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Synthetic Cathinone Adulteration of Illegal Drugs

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Abstract

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 (3,4-methylenedioxymethamphetamine).

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 as well as adverse outcomes associated with adulterated drug use.

Results.—Synthetic cathinone use emerged in the United States by 2009 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 relatively popular illegal drugs, such as ecstasy.

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 improve the accuracy of synthetic cathinone use estimates. Furthermore, we advocate that researchers and clinicians should become better aware that exposure to these potent compounds (e.g., as adulterants) often occurs unknowingly or unintentionally. To improve our understanding of synthetic cathinone adulteration, research utilizing a combinatorial approach (survey and biological testing) will help more accurately determine the prevalence and impact of this public health issue.

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Keywords

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Synthetic Cathinone Adulteration of Illegal Drugs.

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

Evolution of Synthetic Cathinone Use.

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

Cathinone-derived psychostimulant drugs surged in popularity in the late 2000s most notably across the United Kingdom and United States. Novel modifications of the parent compound yielded abuse-prone agents including amphetamine-like 4-methylmethcathinone (4-MMC, “mephedrone”) and 3,4-methylenedioxypropylamphetamine (MDPV), as well as the empathogenic agent 3,4-methylenedioxymethcathinone (MDMC, “methylone”), which structurally resembles MDMA. The surge in use is attributed to marketing on the “dark web” as novel formulations obviated legal persecution for several years by classifying agents as “not for human consumption” with product names including “blue silk,” “vanilla sky,” and “white lightning” (European Monitoring Centre for Drugs and Drug Addiction 2015; Drug Enforcement Agency 2017). The National Forensic Laboratory Information System (NFLIS) reported 34 analytically-confirmed cases of synthetic cathinone seizures across 8 states in 2009. In 2010, NFLIS reported 628 cases across 27 states (NFLIS 2011), and by July 2012, mephedrone and MDPV had become classified as Schedule I by the DEA under emergency order. Consequently, NFLIS reported methylone as the most prevalent synthetic cathinone in 2013 (12,067 cases, 71.8% of all synthetic cathinone cases; NFLIS 2015).

“Second generation” synthetic cathinones surfaced after methylone was scheduled in April 2013 and included 3,4-methylenedioxy-*N*-ethylcathinone (ethylone) and α -pyrrolidinopentiophenone (α -PVP). Synthetic cathinones seized in this “second generation” era possessed ethyl, butyl, pyrrolidinyl, fluoro and benzyl substitutions against cathinone’s backbone (for review, see Majchrzak et al. 2018). Use of the aforementioned synthetic cathinones is associated with health risks ranging from injection site irritation/infection to paranoia/hallucinatory delirium, sympathomimetic toxicity, serotonin syndrome, and sudden cardiac death (Wood et al. 2010; Dorairaj et al. 2012; Carbone et al. 2013). α -PVP, commonly referred to as “flakka,” was linked to 63 deaths in Fort Lauderdale, Florida within a 16-month period (CBS 2016), and the bizarre behavior linked with its use has earned it the street name “zombie drug” (Nóbrega and Dinis-Oliveira 2018). Data as of mid-2017 show β -ketoethylbenzodioxolypentylamine (*N*-ethylpentylone, “ephylone”), which appears to possess appreciably greater potency than MDMA, is the most widely used synthetic cathinone in the United States, with over 2,500 cases reported (DEA 2017; Krotulski et al. 2018). Furthermore, 13 individuals were hospitalized in New Zealand from mistakenly consuming high doses of ephylone in March 2018 (Newshubb 2018). These recent data confirm that novel synthetic cathinones (administered alone or in formulation) continue to be produced and thus pose a threat to public health on an international scale. And while deliberate abuse of synthetic cathinones has ostensibly declined, the variability of drug adulteration obscures the public’s real rates of consumption.

Epidemiology of Synthetic Cathinone Use.

The American Association of Poison Control Center’s (AAPCC) National Poison Data System tracks reported poisonings throughout the United States. AAPCC did not begin receiving reports of exposure to synthetic cathinones until 2009 - this first year, AAPCC received 298 cases of synthetic cathinone poisonings (Wood 2013). In 2011, reports of exposures increased to >6,000 (Wood 2013), and synthetic cathinones were involved in over 20,000 drug-related emergency department (ED) visits (Substance Abuse and Mental Health Services Administration 2011). Between 2011 and 2013, there were nearly 10,000 reported

exposures to synthetic cathinones; however, exposures decreased to fewer than 1,000 between 2014 and mid-2015 (Wood 2013; AAPCC, 2016). Recent public data are not available on hospitalizations or poisonings involving synthetic cathinones in the United States for recent years, but there is evidence to suggest diminution. While national drug-related ED data after 2011 are not available, it should be noted that in light of the prevalence of ecstasy use decreasing dramatically after the early 2000s (Johnston et al. 2018), ED visits related to “ecstasy” use increased several-fold from 4,452 in 2001 to 22,498 in 2011 (Substance Abuse and Mental Health Services Administration 2011). The steep increase in “ecstasy”-related ED visits through 2011 coincided with popularity of use of the drug in powder form (referred to as “Molly”), which may increase likelihood of adulteration (Palamar 2017). It is unknown to what extent synthetic cathinones were unknowingly ingested by users as toxicology testing was not utilized in EDs.

Monitoring the Future (MTF), an annual nationally representative survey of high school seniors (12th graders), is the only national survey in the US to query “bath salts” (synthetic cathinone) use. MTF first asked about “bath salts” in 2012, and 1.3% of students reported past-year use (Johnston et al. 2018). Prevalence of past-year use appears to have decreased with 0.6% reporting use in 2017 (Palamar 2015; Johnston et al. 2018). However, a major limitation of the MTF survey is that “bath salts” are not clearly defined, nor are examples of specific compounds provided. Few studies have examined synthetic cathinone use in greater depth. In 2016, a study of EDM party attendees tested survey methods querying synthetic cathinone use and found that nearly a tenth (9.3%) of those denying overall use of synthetic cathinones then reported use of a specific synthetic cathinone on the following page (Palamar et al. 2017a), reflecting widespread confusion as to what drugs constitute “bath salts.” This was most commonly the case with methylone and mephedrone, which are synthetic cathinones with empathomimetic, ecstasy-like effects. Further, an analysis of type-in responses in the National Survey of Drug Use and Health found that type-in responses of other drugs used led to a severe underestimate of only 0.05% of individuals in the United States ever using synthetic cathinones or other novel phenethylamines or euphorogenic stimulants (Palamar et al. 2015b). These findings reveal that more commonly employed means of assessing drug use (e.g., surveys) may underestimate synthetic cathinone use, in part, due to lack of drug education among users. Few other studies have queried synthetic cathinone use on surveys. One survey of college students in 2011–2012 included a question about use of synthetic cathinones and a specific compound (MDPV), and use was reported by only 1% of the sample (Miller and Stogner 2014). Similarly, a survey of attendees of gay clubs, hip hop clubs, indie rock clubs, and EDM clubs in New York City (NYC) in 2012 asked about use of synthetic cathinones or mephedrone, and similarly, only 1% reported use (Kelly et al. 2013).

Surveys focusing on EDM party attendees, however, have tended to find higher prevalence of reported synthetic cathinone use. We believe higher prevalence is detected in this population for four reasons. First, EDM party attendees are at high risk for using various drugs (Ross et al. 2003; Palamar et al. 2015a, 2017b; Kurtz et al. 2017), and use of other drugs has been found to be a major risk factor for synthetic cathinone abuse (Palamar et al. 2015b, 2017b; Fernández-Calderón et al. 2018). Second, various synthetic cathinone compounds have similar effects to common club drugs such as ecstasy, with some

compounds like mephedrone functioning as counterfeit replacements (Brunt et al. 2011a). Third, surveys of EDM party attendees tend to ask about multiple synthetic cathinone compounds and not just synthetic cathinones as an overall category, and it appears that asking about multiple compounds increases the likelihood of recognizing a specific compound that was used. Finally, EDM party attendees have been found to be at high risk for unknowingly or unintentionally using synthetic cathinones as these compounds are common adulterants in drugs such as ecstasy (Palamar et al. 2016c, 2017c).

A self-selected online sample of past-year drug-using nightclub attendees who participated in the Global Drug Survey in 2013 found that one-out-of-ten (10%) reported ever using at least one synthetic cathinone queried (Palamar et al. 2016b). Most (8%) reported methylone use, 5% reported mephedrone use, and 2% reported MDPV use. More recently, time-space sampling and weighting methods have been used by some studies to yield more accurate estimates of synthetic cathinone use from venue-based recruitment in the EDM scene. A study of young adult (age 18–25) EDM party attendees in 2015 estimated that 7% of attendees had used at least one (of 26) synthetic cathinone compound, with methylone (3%) being the most prevalent (Palamar et al. 2016a). In 2016, similar lifetime prevalence of 7.7% was estimated among EDM attendees in NYC age 18–40 (Palamar et al. 2018); however, in a new 2017 cohort of attendees, estimated prevalence of known use decreased in half to 3.5% (Palamar 2018).

Prevalence estimates of synthetic cathinone use also tend to be underestimates because many users of drugs such as ecstasy consume these compounds unknowingly, as synthetic cathinones are common adulterants or replacements (discussed in detail below). In fact, during a recent survey of EDM party attendees in NYC, 30% of respondents agreed that “bath salts” are sometimes found in Molly, and 15% reported believing they might have unknowingly used “bath salts” (Palamar 2018). This suggests many EDM attendees are aware of the high potential for adulteration, hence extensive interest in “drug checking” in which an individual’s drug is tested for purity (Barratt et al. 2018). To our knowledge, no studies have examined prevalence of adulteration in the United States, and this is likely due to high legal risk for both users and drug checkers. However, studies have begun to analyze biological specimens of users to determine whether they have used synthetic cathinones.

Toxicological Assessment of Synthetic Cathinone Use.

After the presence of synthetic cathinones on the black market became recognized, forensic and clinical laboratories worldwide had to face the analytical challenge of identifying and quantifying these new drugs in various biological matrices. The commercial unavailability of reference standards for the parent drugs and their metabolites, the lack of updated and comprehensive immunoassays for their detection, and the insufficient investigation of their metabolic transformation after intake represented just the main problems toward the identification and quantification of synthetic cathinones (Salomone et al. 2017). At the moment, most of the aforementioned challenges have been at least partially overcome. For example, reference standards for many parent compounds are now available from companies such as Cayman Chemical and Cerillian. Gas chromatography with mass spectrometry (GC-MS) is also employed to assess synthetic cathinone use (Alvarez et al. 2017). The most

recent equipment based on ultra high performance-tandem mass spectrometry (UHPLC-MS/MS) and high resolution mass spectrometry (UHPLC-HRMS) allows the detection of expansive synthetic cathinone panels within a single analytical run. Several laboratories currently embrace this promising advent by offering screening and confirmation analysis for synthetic cathinones (Zuba and Adamowicz 2018; Marchei et al. 2018).

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

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

particular, the occurrence of poly-use and unintentional intake of synthetic cathinones can be revealed by means of hair analysis, possibly combined with surveys.

Synthetic Cathinone Adulteration of Illegal Drugs.

Rust et al. (2012) examined hair samples from 2009 to 2010 from individuals who originally tested positive for amphetamines and/or MDMA (n=325) (Rust et al. 2012). Hair was collected as part of a driving ability assessment and employed liquid chromatography with tandem mass spectrometry (LC-MS/MS) to test for a variety of novel psychoactive substances (NPS), including synthetic cathinones. Of the 120 samples that tested positive for NPS, 10% tested positive for synthetic cathinones (11 samples for mephedrone, 1 sample for methylone). A later study also found high levels of mephedrone in suspected drug users. In France, Martin et al. (2012) found that nearly 20% of hair samples collected from those suspected of narcotic abuse (13 out of 67) tested positive for mephedrone (Martin et al. 2012). While it is unclear whether individuals in either of these studies were aware of synthetic cathinone use, these methods confirm the utility of analyzing hair to assess synthetic cathinone use in suspected users. In 2015, Palamar and colleagues surveyed and analyzed hair samples from 48 EDM attendees in NYC reporting lifetime ecstasy/MDMA/Molly use (Palamar et al. 2016c). Almost half (48%) of hair samples contained butylone and 10% contained methylone. However, of those who reported no lifetime use of synthetic cathinones or unknown pills or powders, 41% tested positive for a synthetic cathinone or other NPS. Specifically, of those denying use of any synthetic cathinones listed on the survey, 38% tested positive for butylone, 9% for methylone, and 3% for the highly potent compound α -PVP (“Flakka”). This study also found that racial/ethnic minorities were more likely to test positive for synthetic cathinones after denying lifetime use. The strongest predictor of testing positive for synthetic cathinones was frequent nightclub/festival attendance.

In 2016, a similar study was conducted with a focus on 90 past-year ecstasy users in the NYC EDM scene (Palamar et al. 2017c). While over a quarter (28%) of attendees tested positive for synthetic cathinones, 68% of those testing positive denied past-year use. Butylone (14%), ethylone (11%), and pentylone (10%) were the most commonly detected synthetic cathinones - strikingly, all participants denied use of these compounds. Methylone was detected in 3% of hair samples, but two of these three participants reported known use of this substance. Unknown α -PVP use was also detected in 2% of samples. These studies demonstrate that many ecstasy-using nightclub/festival attendees are unintentionally administering synthetic cathinones, and that drug checking may be beneficial for those unwilling or unable to abstain.

Synthetic cathinone use at EDM parties has also led to clusters of hospitalizations. In particular, there were at least 22 drug-related hospitalizations at the 2013 Electric Zoo EDM festival in NYC (Ridpath et al. 2014). Of the 22 reported hospitalizations, 9 (41%) were classified as severe, and there were two deaths. Of the 22 patients, 17 were administered toxicological tests, among whom 55% had used “synthetic club drugs.” Four of the 17 tested positive for methylone alone, 3 for methylone and MDMA, 2 for methylone and other illegal drugs other than MDMA, and 2 for MDMA alone. One decedent tested positive for MDMA,

while the other tested positive for both MDMA and methylone. It is unclear whether the second decedent or any of the other patients who tested positive for methylone were fully aware of their drug/formulation intake.

Various drug-testing services throughout Europe have also detected a range of synthetic cathinones in drugs sold as ecstasy. For example, despite the increasing purity of ecstasy tested from 2008–2013 (Brunt et al. 2017), a range of synthetic cathinones including 4-MEC, mephedrone, methylone, and ethylone were detected in submitted substances. The Drug 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 tests. While 60% did report having encountered a patient who admitted to bath salts use, these patients presented with symptoms that could have easily been misattributed to more common drugs of abuse. These symptoms include agitation (81%), aggression or violence (65%), or hallucinations (46%) – all common effects of the widely used drugs that synthetic cathinones may be intended to mimic.

Unintentional Synthetic Cathinone Use, Combinatorial Effects, and Underlying Neurobiology.

Unintentional synthetic cathinone use greatly increases the risk of overdose and death. The two most common causes of death from synthetic cathinone use are overdose and fatal self-

harm (Schifano et al. 2012; Marinetti and Antonides 2013). Our speculation is that overdoses occur because of a fundamental misunderstanding of the mechanisms and potencies of the synthetic cathinone(s) being used. Self-harm associated with synthetic cathinone use may result from serious psychological effects of intoxication such as loss of impulse control, increased risk-taking/sensation-seeking, hallucinations, and paranoia (Elliott and Evans 2014). Moreover, chronic use can lead to persistent neurochemical alterations that underlie extreme depression, thereby triggering self-harm (Banks et al. 2014; Barrio et al. 2016).

In general, the effects of synthetic cathinones are attributed to the neurotransmitters that most illicit drugs act upon including dopamine (DA), noradrenaline (NA) and serotonin (5-HT). Drugs such as cocaine function as DA and NA transporter (reuptake) blockers leading to net elevations in synaptic neurotransmitter levels. Compared to cocaine, MDPV increases synaptic NA with approximately 10-fold- and synaptic DA with approximately 50-fold-greater potency (Baumann et al. 2012). Therefore, if one consumes MDPV under the impression that it is cocaine, the resulting intoxication would be manifold greater than intended. Excitotoxic levels of DA and NA produce hyperthermia and increased heart rate that can lead to multiorgan failure and death (Walter and Carretto 2015).

Drugs such as MDMA, amphetamine, and methamphetamine act as DA, 5-HT, and NA transporter substrates, meaning the drug enters the cell and disrupts vesicular storage and transmitter release dynamics (e.g., Baumann et al. 2013). Transporter substrates produce persistent depletion of neurotransmitters and loss of functional transporters (Baumann et al. 2007, 2013; Gygi et al. 1997; German et al. 2014). Indeed depression and suicide are particularly common in heavy users of both MDMA and the mechanistically similar synthetic cathinone, mephedrone (Cohen 1996; Marinetti and Antonides 2013; Elliott and Evans 2014).

Death from unintentional synthetic cathinone overdose is typified by one of the first reported cases following unintentional “bath salts” consumption. Warrick et al. (2012) describe a 24-year-old female who died after consuming two pills of what turned out to be high doses of methylone and butylone rather than the “ecstasy” she believed she was taking. The patient was found unconscious at a concert and was febrile, tachypnic, and hypertensive. An ED exam revealed that she was diaphoretic, tremulous, hyperflexic, and had sustained clonus. Despite maximal supportive care, optimal ventilation, and improvements in hemodynamics and coagulopathy, within 48 hours of admission the patient developed acute respiratory distress syndrome, renal failure, hypoxemia, lactic acidosis and ultimately expired. Urinalysis and GC/MS testing of pills found on her person similar to the two ingested revealed the sole presence of methylone and butylone, with no traces of MDMA that the “ecstasy” was sold as. While methylone and butylone are 2–6x less potent than MDMA in terms of DA and 5-HT transporter substrate and blocking properties, the excessive quantity of each compound within each pill are the likely reason the patient expired. Ecstasy tablets typically contain 30–150 mg of MDMA, and while methylone and butylone are up to 10x less effective at reducing 5-HT and NA, the three drugs are similarly effective at increasing DA which may explain why the three drugs are consumed recreationally at similar doses (e.g., Hall and Henry 2006; López-Arnau et al. 2012; Warrick et al. 2012). In the case

described by Warrick et al. (2012), each pill contained 422 mg of methylone and 53 mg of butylone - doses that would produce profoundly higher DA levels than what is considered pleasurable or safe.

Unintentional synthetic cathinone use can occur in polydrug users, and a small number of preclinical studies have begun to elucidate the neurotoxic and behavioral effects of drug combinations. Table 1 lists effects observed in animal subjects following exposure to drug combinations that include a synthetic cathinone. Notably, enhancement of neurotoxicity is observed with drugs that have overlapping substrate properties (e.g., mephedrone elevates MDMA-induced DA neurotoxicity; Angoa-Perez 2013). Some combinations, however, produce unexpected protective effects that may be due to the mechanism of one drug minimizing effects of a second drug. For example, the DA transporter blocking properties of MDPV may protect against the DA releasing properties of methamphetamine (Anneken et al. 2015). In addition, many studies fail to account for potential contributions of temperature when examining the neurotoxic effects of synthetic cathinone use (alone or in combination with a second drug). For example, mephedrone potentiates the neurotoxic effects of MDMA under group- but not single-housing conditions (Hadlock et al. 2011) which likely reflects the inherent risk of consuming these combinations in crowded environments (e.g. EDM clubs). The neurotoxicity observed by Hadlock et al. (2011) was persistent yet limited to cells producing 5-HT. In humans, 5-HT depletion has been associated with the negative mood, irritability, and suicidal thoughts experienced in the days after MDMA or mephedrone use (Cohen 1996; Freeman et al. 2012). More research will be needed to reach a clearer understanding of how synthetic cathinones impact the neurochemical and behavioral effects experienced from other drugs when provided, knowingly or unbeknownst to the consumer, in polydrug formulations.

Synthetic cathinone users are at additional risk of experiencing psychosis. There are several reported cases of years-long, intermittent mephedrone users entering drug rehabilitation for delusional thoughts and auditory and visual hallucinations (Barrio 2016). Psychosis can occur in patients with no medical or family history of mental illness demonstrating the profound impact of long-term drug use that may have been consumed unknowingly. MDPV can produce delirium - a state characterized by bizarre behavior, paranoia, and hallucinations. For example, Penders and Gestring (2011) describe 3 cases of individuals experiencing delusions of persecution and harassment from nonexistent sources: one man hallucinated his estranged wife tapping on his window, a young housewife was filmed describing home invaders in an unoccupied room, and a middle-aged man hallucinated burglars shooting him with laser beams. Moreover, the memory disturbances common in MDPV-induced delirium greatly increase the risk of overdose death because patients frequently have no recollection of the amount, frequency, or route of administration. This is especially dangerous in the case of unintentional use of MDPV, of a drug that is over ten times more potent than the more common substance it may have been intended to mimic (e.g. cocaine). These cases demonstrate the great risk involved in consuming a substance that may be far more potent than one conceives.

Finally, unintentional synthetic cathinone use carries with it significant risk of death from self-harm. Self-harm has been cited as the second most common cause of death in synthetic

cathinone users (Schifano et al. 2012; Marinetti and Antonides 2013). A 3-year review of novel psychoactive substances in casework (Elliott and Evans 2014) found that in deaths following synthetic cathinone use, 41% were hangings or other mechanical suicide (i.e., fatal self-harm), which was the highest proportion compared to other classes of drugs. While hangings are the most common form of fatal self-harm, drownings, gunshot wounds, repeated self-lacerations, and jumping from bridges have all been reported (Schifano et al. 2012; Marinetti and Antonides 2013).

Self-harm related to synthetic cathinone use is attributed to impulsivity, paranoia, and violent behavior in response to vivid hallucinations or delusional thoughts (Penders 2012; Penders and Gestring 2011). In a case of fatal self-harm associated with synthetic cathinone use, a 21-year old with no history of depression committed suicide 5 days after ingesting an unknown powder later determined to be MDPV (PBS News, 2018). The decedent experienced days of insomnia and a frightening hallucination of 25 police cars outside his kitchen. Upon being told the police cars did not exist, the patient slit his throat in front of his parents. The self-inflicted laceration was non-fatal and was successfully stitched closed at a hospital. However, 4 hours after returning home from the hospital, and 5 days after initial drug-taking, the decedent committed suicide with a rifle. This case exemplifies how MDPV use can promote self-harm and suicide, possibly as a consequence of withdrawal-associated affective distress. It is likely the decedent was experiencing excitotoxic levels of DA during the psychotic episode. Synthetic cathinone-induced DA excitotoxicity can take days to normalize (Den Hollander et al. 2013; Martínez-Clemente et al. 2014), during which depression and suicidal thoughts may emerge. Indeed, the term “suicide tuesday” emerged to describe the depressive withdrawal state experienced days following initial drug-taking (Psychedelics.com 2018). It is possible that antipsychotic treatment may have prevented death of the patient, as antipsychotic drugs working as DA modulators synthetic cathinone-induced psychosis (Banks et al. 2014; Barrio et al. 2016).

ED clinicians and potential drug users can reduce the risk of overdose and death from unintentional synthetic cathinone use. Clinicians should be aware of the constellation of symptoms typical of synthetic cathinone overdose: agitation, sustained hyperthermia, muscle rigidity, and psychosis. The typical course of treatment involves aggressive cooling, hydration, and antipsychotic medication administration. Additionally, drug users who reject abstinence can make use of pill-testing services that can reliably detect the presence of ‘unknown substances’ in drugs such as cocaine and ecstasy (Saleemi et al. 2017). Drug users and clinicians should also note the potential for self-harm and suicide in patients during intoxication and during withdrawal. Future studies examining the toxicity associated with synthetic cathinone drug combinations are also needed to better address the emerging phenomenon of unintentional synthetic cathinone use.

Concluding Remarks.

Adulteration of illegal drugs with synthetic cathinones is an untenable yet largely unrecognized public health concern, the magnitude of which we are only beginning to appreciate through empirical observation. Traditional approaches used to assess the effects of drugs on public health and safety (e.g., surveys, urinalysis) are likely underestimating

synthetic cathinone use, especially in high-risk populations. Moreover, synthetic cathinone abuse carries with it risks unique to this class of drugs such as overdose, self-harm, and suicide. It is clear that synthetic cathinones mimicking relatively popular illegal drugs such as cocaine (e.g., MDPV) and MDMA (e.g., methylenedioxymethamphetamine) produce similar euphorogenic subjective effects, though typically at fractions of the dose.

We believe the burden of addressing this public health problem is complicated and shared by many. In effort to specifically reduce accidental overdose, we advocate the development and commercial sale of purity detectors (e.g. pill-testing products and services) that can be employed by users. We advocate the dissemination of accurate, empirically-derived information on the effects of synthetic cathinones so users and medical professionals including ED personnel can recognize when an individual - knowingly or not - has consumed a synthetic cathinone. Moreover, ED personnel should be aware of the availability of synthetic cathinone drug-testing products and services. In the future, collaborative work between field observers and basic scientists will (i) clarify the extent to which synthetic cathinones impact the subjective and physiological effects associated with other drug use, (ii) determine how situational factors such as environment influence the effects of synthetic cathinones taken with other drugs, and (iii) aide in the development of medical intervention strategies associated with the unique risks of drug use complicated by synthetic cathinone adulteration.

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Abbreviations.

α-PVP	α -pyrrolidinopentiophenone
4-MMC	4-methylmethcathinone
5-HT	serotonin
AAPCC	American Association of Poison Control Center
DA	dopamine
DEA	Drug Enforcement Administration
ED	emergency department
EDM	electronic dance music
MDMA	3,4-methylenedioxymethamphetamine
MDMC	3,4-methylenedioxymethcathinone
MDPV	3,4-methylenedioxypropylone
NA	noradrenaline

NFLIS	The National Forensic Laboratory Information System
NPS	new psychoactive substance
PCP	phencyclidine
UHPLC-HRMS	ultra high performance-tandem mass spectrometry-high resolution mass spectrometry
UHPLC-MS/MS	ultra high performance liquid chromatography-tandem mass spectrometry

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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	Potentates 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		