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Synthetic cathinone adulteration of illegal drugs.

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(Article begins on next page)

Psychopharmacology

Synthetic Cathinone Adulteration of Illegal Drugs

--Manuscript Draft--

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Full Title:	Synthetic Cathinone Adulteration of Illegal Drugs	
Article Type:	Review	
Funding Information:	National Institute on Drug Abuse (R01 DA039139)	Dr. Scott Rawls
Abstract:	<p>Abstract</p> <p>Rationale Current prevalence estimates of synthetic cathinone ("bath salts") use may be underestimates given that traditional metrics (e.g., surveys, urinalysis) often fail to capture the emergent issue of synthetic cathinone adulteration of more common illegal drugs such as ecstasy.</p> <p>Objectives This review examines the evolution of synthetic cathinones and prevalence of use over the past decade in the United States. We also review methods of self-report and biological testing of these compounds, and adverse outcomes pertaining to adulterated drug use.</p> <p>Results Synthetic cathinone use emerged in the US by 2010 with use associated with tens of thousands of poisonings. Reported poisonings and self-reported use have substantially decreased over the past five years. However, our review suggests that current estimates of use are underestimates due to underreporting, stemming primarily from unknown or unintentional use of adulterated formulations of illegal drugs such as ecstasy. Unintentional synthetic cathinone use can also be associated with adverse outcomes reportedly from use of other drugs individuals believed they were using.</p> <p>Conclusions While intentional synthetic cathinone use has decreased in recent years, evidence suggests prevalence of use is underestimated. Testing of drugs and/or biological specimens can help us better determine exposure to synthetic cathinones and researchers and clinicians should become better aware that unintentional exposure to these potent compounds (e.g., as adulterants) is often unknown or unintentional. Research utilizing both survey and biological testing methods may help more accurately determine the prevalence of use of these compounds.</p>	
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Author Comments:		

Response Letter.

Re: Reviewer response for manuscript
Klaus A. Miczek PhD
Principal Editor of *Psychopharmacology*

Dear Dr. Miczek --

Sincere thanks to you and the reviewing team for considering our manuscript for publication in *Psychopharmacology*. We have addressed each comment, and an itemized reply can be found below this passage. The reviewer comment will be **boldfaced**, and our reply will follow.

We are happy to make additional edits to the manuscript as you and the reviewing team see fit.

Sincerely,
Chicora Oliver.

Editorial Comment

We have now included a Table that specifies effects of synthetic cathinones administered with (or following) other illicit drugs including cocaine and methamphetamine. We believe this Table is a valuable reference that will refer readers to original research reports addressing this critical issue. We regretfully were unable to construct a timeline of historical development of synthetic cathinones but hope the reviewing team finds the written text to be sufficient.

Reviewer 1

(1-2) **“The review comes to a little bit of an abrupt end... (add) recommendation for professional education (ED personnel)...”**. We thank Reviewer 1 for this comment and have expanded our concluding passages. Specifically, we reiterate take-home messages that drugs marketed as something other than synthetic cathinones may, indeed, contain one or more synthetic cathinone agents. We expand on potential factors contributing to suicides associated with synthetic cathinone use.

All minor corrections were performed in the revised manuscript.

Reviewer 2

(1-2) **“In the abstract...identify "ecstasy" by its chemical name.” and “Page 9, line 10 - please define "ersatz".”** We thank Reviewer 2 for noting these issues with clarity. We define ecstasy in the abstract and use the clearer term “counterfeit” in place of “ersatz”.

(3) **“Toxicological Assessment subsection - it should be mentioned that reference standards for many parent compounds are now available (i.e., Cayman Chemical, Cerillian). Also, in this section it should be mentioned that GC-MS methods are also used for detection and analysis.”** These important changes were made to the revised text. Discussion of toxicological assessment now cites the availability of reference standards as well as GC-MS testing methods.

(4) **“ It would be helpful to know, if such information is available, the degree to which some drugs such as MDMA are adulterated with cathinones. For example, in seized MDMA tablets, what percent of the tablets are MDMA vs. cathinones? Likely there are trace amounts, but the relative contamination levels could be useful to discuss briefly.”** We agree with Reviewer 2 that having this information would be incredibly useful. However, such data is not currently available. The coauthors have personally contacted likely sources of this information (e.g. NFLIS) but have been unable to find data relevant to this issue.

(5) **“Consequences subsection - when discussing the ability of cathinones to increase, DA, NE, 5-HT, the authors should briefly clarify that these increases are in extracellular levels, not tissue content, and are achieved by presynaptic transporter blockade or via acting as transporter substrates. The phrase "increase dopamine, norepinephrine, and serotonin..." is too general.”** This important oversight is corrected in the revised text. We made

clear that neurotransmitters modulated by synthetic cathinones are done so in the synapse and result from both transporter blocking and substrate properties of these drugs.

(6) **“The final Conclusions section is very short and could be expanded with a discussion of some critical issues. These could include, but are not limited to, the issue of constant development of new cathinone derivatives, identification of synthetic cathinone metabolites which might have long elimination half lives which better aid in detection in biological samples as markers of prior use, identification of unique behavioral or physiological biomarkers of contaminated drug use, etc.”** We thank Reviewer 2 for this incredibly helpful feedback. The Conclusion (now “Concluding Remarks”) was expanded to discuss the potential for death from overdose or fatal self-harm and how there is a need for more awareness of the symptoms of synthetic cathinone overdose. We also discuss the need for more research on the behavioral and neurotoxic effects of synthetic cathinone drug combinations. We also highlight the need for studies that examine how environmental factors such as temperature alter the effects of synthetic cathinones use. Finally, we close by stating that these efforts may aide in the development of interventions that address the unique problem of synthetic cathinone adulteration of illegal drugs. We believe these changes greatly strengthen the text and hope the reviewing team find these changes to be sufficient.

[Click here to view linked References](#)

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Synthetic Cathinone Adulteration of Illegal Drugs

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4 **Abstract.**
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6 *Rationale.* Current prevalence estimates of synthetic cathinone (“bath salts”) use may be
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8
9 underestimate given that traditional metrics (e.g., surveys, urinalysis) often fail to capture the
10
11 emergent issue of synthetic cathinone adulteration of more common illegal drugs such as ecstasy
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13 (3,4-methylenedioxymethamphetamine).
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16 *Objectives.* This review examines the evolution of synthetic cathinones and prevalence of use
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18 over the past decade in the United States. We also review methods of self-report and biological
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20 testing of these compounds as well as adverse outcomes associated with adulterated drug use.
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24 *Results.* Synthetic cathinone use emerged in the United States by 2009 with use associated with
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26 tens of thousands of poisonings. Reported poisonings and self-reported use have substantially
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28 decreased over the past five years. However, our review suggests that current estimates of use
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30 are underestimates due to underreporting stemming primarily from unknown or unintentional use
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32 of adulterated formulations of relatively popular illegal drugs, such as ecstasy.
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36 *Conclusions.* While intentional synthetic cathinone use has decreased in recent years, evidence
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38 suggests prevalence of use is underestimated. Testing of drugs and/or biological specimens can
39
40 improve the accuracy of synthetic cathinone use estimates. Furthermore, we advocate that
41
42 researchers and clinicians should become better aware that exposure to these potent compounds
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44 (e.g., as adulterants) often occurs unknowingly or unintentionally. To improve our understanding
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46 of synthetic cathinone adulteration, research utilizing a combinatorial approach (survey and
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48 biological testing) will help more accurately determine the prevalence and impact of this public
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50 health issue.
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4 **Keywords.**
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6 Synthetic cathinones; novel psychoactive substances; ecstasy; adulteration; addiction.
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11 **Abbreviations.**
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14 α -PVP - α -pyrrolidinopentiophenone
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16 4-MMC - 4-methylmethcathinone
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18 5-HT - serotonin
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21 AAPCC - American Association of Poison Control Center
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23 DA - dopamine
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26 DEA - Drug Enforcement Administration
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28 ED – emergency department
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30 EDM - electronic dance music
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33 MDMA - 3,4-methylenedioxymethamphetamine
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36 MDMC - 3,4-methylenedioxymethcathinone
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38 MDPV – 3,4-methylenedioxypropylone
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40 NA - noradrenaline
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43 NFLIS - The National Forensic Laboratory Information System
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45 NPS – new psychoactive substance
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47 PCP – phencyclidine
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50 UHPLC-HRMS - ultra high performance-tandem mass spectrometry-high resolution mass
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52 spectrometry
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55 UHPLC-MS/MS - ultra high performance liquid chromatography-tandem mass spectrometry
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9 **Synthetic Cathinone Adulteration of Illegal Drugs.**

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11 A growing number of studies have demonstrated synthetic cathinone adulteration of
12 illegal drugs such as ecstasy or 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) (Rust
13 et al. 2012; Palamar et al. 2016d, 2017b; Salomone et al. 2017). Various synthetic cathinones
14 (colloquially, “bath salts”) produce effects similar to those of MDMA, and therefore adulteration
15 or replacement of ecstasy with synthetic cathinones may go unnoticed by some users. However,
16 synthetic cathinones can be much more potent than the drugs they are intended to mimic
17 (Baumann et al. 2012), and thus the risk of overdose and death can be greatly increased. While
18 growing awareness, legal restrictions, and sensational media reporting seem to have reduced
19 intentional synthetic cathinone use, synthetic cathinones continue to be detected in users unaware
20 of consumption. For example, two recent studies analyzing hair samples of ecstasy-using
21 electronic dance music (EDM) party attendees found that 50-68% of those testing positive for
22 synthetic cathinones denied known use (Palamar et al. 2016c, 2017c). Retrospective analysis of
23 the hair of drug users confirms the presence of synthetic cathinones in those who report MDMA
24 and/or other drug use but deny conscious consumption of synthetic cathinones (Rust et al. 2012;
25 Palamar et al. 2016c, 2017c). These and other studies reviewed in this manuscript indicate that
26 current prevalence estimates of synthetic cathinone use (e.g., in the United States) are likely
27 underestimates, and we believe addressing these potential underestimates is critical for
28 improving public health and safety.

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53 **Evolution of Synthetic Cathinone Use.**
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4 Synthetic cathinones are psychoactive substances manufactured to mimic the stimulating
5 effects of naturally occurring, plant-based cathinones. The psychoactive properties of cathinones
6 have been appreciated for several millennia through the practice of chewing leaves of the
7 cultivated perennial shrub khat, *C. edulis* (native to East Africa/Arabian Peninsula). Subjective
8 effects of khat leaf chewing include allayed fatigue and elated mood (Alles et al. 1961; Numan
9 2004). In the mid-20th century, means of expedited international trade allowed perishable khat to
10 be exported to the United States, United Kingdom and elsewhere. The United Nations Narcotics
11 Laboratory successfully isolated (\pm)-cathinone as the principal psychoactive agent from khat
12 leaves in the early 1970s (for discussion, see Kalix 1984) and noted structural similarity to
13 phenylisopropylamine (amphetamine) with the addition of a ketone at cathinone's β -carbon
14 atom. In 1987, Glennon and colleagues (1987) discovered alarming potency in the amphetamine-
15 like subjective effects of methcathinone among animals, although readers should note the
16 original synthesis of methcathinone was performed in the 1920s in an effort to produce ephedrine
17 homologs (Hyde et al. 1928). In 1994, the Drug Enforcement Agency (DEA) of the United States
18 designated methcathinone as a Schedule I illegal drug (State Department 1994), and use of
19 synthesized cathinones remained low for the subsequent two decades.

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43 Cathinone-derived psychostimulant drugs surged in popularity in the late 2000s most
44 notably across the United Kingdom and United States. Novel modifications of the parent
45 compound yielded abuse-prone agents including amphetamine-like 4-methylmethcathinone (4-
46 MMC, "mephedrone") and 3,4-methylenedioxypropylvalerone (MDPV), as well as the
47 empathogenic agent 3,4-methylenedioxymethcathinone (MDMC, "methylone"), which
48 structurally resembles MDMA. The surge in use is attributed to marketing on the "dark web" as
49 novel formulations obviated legal persecution for several years by classifying agents as "not for
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4 human consumption” with product names including “blue silk,” “vanilla sky,” and “white
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6 lightning” (European Monitoring Centre for Drugs and Drug Addiction 2015; Drug Enforcement
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8 Agency 2017). The National Forensic Laboratory Information System (NFLIS) reported 34
9
10 analytically-confirmed cases of synthetic cathinone seizures across 8 states in 2009. In 2010,
11
12 NFLIS reported 628 cases across 27 states (NFLIS 2011), and by July 2012, mephedrone and
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14 MDPV had become classified as Schedule I by the DEA under emergency order. Consequently,
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16 NFLIS reported methylone as the most prevalent synthetic cathinone in 2013 (12,067 cases,
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18 71.8% of all synthetic cathinone cases; NFLIS 2015).
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23 “Second generation” synthetic cathinones surfaced after methylone was scheduled in
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25 April 2013 and included 3,4-methylenedioxy-*N*-ethylcathinone (ethylone) and α -
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27 pyrrolidinopentiophenone (α -PVP). Synthetic cathinones seized in this “second generation” era
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29 possessed ethyl, butyl, pyrrolidinyl, fluoro and benzyl substitutions against cathinone’s backbone
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31 (for review, see Majchrzak et al. 2018). Use of the aforementioned synthetic cathinones is
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33 associated with health risks ranging from injection site irritation/infection to
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35 paranoia/hallucinatory delirium, sympathomimetic toxicity, serotonin syndrome, and sudden
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37 cardiac death (Wood et al. 2010; Dorairaj et al. 2012; Carbone et al. 2013). α -PVP, commonly
38
39 referred to as “flakka,” was linked to 63 deaths in Fort Lauderdale, Florida within a 16-month
40
41 period (CBS 2016), and the bizarre behavior linked with its use has earned it the street name
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43 “zombie drug” (Nóbrega and Dinis-Oliveira 2018). Data as of mid-2017 show β -keto-
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45 ethylbenzodioxolypentanamine (*N*-ethylpentylone, “ephylone”), which appears to possess
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47 appreciably greater potency than MDMA, is the most widely used synthetic cathinone in the
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49 United States, with over 2,500 cases reported (DEA 2017; Krotulski et al. 2018). Furthermore,
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51 13 individuals were hospitalized in New Zealand from mistakenly consuming high doses of
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4 ephylone in March 2018 (Newshubb 2018). These recent data confirm that novel synthetic
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6 cathinones (administered alone or in formulation) continue to be produced and thus pose a threat
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8 to public health on an international scale. And while deliberate abuse of synthetic cathinones has
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10 ostensibly declined, the variability of drug adulteration obscures the public's real rates of
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12 consumption.
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15 16 **Epidemiology of Synthetic Cathinone Use.** 17

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19 The American Association of Poison Control Center's (AAPCC) National Poison Data
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21 System tracks reported poisonings throughout the United States. AAPCC did not begin receiving
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23 reports of exposure to synthetic cathinones until 2009 - this first year, AAPCC received 298
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25 cases of synthetic cathinone poisonings (Wood 2013). In 2011, reports of exposures increased to
26
27 >6,000 (Wood 2013), and synthetic cathinones were involved in over 20,000 drug-related
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29 emergency department (ED) visits (Substance Abuse and Mental Health Services Administration
30
31 2011). Between 2011 and 2013, there were nearly 10,000 reported exposures to synthetic
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33 cathinones; however, exposures decreased to fewer than 1,000 between 2014 and mid-2015
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35 (Wood 2013; AAPCC, 2016). Recent public data are not available on hospitalizations or
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37 poisonings involving synthetic cathinones in the United States for recent years, but there is
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39 evidence to suggest diminution. While national drug-related ED data after 2011 are not available,
40
41 it should be noted that in light of the prevalence of ecstasy use decreasing dramatically after the
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43 early 2000s (Johnston et al. 2018), ED visits related to "ecstasy" use increased several-fold from
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45 4,452 in 2001 to 22,498 in 2011 (Substance Abuse and Mental Health Services Administration
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47 2011). The steep increase in "ecstasy"-related ED visits through 2011 coincided with popularity
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49 of use of the drug in powder form (referred to as "Molly"), which may increase likelihood of
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4 adulteration (Palamar 2017). It is unknown to what extent synthetic cathinones were
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6 unknowingly ingested by users as toxicology testing was not utilized in EDs.
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9 Monitoring the Future (MTF), an annual nationally representative survey of high school
10 seniors (12th graders), is the only national survey in the US to query “bath salts” (synthetic
11 cathinone) use. MTF first asked about “bath salts” in 2012, and 1.3% of students reported past-
12 year use (Johnston et al. 2018). Prevalence of past-year use appears to have decreased with 0.6%
13 reporting use in 2017 (Palamar 2015; Johnston et al. 2018). However, a major limitation of the
14 MTF survey is that “bath salts” are not clearly defined, nor are examples of specific compounds
15 provided. Few studies have examined synthetic cathinone use in greater depth. In 2016, a study
16 of EDM party attendees tested survey methods querying synthetic cathinone use and found that
17 nearly a tenth (9.3%) of those denying overall use of synthetic cathinones then reported use of a
18 specific synthetic cathinone on the following page (Palamar et al. 2017a), reflecting widespread
19 confusion as to what drugs constitute “bath salts.” This was most commonly the case with
20 methylone and mephedrone, which are synthetic cathinones with empathomimetic, ecstasy-like
21 effects. Further, an analysis of type-in responses in the National Survey of Drug Use and Health
22 found that type-in responses of other drugs used led to a severe underestimate of only 0.05% of
23 individuals in the United States ever using synthetic cathinones or other novel phenethylamines
24 or euphorigenic stimulants (Palamar et al. 2015b). These findings reveal that more commonly
25 employed means of assessing drug use (e.g., surveys) may underestimate synthetic cathinone
26 use, in part, due to lack of drug education among users. Few other studies have queried synthetic
27 cathinone use on surveys. One survey of college students in 2011-2012 included a question about
28 use of synthetic cathinones and a specific compound (MDPV), and use was reported by only 1%
29 of the sample (Miller and Stogner 2014). Similarly, a survey of attendees of gay clubs, hip hop
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4 clubs, indie rock clubs, and EDM clubs in New York City (NYC) in 2012 asked about use of
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6 synthetic cathinones or mephedrone, and similarly, only 1% reported use (Kelly et al. 2013).
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9 Surveys focusing on EDM party attendees, however, have tended to find higher
10 prevalence of reported synthetic cathinone use. We believe higher prevalence is detected in this
11 population for four reasons. First, EDM party attendees are at high risk for using various drugs
12 (Ross et al. 2003; Palamar et al. 2015a, 2017b; Kurtz et al. 2017), and use of other drugs has
13
14 been found to be a major risk factor for synthetic cathinone abuse (Palamar et al. 2015b, 2017b;
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16 Fernández-Calderón et al. 2018). Second, various synthetic cathinone compounds have similar
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18 effects to common club drugs such as ecstasy, with some compounds like mephedrone
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20 functioning as counterfeit replacements (Brunt et al. 2011a). Third, surveys of EDM party
21
22 attendees tend to ask about multiple synthetic cathinone compounds and not just synthetic
23
24 cathinones as an overall category, and it appears that asking about multiple compounds increases
25
26 the likelihood of recognizing a specific compound that was used. Finally, EDM party attendees
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28 have been found to be at high risk for unknowingly or unintentionally using synthetic cathinones
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30 as these compounds are common adulterants in drugs such as ecstasy (Palamar et al. 2016c,
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32 2017c).
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43 A self-selected online sample of past-year drug-using nightclub attendees who
44 participated in the Global Drug Survey in 2013 found that one-out-of-ten (10%) reported ever
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46 using at least one synthetic cathinone queried (Palamar et al. 2016b). Most (8%) reported
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48 methylnone use, 5% reported mephedrone use, and 2% reported MDPV use. More recently, time-
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50 space sampling and weighting methods have been used by some studies to yield more accurate
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52 estimates of synthetic cathinone use from venue-based recruitment in the EDM scene. A study of
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54 young adult (age 18-25) EDM party attendees in 2015 estimated that 7% of attendees had used at
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4 least one (of 26) synthetic cathinone compound, with methylone (3%) being the most prevalent
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6 (Palamar et al. 2016a). In 2016, similar lifetime prevalence of 7.7% was estimated among EDM
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8 attendees in NYC age 18-40 (Palamar et al. 2018); however, in a new 2017 cohort of attendees,
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10 estrimated prevalence of known use decreased in half to 3.5% (Palamar 2018).
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14 Prevalence estimates of synthetic cathinone use also tend to be underestimates because
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16 many users of drugs such as ecstasy consume these compounds unknowingly, as synthetic
17
18 cathinones are common adulterants or replacements (discussed in detail below). In fact, during a
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20 recent survey of EDM party attendees in NYC, 30% of respondents agreed that “bath salts” are
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22 sometimes found in Molly, and 15% reported believing they might have unknowingly used “bath
23
24 salts” (Palamar 2018). This suggests many EDM attendees are aware of the high potential for
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26 adulteration, hence extensive interest in “drug checking” in which an individual’s drug is tested
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28 for purity (Barratt et al. 2018). To our knowledge, no studies have examined prevalence of
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30 adulteration in the United States, and this is likely due to high legal risk for both users and drug
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32 checkers. However, studies have begun to analyze biological specimens of users to determine
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34 whether they have used synthetic cathinones.
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40 41 **Toxicological Assessment of Synthetic Cathinone Use.** 42

43 After the presence of synthetic cathinones on the black market became recognized,
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45 forensic and clinical laboratories worldwide had to face the analytical challenge of identifying
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47 and quantifying these new drugs in various biological matrices. The commercial unavailability of
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49 reference standards for the parent drugs and their metabolites, the lack of updated and
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51 comprehensive immunoassays for their detection, and the insufficient investigation of their
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53 metabolic transformation after intake represented just the main problems toward the
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55 identification and quantification of synthetic cathinones (Salomone et al. 2017). At the moment,
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4 most of the aforementioned challenges have been at least partially overcome. For example,
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6 reference standards for many parent compounds are now available from companies such as
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8 Cayman Chemical and Cerillian. Gas chromatography with mass spectrometry (GC-MS) is also
9
10 employed to assess synthetic cathinone use (Alvarez et al. 2017). The most recent equipment
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12 based on ultra high performance-tandem mass spectrometry (UHPLC-MS/MS) and high
13
14 resolution mass spectrometry (UHPLC-HRMS) allows the detection of expansive synthetic
15
16 cathinone panels within a single analytical run. Several laboratories currently embrace this
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18 promising advent by offering screening and confirmation analysis for synthetic cathinones (Zuba
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20 and Adamowicz 2018; Marchei et al. 2018).

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26 Much is yet to be discovered about the current diffusion of synthetic cathinones among
27
28 the general population and in high-risk populations. Synthetic cathinones are eliminated from the
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30 urine, blood, and saliva of users within hours or days, which limits the ability of toxicological
31
32 confirmation. This is especially concerning in cases of hospitalization and death resulting from
33
34 intentional or unintentional use of synthetic cathinones (Salomone et al. 2017). As a
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36 consequence, a number of unresolved issues are raised, including the number and variety of
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38 synthetic cathinones present in different countries, their frequency of use, and user
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40 demographics. To circumvent the limitations of conventional biological samples (e.g., blood,
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42 urine, saliva), the detection of synthetic cathinones in alternative matrices (i.e., hair samples) was
43
44 proposed as a practical means to provide preliminary information on the black market
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46 penetration of synthetic cathinones (Rust et al. 2012; Salomone et al. 2016b) in specific
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48 territories and populations. The keratin matrix incorporates parent synthetic cathinones
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50 consumed over extended time periods, providing access to a much wider diagnostic window than
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52 blood and urine. This feature, combined with the analytical performance of the latest generation
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4 of UHPLC-MS/MS instruments, allows researchers to obtain significant information about past
5 use – even a single intake of any targeted compound, with older periods of use corresponding to
6 the hair segments more distant from the hair root (Salomone et al. 2016b). In particular,
7 analytical methods must guarantee high sensitivity: due to their high pharmacological potency *in*
8 *vitro*, it is likely that synthetic cathinones are active in relatively low doses (and therefore are
9 consumed in low doses, and present at lower levels in hair).

10
11 Remarkably, the majority of the published studies describing novel synthetic drug
12 detection in hair samples reported the frequent occurrence of polydrug use (Kintz et al. 2015;
13 Salomone et al. 2016a). One explanation for this is because the consumers are unaware of the
14 actual composition of the products. Today, despite the general knowledge that no systematic
15 correspondence exists between the trade or the street name and real content of the
16 pill/powder/crystal/herbal blend, consumers hardly ever have means of verifying what they
17 purchased. This is not surprising as synthetic cathinones are semi-clandestine preparations in
18 which the active ingredients may vary over time. This inconsistency in the content of illegal
19 drugs implies that consumers do not have control of the potency and efficacy of the products to
20 be consumed. Even when synthetic cathinones are purchased online or used intentionally,
21 substantial risk exists that they are mislabeled either because they contain chemical analogs of
22 the ordered drug (e.g., pentedrone instead of 3,4-dimethylcathinone) or because the active agent
23 differs from what was advertised by the dealer or via the website (Brunt et al. 2017). In this
24 scenario, hair testing offers a unique perspective in the investigation of drug consumption,
25 provided a large panel of target analytes. The extended diagnostic time window covered by the
26 keratin matrix (unlike urine, blood, and saliva) allows retrospective investigation of drug
27 prevalence and diffusion of any targeted psychoactive substance. In particular, the occurrence of
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4 poly-use and unintentional intake of synthetic cathinones can be revealed by means of hair
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6 analysis, possibly combined with surveys.
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9 **Synthetic Cathinone Adulteration of Illegal Drugs.**

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11 Rust et al. (2012) examined hair samples from 2009 to 2010 from individuals who
12 originally tested positive for amphetamines and/or MDMA (n=325) (Rust et al. 2012). Hair was
13 collected as part of a driving ability assessment and employed liquid chromatography with
14 tandem mass spectrometry (LC-MS/MS) to test for a variety of novel psychoactive substances
15 (NPS), including synthetic cathinones. Of the 120 samples that tested positive for NPS, 10%
16 tested positive for synthetic cathinones (11 samples for mephedrone, 1 sample for methylone). A
17 later study also found high levels of mephedrone in suspected drug users. In France, Martin et al.
18 (2012) found that nearly 20% of hair samples collected from those suspected of narcotic abuse
19 (13 out of 67) tested positive for mephedrone (Martin et al. 2012). While it is unclear whether
20 individuals in either of these studies were aware of synthetic cathinone use, these methods
21 confirm the utility of analyzing hair to assess synthetic cathinone use in suspected users.
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25 In 2015, Palamar and colleagues surveyed and analyzed hair samples from 48 EDM attendees in
26 NYC reporting lifetime ecstasy/MDMA/Molly use (Palamar et al. 2016c). Almost half (48%) of
27 hair samples contained butylone and 10% contained methylone. However, of those who reported
28 no lifetime use of synthetic cathinones or unknown pills or powders, 41% tested positive for a
29 synthetic cathinone or other NPS. Specifically, of those denying use of any synthetic cathinones
30 listed on the survey, 38% tested positive for butylone, 9% for methylone, and 3% for the highly
31 potent compound α -PVP (“Flakka”). This study also found that racial/ethnic minorities were
32 more likely to test positive for synthetic cathinones after denying lifetime use. The strongest
33 predictor of testing positive for synthetic cathinones was frequent nightclub/festival attendance.
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4 In 2016, a similar study was conducted with a focus on 90 past-year ecstasy users in the
5 NYC EDM scene (Palamar et al. 2017c). While over a quarter (28%) of attendees tested positive
6 for synthetic cathinones, 68% of those testing positive denied past-year use. Butylone (14%),
7 ethylone (11%), and pentylone (10%) were the most commonly detected synthetic cathinones -
8 strikingly, all participants denied use of these compounds. Methylone was detected in 3% of hair
9 samples, but two of these three participants reported known use of this substance. Unknown α -
10 PVP use was also detected in 2% of samples. These studies demonstrate that many ecstasy-using
11 nightclub/festival attendees are unintentionally administering synthetic cathinones, and that drug
12 checking may be beneficial for those unwilling or unable to abstain.
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26 Synthetic cathinone use at EDM parties has also led to clusters of hospitalizations. In
27 particular, there were at least 22 drug-related hospitalizations at the 2013 Electric Zoo EDM
28 festival in NYC (Ridpath et al. 2014). Of the 22 reported hospitalizations, 9 (41%) were
29 classified as severe, and there were two deaths. Of the 22 patients, 17 were administered
30 toxicological tests, among whom 55% had used “synthetic club drugs.” Four of the 17 tested
31 positive for methylone alone, 3 for methylone and MDMA, 2 for methylone and other illegal
32 drugs other than MDMA, and 2 for MDMA alone. One decedent tested positive for MDMA,
33 while the other tested positive for both MDMA and methylone. It is unclear whether the second
34 decedent or any of the other patients who tested positive for methylone were fully aware of their
35 drug/formulation intake.
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50 Various drug-testing services throughout Europe have also detected a range of synthetic
51 cathinones in drugs sold as ecstasy. For example, despite the increasing purity of ecstasy tested
52 from 2008-2013 (Brunt et al. 2017), a range of synthetic cathinones including 4- MEC,
53 mephedrone, methylone, and ethylone were detected in submitted substances. The Drug
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4 Information and Monitoring System in the Netherlands in particular detected mephedrone sold as
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Information and Monitoring System in the Netherlands in particular detected mephedrone sold as ecstasy in a large portion of samples throughout 2009 (Brunt et al. 2011b). A Spanish drug-testing study also examined drug submissions from 2010-2012 and detected 22 different synthetic cathinone compounds (primarily methylone, mephedrone, 4- MEC, and MDPV) in drugs to be sold as ecstasy or ketamine (Caudevilla-Gálligo et al. 2013).

It should be noted that while advanced laboratory methods are now able to detect the presence of many synthetic cathinones, a major limitation to research is that standard drug tests (e.g., urine dip sticks) cannot detect the presence of several dangerous substances. Without a simple form of testing, it is difficult for both researchers and medical professionals (e.g., ED staff) to test body fluids and determine potential exposure to these compounds. Therefore, underestimation of use may continue. However, some harm reduction organizations such as DanceSafe sell drug testing reagents which provide users a color-change metric of purity. Reagent tests are not the most reliable form of testing, but they can improve ability to detect drug adulteration. On-site (e.g., at dance festivals) or off-site testing (e.g., at analytical facilities) can help track what drugs people are really using (Butterfield et al. 2016), and this could identify specific synthetic cathinones and help detect trends in exposure. Most importantly, drug testing is an opportunity for users to discard the drug they plan to use, and results can inform future use or decisions to purchase from specific individuals (Butterfield et al. 2016).

There is a clear need for better testing options and education for clinicians who treat suspected synthetic cathinone overdose. ED clinicians must rely heavily on self-reports to determine the cause of a drug overdose, in part because urine toxicology tests can take days to complete. Vazirian et al. (2015) surveyed ED clinicians and found that 77% do not explicitly ask if a patient has taken synthetic cathinones, and 98% were unaware of bath salt urine toxicology

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4 tests. While 60% did report having encountered a patient who admitted to bath salts use, these
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6 patients presented with symptoms that could have easily been misattributed to more common
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8 drugs of abuse. These symptoms include agitation (81%), aggression or violence (65%), or
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10 hallucinations (46%) – all common effects of the widely used drugs that synthetic cathinones
11
12 may be intended to mimic.
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15 **Unintentional Synthetic Cathinone Use, Combinatorial Effects, and Underlying**

16 **Neurobiology.**

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19 Unintentional synthetic cathinone use greatly increases the risk of overdose and death.
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21 The two most common causes of death from synthetic cathinone use are overdose and fatal self-
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23 harm (citation below). Our speculation is that overdoses occur because of a fundamental
24
25 misunderstanding of the mechanisms and potencies of the synthetic cathinone(s) being used.
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27 Self-harm associated with synthetic cathinone use may result from serious psychological effects
28
29 of intoxication such as loss of impulse control, increased risk-taking/sensation-seeking,
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31 hallucinations, and paranoia (_____). Moreover, chronic use can lead to persistent
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33 neurochemical alterations that underlie extreme depression, thereby triggering self-harm (Banks
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35 et al. 2014; Barrio et al. 2016).
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43 In general, the effects of synthetic cathinones are attributed to the neurotransmitters that
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45 most illicit drugs act upon including dopamine (DA), noradrenaline (NA) and serotonin (5-HT).
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47 Drugs such as cocaine function as DA and NA transporter (reuptake) blockers leading to net
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49 elevations in synaptic neurotransmitter levels. Compared to cocaine, MDPV increases synaptic
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51 NA with approximately 10-fold- and synaptic DA with approximately 50-fold-greater potency
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53 (Baumann et al. 2012). Therefore, if one consumes MDPV under the impression that it is
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55 cocaine, the resulting intoxication would be manifold greater than intended. Excitotoxic levels of
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4 DA and NA produce hyperthermia and increased heart rate that can lead to multiorgan failure
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6 and death (Walter and Carretto 2015).
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9 Drugs such as MDMA, amphetamine, and methamphetamine act as DA, 5-HT, and NA
10 transporter substrates, meaning the drug enters the cell and disrupts vesicular storage and
11 transmitter release dynamics (e.g., Baumann et al. 2013). Transporter substrates produce
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13 persistent depletion of neurotransmitters and loss of functional transporters (Baumann et al.
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15 2007, 2013; Gygi et al. 1997; German et al. 2014). Indeed depression and suicide are particularly
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17 common in heavy users of both MDMA and the mechanistically similar synthetic cathinone,
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19 mephedrone (Cohen 1996; Marinetti and Antonides 2013; Elliott and Evans 2014).
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26 Death from unintentional synthetic cathinone overdose is typified by one of the first
27 reported cases following unintentional “bath salts” consumption. Warrick et al. (2012) describe a
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29 24-year-old female who died after consuming two pills of what turned out to be high doses of
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31 methylone and butylone rather than the “ecstasy” she believed she was taking. The patient was
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33 found unconscious at a concert and was febrile, tachypnic, and hypertensive. An ED exam
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35 revealed that she was diaphoretic, tremulous, hyperflexic, and had sustained clonus. Despite
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37 maximal supportive care, optimal ventilation, and improvements in hemodynamics and
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39 coagulopathy, within 48 hours of admission the patient developed acute respiratory distress
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41 syndrome, renal failure, hypoxemia, lactic acidosis and ultimately expired. Urinalysis and
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43 GC/MS testing of pills found on her person similar to the two ingested revealed the sole presence
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45 of methylone and butylone, with no traces of MDMA that the “ecstasy” was sold as. While
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47 methylone and butylone are 2-6x less potent than MDMA in terms of DA and 5-HT transporter
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49 substrate and blocking properties, the excessive quantity of each compound within each pill are
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51 the likely reason the patient expired. Ecstasy tablets typically contain 30-150 mg of MDMA, and
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4 while methylone and butylone are up to 10x less effective at reducing 5-HT and NA, the three
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6 drugs are similarly effective at increasing DA which may explain why the three drugs are
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8 consumed recreationally at similar doses (e.g., Hall and Henry 2006; López-Arnau et al. 2012;
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10 Warrick et al. 2012). In the case described by Warrick et al. (2012), each pill contained 422 mg
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12 of methylone and 53 mg of butylone - doses that would produce profoundly higher DA levels
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14 than what is considered pleasurable or safe.
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19 Unintentional synthetic cathinone use can occur in polydrug users, and a small number of
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21 preclinical studies have begun to elucidate the neurotoxic and behavioral effects of drug
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23 combinations. Table 1 lists effects observed in animal subjects following exposure to drug
24
25 combinations that include a synthetic cathinone. Notably, enhancement of neurotoxicity is
26
27 observed with drugs that have overlapping substrate properties (e.g., mephedrone elevates
28
29 MDMA-induced DA neurotoxicity; Angoa-Perez 2013). Some combinations, however, produce
30
31 unexpected protective effects that may be due to the mechanism of one drug minimizing effects
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33 of a second drug. For example, the DA transporter blocking properties of MDPV may protect
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35 against the DA releasing properties of methamphetamine (Anneken et al. 2015). In addition,
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37 many studies fail to account for potential contributions of temperature when examining the
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39 neurotoxic effects of synthetic cathinone use (alone or in combination with a second drug). For
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41 example, mephedrone potentiates the neurotoxic effects of MDMA under group- but not single-
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43 housing conditions (Hadlock et al. 2011) which likely reflects the inherent risk of consuming
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45 these combinations in crowded environments (e.g. EDM clubs). The neurotoxicity observed by
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47 Hadlock et al. (2011) was persistent yet limited to cells producing 5-HT. In humans, 5-HT
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49 depletion has been associated with the negative mood, irritability, and suicidal thoughts
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51 experienced in the days after MDMA or mephedrone use (Cohen 1996; Freeman et al. 2012).
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4 More research will be needed to reach a clearer understanding of how synthetic cathinones
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6 impact the neurochemical and behavioral effects experienced from other drugs when provided,
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8 knowingly or unbeknownst to the consumer, in polydrug formulations.
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11 Synthetic cathinone users are at additional risk of experiencing psychosis. There are
12
13 several reported cases of years-long, intermittent mephedrone users entering drug rehabilitation
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15 for delusional thoughts and auditory and visual hallucinations (Barrio 2016). Psychosis can occur
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17 in patients with no medical or family history of mental illness demonstrating the profound impact
18
19 of long-term drug use that may have been consumed unknowingly. MDPV can produce delirium
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21 - a state characterized by bizarre behavior, paranoia, and hallucinations. For example, Penders
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23 and Gestring (2011) describe 3 cases of individuals experiencing delusions of persecution and
24
25 harassment from nonexistent sources: one man hallucinated his estranged wife tapping on his
26
27 window, a young housewife was filmed describing home invaders in an unoccupied room, and a
28
29 middle-aged man hallucinated burglars shooting him with laser beams. Moreover, the memory
30
31 disturbances common in MDPV-induced delirium greatly increase the risk of overdose death
32
33 because patients frequently have no recollection of the amount, frequency, or route of
34
35 administration. This is especially dangerous in the case of unintentional use of MDPV, of a drug
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37 that is over ten times more potent than the more common substance it may have been intended to
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39 mimic (e.g. cocaine). These cases demonstrate the great risk involved in consuming a substance
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41 that may be far more potent than one conceives.
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50 Finally, unintentional synthetic cathinone use carries with it significant risk of death from
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52 self-harm. Self-harm has been cited as the second most common cause of death in synthetic
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54 cathinone users (Schifano et al. 2012; Marinetti and Antonides 2013). A 3-year review of novel
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56 psychoactive substances in casework (Elliott and Evans 2014) found that in deaths following
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4 synthetic cathinone use, 41% were hangings or other mechanical suicide (i.e., fatal self-harm),
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6 which was the highest proportion compared to other classes of drugs. While hangings are the
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8 most common form of fatal self-harm, drownings, gunshots wounds, repeated self-lacerations,
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10 and jumping from bridges have all been reported (Schifano et al. 2012; Marinetti and Antonides
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12 2013).
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16 Self-harm related to synthetic cathinone use is attributed to impulsivity, paranoia, and
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18 violent behavior in response to vivid hallucinations or delusional thoughts (Penders 2012;
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20 Penders and Gestring 2011). In a case of fatal self-harm associated with synthetic cathinone use,
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22 a 21-year old with no history of depression committed suicide 5 days after ingesting an unknown
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24 powder later determined to be MDPV (PBS News, 2018). The decedent experienced days of
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26 insomnia and a frightening hallucination of 25 police cars outside his kitchen. Upon being told
27
28 the police cars did not exist, the patient slit his throat in front of his parents. The self-inflicted
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30 laceration was non-fatal and was successfully stitched closed at a hospital. However, 4 hours
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32 after returning home from the hospital, and 5 days after initial drug-taking, the decedent
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34 committed suicide with a rifle. This case exemplifies how MDPV use can promote self-harm and
35
36 suicide, possibly as a consequence of withdrawal-associated affective distress. It is likely the
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38 decedent was experiencing excitotoxic levels of DA during the psychotic episode. Synthetic
39
40 cathinone-induced DA excitotoxicity can take days to normalize (Den Hollander et al. 2013;
41
42 Martínez-Clemente et al. 2014), during which depression and suicidal thoughts may emerge.
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44 Indeed, the term “suicide tuesday” emerged to describe the depressive withdrawal state
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46 experienced days following initial drug-taking (Psychedelics.com 2018). It is possible that
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48 antipsychotic treatment may have prevented death of the patient, as antipsychotic drugs working
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50 as DA modulators synthetic cathinone-induced psychosis (Banks et al. 2014; Barrio et al. 2016).
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4 ED clinicians and potential drug users can reduce the risk of overdose and death from
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6 unintentional synthetic cathinone use. Clinicians should be aware of the constellation of
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8 symptoms typical of synthetic cathinone overdose: agitation, sustained hyperthermia, muscle
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10 rigidity, and psychosis. The typical course of treatment involves aggressive cooling, hydration,
11
12 and antipsychotic medication administration. Additionally, drug users who reject abstinence can
13
14 make use of pill-testing services that can reliably detect the presence of ‘unknown substances’ in
15
16 drugs such as cocaine and ecstasy (Saleemi et al. 2017). Drug users and clinicians should also
17
18 note the potential for self-harm and suicide in patients during intoxication and during
19
20 withdrawal. Future studies examining the toxicity associated with synthetic cathinone drug
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22 combinations are also needed to better address the emerging phenomenon of unintentional
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24 synthetic cathinone use.
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30 **Concluding Remarks.**

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33 Adulteration of illegal drugs with synthetic cathinones is an untenable yet largely
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35 unrecognized public health concern, the magnitude of which we are only beginning to appreciate
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37 through empirical observation. Traditional approaches used to assess the effects of drugs on
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39 public health and safety (e.g., surveys, urinalysis) are likely underestimating synthetic cathinone
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41 use, especially in high-risk populations. Moreover, synthetic cathinone abuse carries with it risks
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43 unique to this class of drugs such as overdose, self-harm, and suicide. It is clear that synthetic
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45 cathinones mimicking relatively popular illegal drugs such as cocaine (e.g., MDPV) and MDMA
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47 (e.g., methyldone and mephedrone) produce similar euphorogenic subjective effects, though
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49 typically at fractions of the dose.
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55 We believe the burden of addressing this public health problem is complicated and shared
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57 by many. In effort to specifically reduce accidental overdose, we advocate the development and
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4 commercial sale of purity detectors (e.g. pill-testing products and services) that can be employed
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6 by users. We advocate the dissemination of accurate, empirically-derived information on the
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8 effects of synthetic cathinones so users and medical professionals including ED personnel can
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10 recognize when an individual - knowingly or not - has consumed a synthetic cathinone.
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13 Moreover, ED personnel should be aware of the availability of synthetic cathinone drug-testing
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15 products and services. In the future, collaborative work between field observers and basic
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17 scientists will (i) clarify the extent to which synthetic cathinones impact the subjective and
18
19 physiological effects associated with other drug use, (ii) determine how situational factors such
20
21 as environment influence the effects of synthetic cathinones taken with other drugs, and (iii) aide
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23 in the development of medical intervention strategies associated with the unique risks of drug use
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25 complicated by synthetic cathinone adulteration.
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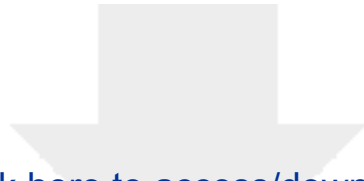
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Tables.

Table 1. Neurotoxic and Behavioral Effects of Synthetic Cathinones in Combination More Commonly Used Illegal Drugs. Synthetic cathinones can potentiate, nullify, or protect against the neurotoxic and behavioral effects of more commonly used drugs (second drug).

Synthetic cathinone	Common Illegal Drug	Effects (neurotoxic or behavioral)	Reference (format)
Mephedrone	MDMA	Potentiate MDMA-induced DA and 5-HT neurotoxicity in group-housed animals	Hadlock et al. 2011
MDPV	Methamphetamine	Reduced methamphetamine-induced DA neurotoxicity	Anneken 2015
Methylone			
Methylone	MDMA	Reduced MDMA-elicited astrogliosis and neurotoxicity markers	Miner 2017
Mephedrone	MDMA	No effect on 5-HT neurotoxicity	Angoa-Perez 2014
	Methamphetamine		
Mephedrone	MDMA	Reduced depression, improved memory consolidation	Budzynska 2017
Mephedrone	Methamphetamine	Enhanced DA neurotoxicity	Angoa-Perez 2013
	Amphetamine		
	MDMA		



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