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Review

E-cigarettes—An unintended illicit drug delivery system

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ABSTRACT

Since the introduction of electronic cigarettes (e-cigarettes) in 2003, the technology has advanced allowing for greater user modifications, with users now able to control voltage, battery power, and constituents of the e-cigarette liquid. E-cigarettes have been the subject of a growing body of research with most research justifiably focused on the chemical makeup and risk analysis of chemicals, metals, and particulates found in e-cigarette liquids and vapor. Little research to date has focused on assessing the risks associated with the drug delivery unit itself and its potential for use as an illicit drug delivery system. In light of this, a range of illicit drugs was researched focusing on pharmacodynamics, usual method of administration, the dosage required for toxicity, toxic effects, and evidence of existing use in e-cigarettes in both literature and online illicit drug forums. A systematic literature search found evidence of current use of e-cigarettes to vape almost all illicit drug types analyzed. This presents both a potential population health risk and a management issue for clinicians. It also raises the issue of policing illicit drugs due to potential altered characteristic smells and storage within e-cigarette fluids. E-cigarettes are a viable illicit drug delivery system with evidence both inside and outside of the formal medical literature detailing their potential use for drug delivery of a wide range of illicit and legal drugs.

1. Introduction

The electronic cigarette (e-cigarette) first appeared in 2003 as an alternative to traditional tobacco cigarettes for nicotine delivery (Schraufnagel et al., 2014). Since its introduction, e-cigarette awareness and use has grown rapidly (Adkison et al., 2013; Schraufnagel et al., 2014) expanding into the global market with United States (U.S.) retail sales expected to approach $10 billion by 2017 (Besaratinia and Tommasi, 2017), and presenting a challenge for tobacco regulatory bodies and health departments (WHO, 2014). The past six years have seen a ten-fold increase in the number of adult smokers seeking to transition from smoking to vaping, with recent estimates showing more than 4 million Americans are using e-cigarette devices (Besaratinia and Tommasi, 2017). In 2014, e-cigarettes became a more common tobacco product among U.S. youth than traditional cigarettes (Eggers et al., 2017) and a survey of students in Wales, UK found that among year 11 students (aged 15–16) 37.3% had used an e-cigarette (ever) where only 26.5% had smoked a traditional cigarette (ever) showing the increased popularity of e-cigarettes among youth (Lacy et al., 2017). This has warranted an influx of research around both the technology and its delivery method.

Most studies to date have examined the chemical composition of e-cigarette vapor and liquid. This has included: nicotine delivery concentrations per puff (Czogala et al., 2014; Goniewicz et al., 2014; Pellegrino et al., 2012); e-cigarette liquid nicotine concentrations (Pisinger and Døssing, 2014); exhaled concentrations of propylene glycol (Pellegrino et al., 2012; Schober et al., 2014; Schripp et al., 2013) and its effects (Werley et al., 2011); glycerine vapor concentrations (Pellegrino et al., 2012) and its effects (Farsalinos and Polosa, 2014); acetone vapor concentrations (Schripp et al., 2013); formaldehyde vapor concentrations (Goniewicz et al., 2014, 2013; Schripp et al., 2013); nitrosonornicotine presence in vapor (Goniewicz et al., 2014; WHO, 2007); tobacco-specific nitrosamine presence in vapor (Farsalinos and Polosa, 2014; McAuley et al., 2012); metals in vapor (Goniewicz et al., 2014; Williams et al., 2013) and flavoring concentrations and toxicity (Bahl et al., 2012; Farsalinos et al., 2015; Khlystov and Samburova, 2016). Particulate matter (PM) levels have also been researched with studies showing that e-cigarettes produce PM_{10}, $PM_{2.5}$ and $PM_{1.0}$ (Pellegrino et al., 2012; Schober et al., 2014), though these levels are lower than traditional cigarettes (Czogala et al., 2014; Pellegrino et al., 2012) and differ depending on e-cigarette liquid brand and composition (Czogala et al., 2014; Schober et al., 2014). Common consensus is that e-cigarette users do not inhale the carcinogens contained in tars (Douglas et al., 2015), and the e-cigarette liquids

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are not heated to the point of combustion, therefore the health effects relating to the use of e-cigarettes are likely to be lower than for traditional cigarettes even though the long-term effects are largely unknown. There has also been a growing interest in the use of e-cigarettes as a tobacco smoking cessation device, with some studies showing promise for its use (Barbeau et al., 2013; Bullen et al., 2013), while others provide conflicting results (Orr and Asal, 2014) or suggest e-cigarettes may be a pathway to increased youth tobacco smoking (Dutra and Glantz, 2014; Leventhal et al., 2015). Despite this influx of research, some concerns have arisen. A serious concern addressed by a meta-analysis by Pisinger and Døssing is that of academic bias. They claimed that 34% of included authors on papers describing e-cigarette toxicity had a conflict of interest and that the majority of their included studies were either funded or supported to some degree by e-cigarette manufacturers (2014).

Another concern identified in the research is the lack of academic focus on the risk analysis of the e-cigarette drug delivery unit. Since the release of the first-generation e-cigarette, which was cigarette-shaped (Rom et al., 2015), three generations have followed. Second generation devices exhibited a change in style as well as introducing elements of larger rechargeable batteries and refillable e-cigarette fluid tanks (Dawkins et al., 2015). Third generation devices added the ability to modify the voltage provided to the atomizer to alter the atomizer temperature (Dawkins et al., 2015), generally up to 212 °C (Giroud et al., 2015), with consequent effects on the amount of vapor production. Further to this, third generation devices, with larger battery capacity and unit size, allowed the attachment of larger tanks allowing for greater e-cigarette liquid storage (Dawkins et al., 2015). These generational changes as well as the advanced user's ability to personally modify devices add a difficult to control variable when assessing the risk of the e-cigarette unit, especially considering the potential to deliver drugs of abuse.

Despite the growing catalog of research and studies surrounding e-cigarettes and the fact that inhalation has been noted as an increasingly common route of administration of illicit drugs due to the rapid onset of action, very little research has focused on possible alternative uses of e-cigarette technology (Bell and Nida, 2015). Since e-cigarettes have proved to be an effective nicotine drug delivery system (Schroeder and Hoffman, 2014), the question arises as to whether other illicit drugs are also able to be effectively delivered by e-cigarettes. Referring to the most commonly abused illicit drugs in Australia (AIHW, 2008) and around the world, the pharmacodynamics and pharmacokinetics of these drugs indicate the potential for the use of e-cigarette technology as a novel drug delivery system. The vaporization of cannabis had been proposed well before the first e-cigarette (Gieringer, 2001) with studies demonstrating that vaporization of medicinal cannabis produces plasma concentrations of Δ-9-tetrahydrocannabinol (Δ-9-THC) comparable to traditional cannabis combustion smoking (Abrams et al., 2007; Gieringer et al., 2004).

Due to the limited pool of literature on illicit drug delivery via e-cigarettes (Giroud et al., 2015), the question arises as to what other illicit drugs are being used via e-cigarette technology. In addition to summarizing the current literature relating to this topic, this paper, investigates the plausibility and risk of e-cigarette technology as a drug delivery system for illicit drugs. Drugs assessed include: cannabis, synthetic cannabinoids (SCs), synthetic cathinones, benzoylmethylecgonine (cocaine), gamma-hydroxybutyric acid (GHB), heroin, fentanyl, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), and methamphetamine. These drugs will be reviewed in terms of their known mechanisms of action, the dosage required for toxicity and toxic effects. Finally, the literature will be reviewed for evidence of e-cigarette use for each drug and where no evidence can be found illicit drug use internet forums will be accessed for preliminary evidence of possible usage.

The term 'vaping' is used both colloquially and in the literature to describe the through mouth inhalation of a vaporized product from a device that uses electrical power to heat the product to the point of vaporization. The product can refer to substances with desired inhalation effects such as nicotine dissolved in e-liquids (usually a mix of propylene glycol and glycerine); crushed plant material placed directly into the vaporizing device; concentrated extracts from plant materials in the form of thick waxes or oils either on their own or diluted in e-liquid; or substances directly dripped onto the hot coil to produce vapor. Vaping devices can be classified into two broad categories portable vaporizing devices, powered by batteries, or table-top vaporizers. For the purposes of this paper 'e-cigarettes' is used as a collective term for all types of portable vaporizing devices, not only those that resemble traditional cigarettes. 'Vaping' can refer to use of either e-cigarettes or table-top vaporizers or both unless specified.

2. Methods

2.1. Search strategy

A systematic search for the use of electronic cigarettes or other vaping devices to vape illicit drugs in the literature was conducted on 14 March 2018. The databases employed were ProQuest, Scopus, Web of Science and PubMed. The literature search was left deliberately broad to ensure all results involving the use of electronic cigarettes or other vaping devices to vape illicit drugs were captured. The search strategy employed for all databases was as follows: ab(cannabis OR THC OR cathinone OR alpha-PVP OR MDPV OR methylone OR mephedrone OR cocaine OR GHB OR "gamma-hydroxybutyric acid" OR heroin OR fentanyl OR oxycodone OR opioid OR MDA OR "3,4-methylenedioxyamphetamine" OR amphetamine OR methamphetamine OR MDMA OR "3,4-methylenedioxymethamphetamine" OR Molly OR ecstasy OR "synthetic cannabinoid" OR cannabinoid OR "bath salts" OR "legal high") AND (vapor OR vapor OR vaping OR vape OR e-cigarette OR "electronic cigarette" OR e-cig OR "e-cig" OR vaporizer OR vaporizer OR vaporizer) limited to English (abstract only). Illicit drug user forums were accessed in lieu of formal medical literature to assess evidence for the use of illicit drugs with e-cigarettes. Forum websites were searched using the same terms as the academic literature search, however, colloquial and street names were used in the search. The following websites were utilized: www.bluelight.org/vb/content/; https://drugs-forum.com/forum/index.php; https://www.reddit.com/r/Drugs/; https://www.quora.com; and https://www.erowid.org. Evidence of use was subjectively assessed via forum threads and user comments directly indicating either personal or known associate use.

2.2. Search selection

The initial database search identified 1603 papers, which once duplicates were removed left 1118 results (Fig. 1). Of those, 935 records were eliminated because of their irrelevance to the topic, and a further 145 were removed following full-text screening as they did not provide specific examples of the use of electronic-cigarette style devices to vape illicit drugs. The remaining 38 articles were used in the final analysis, articles relating to cannabis use in e-cigarettes are marked in the reference list with a *; articles relating to any other type of illicit drug use in e-cigarettes are marked with a ^.

3. Results

3.1. Cannabis

Cannabis (marijuana) is currently the most widely used illicit drug in the world (3.5% adults), with the highest rates of past year usage in Oceania (10.3%) (Gowing et al., 2015). It is usually administered orally or by inhalation (Grotenhermen, 2003; Pillay, 2013). The theory behind vaping cannabis is a reduction in inhalation of smoke-related toxins and carcinogens including tar, carbon monoxide and ammonia (Budney

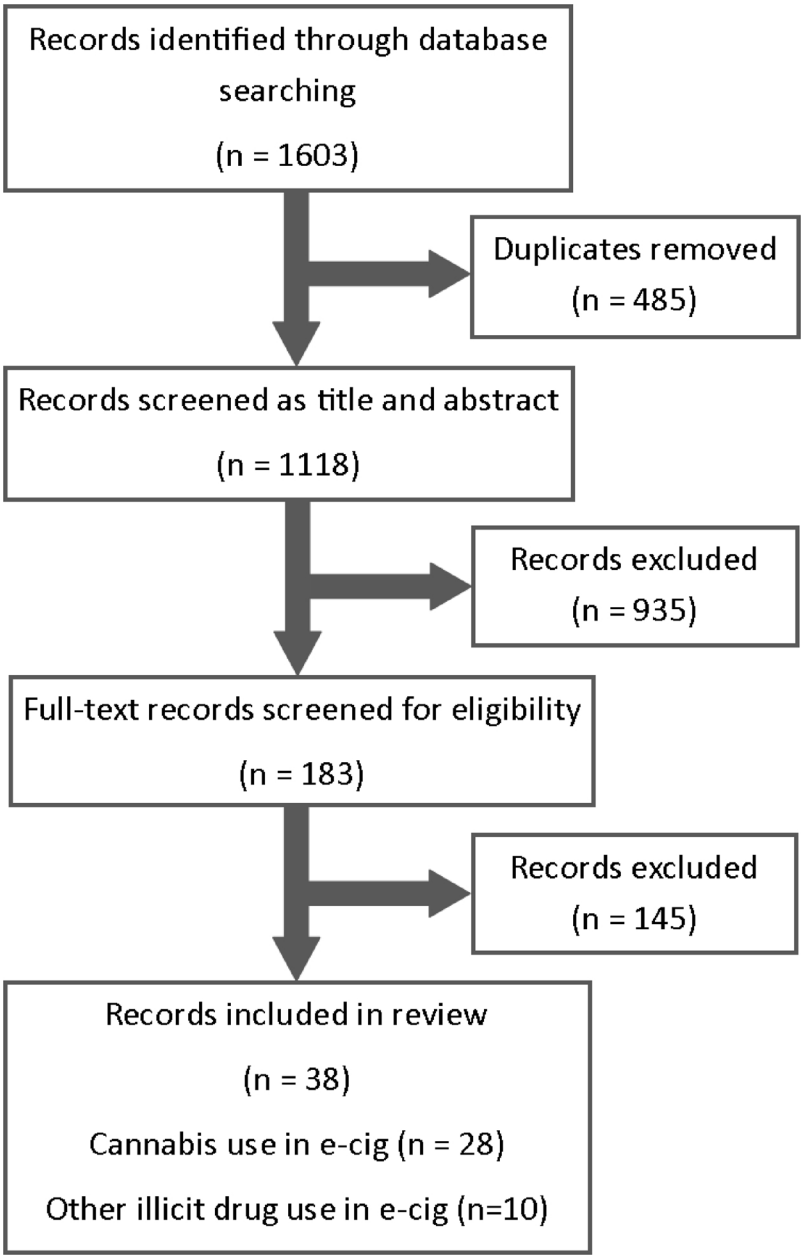

Fig. 1. Systematic review selection process.

et al., 2015), and in particular harm minimization for medicinal cannabis users (Gieringer et al., 2004; Gieringer, 2001; Van Dam and Earleywine, 2010). Cannabis users perceive vaping to be less harmful to their health than smoking methods (Budney et al., 2015) and those who use vaporizers claim to experience less respiratory irritation (Loflin and Earleywine, 2015). A survey of those who had 'ever-vaped' cannabis reported that vaping tastes better than smoking (39.3% of users); is healthier (42.9%); and produces a stronger high (58.1%) (Morean et al., 2015). Vaping of cannabis has the potential to decrease the risk of second-hand smoke inhalation (Cranford et al., 2016) and might reduce the number of youths becoming addicted to nicotine due to 'mulling' of the cannabis with tobacco before smoking (Gartner, 2015).

The main active component of cannabis is Δ-9-tetrahydrocannabinol (Δ-9-THC). Δ-9-THC acts as a partial agonist (Mills et al., 2015) equally upon the cannabinoid receptors CB_1 and CB_2 (Adams and Martin, 1996; Grotenhermen, 2003). CB_1 receptors are primarily present in the central and peripheral nervous system and produce the main effects of drug intoxication, whilst CB_2 receptors are found primarily in immune cells and do not contribute to the effects of intoxication (Grotenhermen, 2003). Activation of these receptors appears to inhibit the release of a number of neurotransmitters including acetylcholine, norepinephrine, GABA, dopamine, serotonin, and prostaglandins (McGuigon, 2006; Pillay, 2013). Δ-9-THC and its active metabolite 11 – OH-THC both contribute to the psychotropic effects of cannabis (Greydanus et al., 2015). Inhalation of vaporized cannabis produces pharmacokinetic curves and plasma concentrations of Δ-9-THC and its active metabolite that are similar to those from smoking cannabis (Hartman et al., 2015; Swortwood et al., 2016).

3.1.1. Dosage required for toxicity

Toxicity is thought to be affected largely by individual prior experience and tolerance level (Benowitz, 2012a). Dosages of up to 9000 mg/kg of Δ-9-THC have been administered to monkeys with no reported deaths (Thompson et al., 1973). Inhaled dosages > 7.5 mg/m^2 can produce symptoms such as hypotension, panic, anxiety, myoclonic jerking, delirium, respiratory depression, and ataxia in adults (Turner

and Agrawal, 2017).

3.1.2. Toxic effects

Effects are dependent on dose (Grotenhermen, 2003; Hoch et al., 2015), as well as the frequency of use and method of preparation (Hoch et al., 2015). Toxic effects can include: reduced psychomotor and cognitive performance (Solowij et al., 2001), anxiety and panic attacks (Benowitz, 2012a; Grotenhermen, 2003), psychotic episodes (Hall, 1994), delusions, hallucinations, slurred speech, mood swings, orthostatic hypotension and tachycardia (Benowitz, 2012a; Cavazos-Rehg et al., 2016; Leikin and Paloucek, 2007). There are reports of increased rates of conjunctivitis regardless of route of administration, as well as the exacerbation of pre-existing psychotic diseases (Turner and Agrawal, 2017) and development of cannabinoid hyperemesis syndrome in long-term users, particularly those consuming cannabis with a high Δ-9-THC content (Galli et al., 2011). There is also a case report of acute respiratory failure in a patient who had vaped cannabis oil approximately once a week for several years but had never smoked (He et al., 2017).

3.1.3. E-cigarette usage

Vaping is a highly prevalent mode of use among medical marijuana patients, with 39% of survey respondents having vaped in the past month. However, it is rarely an explicit route of administration, often combined with others including smoking, oral and topical (Cranford et al., 2016). There have been a number of e-cigarette accessories, including interchangeable coil heads, specifically designed and adapted for use vaping dry plant material, oil concentrates, and cannabis-based e-liquids (Giroud et al., 2015). Numerous survey studies investigating the prevalence of cannabis vaping among adults and youth are summarized in Table 1.

A temperature of approximately 200 °C is sufficient for decarboxylation and vaporization (Lanz et al., 2016) with the cannabinoids vaporizing at temperatures ranging from 157 to 220 °C (Troutt and DiDonato, 2017). Exposure to higher temperatures, or prolonged exposure to the heating coil will result in the subsequent formation of toxic pyrolytic by-products (Giroud et al., 2015). In addition, a study of the common thinning agents mixed with cannabis oil prior to use in e-cigarettes found that at 230 °C a number of toxic aldehydes, including acetaldehyde and formaldehyde were produced (Troutt and DiDonato, 2017). Several brands of bench-top electronic vaporizers were analyzed using a vaporization temperature of 210 °C with vapor recovery of Δ-9-THC varying between 54.6–82.7% and cannabidiol (CBD) from 51.4 to 70.0%. Decarboxylation was > 97.3% for Δ-9-THC for all devices (Lanz et al., 2016).

Following the legalization of marijuana in some U.S. states there has been an influx of e-liquids containing cannabinoids to the marketplace (Peace et al., 2016a) where the sale of prefilled cannabis oil cartridges (for vaporization) in Colorado increased by 163% between February 2015 and February 2016 (Troutt and DiDonato, 2017). However, there is often a significant discrepancy between the labeling of products and the actual contents. Two commercial marijuana e-liquids for use in e-cigarettes which claimed to contain 3.3 mg/ml CBD were found to contain 6.5 and 7.6 mg/ml CBD (Peace et al., 2016a). In a separate study analysis of another cannabis e-liquid which claimed to contain 69.1% Δ-9-THC and 1% CBD was shown to contain 42.6% Δ-9-THC (w/v) and 0.5% CBD (w/v) (Peace et al., 2016b). A study analyzing 84 cannabidiol (CBD) extracts for sale as medical products found that only 31% contained a CBD content that corresponded with the label (within 10%), 43% exceeded the amount shown on the label, and 26% contained less CBD than shown (Bonn-Miller et al., 2017).

In addition to using vaping devices such as e-cigarettes to vape e-liquids and cannabis plant material, the devices are also employed to consume high potency cannabis concentrates (Budney et al., 2015). Concentrates, obtained from solvent extraction of the plant, contain significantly higher Δ-9-THC content (~80% c.f. ~10%) (Cavazos-Rehg et al., 2016; Daniulaityte et al., 2015), and can be easily vaporized (Blundell et al., 2018b). Concentrates can be divided into four general categories: kief from dry extraction processes such as dry-ice; hash oil (also known as bubble) from water extraction; butane honey oil (BHO) (also known as wax, shatter or budder) from butane solvent extraction (other organic solvents can also be used); and CO_2 oil from CO_2 extraction (Raber et al., 2015). Because the extraction process is not regulated and is often performed in clandestine laboratories, there is a wide variation in the purity and potency of these products (Budney et al., 2015). Lifetime cannabis vapers reported a preference for hash oil (45.5%), and dried buds (39.4%) over Δ-9-THC wax (15.2%) (Morean et al., 2015). Analysis of concentrates found that 83.3% of samples contained some residual solvents, with isopentane the most common residual solvent identified (29.8%) (Raber et al., 2015). Pesticides were also identified in 33.3% of concentrate samples (Raber et al., 2015). Recently, there has been a proliferation of advertising in states that have legalized medical marijuana. According to a preliminary study reported by Carlini et al. (2017), approximately 20% of the advertisements they analyzed featured concentrates or devices used to consume concentrates.

A new method of partaking in cannabinoids is via a technique known as 'dabbing' (Greydanus et al., 2015; Krauss et al., 2015). Dabbing involves heating a cannabis concentrate, often BHO, to high temperatures and inhaling the resulting vapor (Cavazos-Rehg et al., 2016) often the 'dab' of oil is vaporized on the end of a glass rod that has been heated with a blowtorch (Giroud et al., 2015; Raber et al., 2015) or used in a vaporizer or electronic cigarette (Zhang et al., 2016). The slang term 'dabs' seems to be used regardless of the type of concentrate (e.g., BHO) being used or the mode of inhalation (e.g., via a dab rig or vape pens; Daniulaityte et al., 2017).

Accurate determination of rates of e-cigarette use for cannabis is difficult to determine due to the wide variation in the types of nomenclature used for these devices. For example, e-cigarettes, vape pens, and e-vaporizers (usually a portable electronic vaporizer that isn't shaped like a traditional cigarette) are all types of portable electronic vaporizers, whereas 'electronic vaporizer' can mean e-vaporizer or can be referring to a table-top non-portable system. E-cigarettes can be used as a general term to describe any portable vaporization device (as it is in this paper) or it might specifically refer to small disposable e-cigarettes which very closely resemble traditional cigarettes. Additionally, terms used interchangeably with e-cigarettes include vape-mod, box-mod, personal vaporizer, and specifically for cannabis use e-joint or vape joint. Hakkarainen (2016) has proposed more defined terminology where the term e-cigarette is used exclusively for tobacco vaporization whereas vape-pen could be used as a term for portable vaporizers for cannabis. The difficulty here is the obvious cross-over between these units with individuals often using their e-cigarettes usually used for nicotine consumption for more illicit drugs including cannabis. Adding to this intricacy is the novel use of existing terminology. A series of semi-structured interviews with young adults revealed an increasing complexity in the use of terms as common as the word 'smoking' with confusion as to whether the word smoking refers to tobacco, cannabis or either. Terminology seemed to vary by geographical location with one respondent claiming that in Colorado the term 'smoke' indicated marijuana use, but in Texas, the term would mean tobacco use (McDonald et al., 2016).

3.2. Synthetic cannabinoids

Synthetic cannabinoids (SCs) consist of hundreds of designer drugs (Castaneto et al., 2014) based off the structure of Δ-9-THC, with 160 SCs currently being monitored by the European Monitoring Centre for Drugs and Drug Addictions (EMCDDA) (Kim et al., 2017). They are particularly attractive to young people due to: a lack of available methods of detection in bodily fluids, largely caused by a regular influx of new structural entities to the market; the perception that the drugs

Table 1
Summary of survey findings describing current use of vaporizers to consume cannabis. Unless specified 'vaporizer' use may be referring to table-top vaporizers, or vape-pen (e-cigarette) style-vaporizers or a combination of both.

Ref.	Year	Study Description	Relevant Findings
(Hindocha et al., 2016)	2013-2014	Global Drug Survey, online, adult, past year cannabis use, n = 33,687	5.8% of Australian cannabis users had used a vaporizer as the route of administration compared to 11.2% of respondents from the United States and 13.3% from Canada.
(Schauer et al., 2016)	2014	United States, Summer Styles Survey, adults, n = 4269	7.6% of past 30-day cannabis users had used a vaporizer or other electronic device to consume cannabis, compared with 9.9% of ever-cannabis users.
(Lankenau et al., 2017)	2014-2015	United States, Los Angeles, young adult (18–26 years), current cannabis users, medical vs recreational use, n = 366	44.3% of users had used an electronic vaporizer such as an e-cigarette or vape-pen in the past 90 days, this value increased to 51.9% when considering only the medical marijuana user.
(Lee et al., 2016)	2014-2015	United States, online, adult, current cannabis users, n = 2910	61% of current cannabis users had administered cannabis via vaping; 37% had vaped in the past 30 days; 20% reported > 100 days of vaping; and 12% reported vaping as their preferred method of administration.
(Morean et al., 2017)	2015	United States, adult, past month nicotine e-cigarette use, n = 522	52.3% of nicotine e-cigarette users reported use of any cannabis; 17.8% reported ever-use of an e-cigarette or vape pen to vaporize cannabis; 11.5% reported vaping cannabis in the past month.
(Shiplo et al., 2016)	2015	Canada, adult, medical cannabis use, n = 364	65.9% of medical cannabis users had ever used a vaporizer as a mode of delivery; 5.27% were current users; and 28.3% stated vaporizers were their preferred mode of delivery. Most of the respondents claimed use of a portable vaporizer (such as an e-cigarette) rather than a table-top vaporizer.
(Daniulaityte et al., 2017)	2016	United States, adult, current cannabis users, n = 673	> 66% of current cannabis users had used marijuana concentrates, with about 13% reporting daily or near daily use. Of those using concentrates 66% reported the use of a vape pen to consume cannabis.
(Morean et al., 2015)	2014	United States, Connecticut, middle and high school students, n = 3847	4.5% had used an e-cigarette to vaporize hash oil; 3.0% had used e-cigarettes to vaporize THC-infused wax; and 6.7% had used a portable electronic vaporizer to vaporize dry cannabis plant material.
(Eggers et al., 2017)	2015	United States, Florida Youth Tobacco Survey, middle and high school students, n = 12,320	3.4% of middle school students and 11.5% of high school students reported ever using a vaping device to consume cannabis.
(Mammen et al., 2016)	2015	Canada, Ontario Student Drug Use and Health Survey, high school students, n = 3171	8% of high school students reported vaping cannabis using an e-cigarette (the value is possibly even higher if other forms of vaporizer are considered).
(Blundell et al., 2018a)	2017	UK, adult (> 16 yrs.), convenience sample, online questionnaire, n = 2501	6.2% of respondents reported vaping cannabis (ever use); 3.6% of respondents reported vaping cannabis (last 30 days); majority (74%) of users used an e-cigarette.
(Borodovsky et al., 2016)	2014-2015	United States, adult, convenience sample of past cannabis users, online survey, n = 2838	53.8% of cannabis users in states without legal medical marijuana had vaped cannabis; 68.6% of cannabis users in states with legal medical marijuana had vaped cannabis
(Borodovsky et al., 2017)	2016	United States, youth (14–18 yrs.), convenience sample of past cannabis users, online survey, n = 2630	35.6% of cannabis users in states without legal medical marijuana had vaped cannabis; 50.8% of cannabis users in states with legal medical marijuana had vaped cannabis
(Cuttler et al., 2016)	–	United States, adult, convenience sample of past cannabis users, online survey, n = 2459	17.3% of male cannabis users and 11.4% of female cannabis users reported their method of use as a vaporizer; 5.4% of males and 3.1% of females reported use of concentrates
(Cranford et al., 2016)	2014-2015	United States, adults (> 21 yrs), medical marijuana users, n = 1485	38.7% past month cannabis vaping; small number used vaping as the only route of administration (5.9%)
(Etter, 2015)	2013-2014	Europe, adults, e-cig or portable e-vaporizer cannabis users, n = 55	11 responders used e-cig; 44 responders used portable e-vaporizer; most common products used in e-cig were buds (45%) and oil (54%), in portable e-vaporizers were buds (77%), oil (21%) and hashish (21%)
(Frohe et al., 2018)	2017	United States, college students > 18 yrs. n = 270	10.7% of respondents had used a vape-pen to vape cannabis
(Johnson et al., 2016)	2013	United States, high school students, Healthy Kids Colorado Survey, n = 25,197	6.2% (weighted) of past 30-day cannabis users stated vaporization was their usual method of consumption of cannabis
(Jones et al., 2016)	2016	United States, college students enrolled in intro Psychology, questionnaire, n = 482	22.5% of respondents had vaped cannabis; 51.2% of past-year cannabis users had vaped cannabis

are natural and therefore legal and/or harmless; and the ease of access, often via both convenience stores and the internet labelled as 'legal high' or 'not for human consumption' (Castellanos and Gralnik, 2016; NDEWS, 2015; Weinstein et al., 2017). Street names for SCs vary by country; the most common are 'K2' in the United States, 'Spice' in Europe, and 'Kronic' in Australia and New Zealand (Zawilska and Andrzejczak, 2015). Several countries have reported the identification of products that are being sold as cannabis resin on the illicit market that consist of synthetic cannabinoids (Castellanos and Gralnik, 2016). SCs are available as a plant preparation, where the cannabinoids are dissolved and sprayed onto various herbs, as capsules and in e-liquid formations (Schifano et al., 2017). The usual routes of administration are inhalational, intranasal, and oral (Vandrey et al., 2012).

Most SCs exhibit a full agonist effect on CB_1 receptors (Koller et al., 2013), and to a lesser extent, CB_2 receptors (Mills et al., 2015) with a faster time to peak of onset effect and a shorter duration of action than natural cannabinoids (DeBruyne and Boisselier, 2015; Schifano et al., 2017). However, some have been identified as full agonists at both the CB_1 and CB_2 receptors which results not only in greater potency but also potentially more severe adverse effects (Blundell et al., 2018b). Activation of CB_1 receptors is associated with the drug's effects (Mills et al., 2015), with most synthetic cannabinoids exhibiting significantly stronger affinity than Δ-9-THC when binding to CB_1 receptors (ElSohly et al., 2014), and some mono-hydroxylated SC metabolites retaining nanomolar binding affinity for CB_1 receptors (Tai and Fantegrossi, 2017). The higher affinity of SCs and the presence of multiple active metabolites may explain the increased morbidity and mortality seen with SC abuse when compared with cannabis (Tai and Fantegrossi, 2017).

3.2.1. Dosage required for toxicity

Dosage of synthetic cannabinoids is often relatively low due to the high affinity of the drugs for CB_1 receptors (Castaneto et al., 2015). Toxic effects have been reported in blood serum levels of JWH-018 lower than 0.10 ng/ml (Hermanns-Clausen et al., 2013), while some regular users who have built up tolerance to the drug can demonstrate

higher serum levels, up to 17 ng/ml, without toxic symptoms occurring (Dresen et al., 2011). To demonstrate the variability in toxic levels, the synthetic cannabinoid JWH-210 can produce similar toxic effects at blood serum levels as low as 0.20 ng/ml and as high as 190 ng/ml (Hermanns-Clausen et al., 2013). Actual toxic dosage levels are similarly difficult to establish. Tonic-clonic seizures have been reported in smoked dosages of 3 g of Spice (Pant et al., 2012). Aggression, agitation, panic attack and vomiting have been reported following a smoked dosage of 300 mg of 'Samurai King' (Derungs et al., 2013), recurrence of cannabis-induced psychosis following 3 g of smoked 'Spice' (Müller et al., 2010) and post-traumatic stress disorder flashbacks and hallucinations following a 1.5 g a day habit of smoked 'Spice' (Peglow et al., 2012).

3.2.2. Toxic effects

Effects are dependent on the individual user, dosage and the particular SC and its mixture (Salani and Zdanowicz, 2015). Nausea and vomiting, hypokalaemia, acute psychosis, panic attack, confusion, agitation, blindness, deafness, mild to intense pain, severe sinus bradycardia or tachycardia (Andonian et al., 2017; Carlier et al., 2016), ventricular dysrhythmias, hypo- or hyperthermia, hypo- or hyperglycaemia (Hermanns-Clausen et al., 2013; Kersten and McLaughlin, 2015), sweating, muscle twitching, chest pain, shortness of breath, myocardial infarction, rhabdomyolysis (Castellanos and Gralnik, 2016; Weaver et al., 2015; Zawilska and Andrzejczak, 2015), ischaemic stroke (Castaneto et al., 2014), excited delirium, acute kidney injury, seizures, hallucinations, cardiotoxic effects, and coma (Trecki et al., 2015) have been reported. Death due to cardiac ischemic event and extreme anxiety leading to suicide have also been reported following SC use (Weaver et al., 2015).

3.2.3. E-cigarette usage

Blundell et al. (2018a) reviewed drug user forums and determined that around 15% of individuals who vaped cannabis have also vaped synthetic cannabinoids (Blundell et al., 2018b). In a survey study by the same group 7.8% of electronic vaping device users admitted to vaping synthetic cannabinoids. A National Early Warning System Report out of Atlanta stated that the use of vaporization techniques involving e-cigarettes is becoming a popular method of use for administration of synthetic cannabinoids (NDEWS, 2015). The manufacture of SCs in liquid cartridges for use in e-cigarettes has also been reported (DEA, 2016; Castellanos and Gralnik, 2016; DeBruyne and Boisselier, 2015). These solutions are colloquially referred to as 'Buddha-blue,' 'C-liquid,' 'herbal e-liquid,' and others (DeBruyne and Boisselier, 2015). In contrast, the more non-polar synthetic cannabinoids are generally sprayed onto aromatic herbs and vaped using a dry-herb coil head fitted to an e-cigarette rather than consumed as an e-liquid due to poor solubility (Giroud et al., 2015).

There have also been several reports of intoxication due to vaporization of synthetic cannabinoids. In 2014 there were a number of teens treated for intoxication with cannabinoid 'Cloud 9.' According to police reports the students were putting drops on their tongues, mixing it with candy or soft drinks and using e-cigarettes to vaporize the drug (Glover, 2014). Literature case reports of patients receiving treatment for intoxication due to suspected or known vaping of synthetic cannabinoids are described in Table 2.

3.3. Methamphetamine

Methamphetamine is a central nervous system stimulant that belongs to both the amphetamine and phenethylamine drug classes (Yu et al., 2015) typical behavioral effects include alertness, energy, and euphoria (Kish, 2008). Usual routes of administration are inhalational, oral, intravenous, and intranasal (Elkashef et al., 2008). Methamphetamine targets and reverses the vesicular monoamine uptake transporter-2 (VMAT) (Elkashef et al., 2008). This results in rapid accumulation of monoamines, dopamine, serotonin and norepinephrine in the presynaptic neuron, followed by their release into the extracellular space due to transporter reversal (Elkashef et al., 2008; Kish, 2008). Methamphetamine is also a weak inhibitor of monoamine oxidase (MAO) resulting in a reduction of monoamine neurotransmitter metabolism, extending their duration of effect in the synaptic cleft (Elkashef et al., 2008).

3.3.1. Dosage required for toxicity

Methamphetamine bioavailability via inhalation (smoking) ranges from 67% to 90% depending upon smoking technique (Cruickshank and Dyer, 2009). Inhaled dosages above 50 mg have the potential to cause some toxicity, but specific toxic dosages are difficult to determine due to significant variability between individuals, particularly in long-term users. Dosages greater than 150 mg are thought to be highly toxic to non-chronic users (Cho, 1990). Long-term chronic users can tolerate higher dosages of up to 1000 mg or more (Lake and Quirk, 1984).

3.3.2. Toxic effects

Restlessness, insomnia, hyperthermia, seizures, agitation, psychosis, paranoia (Elkashef et al., 2008), thirst, diaphoresis, paresthesia, headaches, aggression (Bell, 1973), angina, nausea and vomiting, hallucinations, palpitations, dyspnoea, ventricular fibrillation, myocardial infarction, tooth decay (meth mouth), coma, and renal failure (De-Carolis et al., 2015) as well as rhabdomyolysis and suicidal ideation (Cruickshank and Dyer, 2009) have been reported. An increase in the rate of both hemorrhagic and ischemic stroke in young people (< 45 years) has also been reported with ischemic stroke noted to be more common with an inhalational route of administration (Lappin et al., 2017).

3.3.3. E-cigarette usage

Literature indicates that an increasing number of individuals are using drug vaporization, such as e-cigarettes, as a new method of administration for methamphetamine (NDEWS, 2015). Additionally, researchers have recently shown that methamphetamine is present at reasonable concentrations in vapor from e-cigarettes (McNeill, 2016). While literature evidence on the use of e-cigarettes for the vaping of methamphetamine is currently limited, internet drug forum users have stated that they have used e-cigarettes (Fig. 2), vape pens and/or tabletop units to vaporize methamphetamine.

3.4. MDMA

3-4-Methylenedioxymethamphetamine (MDMA), also known as 'Ecstasy' or 'Molly', is an amphetamine derivative and psychostimulant used primarily as a recreational drug to increase user empathy and euphoria (Green et al., 2012). The usual administration routes are oral, intranasal, inhalational, and via intravenous injection (EMCDDA, 2015c). MDMA blocks the reuptake of monoamine neurotransmitters (norepinephrine, serotonin, dopamine) (De la Torre et al., 2004; Steinkellner et al., 2011), with MDMA exhibiting a stronger affinity for serotonin, and norepinephrine transporters (Rothman et al., 2001). It also acts as a competitive substrate for monoamines and reverses monoamine transportation, further reducing monoamine reuptake (Sitte and Freissmuth, 2010).

3.4.1. Dosage required for toxicity

Tolerance to MDMA develops rapidly with a subsequent increase in adverse effects due to frequent use. Toxic dosage is dependent on individual susceptibility (EMCDDA, 2015c). There is little data on toxicity due to inhalation; however, toxic symptoms such as psychosis and paranoia have been reported with oral dosages of 80–85 mg (Ellenhorn et al., 1997) and fatalities have been recorded following dosages of 300 mg (EMCDDA, 2015c). Severe hyperthermia has been reported at doses of 4–5 mg/kg (Hahn, 2017).

Table 2
Summary of case reports involving known or suspected intoxication with synthetic cannabinoids that had been vaped or were found in e-liquids for vaporization.

Ref	Patient	Clinical Signs	Drug Identification
(Lam et al., 2017)	24 yrs. old male; confusion, agitation, palpitation and vomiting following the oral ingestion of 2 drops of e-cig fluid	GCS – 14/15; BP – 163/93 mmHg; HR – 169 bpm; 12 lead ECG showed sinus tachycardia with multiple ventricular ectopic beats	AB-FUBINACA (serum 5.6 ng/ml) and ADB-FUBINACA (serum 15.6 ng/ml) identified in e-cig fluid and serum
(McCloskey et al., 2016)	36 yrs. old male; found "kicking" and "rolling" around sidewalk; patient was holding an e-cig	BP – 151/56 mmHg; HR – 106 bpm; Non-specific T wave and ST segment changes; creatine kinase 3936 U/L	Patient admitted to placing K2 in e-cig to "get high"
(Mehta et al., 2017)	16 yrs. old obese male; sudden onset of left-sided chest pain following e-cig use	BP – 142/76 mmHg; ECG showed non-specific ST segment changes troponin I 1.63 ng/ml;	Urine screen positive for cannabinoids; suspected intoxication with synthetic cannabinoids; no verification

3.4.2. Toxic effects

Nausea, vomiting, restlessness, tremor, hyperreflexia, irritability, trismus and bruxism, palpitations, confusion, aggression, psychosis, panic attack (De la Torre et al., 2004), hyperthermia, serotonin syndrome, cardiac arrhythmias, hypertension, hyponatremia, seizures, coma, death (Schifano, 2004).

3.4.3. E-cigarette usage

There is evidence on internet drug forums of users employing vaporization techniques, such as e-cigarettes and table-top vaporizers, to vape MDMA. In several cases, users made mention of ensuring the drug was converted into the free-base form before vaporization. A survey by Blundell et al. (2018a) determined that 11.7% of electronic vaping device users have vaped MDMA.

3.5. Synthetic cathinones

One of the major classes of new psychoactive substances is synthetic cathinones which are sold as alternatives to 3,4-methylenedioxymethamphetamine (MDMA) and other amphetamines, with which they share structural similarities, or cocaine (Anizan et al., 2014; Ellefsen et al., 2016). In 2014, 31% of the 101 new psychoactive substances (NPS) identified were synthetic cathinones (Glennon and Dukat, 2017). Cathinones are often marketed as legal highs or labelled as "bath salts,' 'plant food,' or 'research chemicals' often in combination with the warning 'not for human consumption' in order to avoid government legislative control (Abbott and Smith, 2015; Anizan et al., 2014; Backberg et al., 2015; Ellefsen et al., 2016). Chemical purity in commercially available 'bath salts' is often a problem with no quality control in manufacturing (Backberg et al., 2015). A study of 27 'legal high' products identified a wide variety of synthetic cathinones, as well as drugs from other structural classes, and samples rarely contained a single psychoactive ingredient (Araujo et al., 2015). 17% of the samples studied contained caffeine, sometimes at concentrations > 20%, and often samples sold under the same name at different stores showed an utterly different composition (Araujo et al., 2015).

The most common synthetic cathinones in the United States are α-pyrrolidinopentiophenone (α-PVP), 3,4-methylenedioxypyrovalerone (MDPV), and pentedrone; while mephedrone and methylone are more common in Europe (Barrios et al., 2016; Weinstein et al., 2017). Cathinones act to inhibit monoamine transporters for the reuptake of dopamine (DAT), serotonin (SERT) and norepinephrine (NET) blocking the reuptake of these neurotransmitters; however, their activity is complex due to varying selectivity for different transporters (Abbott and Smith, 2015; Matsunaga et al., 2017). Adding to the complexity, most cathinones also act as monoamine releasers, again with varying selectivity for the three neurotransmitters (Abbott and Smith, 2015). Synthetic cathinones have a rapid onset of action for psychostimulant

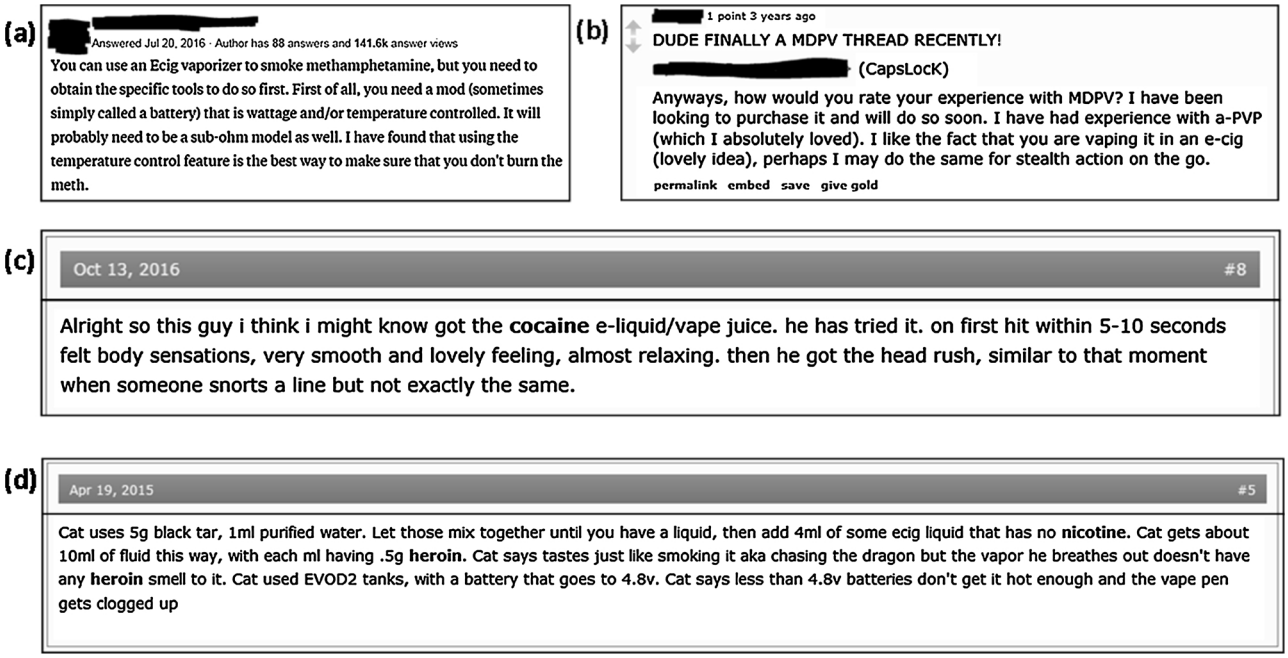

Fig. 2. Screen captures from forums discussing the use of illicit drugs in e-cigarettes or other forms of portable vaporizers. (a) Discussion on Quora.com about whether you can smoke crystal meth from a vaporizer; (b) Discussion on Reddit.com about the use of electronic cigarettes to vape synthetic cathinones; (c) Discussion on drugs-forum.com about cocaine e-liquid available for sale on the dark web; (d) Discussion on drugs-forum.com about vaporizing heroin in an e-cigarette.

effects that can last for minutes to hours depending on the route of administration (Abbott and Smith, 2015). They produce similar effects to amphetamine with users reporting euphoria, increased sociability, sexual arousal, empathy, and increased focus (Abbott and Smith, 2015; Karila et al., 2015).

3.5.1. MDPV

3,4-methylenedioxypyrovalerone (MDPV) was one of the earliest abused synthetic cathinones because of its strong psychostimulant effects (Anizan et al., 2014). *in vitro* data have shown that MDPV is a potent inhibitor of catecholamine uptake at DAT and NET, with significant preference for DAT and NET over SERT, but it does not cause neurotransmitter release (Ellefsen et al., 2016; Kandel and Kandel, 2015; Matsunaga et al., 2017; Solis, 2017). Reported clinical features include agitation, psychosis, paranoia, tachycardia, rhabdomyolysis, hyperthermia, metabolic acidosis, acute renal failure and death (Anizan et al., 2014; Froberg et al., 2015; Valsalan et al., 2017). In a case study of 23 patients who tested positive to MDPV all except one were admitted to hospital and most were admitted to the ICU, with one reported death (Froberg et al., 2015).

3.5.2. α-PVP

Between 2011–2015 there were at least 23 deaths where α-PVP was the direct cause or contributed to the death (Kandel and Kandel, 2015). Its mechanism of action closely resembles that of MDPV (Ellefsen et al., 2016; Karila et al., 2015). It is more potent at both DAT and NET than cocaine or amphetamine (Kandel and Kandel, 2015). Routes of administration of α-PVP include snorting, injection, oral, smoking/inhalation, sub-lingual and rectal (Kandel and Kandel, 2015). User reports on forums have suggested that some believe that smoking, either by vaporization or a pipe, leads to an increase in side effects (Kandel and Kandel, 2015). Dosage reports vary from 20 to 330 mg (Kandel and Kandel, 2015). Features associated with α-PVP include tachycardia, hyperthermia, hypertension, agitation, paranoia, hallucinations, aggression, mydriasis, and insomnia (Kandel and Kandel, 2015; Patel et al., 2017; Umebachi et al., 2016); however, toxic effects are often difficult to ascribe due to polydrug use.

3.5.3. Mephedrone

Dosages of mephedrone vary considerably: oral doses range from 15 to 300 mg; nasal insufflation doses range from 5 to 200 mg; intravenous or intramuscular injection doses are in the range 5–150 mg; and the rectal dose is ~100 mg (Papaseit et al., 2017). There are currently no data in the literature describing vaporization doses. Redosing is common due to a short duration of action, so this can lead to a total dosage of 1–2 g administered in a single session (Busardo et al., 2015) with psychoactive effects, which resemble those of methamphetamine, lasting 1–4 hours (Karila et al., 2015). Mephedrone works on the monoamine receptor systems with inhibition of the reuptake of neurotransmitters at NET, DAT, and SERT, in combination with an increase in the release of all three neurotransmitters (Karila et al., 2015; Luethi et al., 2017). Adverse effects from mephedrone use include a change in body temperature, agitation, mydriasis, slurred speech, blurred vision, nausea, vomiting, and seizure (Busardo et al., 2015; Ellefsen et al., 2016). Acute toxic effects include hypertension, tachycardia, chest pain, paranoia, psychosis, and suicidal ideation (Papaseit et al., 2017). There have been at least 12 documented cases where death was attributed to mephedrone or multiple-drug intoxication involving mephedrone (Busardo et al., 2015).

3.5.4. Methylone

Methylone is a direct MDMA analog with the only structural change being the incorporation of the β-keto group common to all synthetic cathinones. As such its mechanism of action is similar to that of MDMA and mephedrone (Barrios et al., 2016; Karila et al., 2015). There have been at least four reported cases of death in the United States and one in France related to toxicity from methylone use (Barrios et al., 2016).

3.5.5. E-cigarette usage

There is evidence of e-cigarette use of a variety of synthetic cathinones (including derivatives not detailed above) on illicit drug forums, including the user's perceived importance of the ability to consume drugs via stealth in public (Fig. 2). Additionally, there is literature evidence that MDPV has been administered by vaporization (Schifano et al., 2017) and that e-cigarettes are being used to vaporize drugs such as methamphetamine and α-PVP as vaporization has a more rapid onset of effects and a shorter duration of action when compared to nasal inhalation (snorting; Marusich et al., 2016). Blundell et al. (2018a) provided additional evidence of the use of electronic vaping devices to vape synthetic cathinones with a convenience survey suggesting that 8.5% of electronic vaping device users had vaped mephedrone and 7.1% had vaped α-PVP.

3.6. Cocaine

Cocaine is the second most common illicit drug globally and is a central and peripheral nervous system stimulant (Favrod-Coune and Broers, 2010). Cocaine is known colloquially as 'coke' in its hydrochloride salt form and 'crack' in its free base form. Some users distinguish crack from freebase cocaine upon the basis that crack is a more impure form of the drug. Intranasal, intravenous, and inhalational are the most common routes of administration (Benowitz, 2012b). The main mechanism of action of cocaine is blocking the reuptake of monoamine neurotransmitters, norepinephrine, dopamine (Docherty, 2008; Heikkila et al., 1975) and to a lesser extent serotonin (Howell and Kimmel, 2008; Rothman et al., 2001). This results in central and peripheral nervous system stimulation (Favrod-Coune and Broers, 2010). Further to this, cocaine stimulates alpha adrenergic receptors and blocks voltage-gated membrane sodium channels, with a notable effect on myocardial electrical conduction (Magnano et al., 2006; Tisdale et al., 1996).

3.6.1. Dosage required for toxicity

Although inhaled 'crack' cocaine reaches the brain quickly, its short-term effects tend to increase redosing, which leads to a high risk of toxicity and a rapid development of dependence (Garcia et al., 2012). Dosages are also difficult to determine as the user can space the inhalation of the single 'rock' of crack cocaine over several hours. The dosage causing toxicity varies greatly by route of administration and individual tolerance level (Benowitz, 2012b). Ingestion of one gram or more is suggested to be fatal (Benowitz, 2012b) although large ranges have been reported (EMCDDA, 2015a; Heard et al., 2008).

3.6.2. Toxic effects

Possible toxic effects include myocardial infarction, cerebrovascular accident, ventricular tachycardia and ventricular fibrillation, seizures, paranoia, hyperthermia, bizarre and violent behavior (Baselt, 2011), QRS prolongation, Q–T prolongation, respiratory arrest, delirium, psychosis, anxiety, muscle rigidity (Benowitz, 2012b), blurred vision and nausea (Brownlow and Pappachan, 2002). Inhalation of 'crack' cocaine has also been associated with more violent behavior and aggression when compared with the use of the hydrochloride salt of cocaine (Garcia et al., 2012).

3.6.3. E-cigarette usage

Illicit drug forums suggest that cocaine in its free base form (crack cocaine) is being used in electronic cigarette style devices with users stating that e-liquids containing cocaine are available for purchase on the dark web (Fig. 2). Survey data found that 10.9% of electronic vaping device users had vaped cocaine powder and 8.4% had vaped crack cocaine (Blundell et al., 2018a). The majority of the respondents to this survey used e-cigarettes as their preferred vaping device

(74.2%). The melting point for the hydrochloride salt of cocaine is 195 °C however at the vaporization temperature the cocaine decomposes (Hatsukami and Fischman, 1996). Cocaine can be converted from the hydrochloride salt to the freebase form which can be volatilized at ~100 °C, however at temperatures exceeding 200 °C the loss of the benzoyl group via an elimination reaction begins to occur (Bell and Nida, 2015). Thermolytic degradants, which may be generated in the process of heating to vaporization, for cocaine and methamphetamine include both potential carcinogens and psychoactive pyrolysis products (Marusich et al., 2016).

3.7. Heroin

Heroin is an opioid, working as a central nervous system depressant, which is most commonly injected intravenously but can also be inhaled or snorted intranasally. (EMCDDA, 2015b; Rook et al., 2006). Following administration of heroin, it crosses the blood-brain barrier and is rapidly converted into 6-monoacetylmorphine (6-MAM) and then into morphine (Rook et al., 2006; Selley et al., 2001), along with other metabolites such as the toxic morphine-3-glucuronide (M3G) (Rook et al., 2006; Smith, 2000). Heroin, 6-MAM, and morphine show a strong affinity for the μ-opioid receptor and exhibit the effects of heroin via its activation (Selley et al., 2001).

3.7.1. Dosage required for toxicity

The inhalation method known as 'chasing the dragon,' where users inhale heroin vapor from a heated metal surface, has been a common method of administration of heroin for almost a century. However, data on usual dosages and toxic dosages is limited due to the variation in dosage in opioid naïve and tolerate users as well as the nature of the technique which involves many incremental small doses until the desired physical effects are reached. For IV administration, the minimum lethal dosage is claimed to be 200 mg noting larger dosages for chronic uses with built up tolerance (EMCDDA, 2015b). Fatalities have been recorded following 10 mg IV dosages (Clarke and Moffat, 1986).

3.7.2. Toxic effects

Agitation, hallucinations, paranoia, sinus tachycardia, seizures (Dart, 2004), lethargy, hypotonia, apnea, leukoencephalopathy, pulmonary edema, coma, and sudden death have been reported following heroin use (Albertson, 2012). Pyrolysis products from vaporizing heroin at high temperatures have been shown to induce encephalopathy (Bell and Nida, 2015), inhalation of heroin has also been shown to cause acute eosinophilic pneumonia (Eyupoglu et al., 2017).

3.7.3. E-cigarette usage

Illicit drug forums suggest that the freebase form of heroin is being used in personal electronic devices such as e-cigarettes (Fig. 2). A convenience survey found that 7.1% of responding electronic vaping device users had vaped heroin (Blundell et al., 2018a). There is also evidence on illicit drug forums of other opioids including oxycodone and morphine being used in e-cigarettes.

3.8. Fentanyl and derivatives

Fentanyl is an agonist at all opioid receptors with 50–100 times the potency of morphine. The potency of fentanyl analogs varies with carfentanil being 10,000 times more potent than morphine. The high lipophilicity of these compounds results in rapid diffusion through membranes, including the blood-brain barrier, with a subsequent rapid fall in plasma concentration. The lipophilicity also complicates the pharmacokinetics in patients with large amounts of adipose tissue due to storage and slow release of the opioid. Effects of fentanyl and its derivatives are similar to that of other opioids including analgesia, anxiolysis, euphoria, and drowsiness (Suzuki and El-Haddad, 2017). Fentanyl and its derivatives are of particular importance at the moment given their role in the current opioid epidemic, with 19,413 deaths in the United States in 2016 attributed to synthetic opioids, more than double the number in 2015 (Hedegaard et al., 2017).

3.8.1. Dosage required for toxicity

The clinical effects of fentanyl are dosage dependent with dosages varying greatly between analogs. For fentanyl, serum concentrations of 0.3–0.7 ng/ml provide analgesia and concentrations > 3 ng/ml cause a loss of protective airway reflexes and CNS depression in opioid naïve patients (Kumar et al., 1987; Nelson and Schwaner, 2009) however, toxic dosages are far more difficult to predict in those with an opioid tolerance. Postmortem serum concentrations have been in the range of 3–383 ng/ml (Martin et al., 2006).

3.8.2. Toxic effects

Constipation, nausea, pruritus, orthostatic hypotension, chest wall rigidity (Armenian et al., 2017), confusion, hallucinations, weakness, and seizures are all possible toxic effects (DrugAbuse.com, 2018). In cases of overdose, signs include extreme fatigue, obtundation, cardiac arrest, bradypnoea, severe confusion, and respiratory arrest (DrugAbuse.com, 2018).

3.8.3. E-cigarette usage

A survey study by Blundell et al. (2018a) found that 7.3% of electronic vaping device users had vaped fentanyl (2.5% of all survey respondents). In the literature, there is a case report of a 36-year old male presenting to the emergency department with altered mental status following vaping combined with oral consumption of 'synthetic opium' which upon further analysis was discovered to contain acetylfentanyl (Rogers et al., 2016). There is also a case report of a fatal intoxication with fentanyl derivative, 4-fluorobutyrfentanyl (4-FBF). A 26-year old male was found deceased with an e-cigarette near the body. 4-FBF was identified in both biological samples (blood concentration of 4-FBF was 91 ng/ml) and the e-cigarette fluid (Rojkiewicz et al., 2017).

3.9. Other drugs

3.9.1. E-cigarette usage

A sample of resin submitted for testing by a concerned parent was found to be a concentrated resin from the blue lotus flower (*N. caerulea*) for suspected use in an e-cigarette 'dripper-style' device (Poklis et al., 2017). The confiscated resin was shown to contain a very high concentration of Nuciferine (4300 ng/ml), an alkaloid associated with dopamine receptor blockade. Subsequent investigation led to the identification of a number of blue lotus flower e-liquids and resins on sale for use in e-cigarettes (Poklis et al., 2017).

In addition to a number of illicit drugs already discussed respondents to Blundell et al. (2018a) recent survey of e-cigarette users also self-reported use of tryptamines (7.0%), NBOMe (2,5-dimethoxy-4-bromophenethylamine) (6.9%) and ketamine (6.7%).

Of all the drugs analyzed in this study only gamma-hydroxybutyric acid (GHB) and 3,4-methylenedioxyamphetamine (MDA) were found to have no evidence of use in e-cigarettes in either the literature or on illicit drug forums. This may be due to the well-established oral dosing behaviors of GHB, and the less frequent present-day abuse of MDA.

4. Discussion

In highlighting the risk of e-cigarettes being used as illicit drug delivery systems, the focus must be directed on the groups who are at the greatest potential risk, as well as whether this route of drug administration holds a benefit of risk reduction in users. The demographics of e-cigarette users as well as those experimenting with the technology show an alarming trend towards adolescents and young adult use and experimentation (Anand et al., 2015; Goniewicz and Zielinska-Danch, 2012), a pattern which is mirrored in illicit drug

exposure (AIHW, 2008). The use or experimentation with e-cigarettes has also demonstrated the risk of commencing or experimenting with traditional cigarettes (Dutra and Glantz, 2014; Leventhal et al., 2015). Considering that e-cigarettes are being marketed and reported as a safe alternative to smoking (Rom et al., 2015), a statement supported by current youth perceptions (Ambrose et al., 2014; Anand et al., 2015), potential illicit drug administration via this route may present itself as a safer and innocuous method to experiment and try illicit drugs. This view of harm minimization, cleaner administration, potential enticement from liquid flavorings (Durmowicz, 2014) and reduced risk may result in experimentation and use within this at-risk group which may not have otherwise occurred. Adding to this, the benign appearance of e-cigarette fluid may also mask the appearance of illicit drugs resulting in unintended or malicious exposure. With the growth of the e-cigarette industry and user adoption, there has been an observed spike in emergency department visits, and poison hotline calls associated with pediatric accidental exposure to the e-cigarette fluid or inhalational vapor (Cantrell, 2014; Vakkalanka et al., 2014). This raises the possible reality of pediatric exposure to either dissolved illicit drugs in e-cigarette fluid or accidental inhalation of illicit drug vapor.

The implications of illicit drug use via e-cigarettes poses issues for medical practice, public health, and policing forces. The use of illicit drugs via an easy to administer route and tool may result in higher usage levels and maintenance of drug trough levels resulting in higher thresholds for drug toxicity as well as changes in drug withdrawal. It may also lead to unusual patterns of drug use (continuous versus acute administration), potential increases in young adult use, addiction and toxicity, and pediatric accidental exposure. This has important implications for frontline healthcare workers such as general practitioners, emergency physicians and drug and alcohol workers. Many of these facets have carried on implications for public health as well. The debatable efficacy in e-cigarettes as a nicotine cessation device (Orr and Asal, 2014) raises questions of their benefit to society as a harm minimization tool. In relation to police enforcement of illegal drugs, e-cigarettes pose a massive challenge for detection and public place usage. Dissolving illicit drugs into e-cigarette fluid poses problems of visual identification of illicit drugs by police forces. Further to this, some users on illicit drug forums have reported that characteristic smells produced by the combustion of illicit drugs are lost during vaping, potentially allowing users to ingest illicit drugs in public locations without alerting authorities and possibly exposing the general public to second-hand vapor. This is of particular concern in locations where e-cigarettes are not policed under the same restrictions as traditional combustible cigarettes.

Though the current study aimed to highlight the potential risk of e-cigarettes as a novel illicit drug delivery system, as well as highlight potential current usage trends, the authors, acknowledge that the sources used to obtain such trends are not ideal. Future research should continue surveying e-cigarette usage and whether users have considered or used illicit drugs with the technology. Current studies are limited with small sample sizes, such as a study of club patrons in South London which found that 5.9% of individuals (N = 101) had used an e-cigarette to vape substances other than nicotine (Thurtle et al., 2017). A survey study using US college students determined that 6.94% of e-cigarette users have used their e-cigarette to vape something other than nicotine. In the majority of these cases the students identified cannabis (77.9%) as the substance used; however, 16.4% refused to indicate or did not know the identity of the drug vaped (Kenne et al., 2017). Data currently being collected by the Global Health Survey may go some way to rectifying this gap in current understanding (Winstock, 2017). All researchers investigating the use of e-cigarettes or other portable electronic devices as a means of vaping illicit drugs need to ensure that the terms they are using are clearly explained to differentiate between the different types of vaporizing devices. Additionally, survey designers need to be made aware of the changing nature of ‘smoking’ versus ‘vaping’ terminology to ensure the validity of their results.

Perhaps most telling in the examination of the extent of e-cigarettes and other electronic vaping devices to inhale illicit drugs are the recent survey results published by Blundell et al. (2018a). Of the 861 (34.4%) respondents that had used an electronic vaping device, more than one third (39.5%) had used them to vape recreational drugs. The most common drug vaped in this study was cannabis (18.0% of vape device users). However, there was evidence of a wide range of drugs being vaped by electronic vaping device users including: MDMA (11.7%); cocaine powder (10.9%); crack cocaine (8.4%); synthetic cathinones, mephedrone (8.5%) and α-PVP (7.1%); synthetic cannabinoids (7.8%); opioids, heroin (7.1%) and fentanyl (7.3%); and other drugs including tryptamines and ketamine (Blundell et al., 2018a). This paper provides the first evidence in the scientific literature as to the broad range of drugs currently being used in e-cigarette-style devices.

The e-cigarette industry and user base is a rapidly expanding area, along with the foundation of literature reviewing it. This study has highlighted a gap in the literature pertaining to e-cigarettes as a delivery system for illicit drugs. Where the literature fails to account for these emerging behaviors, illicit drug forums provide some insight. This provides the academic community the opportunity to start documenting the use of e-cigarettes with illicit street drugs and start providing advice to health professionals, public health, and policing forces. The adoption by the illicit drug using community demonstrates the viability and risk of e-cigarettes being used as an illicit drug delivery system, and also poses the question of its use as a delivery system for non-illicit drugs, either used legally or illegally, as well as inhalational poisons.

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Authors’ contribution

A.B. and A.J. contributed to conception of the review. A.B. and J.M. reviewed the literature, examined online illicit drug forums and wrote and edited the manuscript text. A.J. supervised the work and revised the manuscript critically for important intellectual content. All authors reviewed the manuscript and have approved the final version.

Conflict of interest

No conflict declared.

References

Abbott, R., Smith, D.E., 2015. The new designer drug wave: a clinical, toxicological, and legal analysis. J. Psychoact. Drugs 47, 368–371. https://doi.org/10.1080/02791072.2015.1094591.

Abrams, D.I., Vizoso, H.P., Shade, S.B., Jay, C., Kelly, M.E., Benowitz, N.L., 2007. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin. Pharmacol. Ther. 82, 572–578. https://doi.org/10.1038/sj.clpt.6100200.

Adams, I.B., Martin, B.R., 1996. Cannabis: pharmacology and toxicology in animals and humans. Addiction 91, 1585–1614. https://doi.org/10.1046/j.1360-0443.1996.911115852.x.

Adkison, S.E., O’Connor, R.J., Bansal-Travers, M., Hyland, A., Borland, R., Yong, H.-H., Cummings, K.M., McNeill, A., Thrasher, J.F., Hammond, D., 2013. Electronic nicotine delivery systems: international tobacco control four-country survey. Am. J. Prev. Med. 44, 207–215. https://doi.org/10.1016/j.amepre.2012.10.018.

Australian Institute of Health and Welfare (AIHW), 2008. 2007 National Drug Strategy Household Survey: Detailed Findings. Accessed 4 January 2018. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442459906.

Albertson, T.E., 2012. Opiates and opioids. In: Olson, K.R. (Ed.), Poisoning and Drug Overdose. McGraw-Hill Education, USA.

Ambrose, B.K., Rostron, B.L., Johnson, S.E., Portnoy, D.B., Apelberg, B.J., Kaufman, A.R., Choiniere, C.J., 2014. Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth. Am. J. Prev. Med. 47, 53–60. https://doi.org/10.1016/j.amepre.2014.04.016.

Anand, V., McGinty, K.L., O’Brien, K., Guenthner, G., Hahn, E., Martin, C.A., 2015. E-cigarette use and beliefs among urban public high school students in. North. Carol. J. Adolesc. Health 57, 46–51. https://doi.org/10.1016/j.jadohealth.2015.03.018.

Andonian, D.O., Seaman, S.R., Josephson, E.B., 2017. Profound hypotension and bradycardia in the setting of synthetic cannabinoid intoxication – a case series. Am. J. Emerg. Med. 35 (940), e945–940. https://doi.org/10.1016/j.ajem.2017.01.011. e946.

Anizan, S., Concheiro, M., Lehner, K.R., Bukhari, M.O., Suzuki, M., Rice, K.C., Baumann, M.H., Huestis, M.A., 2014. Linear pharmacokinetics of 3,4-methylenedioxypyrovalerone (MDPV) and its metabolites in the rat: relationship to pharmcodynamic effects. Addict. Biol. 21, 339–347. https://doi.org/10.1111/adb.12201.

Araujo, A.M., Valente, M.J., Carvalho, M., Silva, D.Dd., Gaspar, H., Carvalho, F., Bastos, Md.L., Pinho, P.G.D., 2015. Raising awareness of new psychoactive substances: chemical analysis and in vitro toxicity screening of 'legal high' packages containing synthetic cathinones. Arch. Toxicol. 89, 757–771. https://doi.org/10.1007/s00204-014-1278-7.

Armenian, P., Vo, K.T., Barr-Walker, J., Lynch, K.L., 2017. Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. Neuropharmacol. 134 (Pt A), 121–132. https://doi.org/10.1016/j.neuropharm.2017.10.016.

Backberg, M., Lindeman, E., Beck, O., Helander, A., 2015. Characteristics of analytically confirmed 3-MMC-related intoxications from the Swedish STRIDA project. Clin. Toxicol. 53, 46–53. https://doi.org/10.3109/15563650.2014.981823.

Bahl, V., Lin, S., Xu, N., Davis, B., Wang, Y.-h., Talbot, P., 2012. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod. Toxicol. 34, 529–537. https://doi.org/10.1016/j.reprotox.2012.08.001.

Barbeau, A.M., Burda, J., Siegel, M., 2013. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. Addict. Sci. Clin. Pract. 8, 5. https://doi.org/10.1186/1940-0640-8-5.

Barrios, L., Grison-Hernando, H., Boels, D., Bouquie, R., Monteil-Ganiere, C., Clement, R., 2016. Death following ingestion of methylone. Int. J. Leg. Med. 130, 381–385. https://doi.org/10.1007/s00414-015-1212-4.

Baselt, R.C., 2011. Disposition of Toxic Drugs and Chemicals in Man, 9th edition. Biomedical Publications, Seal Beach, CA.

Bell, D.S., 1973. The experimental reproduction of amphetamine psychosis. Arch. Gen. Psychiatry. 29, 35–40. https://doi.org/10.1001/archpsyc.1973.04200010020003.

Bell, S., Nida, C., 2015. Pyrolysis of drugs of abuse: a comprehensive review. Drug Test. Anal. 7, 445–456. https://doi.org/10.1002/dta.1794.

Benowitz, N.L., 2012a. Marijuana. In: Olson, K. (Ed.), Poisoning and Drug Overdose, 6th edition. McGraw-Hill Education, USA.

Benowitz, N.L., 2012b. Cocaine. In: Olson, K. (Ed.), Poisoning and Drug Overdose, 6th edition. McGraw-Hill Education, USA.

Besaratinia, A., Tommasi, S., 2017. An opportune and unique research to evalute the public health impact of electronic cigarettes. Cancer Causes Control 28, 1167–1171. https://doi.org/10.1007/s10552-017-0952-5.

Blundell, M., Dargan, P., Wood, D., 2018a. A cloud on the horizon - a survey into the use of electronic vaping devices for recreational drug and new psychoactive substance (NPS) administration. QJM 111, 9–14. https://doi.org/10.1093/qjmed/hcx178.

Blundell, M.S., Dargan, P.I., Wood, D.M., 2018b. The dark cloud of recreational drugs and vaping. QJM 111, 145–148. https://doi.org/10.1093/qjmed/hcx049.

Bonn-Miller, M.O., Loflin, M.E., Thomas, B.F., Marcu, J.P., Hyke, T., Vandrey, R., 2017. Labeling accuracy of cannabidiol extracts sold online. JAMA 318, 1708–1709. https://doi.org/10.1001/jama.2017.11909.

Borodovsky, J.T., Crosier, B.S., Lee, D.C., Sargent, J.D., Budney, A.J., 2016. Smoking, vaping, eating: Is legalization impacting the way people use cannabis? Int. J. Drug Policy 36, 141–147. https://doi.org/10.1016/j.drugpo.2016.02.022.

Borodovsky, J.T., Lee, D.C., Crosier, B.S., Gabrielli, J.L., Sargent, J.D., Budney, A.J., 2017. U.S. cannabis legalization and use of vaping and edible products among youth. Drug. Alcohol. Depend. 177, 299–306. https://doi.org/10.1016/j.drugalcdep.2017.02.017.

Brownlow, H.A., Pappachan, J., 2002. Pathophysiology of cocaine abuse. Eur. J. Anaesthesiol. 19, 395–414. https://doi.org/10.1017/S0265021502000650.

Budney, A.J., Sargent, J.D., Lee, D.C., 2015. Vaping cannabis (marijuana): parallel concerns to e-cigs? Addiction 110, 1699–1704. https://doi.org/10.1111/add.13036.

Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Williman, J., Walker, N., 2013. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 382, 1629–1637. https://doi.org/10.1016/S0140-6736(13)61842-5.

Busardo, F.P., Kyriakou, C., Napoletano, S., Marinelli, E., Zaami, S., 2015. Mephedrone related fatalities: a review. Eur. Rev. Med. Pharmacol. Sci. 19, 3777–3790.

Cantrell, F., 2014. Adverse effects of e-cigarette exposures. J. Commun. Health 39, 614–616. https://doi.org/10.1007/s10900-013-9807-5.

Carlier, J., Scheidweiler, K.B., Wohlfarth, A., Salmeron, B.D., Baumann, M.H., Huestis, M.A., 2016. Quantification of [1-(5-fluoropentyl)-1H-indol-3-yl](naphthalene-1-yl) methanone(AM-2201) and 13 metabolites in human and rat plasma by liquid chromatography-tandem mass spectrometry. J. Chromatogr. A 1451, 97–106. https://doi.org/10.1016/j.chroma.2016.05.020.

Carlini, B.H., Garrett, S.B., Harwick, R.M., 2017. Beyond joints and brownies: marijuana concentrates in the legal landscape of WA State. Int. J. Drug Policy 42, 26–29. https://doi.org/10.1016/j.drugpo.2017.01.004.

Castaneto, M.S., Gorelick, D.A., Desrosiers, N.A., Hartman, R.L., Pirard, S., Huestis, M.A., 2014. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend. 144, 12–41. https://doi.org/10.1016/j.drugalcdep.2014.08.005.

Castaneto, M.S., Wohlfarth, A., Desrosiers, N.A., Hartman, R.L., Gorelick, D.A., Huestis, M.A., 2015. Synthetic cannabinoids pharmacokinetics and detection methods in biological matrices. Drug Metab. Rev. 1–51. https://doi.org/10.3109/03602532.2015.1029635.

Castellanos, D., Gralnik, L.M., 2016. Synthetic cannabinoids 2015: an update for pediatricians in clinical practice. World J. Clin. Pediatr. 5, 16–24. https://doi.org/10.5409/wjcp.v5.i1.16.

Cavazos-Rehg, P.A., Sowles, S.J., Krauss, M.J., Agbonavbare, V., Grucza, R., Bierut, L., 2016. A content analysis of tweets about high-potency marijuana. Drug. Alcohol. Depend. 166, 100–108. https://doi.org/10.1016/j.drugalcdep.2016.06.034.

Cho, A.K., 1990. Ice: a new dosage form of an old drug. Science 249, 631. https://doi.org/10.1126/science.249.4969.631.

Clarke, E.G.C., Moffat, A.C., 1986. Clarke's Isolation and Identification of Drugs in Pharmaceuticals, 2nd edition. The Pharmaceutical Press, London.

Cranford, J.A., Bohnert, K.M., Perron, B.E., Bourque, C., 2016. Prevalence and correlates of' vaping' as a route of cannabis administration in medical cannabis patients. Drug Alcohol Depend. 169, 41–47. https://doi.org/10.1016/j.drugalcdep.2016.10.008.

Cruickshank, C.C., Dyer, K.R., 2009. A review of the clinical pharmacology of methamphetamine. Addiction 104, 1085–1099. https://doi.org/10.1111/j.1360-0443.2009.02564.x.

Cuttler, C., Mischley, L.K., Sexton, M., 2016. Sex differences in cannabis use and effects: a cross-sectional survey of cannabis users. Cannabis Cannab. Res. 1, 166–175. https://doi.org/10.1089/can.2016.0010.

Czogala, J., Goniewicz, M.L., Fidelus, B., Zielinska-Danch, W., Travers, M.J., Sobczak, A., 2014. Secondhand exposure to vapors from electronic cigarettes. Nicotine Tob. Res. 16, 655–662. https://doi.org/10.1093/ntr/ntt203.

Daniulaityte, R., Nahhas, R.W., Wijeratne, S., Carlson, R.G., Lamy, F.R., Martins, S.S., Boyer, E.W., Smith, G.A., Sheth, A., 2015. "Time for dabs": analyzing twitter data on marijuana concentrates across the U.S. Drug Alcohol Depend. 155, 307–311. https://doi.org/10.1016/j.drugalcdep.2015.07.1199.

Daniulaityte, R., Lamy, F.R., Barratt, M., Nahhas, R.W., Martins, S.S., Boyer, E.W., Sheth, A., Carlson, R.G., 2017. Characterizing marijuana concentrate users: a web-based survey. Drug Alcohol Depend. 178, 399–407. https://doi.org/10.1016/j.drugalcdep.2017.05.034.

Dart, R.C., 2004. Medical Toxicology. Lippincott Williams & Wilkins, Philadelphia, PA.

Dawkins, L., Kimber, C., Puwanesarasa, Y., Soar, K., 2015. First-versus second-generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. Addiction 110, 669–677. https://doi.org/10.1111/add.12807.

De La Torre, R., Farré, M., Roset, P.N., Pizarro, N., Abanades, S., Segura, M., Segura, J., Camí, J., 2004. Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. Ther. Drug Monit. 26, 137–144.

Drug Enforcement Administration (DEA), 2016. 2016 National Drug Threat Assesment Summary. Accessed 23 November 2017. https://www.hsdl.org/?abstract&did=797265.

DeBruyne, D., Boisselier, R.L., 2015. Emerging drugs of abuse: current perspectives on synthetic cannabinoids. Subst. Abuse Rehabil. 6, 113–129. https://doi.org/10.2147/SAR.S73586.

De-Carolis, C., Boyd, G.-A., Mancinelli, L., Pagano, S., Eramo, S., 2015. Methamphetamine abuse and "meth mouth" in Europe. Med. Oral Patol. Oral Cir. Bucal. 20, e205. https://doi.org/10.4317/medoral.20204.

Derungs, A., Schwaninger, A.E., Mansella, G., Bingisser, R., Kraemer, T., Liechti, M.E., 2013. Symptoms, toxicities, and analytical results for a patient after smoking herbs containing the novel synthetic cannabinoid MAM-2201. Forensic Toxicol. 31, 164–171. https://doi.org/10.1007/s11419-012-0166-1.

Docherty, J.R., 2008. Pharmacology of stimulants prohibited by the world anti-doping agency (WADA). Br. J. Pharmacol. 154, 606–622. https://doi.org/10.1038/bjp.2008.124.

Douglas, H., Hall, W., Gartner, C., 2015. E-cigarettes and the law in Australia. Aust. Fam. Physician. 44, 415–418.

Dresen, S., Kneisel, S., Weinmann, W., Zimmermann, R., Auwärter, V., 2011. Development and validation of a liquid chromatography–tandem mass spectrometry method for the quantitation of synthetic cannabinoids of the aminoalkylindole type and methanandamide in serum and its application to forensic samples. J. Mass. Spectrom. 46, 163–171. https://doi.org/10.1002/jms.1877.

DrugAbuse.com, 2018. In: Lautieri, A. (Ed.), The Effetcs of Fentanyl Use, Accessed 13 April 2018. https://drugabuse.com/library/the-effects-of-fentanyl-use/.

Durmowicz, E.L., 2014. The impact of electronic cigarettes on the paediatric population. Tob. Control. 23, ii41–ii46. https://doi.org/10.1136/tobaccocontrol-2013-051468.

Dutra, L.M., Glantz, S.A., 2014. Electronic cigarettes and conventional cigarette use among US adolescents: a cross-sectional study. JAMA Pediatr. 168, 610–617. https://doi.org/10.1001/jamapediatrics.2013.5488.

Eggers, M.E., Lee, Y.O., Jackson, K., Wiley, J.L., Porter, L., Nonnomaker, J.M., 2017. Youth use of electronic vapor products and blunts for administering cannabis. Addict. Behav. 70, 79–82. https://doi.org/10.1016/j.addbeh.2017.02.020.

Elkashef, A., Vocci, F., Hanson, G., White, J., Wickes, W., Tiihonen, J., 2008. Pharmacotherapy of methamphetamine addiction: an update. Subst. Abuse. 29, 31–49. https://doi.org/10.1080/08897070802218554.

Ellefsen, K.N., Concheiro, M., Huestis, M.A., 2016. Synthetic cathinone pharmacokinetics, analytical methods, and toxicological findings from human performance and postmortem cases. Drug Metab. Rev. 48, 237–265. https://doi.org/10.1080/03602532.2016.1188937.

Ellenhorn, M.J., Schonwald, S., Ordog, G., Wasserberger, J., 1997. Ellenhorn'S Medical Toxicology: Diagnosis and Treatment of Human Poisoning, 2nd edition. Williams & Wilkins, Baltimore, MD.

ElSohly, M.A., Gul, W., Wanas, A.S., Radwan, M.M., 2014. Synthetic cannabinoids: analysis and metabolites. Life Sci. 97, 78–90. https://doi.org/10.1016/j.lfs.2013.12.212.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2015a. Cocaine and Crack Drug Profile. Accessed 2 September 2015. http://www.emcdda.europa.eu/publications/drug-profiles/cocaine.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2015b. Heroin Drug Profile. Accessed 2 September 2015. http://www.emcdda.europa.eu/publications/drug-profiles/heroin.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2015c.

Methylenedioxymethamphetamine (MDMA or' Ecstasy') Drug Profile. Accessed 2 September 2015. http://www.emcdda.europa.eu/publications/drug-profiles/mdma.
Etter, J.F., 2015. Electronic cigarettes and cannabis: an exploratory study. Eur. Addict. Res. 21, 124–130. https://doi.org/10.1159/000369791.
Eyupoglu, D., Ortac Ersoy, E., Rollas, K., Topeli, A., 2017. Acute eosinophilic pneumonia secondary to heroin inhalation. Tuberk Toraks 65, 154–156. https://doi.org/10.5578/tt.10438.
Farsalinos, K.E., Polosa, R., 2014. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther. Adv. Drug Saf. 5, 67–86. https://doi.org/10.1177/2042098614524430.
Farsalinos, K.E., Kistler, K.A., Gillman, G., Voudris, V., 2015. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. Nicotine Tob. Res. 17, 168–174. https://doi.org/10.1093/ntr/ntu176.
Favrod-Coune, T., Broers, B., 2010. The health effect of psychostimulants: a literature review. Pharmaceuticals 3, 2333–2361. https://doi.org/10.3390/ph3072333.
Froberg, B.A., Levine, M., Beuhler, M.C., Judge, B.S., Moore, P.W., Engebretsen, K.M., Mckeown, N.J., Rosenbaum, C.D., Young, A.C., Rusyniak, D.E., 2015. Acute methylenedioxypyrovalerone toxicity. J. Med. Toxicol. 11, 185–194. https://doi.org/10.1007/s13181-014-0446-8.
Frohe, T., Leeman, R.F., Patock-Peckham, J., Ecker, A., Kraus, S., Foster, D.W., 2018. Correlates of cannabis vape-pen use and knowledge among U.S. College students. Addict. Behav. Rep. 7, 32–39. https://doi.org/10.1016/j.abrep.2017.11.004.
Galli, J.A., Sawaya, R.A., Friedenberg, F.K., 2011. Cannabinoid hyperemesis syndrome. Curr. Drug Abuse Rev. 4, 241–249.
Garcia, R.C.T., Dati, L.M.M., Fukuda, S., Torres, L.H.L., Moura, S., de Carvalho, N.D., Carrettiero, D.C., Camarini, R., Levada-Pires, A.C., Yonamine, M., Negrini-Neto, O., Abdalla, F.M.F., Sandoval, M.R.L., Afeche, S.C., Marcourakis, T., 2012. Neurotoxicity of anhydroecgonine methyl ester, a crack cocaine pyrolysis product. Toxicol. Sci. 128, 223–234. https://doi.org/10.1093/toxsci/kfs140.
Gartner, C., 2015. Mull it over: Cannabis vaporizers and harm reduction. Addiction 110, 1709–1710. https://doi.org/10.1111/add.13139.
Gieringer, D.H., 2001. Cannabis "vaporization" a promising strategy for smoke harm reduction. J. Cannabis Ther. 1, 153–170. https://doi.org/10.1300/J175v01n03_10.
Gieringer, D., St, Laurent, J., Goodrich, S., 2004. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. J. Cannabis Ther. 4, 7–27. https://doi.org/10.1300/J175v04n01_02.
Giroud, C., de Cesare, M., Berthet, A., Varlet, V., Concha-Lozano, N., Favrat, B., 2015. E-cigarettes: a review of new trends in cannabis use. Int. J. Environ. Res. Publ. Health. 12, 9988–10008. https://doi.org/10.3390/ijerph120809988.
Glennon, R.A., Dukat, M., 2017. Structure-activity relationships of synthetic cathinones. In: Baumann, M.H., Glennon, R.A., Wiley, J.L. (Eds.), Neuropharmacology of New Psychoactive Substances (NPS): The Science Behind the Headlines. Springer International Publishing, pp. 19–48.
Glover, C., 2014. 6 Teens Hospitalized so Far from' Cloud 9' Drug. Accessed 28 September 2017. https://www.clickondetroit.com/news/6-teens-hospitalized-so-far-from-cloud-9-drug.
Goniewicz, M.L., Kuma, T., Gawron, M., Knysak, J., Kosmider, L., 2013. Nicotine levels in electronic cigarettes. Nicotine Tob. Res. 15, 158–166. https://doi.org/10.1093/ntr/nts103.
Goniewicz, M.L., Knysak, J., Gawron, M., Kosmider, L., Sobczak, A., Kurek, J., Prokopowicz, A., Jablonska-Czapla, M., Rosik-Dulewska, C., Havel, C., 2014. Levels of selected carcinogens and toxicants in vapor from electronic cigarettes. Tob. Control 23, 133–139. https://doi.org/10.1136/tobaccocontrol-2012-050859.
Goniewicz, M.L., Zielinska-Danch, W., 2012. Electronic cigarette use among teenagers and young adults in Poland. Pediatrics 130, 879–885. https://doi.org/10.1542/peds.2011-3448.
Gowing, L.R., Ali, R.L., Allsop, S., Marsden, J., Turf, E.E., West, R., Witton, J., 2015. Global statistics on addictive behaviours: 2014 status report. Addiction 110, 904–919. https://doi.org/10.1111/add.12899.
Green, A.R., King, M.V., Shortall, S.E., Fone, K.C.F., 2012. Lost in translation: preclinical studies on 3, 4-methylenedioxymethamphetamine provide information on mechanisms of action, but do not allow accurate prediction of adverse events in humans. Br. J. Pharmacol. 166, 1523–1536. https://doi.org/10.1111/j.1476-5381.2011.01819.x.
Greydanus, D., Kaplan, G., Baxter Sr, L.E., Patel, D., Feucht, C., 2015. Cannabis: the never-ending, nefarious nepenthe of the 21st century: what should the clinician know? Dis. Mon. 61, 118–175. https://doi.org/10.1016/j.disamonth.2015.01.004.
Grotenhermen, F., 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin. Pharmacokinet. 42, 327–360. https://doi.org/10.2165/00003088-200342040-00003.
Hahn, I., 2017. In: Pritchard Taylor, J. (Ed.), MDMA Toxicity, New York, NY. https://emedicine.medscape.com/article/821572-overview#showall Accessed 19 April 2018.
Hakkarainen, P., 2016. Vaporizing the Pot World - Easy, Healthy, and Cool, vol. 16. pp. 185–193.
Hall, W., 1994. The health and psychological effects of cannabis use. Curr. Issues Crim. Just. 6, 208–220. https://doi.org/10.1108/DAT-10-2015-0062.
Hartman, R.L., Brown, T.L., Milavetz, G., Spurgin, A., Gorelick, D.A., Gaffney, G., Huestis, M.A., 2015. Controlled cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol. Clin. Chem. 61, 850–869. https://doi.org/10.1373/clinchem.2015.238287.
Hatsukami, D.K., Fischman, M.W., 1996. Crack cocaine and cocaine hydrochloride: are the differences myth or reality? JAMA 276, 1580–1588. https://doi.org/10.1001/jama.1996.03540190052029.
He, T., Oks, M., Esposito, M., Steinberg, H., Makaryus, M., 2017. 'Tree-in-bloom': severe acute lung injury induced by vaping cannabis oil. Ann. Am. Thorac. Soc. 13, 468–470. https://doi.org/10.1513/AnnalsATS.201612-974LE.
Heard, K., Palmer, R., Zahniser, N.R., 2008. Mechanisms of acute cocaine toxicity. Open Pharmacol. J. 2, 70. https://doi.org/10.2174/1874143600802010070.
Hedegaard, H., Warner, M., Miniño, A., 2017. Drug overdose deaths in the United States, 1999-2016. NCHS Data Brief, No 294. National Center for Health Statistics, Hyattsville, MD 2017.
Heikkila, R.E., Orlansky, H., Cohen, G., 1975. Studies on the distinction between uptake inhibition and release of [3 H] dopamine in rat brain tissue slices. Biochem. Pharmacol. 24, 847–852. https://doi.org/10.1016/0006-2952(75)90152-5.
Hermanns-Clausen, M., Kneisel, S., Szabo, B., Auwärter, V., 2013. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction 108, 534–544. https://doi.org/10.1111/j.1360-0443.2012.04078.x.
Hindocha, C., Freeman, T.P., Ferris, J.A., Lynskey, M.T., Winstock, A.R., 2016. No smoke without tobacco: a global overview of cannabis and tobacco routes of administration and their association with intention to quit. Front. Psychiatry 7, 104. https://doi.org/10.3389/fpsyt.2016.00104.
Hoch, E., Bonnet, U., Thomasius, R., Ganzer, F., Havemann-Reinecke, U., Preuss, U.W., 2015. Risks associated with the non-medicinal use of cannabis. Dtsch. Arztebl. Int. 112, 271. https://doi.org/10.3238/arztebl.2015.0271.
Howell, L.L., Kimmel, H.L., 2008. Monoamine transporters and psychostimulant addiction. Biochem. Pharmacol. 75, 196–217. https://doi.org/10.1016/j.bcp.2007.08.003.
Johnson, R.M., Brooks-Russell, A., Ma, M., Fairman, B.J., Tolliver, R.L., Levinson, A.H., 2016. Usual modes of marijuana consumption among high school students in Colorado. J. Stud. Alcohol. Drugs. 77, 580–588. https://doi.org/10.15288/jsad.2016.77.580.
Jones, C.B., Hill, M.L., Pardini, D.A., Meier, M.H., 2016. Prevalence and correlates of vaping cannabis in a sample of young adults. Psych. Adict. Behav. 30, 915–921. https://doi.org/10.1037/adb0000217.
Kandel, D., Kandel, E., 2015. The gateway hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatrica. 104, 130–137. https://doi.org/10.1111/apa.12851.
Karila, L., Megarbane, B., Cottencin, O., Lejoyeux, M., 2015. Synthetic cathinones: a new public health problem. Curr. Neuropharmacol. 13, 12–20. https://doi.org/10.2174/1570159X13666141210224137.
Kenne, D.R., Fischbein, R.L., Tan, A.S., Banks, M., 2017. The use of substances other than nicotine in electronic cigarettes among college students. J. Subst. Abuse Treat. 11, 1–8. https://doi.org/10.1177/1178221817733736.
Kersten, B.P., McLaughlin, M.E., 2015. Toxicology and management of novel psychoactive drugs. J. Pharm. Pract. 28, 50–65. https://doi.org/10.1177/0897190014544814.
Khlystov, A., Samburova, V., 2016. Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping. Environ. Sci. Technol. 50, 13080–13085. https://doi.org/10.1021/acs.est.6b05145.
Kim, J.-H., Kwon, S.-S., Kong, T.Y., Cheong, J.C., Kim, H.S., In, M.K., Lee, H.S., 2017. AM-2201 inhibits multiple cytochrome P450 and uridine 50-diphospho-glucuronosyltransferase enzyme activities in human liver microsomes. Molecules 22, E443. https://doi.org/10.3390/molecules22030443.
Kish, S.J., 2008. Pharmacologic mechanisms of crystal meth. CMAJ. 178, 1679–1682. https://doi.org/10.1503/cmaj.071675.
Koller, V.J., Zlabinger, G.J., Auwärter, V., Fuchs, S., Knasmueller, S., 2013. Toxicological profiles of selected synthetic cannabinoids showing high binding affinities to the cannabinoid receptor subtype CB1. Arch. Toxicol. 87, 1287–1297. https://doi.org/10.1007/s00204-013-1029-1.
Krauss, M.J., Sowles, S.J., Mvylaganam, S., Zewdie, K., Beirut, L.J., Cavazos-Rehg, P.A., 2015. Displays of dabbing marijuana extracts on YouTube. Drug. Alcohol. Depend. 155, 45–51. https://doi.org/10.1016/j.drugalcdep.2015.08.020.
Kumar, K., Morgan, D.J., Crankshaw, D.P., 1987. Determination of fentanyl and alfentanil in plasma by high-performance liquid chromatography with ultraviolet detection. J. Chromatogr. B. 419, 464–468. https://doi.org/10.1016/0378-4347(87)80317-1.
Lacy, Ed., Fletcher, A., Hewitt, G., Murphy, S., Moore, G., 2017. Cross-sectional study examining the prevalence, correlates and sequencing of electronic cigarette and tobacco use among 11-16-year olds in schools in Wales. BMJ Open 6, e012784. https://doi.org/10.1136/bmjopen-2016-012784.
Lake, C.R., Quirk, R.S., 1984. CNS stimulants and the look-alike drugs. Psychiatr. Clin. North. Am. 7, 689–701.
Lam, R., Tang, M., Leung, S., Chong, Y., Tsui, M., Mak, T., 2017. Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: a case report with quantitative anaylsis of serum drug concentrations. Clin. Toxicol. 55, 662–667. https://doi.org/10.1080/15563650.2017.1307385.
Lankenau, S.E., Fedorova, E.V., Reed, M., Schrager, S.M., Iverson, E., Wong, C.F., 2017. Marijuana practices and patterns of use among young adult medical marijuana patients and non-patient users. Drug. Alcohol. Depend. 170, 181–188. https://doi.org/10.1016/j.drugalcdep.2016.10.025.
Lanz, C., Mattsson, J., Soydaner, U., Brenneisen, R., 2016. Medicinal cannabis: in vitro validation of vaporizers for the smoke-free inhalation of cannabis. PLoS One 11, e0147286. https://doi.org/10.1371/journal.pone.0147286.
Lappin, J.M., Darke, S., Farrell, M., 2017. Stroke and methamphetamine use in young adults: a review. J. Neurol. Neurosurg. Psychiatry 88, 1079–1091. https://doi.org/10.1136/jnnp-2017-316071.
Lee, D.C., Crosier, B.S., Borodovsky, J.T., Sargent, J.D., Budney, A.J., 2016. Online survey characterizing vaporizer use among cannabis users. Drug Alcohol. Depend. 159, 227–233. https://doi.org/10.1016/j.drugalcdep.2015.12.020.
Leikin, J.B., Paloucek, F.P., 2007. Poisoning and Toxicology Handbook. Taylor & Francis, U.S.
Leventhal, A.M., Strong, D.R., Kirkpatrick, M.G., Unger, J.B., Sussman, S., Riggs, N.R., Stone, M.D., Khoddam, R., Samet, J.M., Audrain-McGovern, J., 2015. Association of

electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. JAMA 314, 700–707. https://doi.org/10.1001/jama.2015.8950.
Loflin, M., Earleywine, M., 2015. The case for medical marijuana: an issue of relief. Drug. Alcohol Depend. 149, 293–297. https://doi.org/10.1016/j.drugalcdep.2015.01.006.
Luethi, D., Kolaczynska, K.E., Docci, L., Krahenbuhl, S., Hoener, M.C., Liechti, M.E., 2017. Pharmacological profile of mephedrone analogs and related new psychoactive substances. Neuropharmacol 134 (Pt A), 4–12. https://doi.org/10.1016/j.neuropharm.2017.07.026.
Magnano, A.R., Talathoti, N.B., Hallur, R., Jurus, D.T., Dizon, J., Holleran, S., Bloomfield, D.M., Collins, E., Garan, H., 2006. Effect of acute cocaine administration on the QTc interval of habitual users. Am. J. Cardiol. 97, 1244–1246. https://doi.org/10.1016/j.amjcard.2005.11.046.
Mammen, G., Rehm, J., Rueda, S., 2016. Vaporizing cannabis through e-cigarettes: prevalence and socio-demographic correlates among Ontario high school students. Can. J. Public Health. 107, e337. https://doi.org/10.17269/CJPH.107.5747.
Martin, T.L., Woodall, K.L., McLellan, B.A., 2006. Fentanyl-related deaths in Ontario, Canada: toxicological findings and circumstances of death in 112 cases (2002–2004). J. Anal. Toxicol. 30, 603–610. https://doi.org/10.1093/jat/30.8.603.
Marusich, J.A., Lefever, T.W., Blough, B.E., Thomas, B.F., Wiley, J.L., 2016. Pharmacological effects of methamphetamine and alpha-PVP vapor and injection. Neurotoxicology 55, 83–91. https://doi.org/10.1016/j.neuro.2016.05.015.
Matsunaga, T., Morikawa, Y., Kamata, K., Shibata, A., Miyazono, H., Sasajima, Y., Suenami, K., Sato, K., Takekoshi, Y., Endo, S., El-Kabbani, O., Ikari, A., 2017. α-pyrrolidinononanophenone provokes apoptosis of neuronal cells through alterations in antioxidant properties. Toxicology 386, 93–102. https://doi.org/10.1016/j.tox.2017.05.017.
McAuley, T.R., Hopke, P.K., Zhao, J., Babaian, S., 2012. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal. Toxicol. 24, 850–857. https://doi.org/10.3109/08958378.2012.724728.
McCloskey, K., Vearrier, D., McKeever, R.G., Greenberg, M., 2016. E-cigarettes and synthetic cannabinoids: a new trend. 36th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) Vol. 55, 344–519.
McDonald, E.A., Popova, L., Ling, P.M., 2016. Traversing the triangulum: the intersection of tobacco, legalised marijuana and electronic vaporizers in Denver, Colorado. Tob. Control. 25, i96–i102. https://doi.org/10.1136/tobaccocontrol-2016-053091.
McGuigon, M., 2006. Cannabinoids. In: Flomenbaum, N.E., Goldfrank, L.R., Hoffman, R., Howland, M.A., Lewin, N.A., Nelson, L. (Eds.), Goldfrank's Toxicological Emergencies, 8th ed. McGraw-Hill, New York, pp. 1212–1220.
McNeill, B., 2016. Researchers Study the Use of E-Cigarettes for Illicit Drugs. Accessed 13 December 2017. https://medicalxpress.com/news/2016-06-e-cigarettes-illicit-drugs.html.
Mehta, J.J., Mahendran, A.K., Bajaj, R.K., Doshi, A.R., 2017. Myocardial ischemia with cannabinoid use in an adolescent. Cureus 9, e1899. https://doi.org/10.7759/cureus.1899.
Mills, B., Yepes, A., Nugent, K., 2015. Synthetic cannabinoids. Am. J. Med. Sci. 350, 59–62. https://doi.org/10.1097/MAJ.0000000000000466.
Morean, M.E., Kong, G., Camenga, D.R., Cavallo, D.A., Krishnan-Sarin, S., 2015. High school students' use of electronic cigarettes to vaporize cannabis. Pediatrics 136, 611–616. https://doi.org/10.1542/peds.2015-1727.
Morean, M.E., Lipshie, N., Josephson, M., Foster, D., 2017. Predictors of adult e-cigarette users vaporizing cannabis using e-ciragettes and vape-pens. Subst. Use Misuse 52, 974–981. https://doi.org/10.1080/10826084.2016.1268162.
Müller, H., Sperling, W., Köhrmann, M., Huttner, H.B., Kornhuber, J., Maler, J.-M., 2010. The synthetic cannabinoid spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. Schizophr. Res. 118, 309–310. https://doi.org/10.1016/j.schres.2009.12.001.
National Drug Early Warning System, 2015. National Drug Early Warning System (NDEWS) Sentinel Community Site Profile 2015: Atlanta Metro. Accessed 23 November 2017. https://ndews.umd.edu/sites/ndews.umd.edu/files/SCS%20Atlanta%20Metro%202015%20Final%20Web.pdf.
Nelson, L., Schwaner, R., 2009. Transdermal fentanyl: pharmacology and toxicology. J. Med. Toxicol. 5, 230. https://doi.org/10.1007/BF03178274.
Orr, K.K., Asal, N.J., 2014. Efficacy of electronic cigarettes for smoking cessation. Ann. Pharmacother. 48, 1502–1506. https://doi.org/10.1177/1060028014547076.
Pant, S., Deshmukh, A., Dholaria, B., Kaur, V., Ramavaram, S., Ukor, M., Teran, G.A., 2012. Spicy seizure. Am. J. Med. Sci. 344, 67–68. https://doi.org/10.1097/MAJ.0b013e31824cf5c2.
Papaseit, E., Molto, J., Muga, R., Torrens, M., Torre, Rd.l, Farre, M., 2017. Clinical pharmacology of the synthetic cathinone mephedrone. In: Baumann, M.H., Glennon, R.A., Wiley, J.L. (Eds.), Neuropharmacology of New Psychoactive Substances (NPS) : The Science Behind the Headlines. Springer International Publishing, pp. 313–332.
Patel, N., Ford, L., Jones, R., Bradberry, S.M., Vale, J.A., 2017. Poisoning to α-pyrrolidinovalerophenone (α-PVP), a synthetic cathinone. Clin. Toxicol. 55, 159–160. https://doi.org/10.1080/15563650.2016.1248291.
Peace, M.R., Butler, K.E., Wolf, C.E., Poklis, J.L., Poklis, A., 2016a. Evaluation of two commercially available cannabidiol formulations for use in electronic cigarettes. Front. Pharmacol. 7, 279. https://doi.org/10.3389/fphar.2016.00279.
Peace, M.R., Stone, J.W., Poklis, J.L., Turner, J.B.M., Poklis, A., 2016b. Analysis of a commercial marijuana e-cigarette formulation. J. Anal. Toxicol. 40, 374–378. https://doi.org/10.1093/jat/bkw021.
Peglow, S., Buchner, J., Briscoe, G., 2012. Synthetic cannabinoid induced psychosis in a previously nonpsychotic patient. Am. J. Addict. 21, 287–288. https://doi.org/10.1111/j.1521-0391.2012.00222.x.
Pellegrino, R.M., Tinghino, B., Mangiaracina, G., Marani, A., Vitali, M., Protano, C., Osborn, J.F., Cattaruzza, M.S., 2012. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). Ann. Ig. 24, 279–288.
Pillay, V.V., 2013. Modern Medical Toxicology. Jaypee Brothers, New Delhi.
Pisinger, C., Døssing, M., 2014. A systematic review of health effects of electronic cigarettes. Prev. Med. 69, 248–260. https://doi.org/10.1016/j.ypmed.2014.10.009.
Poklis, J.L., Mulder, H.A., Halquist, M.S., Wolf, C.E., Poklis, A., Peace, M.R., 2017. The blue lotus flower (nymphea caerulea) resin used in a new type of electronic cigarette, the re-buildable dripping atomizer. J. Psychoact. Drugs 49, 175–181. https://doi.org/10.1080/02791072.2017.1290304.
Raber, J.C., Elizinga, S., Kaplan, C., 2015. Understanding dabs: contamination concerns of cannabis concentrates and cannabinoids transfer during the act of dabbing. J. Toxicol. Sci. 40, 797–803. https://doi.org/10.2131/jts.40.797.
Rogers, J.S., Rehrer, S.J., Hoot, N.R., 2016. Acetylfentanyl: an emerging drug of abuse. J. Emerg. Med. 50, 433–436. https://doi.org/10.1016/j.jemermed.2015.10.014.
Rojkiewicz, M., Majchrzak, M., Celinski, R., Kus, P., Sajewicz, M., 2017. Identification and physicochemical characterization of 4-fluorobutyrfentanyl (1-((4-fluorophenyl)(1-phenethylpiperidin-4-yl)amino)butan-1-one, 4-FBF) in seized materials and post-mortem biological samples. Drug Test. Anal. 9, 405–414. https://doi.org/10.1002/dta.2135.
Rom, O., Pecorelli, A., Valacchi, G., Reznick, A.Z., 2015. Are e-cigarettes a safe and good alternative to cigarette smoking? Ann. N. Y. Acad. Sci. 1340, 65–74. https://doi.org/10.1111/nyas.12609.
Rook, E.J., Van Ree, J.M., Van Den Brink, W., Hillebrand, M.J., Huitema, A.D.R., Hendriks, V.M., Beijnen, J.H., 2006. Pharmacokinetics and pharmacodynamics of high doses of pharmaceutically prepared heroin, by intravenous or by inhalation route in opioid-dependent patients. Basic. Clin. Pharmacol. Toxicol. 98, 86–96. https://doi.org/10.1111/j.1742-7843.2006.pto_233.x.
Rothman, R.B., Baumann, M.H., Dersch, C.M., Romero, D.V., Rice, K.C., Carroll, F.I., Partilla, J.S., 2001. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. Synapse 39, 32–41. https://doi.org/10.1002/1098-2396(20010101)39:1<32::AID-SYN5>3.0.CO;2-3.
Salani, D.A., Zdanowicz, M.M., 2015. Synthetic cannabinoids: the dangers of spicing it up. J. Psychosoc. Nurs. Ment. Health Serv. 53, 36–43. https://doi.org/10.3928/02793695-20150422-01.
Schauer, G.L., King, B.A., Bunnell, R.E., Promoff, G., McAfee, T.A., 2016. Toking, vaping, and eating for health or fun: marijuana use patterns in adults, US, 2014. Am. J. Prev. Med. 50, 1–8. https://doi.org/10.1016/j.amepre.2015.05.027.
Schifano, F., 2004. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. Psychopharmacology 173, 242–248. https://doi.org/10.1007/s00213-003-1730-5.
Schifano, F., Orsolini, L., Papanti, D., Corkery, J., 2017. NPS: medical consequences associated with their intake. In: Baumann, M.H., Glennon, R.A., Wiley, J.L. (Eds.), Neuropharmacology of New Psychoactive Substances (NPS): The Science Behind the Headlines. Springer International Publishing, pp. 351–380.
Schober, W., Szendrei, K., Matzen, W., Osiander-Fuchs, H., Heitmann, D., Schettgen, T., Jörres, R.A., Fromme, H., 2014. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. Int. J. Hyg. Environ. Health. 217, 628–637. https://doi.org/10.1016/j.ijheh.2013.11.003.
Schraufnagel, D.E., Blasi, F., Drummond, M.B., Lam, D.C., Latif, E., Rosen, M.J., Sansores, R., Van Zyl-Smit, R., 2014. Electronic cigarettes. A position statement of the forum of international respiratory societies. Am. J. Respir. Crit. Care Med. 190, 611–618. https://doi.org/10.1164/rccm.201407-1198PP.
Schripp, T., Markewitz, D., Uhde, E., Salthammer, T., 2013. Does e-cigarette consumption cause passive vaping? Indoor Air. 23, 25–31. https://doi.org/10.1111/j.1600-0668.2012.00792.x.
Schroeder, M.J., Hoffman, A.C., 2014. Electronic cigarettes and nicotine clinical pharmacology. Tob. Control. 23, ii30–ii35. https://doi.org/10.1136/tobaccocontrol-2013-051469.
Selley, D.E., Cao, C.-C., Sexton, T., Schwegel, J.A., Martin, T.J., Childers, S.R., 2001. μ opioid receptor-mediated G-protein activation by heroin metabolites: evidence for greater efficacy of 6-monoacetylmorphine compared with morphine. Biochem. Pharmacol. 62, 447–455.
Shiplo, S., Asbridge, M., Leatherdale, S.T., Hammond, D., 2016. Medical cannabis use in Canada: vaporization and modes of delivery. Harm Reduct. J. 13. https://doi.org/10.1186/s12954-016-0119-9.
Sitte, H.H., Freissmuth, M., 2010. The reverse operation of Na+/Cl−-coupled neurotransmitter transporters–why amphetamines take two to tango. J. Neurochem. 112, 340–355. https://doi.org/10.1111/j.1471-4159.2009.06474.x.
Smith, M.T., 2000. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. Clin. Exp. Pharmacol. Physiol. 27, 524–528.
Solis, E., 2017. Electrophysiological actions of synthetic cathinones on monoamine transporters. In: Baumann, M.H., Glennon, R.A., Wiley, J.L. (Eds.), Neuropharmacology of New Psychoactive Substances (NPS) : The Science Behind the Headlines. Springer International Publishing, pp. 73–92.
Solowij, N., Grenyer, B.F., Grotenhermen, F., Russo, E., 2001. Long Term Effects of Cannabis on Psyche and Cognition. pp. 299–311.
Steinkellner, T., Freissmuth, M., Sitte, H.H., Montgomery, T., 2011. The ugly side of amphetamines: short-and long-term toxicity of 3, 4-methylenedioxymethamphetamine (MDMA,'Ecstasy'), methamphetamine and D-amphetamine. Biol. Chem. 392, 103–115. https://doi.org/10.1515/BC.2011.016.
Suzuki, J., El-Haddad, S., 2017. A review: fentanyl and non-pharmaceutical fentanyls. Drug. Alcohol. Depend. 171, 107–116. https://doi.org/10.1016/j.drugalcdep.2016.11.033.
Swortwood, M.J., Newmeyer, M.N., Andersson, M., Abulseoud, O.A., Scheidweiler, K.B., Huestis, M.A., 2016. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. Drug. Test. Anal. 9, 905–915. https://doi.org/10.1002/dta.2092.

Tai, S., Fantegrossi, W.E., 2017. Pharmacological and toxicological effects of synthetic cannabinoids and their metabolites. In: Baumann, M.H., Glennon, R.A., Wiley, J.L. (Eds.), Neuropharmacology of New Psychoactive Substances (NPS) : The Science Behind the Headlines. Springer International Publishing, pp. 249–262.

Thompson, G.R., Rosenkrantz, H., Schaeppi, U.H., Braude, M.C., 1973. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. Toxicol. Appl. Pharmacol. 25, 363–372.

Thurtle, N., Abouchedid, R., Archer, J.R.H., Ho, J., Yamamoto, T., Dargan, P.I., Wood, D.M., 2017. Prevalence of use of electronic nicotine delivery systems (ENDS) to vape recreational drugs by club patrons in South London. J. Med. Toxicol. 13, 61–65. https://doi.org/10.1007/s13181-016-0583-3.

Tisdale, J.E., Shimoyama, H., Sabbah, H.N., Webb, C.R., 1996. The effect of cocaine on ventricular fibrillation threshold in the normal canine heart. Pharmacotherapy 16, 429–437.

Trecki, J., Gerona, R.R., Schwartz, M.D., 2015. Synthetic cannabinoid-related illnesses and deaths. New Engl. J. Med. 373, 103–107. https://doi.org/10.1056/NEJMp1505328.

Troutt, W.D., DiDonato, M.D., 2017. Carbonyl compounds produced by vaporizing cannabis oil thinning agents. J. Altern. Complement. Med. https://doi.org/10.1089/acm.2016.0337.

Turner, A.R., Agrawal, S., 2017. Marijuana. StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL). 2018 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430801/.

Umebachi, R., Aoki, H., Sugita, M., Taira, T., Wakai, S., Saito, T., Inokuchi, S., 2016. Clinical characteristics of α-pyrrolidinovalerophenone (α-PVP) poisoning. Clin. Toxicol. 54, 563–567. https://doi.org/10.3109/15563650.2016.1166508.

Vakkalanka, J.P., Hardison, L.S., Holstege, C.P., 2014. Epidemiological trends in electronic cigarette exposures reported to U.S. Poison centers. Clin. Toxicol. 52, 542–548. https://doi.org/10.3109/15563650.2014.913176.

Valsalan, R., Varghese, B., Soman, D., Buckmaster, J., Yew, S., Cooper, D., 2017. Multi-organ dysfunction due to bath salts: are we aware of this entity? Intern. Med. 47, 109–111. https://doi.org/10.1111/imj.13307.

Van Dam, N.T., Earleywine, M., 2010. Pulmonary function in cannabis users: support for a clinical trial of the vaporizer. Int. J. Drug. Policy. 21, 511–513. https://doi.org/10.1016/j.drugpo.2010.04.001.

Vandrey, R., Dunn, K.E., Fry, J.A., Girling, E.R., 2012. A survey study to characterize use of spice products (synthetic cannabinoids). Drug Alcohol. Depend. 120, 238–241. https://doi.org/10.1016/j.drugalcdep.2011.07.011.

Weaver, M.F., Hopper, J.A., Gunderson, E.W., 2015. Designer drugs 2015: assessment and management. Addict. Sci. Clin. Pract. 10. https://doi.org/10.1186/s13722-015-0024-7.

Weinstein, A.M., Rosca, P., Fattore, L., London, E.D., 2017. Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. Front. Psychiatry 8, 156. https://doi.org/10.3389/fpsyt.2017.00156.

Werley, M.S., McDonald, P., Lilly, P., Kirkpatrick, D., Wallery, J., Byron, P., Venitz, J., 2011. Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in sprague-Dawley rats and beagle dogs. Toxicology 287, 76–90. https://doi.org/10.1016/j.tox.2011.05.015.

World Health Organisation (WHO) International Agency for Research on Cancer (IARC), 2007. Smokeless Tobacco and Some Tobacco-Specific N-Nitrosamines, vol. 89 Accessed 4 January 2018. http://monographs.iarc.fr/ENG/recentpub/mono89.pdf.

World Health Organisation (WHO) Framework Convention on Tobacco Control, 2014. Electronic Nicotine Delivery Systems. Accessed 4 January 2018. http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10Rev1-en.pdf?ua=1.

Williams, M., Villarreal, A., Bozhilov, K., Lin, S., Talbot, P., 2013. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PLoS One 8, 1–11. https://doi.org/10.1371/journal.pone.0057987.

Winstock, A.R., 2017. Vaping Drugs - Tech, Drugs and Profit - the Perfect Storm or Just a Better High? Accessed 13 December 2017. https://www.globaldrugsurvey.com/gds2017-launch/vaping-drugs-tech-drugs-and-profit-the-perfect-storm-or-just-a-better-high/.

Yu, S., Zhu, L., Shen, Q., Bai, X., Di, X., 2015. Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. Behav. Neurol. 2015. https://doi.org/10.1155/2015/103969.

Zawilska, J.B., Andrzejczak, D., 2015. Next generation of novel psychoactive substances on the horizon - a complex problem to face. Drug. Alcohol. Depend. 157, 1–17. https://doi.org/10.1016/j.drugalcdep.2015.09.030.

Zhang, Z., Zheng, X., Zeng, D.D., Leischow, S.J., 2016. Tracking dabbing using search query surveillance: a case study in the United States. J. Med. Internet Res. 18, e252. https://doi.org/10.2196/jmir.5802.