding urine samples

Further details and further publications not listed here can be found in the text. Articles are sorted by first author's name

stable psychotic symptoms or trigger new-onset psychosis (Fattore 2016). She discussed the evidence of psychotic symptoms induced by ingestion of synthetic cannabinoids and their pharmacology and toxicology with particular reference to their psychoactive effects. She found that synthetic cannabinoids with a high affinity and intrinsic activity at cannabinoid receptor (CB) 1 receptors exert stronger physiological and psychological effects than tetrahydrocannabinol (THC), which might partially explain their high potential to trigger psychotic-like symptoms. Hence, intake of synthetic cannabinoids should be considered in patients known to abuse drugs and who are presenting psychiatric symptoms.

Similar findings were published by van Amsterdam et al. (2015) after reviewing the general toxicity profile and the adverse effects of synthetic cannabinoids again with focus on their psychosis-inducing risk. Synthetic cannabinoids were found to cause more frequent and more severe unwanted negative effects, compared to traditional cannabis, which was again mainly attributed to their high potency. They also emphasized studies on the relative risk of synthetic cannabinoids compared with natural cannabis to induce or evoke psychosis. A comment on the article was published by Whiting (2015).

A further overview article on synthetic cannabinoids by Castaneto et al. (2015) included chapters about animal

Table 3 Overview on qualitative metabolism studies on stimulants, entactogens, and synthetic cannabinoids

References	Compound(s) studied	Metabolism studied in
Stimulants and entactogens		
Ellefsen et al. (2016)	4-Methoxy-alpha-PVP	Human hepatocytes
Ibanez et al. (2016)	MDPV	Human urine
Lai et al. (2015)	Seven phenethylamines	Human liver cytosol and microsomes
Negreira et al. (2016)	Ethylphenidate	Human liver cytosol and microsomes
Paul et al. (2015)	Alpha-PHP	Human urine
Swortwood et al. (2016)	Alpha-PVT	Human hepatocytes and human urine
Synthetic cannabinoids		
Andersson et al. (2016)	AMB and 5F-AMB	Human hepatocytes and human liver microsomes
Bertol et al. (2015)	AM-694	Human plasma and urine
Diao et al. (2016a)	FDU-PB-22 and FUB-PB-22	Human hepatocytes, human liver microsomes, and human urine
Diao et al. (2016b)	THJ-018 and THJ-2201	Human hepatocytes
Franz et al. (2016)	3,5-AB-CHMFUPPYCA and 5,3-AB-CHMFUPPYCA	Human liver microsomes
Jang et al. (2016)	XLR-11 and UR-144	Human liver microsomes and human urine
Kanamori et al. (2015)	XLR-11 and XLR-11 degradant	HepaRG cells and human urine
Kim et al. (2016)	EAM-2201	Human liver microsomes and recombinant human CYP
Mardal et al. (2016)	WIN 55,212-2	Human liver microsomes
Vikingsson et al. (2015)	AKB-48 and 5F-AKB-48	Human liver microsomes and human urine
Watanabe et al. (2016)	JWH-018, JWH-073, and AM2201	Cunninghamella elegans
Wurita et al. (2016)	AB-CHMINACA	Human urine
Wiley et al. (2015)	AB-PINACA, AB-CHIMINACA, and FUBIMINA	Mice urine

Articles are sorted by first author's name

pharmacokinetics and human pharmacokinetics, including absorption, distribution, and biotransformation studies. Biotransformation studies performed in vitro with and without confirmation in authentic specimens were discussed, and finally, analytical methods for detection of synthetic cannabinoids in human biosamples were summarized. Findings included that only a few studies were available on absorption/distribution but that synthetic cannabinoids seemed to be distributed quickly into fat tissue, where they could accumulate leading to a rapid decline of parent concentration in blood after administration. This should lead to long detection windows after chronic consumption. Synthetic cannabinoids were also expected to cross the blood–brain barrier and to accumulate in brain tissue as demonstrated by brain-to-blood ratios >1. All metabolism studies demonstrated that synthetic cannabinoids underwent extensive metabolism and followed typical pathways, which were summarized in a comprehensive table.

Zendulka et al. (2016) reviewed the interactions between CYPs and the endocannabinoid system and its ligands. They discussed the role of CYPs in the metabolism of cannabinoids and vice versa the role of cannabinoids in the regulation of CYP activity. The article also contained some publications on synthetic cannabinoids abused as NPS and found in accordance with the other authors that they were extensively metabolized. CYPs-mediated oxidative metabolism formed preferably mono-, di-, and tri-hydroxylated, carboxylated, and *N*-dealkylated metabolites. Interestingly, some of the metabolites still showed a high affinity for the CB1 and/or CB2 receptor.

Concerning the potential of synthetic cannabinoids as therapeutics, Eisenstein and Meissler found that CB2 selective agonists such as JWH-133 (3-(1,1-dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran) may be a promising new class of immunosuppressants and anti-inflammatory drugs that may help in a variety of conditions, such as autoimmune diseases (Eisenstein and Meissler 2015).

Further NPS

Owen et al. (2015) reviewed the desired and adverse effects of phenibut (β-phenyl-γ-aminobutyric acid), a $GABA_B$ agonist, and found effects similar to other gamma-aminobutyric acid receptor agonists such as baclofen and gamma-hydroxybutyric acid. Concerning acute toxicity, no reports are available so far of deaths associated with the use of phenibut.

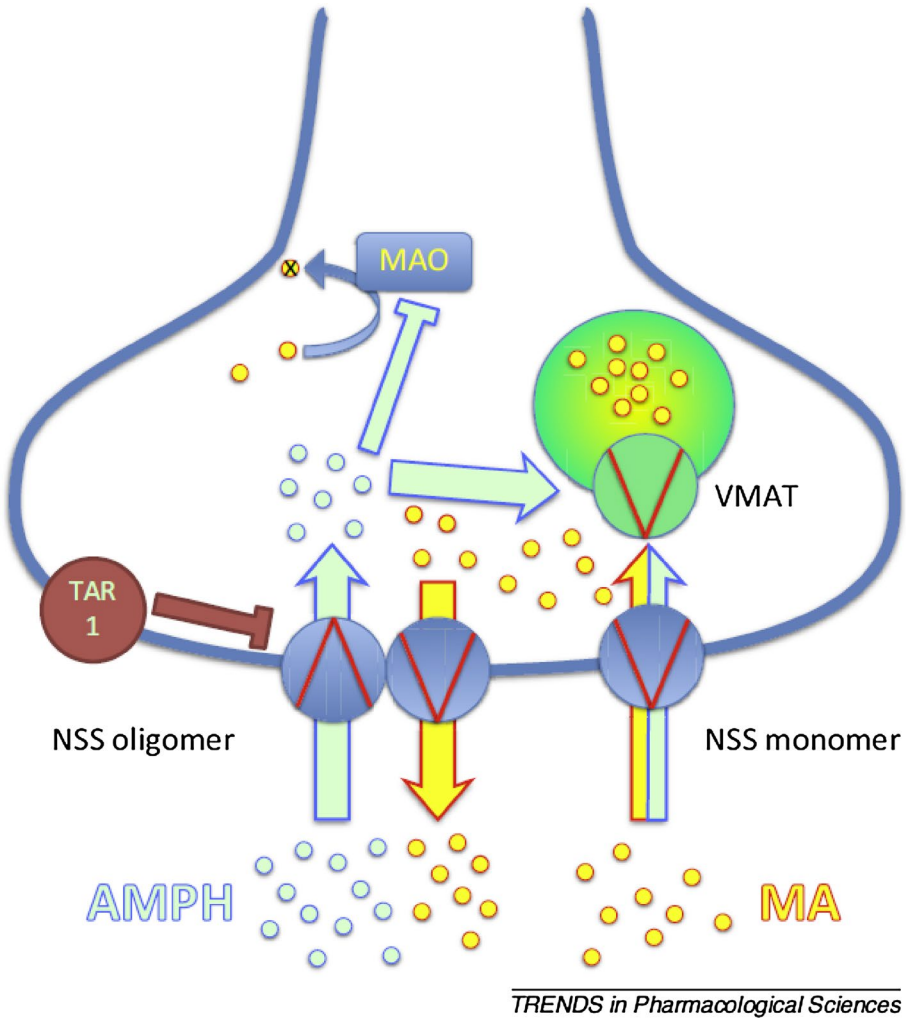

Fig. 1 Molecular effects of amphetamines. Schematic illustration of the effects of amphetamines (AMPH, *light-green circles*) on the reverse operation of neurotransmitter:sodium symporters (NSS). NSS are present in the plasma membrane either as monomers or oligomers (Anderluh et al. 2014). They are physically linked to the vesicles, and this allows their efficient refilling with monoamines (MA, *yellow circles*) (Robertson et al. 2009). The oligomer-based counter-transport model (Seidel et al. 2005) is shown on the left side of the figure and illustrates that the effect of amphetamine relies, at least in part, on an intact oligomer. Amphetamines target the vesicular monoamine transporter (VMAT) and lead to either inhibition and/or reversal of the transport direction to increase the cytosolic concentration of MA, thereby enabling reverse transport. Furthermore, amphetamines inhibit enzymes such as monoamine oxidases A and B (MAO) and thereby prevent the degradation of MA. Abbreviation: TAR1, trace amine receptor 1. Figure and legend taken from Sitte and Freissmuth (2015)

Zanda et al. (2016) reviewed pharmacological effects found in case reports and preclinical studies of the ketamine-like compound methoxetamine (MXE). MXE showed noncompetitive glutamate *N*-methyl-D-aspartate receptor (NMDA) antagonist properties, and the preclinical data highlighted a stimulatory effect of MXE on dopamine neurotransmission within the mesolimbic pathway. The authors also recognized the stimulatory effect of MXE on dopamine neurotransmission within the mesolimbic pathway and its hypothetical rapid antidepressant activity, which should deserve further investigations.

Wood et al. (2015) focused on the acute toxicity of so-called NBOMes, 5-HT_{2A} receptor agonists with an *N*-2-methoxybenzyl moiety, via reviewing 29 published cases. Reported symptoms included tachycardia, hypertension, and agitation/aggression. In five cases, acute kidney injury was reported and 25I-NBOMe has additionally been detected in eight fatalities but has not directly been associated with them.

Siddiqi et al. (2015) searched the scientific literature and "grey literature" to review the availability, use, and desired and unwanted effects of MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine), an opioid-like NPS. They found one paper reporting the acute harms in nine cases after MT-45 intake and desired and unwanted effects were described to be similar to those seen with common opioids and that the opioid antagonist naloxone might be a treatment option.

Katselou et al. (2015a, b) published two reviews on the chemistry, synthesis, analysis in biosamples, and pharmacological and toxicological aspects of 5-IT (5-(2-aminopropyl)indole) and AH-7921 (3,4-dichloro-*N*-[1-(dimethylamino)cyclohexyl]methyl-benzamide), respectively. They summarized information published in NPS-related cases, fatalities, intoxications, or self-reports. In the case of 5-IT, information about the pharmacological and toxicological effects was limited, but AH-7921 was characterized in the 1980s and it was tested as anti-nociceptive

drug. However, in both reviews, the data were presented in text form only and summarizing tables providing a quick overview (e.g. blood concentration, toxidromes) were missing. Nonetheless, they provide a rather comprehensive overview on the available information regarding the toxicodynamics and toxicokinetics of both NPS. 5-IT generally possesses stimulant properties similar to amphetamines and AH-7921 should act similar to morphine.

Warner et al. (2016) reviewed the literature on the toxicodynamics and toxicokinetics of *Mitragyna speciosa* (Kratom), a psychoactive plant. It was reported that mitragynine and 7-hydroxymitragynine should be the primary active alkaloids in the plant. Mitragynine was supposed to have morphine-like effects, but 7-hydroxymitragynine seems to be even four times more potent in its central nervous system stimulant and depressant effects. Mitragynine and 7-hydroxymitragynine are selective and full agonists of μ-opioid subtype receptors, and mitragynine causes analgesic effects via its activity on supraspinal μ- and δ-opioid receptors. Pharmacokinetic data from human and rat including metabolism, terminal half-life, and apparent volume of distribution were summarized in figures and tables.

Nearly in parallel, Cinosi et al. (2015) also summarized pharmacological data of Kratom after reviewing the literature (1967–2015) and over 200 websites, drug forums, and other online resources on Kratom and its main components. Similar conclusions were given here.

Tittarelli et al. (2015) reviewed the NPS group of tryptamines with regard to their effects in relation to routes of administration, their pharmacology and toxicity including papers reporting tryptamine-associated fatalities. Information was taken from published scientific literature but also from nonpeer-reviewed information sources, such as books, government publications, and drug user web forums. The review offered a comprehensive overview starting with the classification of tryptamines based on their chemical structures. Afterwards, a discussion followed on their toxicodynamics and toxicokinetics including metabolism data in relation to the route of administration and chemical structures. Different types of tryptamines were considered such as ring unsubstituted compounds including alpha-methyltryptamine (AMT) and 4-position modified tryptamines such as psilocin. The next chapter summarized effects of tryptamines, which were reported at websites. The next chapters were then dedicated to case reports of intoxications and fatalities involving tryptamines. A final chapter was summarizing some bioanalytical procedures. Each chapter contained tables, providing an excellent overview on the reviewed topics. One overall finding was that toxicodynamics of tryptamines are different depending on their chemical structure. They lead from release of dopamine and its re-uptake inhibition and MAO inhibition in the case of AMT to agonism at 5-HT_{2A} and partial agonism at 5-HT_{1A} receptors in the case of diisopropyl-tryptamine. They all have in part a very long duration of action up to 48 h, and routes of administration are known to include oral ingestion, nasal insufflation, and sublingual application.

Reviews on NPS in general (chronological order)

Liechti summarized the pharmacology of NPS, particularly modulators of monoamine signalling (Liechti 2015). He concluded that stimulants inhibit the DAT and/or norepinephrine transporter (NET) or induce the release of neurotransmitters. Entactogens enhance 5-HT release, and hallucinogens act as agonist at 5-HT_{2A} receptors. The in vitro determined DAT/SERT transporter inhibition ratio could be helpful to predict the effects but also the addiction potential of NPS. Acute toxic and unwanted side effects of serotonergic NPS are expected to include serotonin syndrome, hyperthermia, and seizures. Addiction, agitation, and psychosis are expected for dopaminergic NPS. Besides these modulators of monoamine signalling, consume of CB1 receptor agonists may lead to hypertension, rarely to myocardial infarction and renal failure (Liechti 2015).

In the review by Schifano et al. (2015), several drug classes were introduced and their general toxicodynamic properties were described, partially based on "grey literature". However, the general overview was followed by introducing the latest compounds (such as the synthetic opioids AH-7921 and MT-45) in each group also summarizing their key facts if available. The comprehensive herbs/plants section covered *Salvia divinorum*, *Mitragyna speciosa, Piper methysticum, Ayahuasca, Ibogaine, Hydrangea paniculata, Datura stramonium,* and *Nauclea latifolia*. The authors also raised the issue of prescription drug misuse (e.g. pregabalin or gabapentin). They concluded that the NPS abuse was usually associated with the imbalance of a range of neurotransmitter pathways/receptors and that occurrence of psychosis has been related to numerous NPS classes, which increased central dopamine levels, activating CB1 and 5-HT_{2A} receptors, showed antagonism at NMDA receptors, and which were activating kappa-opioid receptors.

The review by Baumeister et al. (2015) described the pharmacodynamic actions, subjective and physical effects, harmfulness, risk of dependency, and, where appropriate, putative clinical potentials of five NPS groups. One of the highlights is a table summarizing the groups of substances ordered by their primary mechanism of action and containing exemplar agents and effects.

Zawilska and Andrzejczak presented updated information on compounds that have been introduced as replacements of scheduled NPS (Zawilska and Andrzejczak 2015).

They summarized the history of each class with a brief description of the toxicodynamics and toxicokinetics with a focus on metabolism.

Davidson and Schifano briefly summarized the pharmacological properties of nine NPS groups and hypothesized about their possible clinical use (Davidson and Schifano 2016). They concluded that it might be likely that a new stimulant, used at correct dose via the correct route, will appear that has some clinical use in conditions such as attention deficit hyperactivity disorder and narcolepsy.

Concluding opinion

The biggest issue in reading and writing review articles with the topic "NPS" is the high turnover rate of this class of compounds. At the time point, the reviews are published and are accessible to readers, and most of the discussed NPS are already history. They have been disappeared from the market and replaced by congeners, so-called second-class NPS. Therefore, highly frequent update reviews easy to write and to be reviewed by referees and published on an annually basis are highly encouraged and would allow scientist to keep pace with the development and have also their analytical methods updated.

A further issue, which was realized in reading the above-discussed articles, was the missing information on the reviewed time span. Often it was hard to find out until which date publications were considered. The only way in several cases was to look at the submission date (sometimes given by the publisher) and estimate the cut-off date. Therefore, I would encourage scientists writing review articles particularly on such highly dynamic field as the NPS are, to clearly state, which time frame was considered in writing the article.

Selected original research papers on toxicodynamics and toxicokinetics of NPS published between January 2015 and April 2016

The following chapter is divided into paragraphs devoted to different NPS classes based on available published papers since January 2015. The NPS classes are first briefly introduced, and afterwards, latest studies are summarized and discussed. Key aspects of selected papers can also be found as overview in Table 2.

Stimulants and entactogens

This section contains information about compounds acting mainly similar to amphetamine (stimulants) and/or MDMA (entactogens). The most frequent NPS group associated with this pharmacological profile is that of the synthetic cathinones. Simplified, synthetic cathinones exert their action by increasing extracellular levels of norepinephrine, dopamine, and 5-HT (Zawilska and Andrzejczak 2015).

Toxicodynamics

Systematic studies were recently published on the pharmacological profile or toxicity of para-halogenated amphetamines and pyrovalerones (Rickli et al. 2015a), benzofurans (Rickli et al. 2015b), and synthetic cathinones (Araujo et al. 2015). Para-halogenated amphetamines and pyrovalerones were tested for their transporter and receptor interaction profiles using human embryonic kidney 293 cells (Rickli et al. 2015a). Amongst the tested NPS, para-halogenated amphetamines were more serotonergic than non-substituted analogues, which should lead to MDMA-like subjective and acute toxic effects. Pyrovalerone cathinones were found to be potent NET and DAT inhibitors, which is usually associated with stimulant-type effects, toxicity, and a high risk of addiction. Similar studies were done to elucidate the pharmacological profile of benzofurans, which were shown to be monoamine transporter blockers, monoamine releasers, and to interact with 5-HT receptors (Rickli et al. 2015b). Effects should therefore be again similar to MDMA with additional hallucinogenic properties. 2C-B-FLY (2-(4-bromo-2,3,6,7-tetrahydrofuro[2,3-f][1]benzofuran-8-yl)ethanamine) was expected to act as potent hallucinogen with a risk of vasoconstriction leading to ischaemia and hypertension.

Arujo et al. (2015) evaluated the in vitro hepatotoxic effects of methylone, pentedrone, 4-methylethcathinone (4-MEC), MDPV, and MDMA in primary cultured rat hepatocytes via the MTT reduction assay. Pentedrone and MDPV were the most potent agents, with EC_{50} values of around 0.7 mM, which was in the range of MDMA. EC_{50} values of 4-MEC and methylone were 1.29 and 1.18 mM, respectively. However, the study provided no insights into molecular mechanisms by which NPS act hepatotoxic.

Monamine transporter activity was also studied for 5-IT, 6-IT, cis/trans isomers of 3′,4′-methylenedioxy-4-methylaminorex (MDMAR), and cis/trans isomers of DMAR (Marusich et al. 2016; McLaughlin et al. 2015). 5-IT and 6-IT were identified as potent substrates at DAT, NAT, and SERT, but 5-IT showed greater potency for release at DAT than SERT, while 6-IT displayed greater potency for release at SERT than DAT. Additionally, in vivo experiments in mice revealed that 5-IT might have a higher abuse potential than 6-IT. As 5-IT is also a known monoamine oxidase (MAO) A inhibitor (Herraiz and Brandt 2014), particularly co-administration with other monoaminergic drugs might be dangerous. Both MDMAR isomers and both DMAR isomers were more potent substrate releasers at the DAT and NET transporters in rat brain tissue compared to MDMA.

These data are in line with the review of Glanville et al. (2015), who expected the desired and unwanted effects of DMAR to be similar to those of MDMA.

Symptoms in several intoxication cases involving 3-methylmethcathinone (3-MMC) (Backberg et al. 2015c) and MDPV (Beck et al. 2015) were reported as outcome from the Swedish STRIDA project. This project monitors the occurrence of NPS and collects information about associated clinical symptoms and toxicity as well as serum concentration of detected NPS (Helander et al. 2013, 2014). For both drugs, co-ingestion of other drugs was frequently observed, but also mono-intoxications were found. The most frequent clinical symptoms were tachycardia and agitation but also hypertension and hyperthermia. The majority of patients with 3-MMC or MDPV exposure suffered from a more or less severe sympathomimetic toxidrome, which is in line with the previous discussed in vitro studies. However, the high incidence of co-exposure to other drugs made the clinical interpretation difficult in most of the cases.

Toxicokinetics

Interesting key information from case reports (Adamowicz et al. 2016; Adamowicz and Lechowicz 2015; Anne et al. 2015; Backberg et al. 2015c; Beck et al. 2015; Liveri et al. 2016; Maskell et al. 2016; McIlroy et al. 2016; McKeever et al. 2015; Obafemi et al. 2015; Schep et al. 2015; Thornton et al. 2015; Tyndall et al. 2015) such as blood concentrations is given in Table 2.

Backberg et al. (2015c) and Beck et al. (2015) reported useful toxicokinetic data in addition to toxicodynamic data mentioned above after intake of 3-MMC or MDPV. Unfortunately, most of the reported serum concentrations were measured without detailed knowledge about the exact amount of drug taken and the exact time span between intake and sampling. However, this was also an issue in other reports (Liveri et al. 2016; Maskell et al. 2016). In the cases summarized by Maskell et al., even the cause of death was often not drug related.

Metabolism studies published in the beginning of 2015 (Helfer et al. 2015; Negreira et al. 2015; Welter et al. 2015a, b) have already been reviewed (Nugteren-van Lonkhuyzen et al. 2015; Tyrkko et al. 2016; Zawilska and Andrzejczak 2015) and will not be discussed again. A comprehensive overview on recent studies is given in Table 3.

In most cases, metabolism studies were done using different in vitro tools such as human hepatocytes (Ellefsen et al. 2016; Swortwood et al. 2016) or human liver microsomes (HLM) (Lai et al. 2015; Negreira et al. 2016). In some cases, urine sample of abusers was available for confirmation of predicted in vivo metabolites (Swortwood et al. 2016). In contrast to the synthetic cannabinoids discussed below, synthetic cathinones and other stimulants are not that extensively metabolized, and besides several metabolites, also the parent compound could often be found in authentic human urine samples (Ibanez et al. 2016; Paul et al. 2015; Swortwood et al. 2016). However, excretion patterns of drugs are usually dose and time dependent and compounds detected in intoxication cases and overdosing cases may be different from compounds detected after consuming recreational doses or in later excretion phases.

Ellefsen et al. (2016) also studied the HLM half-life (79.7 min), intrinsic clearance (8.7 µL/min/mg), and predicted 4-methoxy-alpha-PVP to be a low-clearance drug with an estimated human hepatic clearance of 8.2 mL/min/kg. 4-Methoxy-alpha-PVP was metabolized similar to structurally related pyrrolidinophenones, including reactions such as multiple hydroxylations, carbonylation to the lactam, ring opening and oxidation reactions, ketone reduction, and *O*-demethylation.

Synthetic cannabinoids

Synthetic cannabinoids or cannabimimetics are abused as alternative to marijuana, and most of them are CB1 receptor agonists with much higher affinity than THC (Castaneto et al. 2015). However, there were also synthetic cannabinoids described to bind at CB1 and CB2 receptors (e.g. 5F-UR-144 (1-(5-fluoropentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclo-propyl)methanone) or mainly at CB2 receptors (e.g. UR-144) (Zawilska and Andrzejczak 2015).

Toxicodynamics

In the following section, selected papers published since January 2015 containing new insights into the toxicodynamics of synthetic cannabinoids will be summarized. Case reports after ingestion of only suspected or unknown amounts or suspected or unknown ingestion time will not be comprehensively discussed in detail here. However, an interesting case report was published by Obafemi et al. (2015) about 11 patients who unintendedly ingested pastries laced with analytically confirmed AM-2201 (1-(5-fluoropentyl)-3-(1-naphthoyl)indole). They showed up with mostly neuropsychiatric and cardiovascular symptoms including memory impairment (10/11) and inappropriate giggling (4/11) as well as light headedness, dry mouth, difficulty focusing/blurring of vision, and sluggishness. Similar symptoms have been reported after ingestion of THC. Unfortunately, no blood concentrations were contained in the report.

Concerning in vitro pharmacology, very interesting results were reported by Aguirre-Rueda et al. (2015) who

found that WIN 55,212-2 ([2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-napthalenylmethanone) increased cell viability and anti-inflammatory response in astrocytes in primary culture and prevented induced cell death. It also increased expression of the antioxidant Cu/Zn superoxide dismutase and was able to prevent induced inflammation. This data implicate neuroprotective effects of WIN 55,212-2 in Alzheimer's disease, which need clinical studies for verification. In contrast, recent studies indicated that CP-47,497-C8 (2-[(1*S*,3*R*)-3-hydroxycyclohexyl]-5-(2-methyloctan-2-yl) phenol-C8 homologue) may cause adverse health effects in users such as induction of inflammation via up-regulation of pro-inflammatory cytokines (Bileck et al. 2016). However, concentrations used in the in vitro experiments were several orders of magnitude higher than common synthetic cannabinoid blood levels, but, as also mentioned by the authors, concentrations may be much higher in particular organs such as lungs after smoking or in the liver and kidneys.

Studies on the cannabinoid receptor binding affinity

Studies on the CB1 receptor binding affinity of synthetic cannabinoids in dependence of terminal fluorination were published by Banister et al. (2015). They studied the in vitro functional activities of JWH-018 (1-pentyl-3-(1-naphthoyl)indole), UR-144, PB-22 (1-pentyl-1*H*-indole-3-carboxylic acid 8-quinolinyl ester), and APICA (*N*-(1-adamantyl)-1-pentyl-1*H*-indole-3-carboxamide), and their respective terminally fluorinated analogues AM-2201, XLR-11, 5F-PB-22, and STS-135 at human CB1 and CB2 receptors. They all were found to have agonist activity at CB1 and CB2 receptors, but the fluorinated analogues showed an approximately 2 to 5 times increased CB1 activity. All tested drugs also showed a dose-dependent hypothermia (PB-22 > 5F-PB-22 = JWH-018 > AM-2201 > APICA = STS-135 = XLR-11 > UR-144) in rat but without increased potency of the fluorinated analogues.

Instead of an in vitro set-up, Paulke et al. used an in silico approach (quantitative structure–activity relationship model, QSAR) to determine the CB1 affinity of synthetic cannabinoids and predicted the K_i values of sixteen compounds to range from 20 nM for RCS-8 (1-(2-cyclohexylethyl)-3-(2-methoxyphenylacetyl)indole) to 468 nM for RCS-8 4-methoxy isomer (Paulke et al. 2016). THC was reported to have a CB1 receptor K_i of about 40 nM. This interesting approach, very common in the field of medicinal and pharmaceutical chemistry, seems to offer a simple way to get a first idea on the possible biological activity of synthetic cannabinoids. However, no conclusions about bioavailability and actual intrinsic activity should be made based on these data.

That intrinsic activity is often rather complex to understand was demonstrated by Smoum et al. (2015) for the two synthetic cannabinoid enantiomers HU-433 ([(1*S*,2*S*,5*S*)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]) and HU-308 ([(1*R*,2*R*,5*R*)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl) phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]methanol). They both were specific CB2 agonists, but whereas HU-433 was much more potent than HU-308 in its CB2-mediated anti-osteoporotic and anti-inflammatory effects, its binding to the CB2 receptor is substantially lower compared with HU-308. A molecular-modelling analysis suggested that HU-433 and HU-308 have two different binding conformations within CB2, with one of them possibly responsible for the affinity difference. Hence, different ligands may have different orientations relative to the same binding site.

Wiley et al. (2015) examined the in vitro and in vivo pharmacology of AB-CHMINACA (*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide), AB-PINACA (*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-1-pentyl-1*H*-indazole-3-carboxamide), FUBIMINA ((1-(5-fluoropentyl)-1*H*-benzo[d]imidazol-2-yl)(naphthalen-1-yl)methanone), and AM-2201 including binding and activation of CB1 receptors and pharmacological equivalence with THC discrimination in mice. AB-CHMINACA, AB-PINACA, and FUBIMINA bound to and activated CB1 and CB2 receptors, and produced locomotor suppression, anti-nociception, hypothermia, and catalepsy. They also substituted for THC in THC discrimination. AB-CHMINACA and AB-PINACA also exhibited higher efficacy than most known full agonists of the CB1 receptor. The rank order of potency correlated with their CB1 receptor binding affinities was as follows: FUBIMINA < THC < AB-PINACA < AB-CHMINACA. AB-CHMINACA and FUBIMINA were also identified to be full dual CB1/CB2 agonists, but FUBIMINA exhibited several-fold greater CB2 receptor selectivity than AB-CHMINACA.

Toxicokinetics

Key information from case reports (Adamowicz and Lechowicz 2015; McIlroy et al. 2016; McKeever et al. 2015; Obafemi et al. 2015; Schep et al. 2015; Thornton et al. 2015; Tyndall et al. 2015) such as blood concentrations if available is given in Table 2.

Karinen et al. (2015) reported blood concentrations of APINACA (*N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide), 5F-APINACA, UR-144, and UR-144 degradant

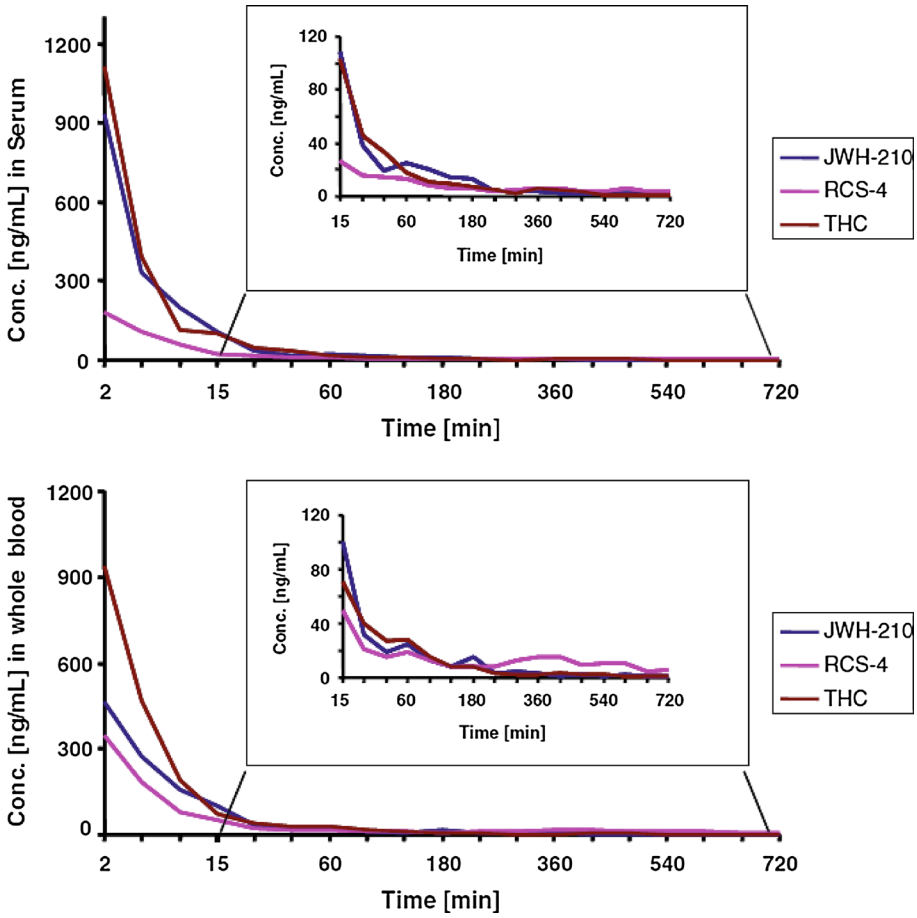

Fig. 2 Concentration time profiles of JWH-210, RCS-4, and THC in pig serum (*upper part*) and in whole blood (*lower part*). Figure and legend taken from Schaefer et al. (2015)

in driving under the influence of drug (DUID) cases and compared values to concentrations previously reported for other synthetic cannabinoids. 5F-APINACA and APINACA concentrations were 900 and 2200 µg/L, 6500 and 240 µg/L, and 2200 and 24,500 µg/L in three different cases. 5F-APINACA was determined at 5300 µg/L, UR-144 at 220 µg/L and 470 µg/L, and its UR-144 degradant at 150 µg/L. One highlight of the paper was the summary of previously reported synthetic cannabinoid concentrations reported in DUID cases, intoxication cases, autopsy cases, and pharmacokinetic studies. Finally, authors pointed out the need of more reports on concentrations of synthetic cannabinoids from different case types. The knowledge of concentration ranges and concentrations in single cases might be helpful to set up appropriate analytical methods and to evaluate possible harmful concentration ranges.

Zaitsu et al. (2015) quantified MAM-2201 (4′-methyl-AM-2201), AM-1220 ((*R*)-(1-((1-methylpiperidin-2-yl) methyl)-1*H*-indol-3-yl)(naphthalen-1-yl)methanone), AM-2232 (1-(4-cyanobutyl)-3-(naphthalen-1-oyl) indole), and some of their metabolites in post-mortem plasma. Based on the values, defluorination was attributed as the major metabolic pathway for MAM-2201, and *N*-dealkylation as a common but minor pathway for naphthoylindole-type synthetic cannabinoids, which is in line with previous findings (Castaneto et al. 2015). Quantitation results also revealed site differences between left heart, right heart, and femoral post-mortem plasma concentrations (e.g. MAM-2201 85.8, 30.7, 16.3 µg/L, respectively), and not surprisingly, post-mortem redistribution was suggested as reason.

Schaefer et al. (2015) developed an interesting pig model for assessing toxicokinetics of NPS, particularly synthetic cannabinoids. Toxicokinetic data following intravenous administration of a mixture of 200 µg/kg body mass dose each of JWH-210 (4-ethylnaphthalen-1-yl-(1-pentylindol-3-yl)methanone), RCS-4 (1-pentyl-3-(4-methoxybenzoyl) indole), and THC were studied. Example concentration time profiles of JWH-210, RCS-4, and THC in pig serum are shown in Fig. 2. Following analysis of urine samples, only THC could be detected as the others were most probably completely metabolized prior to excretion. A further publication by the same authors aimed to demonstrate whether domestic pigs can be used for prediction of human toxicokinetics of synthetic cannabinoids after, unfortunately only, i.v. administration of JWH-210 and RCS-4 (Schaefer et al.

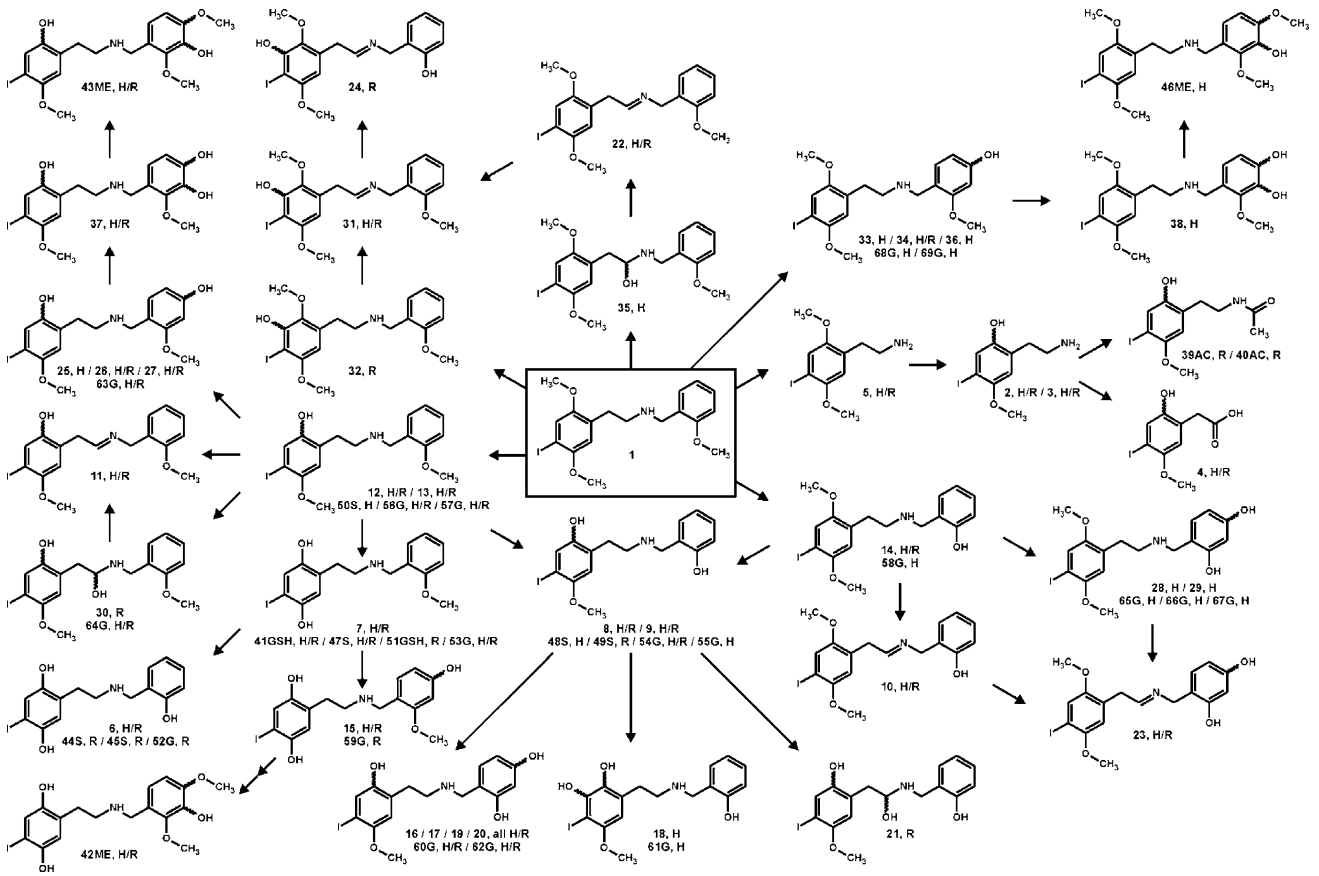

Fig. 3 Metabolic pathways of 25I-NBOMe in human (H) and rat (R). Phase II metabolites: glucuronides (G), sulphates (S), glutathione conjugates (GSH), acetyl conjugates (AC), *O*-methyl conjugates (ME). Undefined position of O-demethylation or hydroxylation indicated by tildes. Figure and legend taken from Caspar et al. (2015)

2016). The population PK analysis revealed that a three-compartment model described best the toxicokinetic data of the tested synthetic cannabinoids. Additional studies with THC showed that pigs together with toxicokinetics modelling may serve as a suitable predictive tool.

Concerning metabolism, studies published in the beginning of 2015 (Erratico et al. 2015; Gandhi et al. 2015; Holm et al. 2015a, b; Sobolevsky et al. 2015; Thomsen et al. 2015; Wohlfarth et al. 2015) have already been reviewed (Castaneto et al. 2015; Zendulka et al. 2016) and will not be discussed again. However, most studies were again published using in vitro tools (Andersson et al. 2016; Diao et al. 2016b; Franz et al. 2016; Mardal et al. 2016) but also using urine specimens from abusers (Bertol et al. 2015; Wurita et al. 2016). An overview on these studies is given in Table 3. All studies implicated that synthetic cannabinoids were extensively metabolized and most probably excreted mainly as metabolites in urine. In vitro metabolism data on the following synthetic cannabinoids have become available recently: AMB (methyl (1-pentyl-1*H*-indazole-3-carbonyl)-L-valinate)) and its 5-fluoro analogue 5F-AMB using human hepatocytes (Andersson et al. 2016), THJ-018 (1-naphthalenyl(1-pentyl-1*H*-indazol-3-yl)-methanone) and its 5-fluoro analogue THJ-2201 using human hepatocytes (Diao et al. 2016b), 3,5-AB-CHMFUPPYCA (*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide) using pooled HLM (Franz et al. 2016), and WIN 55,212-2 using pooled HLM (Mardal et al. 2016). AB-CHMINACA and AM-694 (1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole) metabolism were studied using human urine samples (Bertol et al. 2015; Wurita et al. 2016). Besides qualitative metabolism, Andersson et al. and Mardal et al. also reported in vitro metabolic stability data expressed as in vitro half-life values, which were 1.1 min and 1.0 min for AMB and 5F-AMB, respectively, and 8.3 min for WIN 55,212-2 (Andersson et al. 2016; Mardal et al. 2016). Mardal et al. also determined the plasma protein binding of WIN 55,212-2 to be 95 % in vitro.

Tryptamines, NBOMes, and phencyclidine-like drugs

The desired recreational effects of tryptamines, visual hallucinations and alterations in sensory perception, result from agonist activities at 5-HT_{2A} receptors and serotonin transporter inhibition (Schifano et al. 2015). Similar effects and a similar pharmacological profile, full agonism at 5-HT_{2A} but also 5-HT_{2C} receptors, are known for *N*-benzyl-substituted 2C-phenylethylamines also known as NBOMes (Braden et al. 2006).

Phencyclidine-like drugs or dissociative drugs are characterized mainly by NMDA receptor antagonism besides again 5-HT_{2A} agonism, and affinity for different opioid receptors (Davidson and Schifano 2016; Schifano et al. 2015).

Toxicodynamics

The only data available were from analytically confirmed nonfatal intoxication cases involving diphenidine, methoxphenidine (MXP), 3-MeO-PCP (3-methoxyphencyclidine), or 4-MeO-PCP (Backberg et al. 2015a; Helander et al. 2015). The effects in cases involving diphenidine or MXP were similar to those reported for related drugs such as ketamine and MXE and included hypertension, tachycardia, and anxiety (Helander et al. 2015). 3-MeO-PCP intake leads to similar symptoms, but in both studies poly-substance use was found to be common (e.g. poly-drug use $n = 52$, 3-MeO-PCP only $n = 7$) and observed effects could often not exclusively be attributed to one single compound (Backberg et al. 2015a; Helander et al. 2015). Thus, it was difficult for authors to identify a unique toxidrome related to methoxylated PCP analogues as well as diphenidine or MXP.

Dinger et al. aimed to evaluate tryptamine-derived NPS for their in vitro inhibition potential towards human CYP isozymes (Dinger et al. 2016b). In addition, the inhibition potential of 5-methoxy-*N,N*-diallyltryptamine against CYP1A2 was confirmed in vivo using rats and caffeine as test substrate. They could show that nearly all tested drugs showed inhibited activity of CYP isoforms. For example, diallyl tryptamines inhibited CYP2D6 activity similar to paroxetine and quinidine and CYP1A2 activity comparable to fluvoxamine. The influence of 5-methoxy-*N,N*-diallyltryptamine on the caffeine metabolism in rats was shown to be consistent with in vitro results. They finally concluded that the CYP inhibition by tryptamine-derived NPS might be clinically relevant, but clinical studies should be encouraged to explore this further.

Toxicokinetics

The observed serum 3-MeO-PCP concentrations in the study by Backberg et al. were typically below 110 µg/L and those of 4-MeO-PCP typically below 200 µg/L (Backberg et al. 2015a). This is in line with the assumed lower affinity of 4-MeO-PCP on the glutamate NMDA receptors (Roth et al. 2013). Observed diphenidine concentration in serum ranged between 2 and 262 µg/L and the MXP values in two cases were 187 and 409 µg/L (Helander et al. 2015). Sampling was typically done within a few hours of admission to the emergency department, but exact time of intake and dosage was of course unknown in all cases.

Studies are available reporting the metabolism of 25B-NBOMe and 25I-NBOMe (Boumrah et al. 2016; Caspar et al. 2015), methoxypiperamide (Meyer et al. 2015a), *N,N*-diallyltryptamine (DALT) and 5-methoxy-DALT (Michely et al. 2015), and diphenidine (Wink et al. 2016). All of these studies were done to demonstrate the toxicological detectability in human urine samples by mass spectral techniques after elucidation of their in vivo and/or in vitro metabolism. Also data were included on the in vitro involvement of CYP isoforms in the initial metabolic steps (Caspar et al. 2015; Meyer et al. 2015a; Michely et al. 2015; Wink et al. 2016). Contributions were as follows: 25I-NBOMe was initially metabolized by CYP1A2, CYP3A4, CYP2C9, and CYP2C19; methoxypiperamide by CYP1A2, CYP2C19, CYP2D6, and CYP3A4; DALT and 5-methoxy-DALT by CYP2C19, CYP2D6, CYP1A2, and CYP3A4; and diphenidine by CYP1A2, CYP2B6, CYP2D6, CYP2C9, and CYP3A4. As different CYPs were found to be involved in all initial metabolic steps, genetic polymorphisms and/or interactions should be of minor relevance. In the metabolism study on 25I-NBOMe by Caspar et al., an impressive number of 68 in vivo metabolites could be identified, which are summarized in Fig. 3 (Caspar et al. 2015). Besides studies in rat urine samples after controlled administration, the authors also studied human urine samples collected in an intoxication case after unknown dosage. However, *O*-demethylation seemed to be the main metabolic pathway and *N*-demethoxybenzylation to 2C–I only a minor one in humans but also in rats.

Benzodiazepines and opioids

So-called designer benzodiazepines have become of interest as NPS particularly in the last two years and were represented by compounds such as diclazepam, flubromazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazolam, nifoxipam, and meclonazepam (Lukasik-Glebocka et al. 2016; Meyer et al. 2016; Moosmann et al. 2015). Some were initially synthesized as drug candidates but were never further approved. Chemistry and pharmacology were described already in the early 1970s for compounds bearing; for instance, the 1,4-benzodiazepine skeleton and detailed structure activity relationships studies are available (Sternbach 1971).

A similar phenomenon could be observed for the so-called designer opioids such as the potent opioids MT-45, AH-7921, and some fentanyl analogues. They were associated with severe adverse effects and fatalities (Backberg et al. 2015b; Helander et al. 2016; Siddiqi et al. 2015). Most of these drugs have been developed decades ago but never approved as pharmaceuticals and have now found their way into the laboratories of drug designer. An example is the group of piperidylidene-2-sulfon(cyan)amide derivatives developed in the 1980s (Knaus et al. 1989), which are considered as the next big thing in the world of opioid-like NPS. They were also briefly pharmacologically tested using the phenylquinone writhing test (Collier et al. 1968), which lead to the identification of compounds with an over one thousand times higher analgesic agonist activity than morphine (Gussow 2016).

Toxicodynamics

Lukasik-Glebocka recently described a case of a severe intoxication after intake of flubromazolam in a 27-year-old man, showing deep coma, bilateral pinpoint unreactive pupils, acute respiratory failure, hypotension, and hypoxic ischaemic changes in the central nervous system (Lukasik-Glebocka et al. 2016). Administration of flumazenil improved patient consciousness and after further treatment including mechanical ventilation, the patient could be transferred to another department after the ninth day of hospitalization. Authors stated that intoxications with flubromazolam and related compounds might lead to prolonged, severe intoxication associated with coma, hypotension, and rhabdomyolysis.

Backberg et al. (2015b) reported about five intoxications involving butyrfentanyl or 4-fluorobutyrfentanyl after use of nasal spray or powder. Very little is known about their clinical and adverse effects, but Backberg et al. mentioned that "butyrfentanyl was indicated to be less potent than fentanyl, and fluorinated fentanyl analogues to be generally less potent than their nonfluorinated parent compounds" (Backberg et al. 2015b; Cole et al. 2015). The symptoms observed in those cases included in part severe respiratory depression and loss of consciousness. One issue arising was mislabelling of the purchased NPS preparations. Two products were sold and labelled as butyrfentanyl but mainly contained the more potent fentanyl. Hence, dose adaption based on recommendations in Internet forums may lead to intoxications and even fatalities due to unintended overdosing. The same group reported about 14 intoxications involving acetylfentanyl, 4-methoxybutyrfentanyl, and furanylfentanyl (Helander et al. 2016). Again, clinical features included respiratory depression and decreased consciousness.

Toxicokinetics

Quantification of flubromazolam in a severe intoxication case showed serum values at 59 µg/L about 19 h after ingestion of 3 mg dose (Lukasik-Glebocka et al. 2016). Backberg et al. reported serum concentrations of butyrfentanyl and estimated serum concentrations of 4-fluorobutyrfentanyl in intoxications cases of 0.9 and 0.6 µg/L and 15.0 µg/L. It should be considered that both cases involving butyrfentanyl and fentanyl were also detected at serum concentrations of 4.3 and 10.2 µg/L. The exact amount and time of ingestion was not known in all cases. The second report from the group described serum acetylfentanyl concentrations ranging from 0.6 to 51.6 µg/L, serum 4-methoxybutyrfentanyl concentrations ranging from 1.3 to 3.1 µg/L, and furanylfentanyl serum concentrations ranging from 4.4 to 148 µg/L (Helander et al. 2016). Application was again either using nasal sprays or tablets.

Meyer et al. (2016) reported about the metabolism and main human urinary metabolites of the nitrobenzodiazepines clonazolam, meclonazepam, and nifoxipam. The urine was taken from routine toxicological analysis and cases from acute NPS intoxication presenting in emergency departments and intensive care units but without knowledge of the dose or the time of sampling after ingestion. They found that all studied drugs were extensively metabolized and mainly excreted as their amino and acetamino metabolites, which were also recommended to be suitable analytical targets. A further finding of their study included the recommendation to perform in vitro metabolism studies if in vivo studies are not possible, always including necessary co-substrates for expected reactions. In the case of the nitrobenzodiazepines, particularly acetyl-CoA and suitable enzyme sources containing *N*-acetyltransferases should be added to observe the main metabolic reactions.

Toxicodynamic and/or toxicokinetic studies covering several classes of NPS

Some studies are available describing the acute NPS toxicity (Dines et al. 2015; Liakoni et al. 2015), their managements (Kersten and McLaughlin 2015), NPS consume amongst recently discharged psychiatric inpatients (Stanley et al. 2016), or NPS-related fatalities (McAuley et al. 2015). Liakoni et al. collected data about the acute toxicity of NPS besides traditional recreational drugs in cases presented at their emergency department. Over the period of one year, only two cases involving NPS (2C-B and pentylone) have been observed. The study by Dines et al. summarized further data on all acute drug toxicity presentations to

emergency rooms in sixteen centres across Europe (Dines et al. 2015). NPS were involved in 5.6 % of these cases, but the "top five" of involved drugs were traditional drugs of abuse such as heroin, cocaine, and cannabis. In most of the cases, serious clinical features were not seen, but a total of 27 fatalities (out of 5529 cases) associated with opiate use occurred. However, neuropsychiatric and cardiovascular toxicities were amongst the most common features, which may lead to severe and even life-threatening events (Kersten and McLaughlin 2015). Management strategies were based on supportive and symptomatic care due to the limited data on alternatives.

Information on health risks related to NPS consumption and their pharmacology, toxicity, management, detection, and legal status was comprehensively discussed in a continuing education manuscript (Kersten and McLaughlin 2015), which is highly recommended to interested readers.

In 2012, 23 deaths associated with NPS consume were identified in Scotland and the most frequently NPS involved was phenazepam (McAuley et al. 2015). Further NPS-implicated deaths were most probably due to stimulant abuse such as AMT and 6-APB. However, usually more than one drug was recorded, making the interpretation difficult. Typically involved combinations were opioids and benzodiazepines. More details on characteristics of individuals involved and circumstances surrounding each NPS-implicated death can be found in the original paper (McAuley et al. 2015).

In vitro studies on the CYP inhibition potential of methylenedioxy (MD)-derived designer drugs and NPS were published by Dinger et al. (Dinger et al. 2016a). They found that most of the MD-derived drugs showed inhibition against CYP2D6 activity even in the range of the well-known CYP2D6 inhibitors quinidine and fluoxetine (Dinger et al. 2016a). Drugs bearing an additional beta-keto moiety showed additional inhibition of the activity of CYP2B6, 5,6-MD-DALT of CYP1A2 and CYP3A, and MDAI (5,6-methylenedioxy-2-aminoindane) of CYP2A6, all in the range of clinically relevant inhibitors. Further details are contained in Table 2. However, clinical studies are of course needed to see the actual impact of these drugs on the enzyme activities. Concerning possible P-glycoprotein interactions, the NPS glaucine, JWH-200 (1-(2-morpholin-4-ylethyl)indol-3-yl)-naphthalen-1-ylmethanone), mitragynine, and WIN 55,212-2 could be identified in Caco-2 transport studies as nontransported substrates, but inhibitors of P-gp activity (Meyer et al. 2015b). Thus, drug–drug or drug–food interactions should be very likely for these compounds.

Interestingly, Albadareen et al. (2015) reported about a case of an adolescent who developed prolonged encephalopathy after ingesting methylenedioxybenzylpiperazine. Authors assumed that the prolonged encephalopathy may be in part due to CYP2D6 inhibition caused by the NPS. These findings are somehow supported by the in vitro data discussed above where methylenedioxybenzylpiperazine was found to have an IC_{50} value of 26 μM on CYP2D6

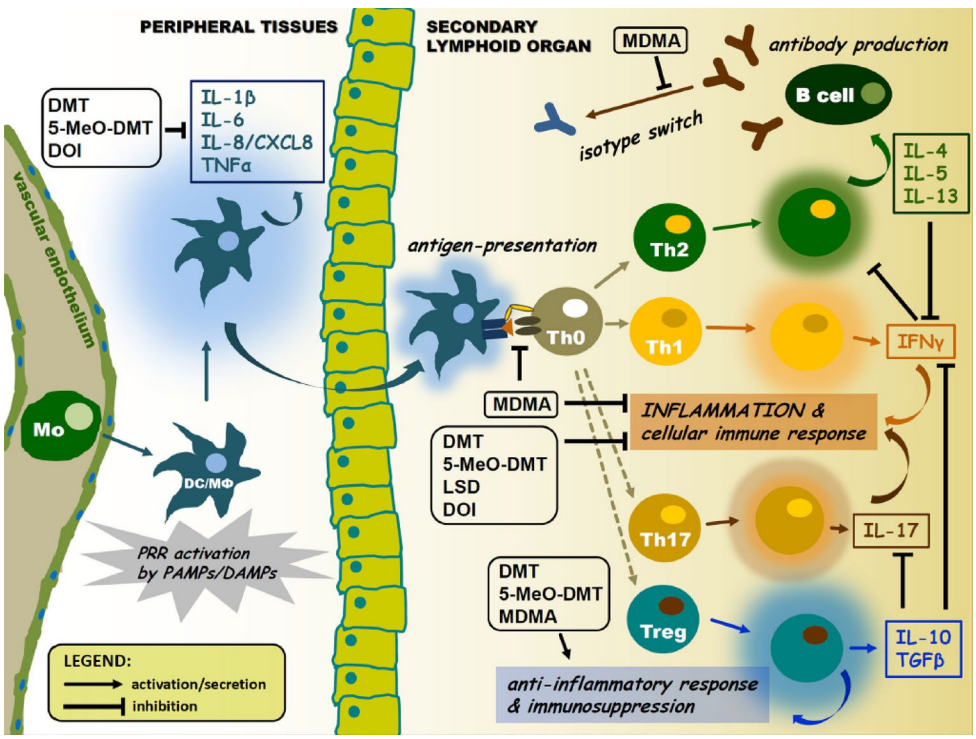

Fig. 4 Pharmacological modulation of APC and lymphocyte cytokine signalling by psychedelics. Psychedelics can significantly interfere with immune cell cytokine profiles. This may lead to suppression of antigen presentation and inflammatory cytokine and chemokine secretion, as well as inhibition of isotype switching or elevated levels of anti-inflammatory cytokines in the tissue environment. *Arrows* represent activation or migration of cells, or secretion of cytokines. *T-arrows* mean inhibition. Abbreviations: Mo, monocyte; DC, dendritic cell; MΦ, macrophage; coloured halos around cells represent activation/cytokine secretion. Figure and legend taken from Szabo (2015)

activity (Dinger et al. 2016a). The patient's response to high dose corticosteroids further suggests an additional inflammatory effect.

Finally, the immunomodulatory potential of classic serotonergic psychedelics, including some tryptamines and LSD, was discussed in a recent paper (Szabo 2015). Drugs modulating the activity of 5-HT_1, 5-HT_2, and sigmar-1 receptors seem to be very promising candidates in many diseases with chronic inflammatory aetiology and pathology, such as atherosclerosis, psoriasis, and rheumatoid arthritis. The pharmacological modulation of APC and lymphocyte cytokine signalling is shown in Fig. 4.

Concluding opinion

Controlled in vivo studies on the toxicodynamics and toxicokinetics of NPS are usually not available due to ethical reasons and due to lack of further data such as pre-clinical toxicology data. In part, such data were elucidated using in vitro studies, but their impact on human is still questionable particularly as, for instance, the amount of NPS ingested by users is often not known as it is for therapeutics or using in vivo animal studies with the difficulty of inter-species differences. Hence, dose-dependent effects are hardly to predict and such data have to be extracted from various papers reporting the acute toxicity and symptoms after NPS intake. Again, the dosage and time point of intake is often unknown even in these cases. Blood or serum/plasma concentrations measured in samples taken very close to the admission to the hospital as it is done in the STRIDA project can help to correlate concentrations and effects. However, one big issue is often the co-consumption of NPS with other NPS or drugs of abuse and/or medicaments, which makes the interpretation complicate. Such co-consumption is also asking for studies predicting possible interactions such as metabolizing enzyme inhibition or inhibition of drug transporters.

General pharmacological profiles were also studied in vitro for particular NPS or NPS groups and are very helpful to get a first idea on their possible biological activity. However, further data, particularly their chronic toxicity, are still lacking despite they should be of high interest not only for physicians but also for the consumers. The best-documented toxicokinetic parameter is the metabolism of NPS as it is comparably easy to study using in vitro systems such as HLM. Nevertheless, such studies are urgently needed to allow detection of the drugs and/or their metabolites in biological matrices in acute intoxications but also in the case of chronic consumption or as substitute for scheduled drugs of abuse.

Acknowledgments The author would like to thank Hans H. Maurer and Lea Wagmann for their support.

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