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Abbreviations

AB-PINACA, N-[1-(aminocarbonyl)-2-methylpropyl]-1-pentyl-1H-indazole-3-carboxamide;
2C-B, 4-bromo-2,5-dimethoxyphenethylamine;
2-Cl-4,5-MDMA, 2-chloro-4,5-methylenedioxymethamphetamine;
25I-NBOMe, 4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine;
3-CMC, 3-chloromethcathinone;
4F-MDMB-BINACA, methyl 2-(1-(4-fluorobutyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate;
3-FEA, 3-fluoroethamphetamine;
4-CMC, 4-chloromethcathinone;
ATP, adenosine triphosphate;
CanTEST, Canberra's health and drug checking service;
CNS, central nervous system;
CPu, caudate-putamen nucleus;
CYP, Cytochrome P450;
DA, dopamine;
DAergic, dopaminergic;
DAT, DA transporter;
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction;
EUDA, European Drug Agency
5-HT, serotonin;
MDAI, 5,6-methylenedioxy-2-aminoindane;
MDMA, 3,4-methylenedioxymethamphetamine;
3-MMC, 3-methylmethcathinone;
4-MMC, 4-methylmethcathinone;
NAc, nucleus accumbens;
NET, noradrenaline transporter;
NMDA, N-methyl-D-aspartate;
NSO, novel synthetic opioids;
PFC, prefrontal cortex;
PMA paramethoxyamphetamine;
PMMA, para-methoxymethamphetamine;
PPI, pre-pulse inhibition of acoustic startle;
ROS, reactive oxygen species;
SERT, 5-HT transporter;
UNODC, United Nations Office on Drugs and Crime;
WDR, World Drug Report;
WEDINOS, Welsh Emerging Drugs and Identification of Novel Substances.

Abstract

Introduction. Preclinical and clinical studies show 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') can cause adverse effects in the central nervous system (CNS). Recently, preclinical studies have demonstrated that certain psychoactive substances may exacerbate the noxious central effects of MDMA when co-administered, including substances that are contained as adulterants in tablets sold as "MDMA" in the illegal market. Since the quality and quantity of adulterants in tablets sold as "MDMA" vary based on factors such as the year and the geographical region of production, this may result in diverse health risks for people who use MDMA.
Methods. This review provides a concise overview of: i) composition of tablets sold as "MDMA" in Continental Europe, UK, USA and Australia in the post COVID-19 pandemic period; ii) recent preclinical and clinical findings about the central effects of the psychoactive adulterants most commonly found in tablets sold as "MDMA" in the above areas; iii) the possible adverse CNS effects of these adulterants in humans when taken in combination with MDMA.
Results. Tablets sold as "MDMA" are frequently and differently adulterated among Continental Europe, UK, USA and Australia.
Discussion. The possible interactions between MDMA and psychoactive adulterants contained in tablets sold as MDMA deserve attention, since they may potentially explain some of the noxious neurological and psychiatric effects that have been described in people who use MDMA.
Conclusions. Ongoing public health efforts and expansion of drug checking are essential to properly inform MDMA users about the risks associated with psychoactive contaminants, first responders, healthcare professionals, and the general public about the possible detrimental consequences for health associated with the use of MDMA coming from illicit sources and unintended contaminant consumption.

Key words: amphetamines, drugs of abuse, ecstasy, nitazenes, phenethylamines, synthetic cathinones.

3. Introduction

The psychostimulant 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is an amphetamine-related drug with abuse liability and psychedelic properties. According to the World Drug Report [1] released by the United Nations Office on Drugs and Crime (UNODC), several countries are experiencing a "psychedelic renaissance". Thus, after a worldwide trend towards decreased use in 2021, possibly related to the COVID-19 pandemic, a rise in the seizures of tablets sold as "MDMA" was reported in recent years, in Europe [2] but not Australia where have still not returned to pre-COVID-19 pandemic levels [3-5]. Interestingly, European countries are identified (83%) as the main region of production of MDMA over the period 2018-2022, followed by North America [2]. Conversely, the number of MDMA seizures in England and Wales in 2023 decreased (36%) compared to 2022 [6].

Low doses of MDMA taken on single occasions, such as raves and club parties, induce effects on the emotional state that include feelings of pleasure and well-being, increased sociability and closeness with others [7,8]. Importantly, tolerance may occur to the pleasurable effects that MDMA elicits on the emotional state. MDMA also induces acute and long-term adverse effects in the central nervous system (CNS); the intensity and occurrence of these effects may be influenced by multiple factors, including the dose and regimen of administration, the sex and age of users, and the social context in which MDMA is consumed [9]. High purity has important implications for MDMA use and harms, as research has shown that use of MDMA where the dose exceeds 120 mg increases the risk of adverse events [10]. MDMA toxicity, due to consumption of: 1) high dose of MDMA; 2) MDMA adulterated with other toxic substances; or 3) consumption of MDMA concomitantly with other substances, can result in death, albeit at relatively low prevalence [11]. MDMA-related deaths have been documented in several European countries and in Australia [12]. Regarding the effects on specific neuronal pathways, preclinical studies have demonstrated that MDMA mostly affects serotonergic and dopaminergic (DAergic) circuits [13]. Concerning the effects of MDMA on serotonergic systems, studies in rats and non-human primates have demonstrated that prolonged and/or repeated exposure to MDMA can affect cortical, hypothalamic, limbic and striatal brain regions, by: i) decreasing the levels of serotonin (5-HT) and of its major metabolite, 5-hydroxyindoleacetic acid [14-17]; ii) reducing the density of the 5-HT transporter (SERT) [18]; iii) decreasing the activity of tryptophan hydroxylase, the rate-limiting enzyme for 5-HT synthesis [16,19]. Importantly, a reduction in SERT density has also been described in several regions of the brain in people with heavy MDMA use histories (i.e., anterior and posterior cingulate cortices, hippocampus, parietal, temporal and occipital lobe, thalamus) [20] although other authors have hypothesized that this reduction may be reversible after MDMA discontinuation [21]. With regard to the effects of MDMA on DAergic systems, studies in mice and certain studies in rats and in non-human primates found that the prolonged and/or repeated administration of MDMA decreased the levels of dopamine (DA) and the density of the DA transporter (DAT) in the caudate-putamen (CPu) [13,22-28] as well as the immunoreactivity for tyrosine hydroxylase, the rate-limiting enzyme for DA synthesis, in both the CPu and substantia nigra *pars compacta* [6,28-31]. The existence of noxious effects of MDMA on the DAergic systems of the human brain is controversial, although some studies reported abnormalities in certain mediators related to DA transmission in the brains of people who use MDMA [32].

Several preclinical investigations have proposed different mechanisms that may be responsible for the effects that MDMA elicits on serotonergic and DAergic systems, including the generation of toxic metabolites of MDMA, the increase in oxidative stress and production of DA-based quinones, the occurrence of mitochondrial dysfunction, the activation of glial cells, the occurrence of excitotoxic events and the induction of hyperthermia [33,34]. Moreover, disfunctions in the GABAergic system have been demonstrated in experimental animals [27] and humans [35] exposed to MDMA. As of today, the relative importance of each potential mechanism of MDMA toxicity is still unclear, and so is the existence of possible synergistic interactions among the different mechanisms of MDMA toxicity. Interestingly, a recent clinical study has found a significantly high iron deposition in the striatum of MDMA user, which has been hypothesized to contribute to neuronal toxicity [36]. Importantly, although some toxicological reports found MDMA was the sole psychoactive substance contained in tablets (as in MDMA tablet seized in Poland between 2019-2020, [37], other reports found seized MDMA tablets to contain at least one other psychoactive substance [2]. The type and number of psychoactive adulterants found in MDMA tablets may occur for different reasons. One possible explanation is that people who supply MDMA can increase their profit by preparing a high number of doses with a low concentration of the active ingredient. Another possible explanation is that psychoactive substances are added to MDMA to magnify the desired effects, but also to counteract their unpleasant effects. Additionally, in some cases, poor manufacturing processes (such as lack of equipment cleaning between different drugs) may lead to contamination. These different explanations may vary by geographic region (Figure 1). Building on the epidemiological and toxicological data reported above, this review provides a concise overview of the content of tablets sold as "MDMA" in the post-COVID-19 pandemic era in Continental Europe, UK, USA and Australia (Figure 1). Moreover, this review outlines the findings obtained in the last 5 years from preclinical and clinical studies that evaluated the central effects of psychoactive adulterants (i.e., amphetamines, cathinones, ketamine, nitazenes, phenethylamines and synthetic cathinones), found in tablets sold as "MDMA".

4. Methodology

To this end, we began with an extensive search strategy to conduct a comprehensive review of the relevant literature, focusing on original research articles, meta-analyses, and review articles published in the last 5 years (2020-2025). Articles were searched by using the specific search terms "adulterants" AND "MDMA tablets" AND "COVID-19" in

PubMed, to focus on articles on psychoactive synthetic adulterants in tablets sold as "MDMA" after the COVID-19 pandemic. After reading the titles and abstracts of these articles, we included in the search strategy a series of additional keywords (e.g., the name of specific adulterant). When a limited number of relevant articles were found, we adjusted the search criteria, for example by extending the search period to the most recent articles available, in order to obtain more relevant literature. Finally, we browsed the main search engines (Google) and the websites of the Continental Europe, UK, USA and Australia regulatory agencies.

5. Results

5.1 The situation in Continental Europe

In the years between 2017 and 2020, certain Continental European countries such as the Netherlands recorded relatively large (e.g., more than 1000 kg) border seizures of tablets sold as MDMA (https://dataunodc.un.org/dp-drug-seizures), indicating a strong market for MDMA. Nonetheless, during 2021, there was a general decline in seizures of tablets sold as MDMA in these countries. In 2022, the number of seizures of the MDMA precursors piperonyl methyl ketone, its glycidic derivatives, and other related chemicals reflected an increase in the production of MDMA, after a period of generalized decrease during the COVID-19 pandemic [2].

Reports from the beginning of 2023, based on data from drug checking services in 18 cities of 10 Continental European countries showed the content of tablets sold as MDMA, contained an average of 134 mg of MDMA (purity of 80%) [2], while in the same period of 2022, tablets were found to contain an average of 139 mg of MDMA (purity of 78%). In 2023, a total of 1541 tablets sold as MDMA were tested for purity by 12 drug checking services in 9 Continental European countries [2]. MDMA was the only psychoactive ingredient in 1325 samples, while the remaining 216 samples contained at least one adulterant substance with psychoactive properties. Notably, synthetic cathinones were the psychoactive adulterants most frequently detected in tablets sold as MDMA, representing 44% of all the detected psychoactive components other than MDMA [2]. Indeed, the presence of synthetic cathinones in tablets sold as MDMA in 2023 was reported by checking services in 9 Continental European countries, with all services reporting synthetic cathinones to be present in at least one sample. The synthetic cathinones most frequently detected were: 3-chloromethcathinone (3-CMC), 4-chloromethcathinone (clephedrone, 4-CMC), 3-methylmethcathinone (3-MMC), 4-methylmethcathinone (mephedrone, 4-MMC), 3-fluoroethamphetamine (3-FEA) and dipentylone [2] (Figure 1). Although the pharmacological and toxicological profiles of these synthetic cathinones are only partially known, as detailed below, they all elicit CNS effects of various severity. After cathinones, caffeine was the second adulterant with psychoactive properties most found in 12% of tablets sold as MDMA in Continental Europe and UK [2,38]. Although typical use of caffeine is regarded as relatively safe, several preclinical studies indicate that caffeine may potentiate the adverse effects of other psychoactive substances that are taken concomitantly with it [34,39-42]. Finally, hallucinogens, as a class, are the third most common psychoactive adulterants, detected in 10% of tablets sold as MDMA, with 4-bromo-2,5-dimethoxyphenethylamine (2C-B) being the most frequently detected hallucinogen in those samples [2,43] (Figure 1). Interestingly, the European Drug Report [2,43] reported that 2C-B may also be added to MDMA powders and tablets sold as 'pink cocaine', often in combination with other psychoactive drugs, such as ketamine and cocaine.

5.2 The situation in the UK

The 2022-2023 House of Commons Home Affairs Committee (UK) reported MDMA as one of the most used drugs in England and Wales, with 246,000 users aged 16–59. Between April and September 2020, the Release report [44] examined the UK drug market's response to COVID-19 pandemic, highlighting shifts in MDMA use. Purchases were infrequent compared to cannabis due to reduced social opportunities, while darknet sales surged, with 13% of users buying there for the first time. Despite price increases, purity remained stable or improved, suggesting suppliers adjusted prices or deal sizes rather than resorting to adulteration. The UK recorded significant MDMA seizures in powder/crystal form, totalling approximately 16 kg (84% purity) in 2017, 9 kg (88%) in 2018, and 9 kg (91%) in 2019. In 2020, seizures surged to 27 kg (89% purity). The seizures of tablets sold as MDMA numbered around 27,000 in 2017 (153 mg/tablet), 34,000 in 2018 (152 mg), and 36,000 in 2019 (147 mg), before rising sharply to 79,000 in 2020 (150 mg) [45]. In 2021 and 2022, the seizures of tablets sold as MDMA declined to approximately 18 kg and 5 kg, respectively, with average purities slightly reduced to 87% and 82%. Similarly, the seizures of tablets sold as MDMA also decreased during this period, totalling around 18,000 in 2021 (average MDMA content of 161 mg per tablet/capsule) and 17,000 tablets/capsules in 2022 (average content 124 mg per tablet/capsule). In 2021 and 2022, crystalline sold as MDMA, that contained caffeine, became widespread [46].

The Welsh Emerging Drugs and Identification of Novel Substances project by Public Health Wales [47] anonymously tests substances from individuals, amnesty bins, and nightlife venues. Between 2015 and 2022, MDMA was the second most identified drug after cocaine, except in 2020 during the COVID-19 pandemic, when it dropped to eighth [46]. COVID-19 pandemic/post-pandemic data revealed a complex MDMA use landscape [47]. For the year ending March 2020, 1.4% of adults aged 16–59 in England and Wales (471,000) reported MDMA use, with 82 of 4,561 drug poisoning deaths involving the drug [48-49]. In the 2019–2020 period, 607 samples were submitted as MDMA, but 33% (203 samples) contained none. Common substitutes included caffeine (96 samples) and cathinones like eutylone and mephedrone (77 samples) (Figure 1). MDMA was the second most identified psychoactive substance after cocaine, with substitution issues evident, often involving caffeine or a mix of MDMA and 2C-B [46] (Figure 1). In 2020-2021, MDMA

was the eighth most identified psychoactive substance, and common substitutes were temazepam, 2C-B, and synthetic cannabinoids like methyl 2-[[1-(4-fluorobutyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate, methyl 2-(1-(4-fluorobutyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate (4F-MDMB-BINACA) and N-[1-(aminocarbonyl)-2-methylpropyl]-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA), sold as cannabis vape liquids [46] (Figure 1). In 2021–2022, MDMA remained the second most identified psychoactive substance after cocaine, frequently combined with diazepam, while certain cocaine-labelled samples included MDMA (Figure 1). A few tablets sold as MDMA also contained 2C-B [46] (Figure 1).

Regarding trends at English music festivals, the analysis of 417 samples from 2019 and 377 samples from 2021 found that the detection of MDMA dropped sharply from 93% to 55% between the two years. In 2021, synthetic cathinones (e.g., 4-CMC, 3-MMC, and eutylone) and caffeine each accounted for roughly 20% of samples, despite being virtually absent in 2019. Survey data indicated that over 35% of attendees intended to use MDMA, but fewer than 1% knowingly used cathinones or caffeine, highlighting unintentional consumption. This surge in adulteration coincided with MDMA shortages caused by Brexit, prolonged COVID-19 lockdowns, and regulatory changes, driving substitution with other substances readily available in the Netherlands [38].

5.3 The situation in the USA

Similar to observations in Continental Europe and UK, between 2017 and 2020, and particularly in 2019, the USA recorded large numbers of border seizures of tablets sold as MDMA (e.g., more than 4,000 kg) and 2020 (e.g., more than 6,000 kg) [50]. Moreover, similarly to UK and Australia, in 2021 and 2022 the USA Customs and Border Protection recorded a decline in seizures of tablets sold as MDMA at the coastal, northern and southwest borders (more than 400 kg in 2021 and 300 kg in 2022), which continued in 2023 and 2024, (294 kg in 2023 and 250 kg in 2024 [50].

Limited information is available about the purity of the tablets sold as MDMA seized in USA, particularly of those seized after the onset of the COVID-19 pandemic [51]. In 2022, the National Forensic Laboratory Information System of the Drug Enforcement Administration identified more than 300,000 reports regarding phenethylamine derivatives, including MDMA, representing 31% of all drug reports. However, the number of reports on tablets sold as MDMA was 3,265, representing less than 1% of all drug reports [52]. Nevertheless, according to reports collected before the COVID-19 pandemic, MDMA purity trends in the USA do not fully mirror those in Continental Europe and Australia. Thus, reports that analyzed hair samples from MDMA users in the timespan between 2015-2020 found that the most common likely psychoactive adulterants in tablets sold as MDMA included ketamine [53], methamphetamine [53] and synthetic cathinones, such as butylone, ethylone, pentylone [53-55] (Figure 1). Finally, Krotulski et al. [56] published a report of 18 medicolegal death investigations. One deceased individual had high blood concentrations of MDMA paired with high concentrations of isotonitazene (ITZ), a novel synthetic opioid (NSO). As detailed below, ITZ consumption may be intentional but is most commonly unintentional, as nitazenes are frequently sold in falsified opioid medicines or mixed with other drugs (e.g., heroin, fentanyl) to increase potency and cut costs, or inadvertently present as adulterants due to poor manufacturing processes. This poses a major challenge since little is known about the possible detrimental effects arising from pharmacodynamic or pharmacokinetic interactions between nitazenes and MDMA. The lack of opioid tolerance among people who use MDMA also places them at considerable risk of overdose due to inadvertent exposure.

5.4 The situation in Australia

Between 2017 and 2020, and particularly in 2020 Australia recorded relatively large (e.g., more than 2,000 kg) border seizures of tablets sold as MDMA (https://dataunodc.un.org/dp-drug-seizures), indicating a strong market for MDMA in Australia. Seizure weights declined (to 265 kg) in 2021 and have still not returned to pre-COVID-19 pandemic levels (https://dataunodc.un.org/dp-drug-seizures). As most of the tablets sold as MDMA consumed in Australia are imported from Continental Europe [2] declines are likely due to international border restrictions imposed during the COVID-19 pandemic.

In 2023, several legislative changes regarding MDMA have occurred in Australia: i) MDMA was legalized for medical use in limited contexts (July 1st 2023), allowing authorized psychiatrists to prescribe MDMA for the treatment of post-traumatic stress disorder [57]; and ii) the possession of small amounts of MDMA for personal use was decriminalized (October 28th 2023) in one jurisdiction (the Australian Capital Territory) [51].While it is possible that heightened media attention may influence patterns in illicit markets, it is too early to evaluate the outcomes of these changes.

Responses to reduce illegal MDMA harms in Australia include expanding drug checking services across the country. Three Australian jurisdictions have approved these services, two of which are in operation: Canberra's health and drug checking service (CanTEST) and Queensland's service CheQpoint [58]. Victoria has commenced its first drug checking services, with a mobile service operating at 5 festivals over the 2024-25 summer. Of the 20 notifications issued in the first 2 years by Australia's first fixed site drug checking service, CanTEST, 9 are related to MDMA [58]. Four of these alerts are related to "high dose" MDMA, including one linked to a "blue punisher" tablet (i.e. a tablet that was blue in appearance with the common street name "blue punisher"), with the same appearance as an MDMA tablet which the Victorian Coroners attributed to a death in Victoria in 2023 [59,60].

Five alerts related to adulterants detected in MDMA through drug checking in Australia. These detections included synthetic cathinones (dipentylone and 4-MMC), nitazenes and methamphetamine [58] (Figure 1). In the first year CanTEST operated, 27% of tested tablets sold as MDMA had other psychoactive substances detected, in particular

dipentylone and caffeine [58] (Figure 1). In the Australian state of New South Wales, most public health alerts, issued by the Ministry of Health were for high or variable doses of MDMA contained in tablets sold as MDMA, while one warning was issued when tablets sold as MDMA were found to contain a nitazene [61]. In Victoria, since 2020, the Department of Health has issued fourteen drug alerts, with five involving MDMA [59]. One alert related to use of MDMA in hot environments, and four alerts reported that other substances such as hallucinogens (para-methoxymethamphetamine, PMMA) and synthetic cathinones (dipentylone, pentylone and N-ethylpentylone) were present in tablets sold as MDMA, resulting in emergency department presentations or other unwanted effects [62] (Figure 1).

6. Central effect of psychoactive adulterants found in tablets sold as MDMA: recent advances

6.1 Synthetic cathinones

Synthetic cathinones, also known as "Bath salts", are all substances with a chemical structure that resembles that of cathinone, the ephedrine analogue found in *Catha edulis* (Khat). Most of the known synthetic cathinones with abuse liability are scheduled in Continental Europe, UK, USA and Australia. Desired and adverse effects of synthetic cathinones largely overlap with those of psychostimulants such as amphetamine, cocaine, and MDMA. Similar to other psychostimulants, synthetic cathinones inhibit the reuptake of monoamines via the DAT, SERT or norepinephrine transporter (NET) [63,64]. The differences in the affinity that the various synthetic cathinones display for DAT, SERT or NET and in the severity of their effects result in varying clinical and toxicological profiles. The synthetic cathinones that chiefly stimulate DAergic transmission (3-CMC, 3-MMC, dipentylone) can induce psychostimulant and reinforcing effects, whereas those that act also on the noradrenergic transmission (3-CMC, 3-MMC) can induce sympathomimetic effects [65].

As mentioned above, 3-CMC, 4-CMC, 3-MMC, 3-FEA and dipentylone are the synthetic cathinones most frequently detected in tablets sold as MDMA in Continental Europe [2], UK [38], USA [53-55] and Australia [66]. For this reason, the present review will focus on the central effects of these compounds.

Although the toxicological profiles of 3-CMC, 4-CMC, 3-MMC, 3-FEA and dipentylone are only partially characterized, these synthetic cathinones generally exhibit less pronounced neurotoxic effects compared with MDMA and other amphetamine-related drugs like methamphetamine [65].

In vitro studies of cytotoxicity in undifferentiated SHSY5Y cells showed that the toxic effects of 3-CMC and 4-CMC depend on drug concentration and duration of drug exposure. Wojcieszak and colleagues evaluated the viability of SHSY5Y cells after exposure to either 3-CMC or 4-CMC [67]. They found cell viability to decline to a maximum of 49% of controls after exposure to 3-CMC for 72 hours, but not 24 hours (concentration range of 50–300 μM). Similarly, the viability of SHSY5Y cells declined to a maximum of 50% of controls after exposure to 4-CMC for 72 hours (concentration range of 100–300 μM). Interestingly, 200 μM and 300 μM of 4-CMC were able to decrease the viability of SHSY5Y cells by 11-12%, after exposure for 24 hours, and by 18% after exposure for 48 hours, compared with controls [67]. Other *in vitro* studies about the cytotoxic properties of 4-CMC showed that differentiated SHSY5Y cells were less sensitive to toxic damage, compared with undifferentiated SHSY5Y cells, at least when evaluated at room temperature [68] When undifferentiated SHSY5Y cells were exposed to 4-CMC at 40.5 °C (concentration range: from 200 to 2000 μM), a decrease in cellular adenosine triphosphate (ATP) and an increase in both mitochondrial formation of reactive oxygen species (ROS) and plasma membrane damage were observed [68].Studies in experimental animals have observed divergent results depending on the number of administrations of synthetic cathinones. The acute administration of either 3-CMC or 4-CMC to male DBA/2J mice at the doses of 5, 10, or 20 mg/kg stimulated horizontal locomotor activity in a dose-dependent manner, with 4-CMC also increasing vertical locomotor activity at the dose of 10 mg/kg [67]. A similar elevation in locomotor activity was observed in male Swiss-Webster mice after the acute administration of 4-CMC at doses of 2.5 or 5 mg/kg [69]. Gatch and colleagues (2021) [70] also tested male Swiss-Webster mice for their locomotor response after the acute administration of dipentylone at doses of 2.5, 5, 10, 25 or 50 mg/kg. Increased locomotor activity was observed after the doses of 10 and 25 mg/kg, which occurred within 10 min and lasted 6 hours after administration [70]. Regarding the repeated administration of synthetic cathinones, Wojcieszak and colleagues performed a 14-day intermittent treatment with 4-CMC at the dose of 10 mg/kg, followed by 48 hours of withdrawal, in DBA/2J mice that were subsequently evaluated for the presence of depressive-like symptoms (tail suspension test, forced swim test, sucrose preference test) and for motor performance (spontaneous locomotor activity, rotarod). They found no significant alterations in the behavioral readouts evaluated, which may suggest that the repeated administration of 4-CMC did not affect the neurocircuits that regulate emotional states and motor function [67]. A recent study in C57BL/6J mice has evaluated the effects of the repeated administration of the halogenated-derivative 3-FEA, given twice a day for 7 days, at doses of 1 and 10 mg/kg (Jo et al., 2023). The study focused on withdrawal score, hyperactivity evaluated in the open field, elevated plus maze, cliff avoidance test, and depressive-like behavior, assessed in the forced-swim test. Jo and colleagues found that withdrawal score increased after 16 and 40 hours from the last administration of 3-FEA. Moreover, they found that 3-FEA administration significantly increased hyperactivity and depressive-like behavior in all the tests performed [71].

Limited data are currently available about the central toxicity that synthetic cathinones may induce in humans. In general, 3-CMC, 4-CMC, 3-MMC and 3-FEA all have been reported to induce episodes of psychosis [63,72]. Reports to the Welsh Emerging Drugs and Identification of Novel Substances Project indicated that the oral intake of dipentylone may induce agitation, confusion, hallucinations, insomnia, memory loss, panic attacks, and paranoia [46]. In addition to the substantial

lack of clinical studies about the central toxicity of synthetic cathinones, tablets sold as MDMA usually contain synthetic cathinones in combination with other adulterants such as PMMA [68], meaning that the central effects elicited by each specific substance are difficult to separate from one another.

6.2 Amphetamines, phenylethylamines, and ketamine

Synthetic compounds with psychedelic and entactogenic effects are available as substitutes of MDMA. Thus, mainly amphetamine and phenylethylamine derivatives, but also ketamine, have been detected in some "MDMA" preparation' seizures (Figure 1). Similar to synthetic cathinones, most of the known amphetamine and phenylethylamine derivatives with abuse liability are scheduled in Europe, USA and Australia. Amphetamine and phenylethylamine derivatives are large classes of compounds that include several methoxy-derivatives such as paramethoxyamphetamine (PMA) and PMMA, mostly found in Australia [62,68], methoxyphenethyl-derivatives, such as 2C-B, and ketamine, frequently detected in tablets sold as MDMA in Europe [2,43]. Desired and adverse effects of these compounds largely overlap with those of MDMA and other amphetamine-related drugs. The para-substituted amphetamines PMA and PMMA are potent inhibitors of the NET and SERT, and their use is associated with higher mortality rates compared with MDMA [73-75]. Derivatives in the 2C-B series increase neurotransmitter levels in the brain, primarily DA [76] and likely also 5-HT and NE [77]. These psychedelics can act as either agonists [78,79] or antagonists [80] of 5-HT2A and alpha-adrenergic receptors. All the halogenated derivatives inhibit the NET, whereas the selectivity of the different compounds to inhibit the DAT versus SERT decreases with the increasing size of the para-substituent [79]. Ketamine is a phencyclidine derivative that primarily acts as a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) glutamate receptors but also has activity at other receptors, as it is an antagonist of muscarinic and nicotinic acetylcholine receptors and an agonist of μ- and κ-opioid receptors, dopamine D2 and serotonin 5-HT2 receptors [81]

In vitro studies contributed to the understanding of PMMA transport through the blood brain barrier, which can be relevant for both its desired and toxic central effects. Sachkova and colleagues [82] used the hCMEC/D3 cell line to model the blood brain barrier, showing that PMMA is one of the amphetamines with the highest concentration-dependent ability to be uptaken into hCMEC/D3 cells by H+/OC-antiporter [82]. Another study in differentiated SHSY5Y cells found that application of the phenylethylamine 2-chloro-4,5-methylenedioxymethamphetamine (2-Cl-4,5-MDMA) for 24 hours, decreased cell viability (1000 μM; 76% of reduction), increased ROS production (125, 250 μM; about 38 fold), and activated apoptotic processes (125, 250 μM; about 25% and 45% of activation, respectively), compared with controls [83]. Regarding methoxyphenethyl- derivatives, a marked concentration-dependent cytotoxic effect has been demonstrated in differentiated SHSY5Y cells treated with 2C-B (100, 150 and 250 μM) [84]. Specifically, 2C-B inhibited the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP2D6, involved in the bioactivation of 2C-B, and induced mitochondrial membrane depolarization and depletion of intracellular glutathione and ATP [84]. Furthermore, acute application of 2C-B (1–300 μM) has been found to induce a concentration-dependent reduction in neuronal activity in rat primary cortical cultures [85] Reduction in neuronal activity was found to persist up to 19 hours after the application of the highest concentration of 2C-B tested, although recovery of neuronal activity was observed after a 19-hour washout period following the exposure to the lowest concentration of 2C-B tested [85]. Finally, a study performed in human TK6 lymphoblast cells has demonstrated that 2C-B, reduced cell viability (35, 50 and 75 μM), activated apoptotic processes (25 and 35 μM) and increased ROS production (12,5 μM), compared with controls; all these effects were evident at 26 hours after drug application [86]. Notably, the same effects were not observed after the application of MDMA (6.25–75 μM) [86]. Regarding ketamine, treatment of mouse neuronal progenitor STHdhQ7/Q7 cells with 10 μM, 100 μM, and 1 mM for 9, 12, 24, 48, and 72 hours induced a time and concentration-dependent decrease in cell viability, probably mediated by the disruption of the endoplasmic reticulum homeostasis [87].

Regarding the central effects of amphetamine derivatives that may be contained in tablets sold as MDMA, studies in experimental animals have found that the acute administration of PMA: i) caused a marked hyperthermic response in Sprague-Dawley rats at the dose of 10 mg/kg [88]; ii) impaired motor and sensorimotor responses in male CD-1 mice, at the doses of 10 or 30 mg/kg; iii) elicited conditioned place preference accompanied by hallucinatory behavior in zebrafish at the dose of 0.1 mg/kg[89], and iv) reduced aggressive behavior in male OF.1 mice at doses between 2–12 mg/kg [90]. These behavioral effects of PMA were associated with modest damage to DAergic and serotonergic neurons [91]. Moreover, PMA seems to have limited ability to reinforce self-administration behavior, unlike amphetamine and MDMA, as suggested by a study performed in Long-Evans rats [92]. Studies on the central effects of PMMA performed in male Wistar rats showed that it increased locomotion and body temperature at the dose of 20 mg/kg and dose-dependently decreased the pre-pulse inhibition of acoustic startle reflex (PPI) at the doses of 5 and 20 mg/kg, an effect indicative of a detrimental effect of PMMA on sensorimotor gating [93]. Moreover, administration of PMMA to male Wistar-Han rats (5 and 10 mg/kg) increased the DA tissue content in the CPu and nucleus accumbens (NAc), and the 5-HT content in the CPu, while decreased the DA levels in the prefrontal cortex (PFC) [74]. In general, PMMA has been reported to induce primarily neurotoxic effects in the serotonergic systems in rats [93,94]and in the DAergic systems in mice [95], respectively. Animal studies also found changes in the DAergic and serotonergic system after the administration of the phenylethylamine 2-Cl-4,5-MDMA, another amphetamine-like adulterant found in tablets sold as MDMA (see above). When administered to male Sprague-Dawley rats 2-Cl-4,5-MDMA (5 mg/kg) increased extracellular DA in the NAc shell and medial PFC to a higher extent in adult than adolescent rats, whilst the opposite was observed on extracellular 5-HT in the NAc shell [96]. This finding suggests that the age at which 2-Cl-4,5-MDMA is consumed could be a critical factor

that shapes the effects that this phenylethylamine may have on the brain and also influence the interactions between 2-Cl-4,5-MDMA and other psychoactive substances that are taken concomitantly with it (e.g., MDMA) [96].

Concerning the central effects of methoxyphenethyl derivatives that may be contained in tablets sold as MDMA, a study in adult male Wistar rats has shown that 2C-B (2.5, 10, 25 or 50 mg/kg) induced a deficit in PPI [76]. The same study also found that the lower doses of 2C-B tested induced a decrease in electroencephalography power spectra and coherence, whereas the dose of 50 mg/kg had a temporally biphasic effect, since it induced an initial decrease followed by an increase in electroencephalography power [76]. An *in vivo* brain microdialysis study performed in male and female Sprague-Dawley rats found that the 2C-B derivative 4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe) stimulated DA transmission in the NAc shell in both sexes at the dose of 0.3 mg/kg, whereas it stimulated 5-HT transmission in the NAc shell of female rats only [97]. The same study also found that 25I-NBOMe (1 mg/kg) impaired visual responses in both sexes, decreased the core temperature in females, and the nociception in male rats [97].

With regard to the central effects of ketamine, Ikonomidou and colleagues [98] first revealed that ketamine administration triggered widespread apoptotic neurodegeneration in rat pups [98]. Subsequent studies revealed that high and prolonged dosing of ketamine negatively affects adolescent brain function and behavior [99]. In adolescent male and female rats, long-term ketamine exposure at doses ranging from 10 to 80 mg/kg increased hippocampal oxidative damage [100] and markers of hippocampal and cortical apoptosis [101-104]. Long-term ketamine exposure in rodents has been shown to alter several neurotransmitter systems. Repeated ketamine exposure (15 to 30 mg/kg) in adolescent male rats increased cortical and hippocampal glutamate levels [102-104], along with DA levels [104], and reduced GABA transmission [105].

Limited data are currently available regarding the central toxicity induced by phenylethylamine and methoxyphenethyl derivatives and ketamine in humans. Antemortem neurobehavioral evaluation has shown that PMMA can induce delirium, altered and incoherent speech and seizures in people who have used it [106]. Besides, 2C-B was found to elicit serotonin syndrome, seizures and brain edema in an 18-year-old man [107]. Structural MRI studies in chronic ketamine users have found widespread reductions in gray matter and white matter volumes, and in cortical thickness at the level of the prefrontal, parietal, temporal, left isthmus cingulate cortex, fusiform cortex, and lateral occipital cortices [108] In addition, chronic ketamine use has been found to be associated with higher right caudate volume [109] and impaired striatal functional connectivity [108] , as well as to reduced functional connectivity between the thalamus and PFC, posterior parietal cortex, the motor cortex/supplementary motor areas, and temporal cortex [110,111]. Moreover, an increase in neurofilament light chain, a blood marker of brain damage, has been reported in chronic ketamine users [112,113]. Furthermore, ketamine has been reported to affect brain development by reducing the gray matter volume in the right insula, left inferior parietal lobule, left dorsolateral PFC/superior frontal gyrus, and left medial orbitofrontal cortex of adolescents who use ketamine, compared with those who do not [114]. Like synthetic cathinones, amphetamines, phenylethylamines and ketamine are usually combined with other adulterants in tablets sold as MDMA, meaning that the central effects elicited by specific substances are difficult to separate from one another.

6.3 Novel synthetic opioids (NSOs): nitazenes

"Nitazenes" is the common name of the 2-benzylbenzimidazole opioid derivatives, which were developed in the 1950s as analgesics by the pharmaceutical company CIBA [115] but did not progress to therapeutic use due to their high risk of adverse effects. From 2019, nitazenes have emerged in the NSOs illicit market, mainly as an alternative to fentanyl derivatives [116]. Many nitazenes are highly potent μ-opioid receptor (MOR) agonists and elicit heroin- or fentanyl-like effects. Nonmedical use of nitazenes has frequently been associated with a high risk of fatal overdose, and in some cases nitazenes do not respond to standard naloxone dosages, requiring multiple administrations of naloxone to effectively reverse the overdose [117]. In Europe, NSOs have been linked to drug-induced fatalities in reports collected prior to COVID-19 pandemic in Estonia, Latvia and Lithuania and, in 2022, at least 163 fatalities were associated with fentanyl and fentanyl-derivates [2] Among the seven new NSOs formally notified in 2023 by the UNODC Early Warning Advisory, six of these were nitazenes [118]. Several studies have shown that some nitazenes display a potency up to 500 times higher than morphine [108,119-122]. Among nitazenes, ITZ, was the first identified in the illicit drug market in 2019 and was internationally scheduled in June 2021 [118]. It has since been widely pharmacologically characterized.

In vitro studies have shown that ITZ is a highly potent and effective MOR agonist [119-123] and displays a higher potency and affinity than [D-Ala^2, *N*-MePhe^4, Gly-ol]-enkephalin (DAMGO), another synthetic opioid with high MOR specificity, in both rat membrane homogenates (EC_{50}:0.99; Ki:0.06 nM) and Chinese hamster ovary (CHO)-MOR cells (EC_{50}:0.71; Ki: 0.05 nM), with no difference in maximal efficacy [124]. Studies in male Sprague Dawley rats have shown that ITZ possesses higher analgesic potency than fentanyl and morphine and activates DA transmission in the NAc shell. Of note, ITZ (0.01 mg/kg) elicited an increase in DA (max. about 200% over basal value) comparable to that elicited by a 100-fold higher dose of morphine (1 mg/kg), but higher than that elicited by an equal dose of fentanyl (0.01 mg/kg); moreover, ITZ has long lasting dose-dependent analgesic properties at dosages lower than both fentanyl and morphine. Also, ITZ (0.01 mg/kg iv) elicits a peculiar pattern of sedation, when compared to morphine (1 mg/kg iv); thus, while the decrement of activity induced by morphine progressively fades away by 30 min post-injection, the robust sedation induced by ITZ lasts up to 120 min [124].

In humans, nitazenes' overdose symptoms, which are increased by concomitant consumption of sedative drugs (such as alcohol or benzodiazepines), share several features typical of an opioid overdose [125,126].

7. Conclusions

In this review, we have summarized the evidence concerning synthetic substances that are most frequently found as adulterants in tablets sold as MDMA (i.e., cathinones, amphetamines, phenethylamines, ketamine and nitazenes). These substances can alter homeostasis, reduce viability in *in vitro* systems and can induce noxious central effects of different degrees of severity in experimental animals. Although there is increasing evidence to suggest that MDMA can cause neurotoxic effects in humans, no conclusive demonstration of long-lasting neurotoxic damage in serotonergic and/or DAergic system has been obtained so far in people who use MDMA. The possible interactions between MDMA and psychedelic adulterants contained in tablets sold as MDMA deserve attention, since, if taken often enough and in high enough doses, may potentially explain some of the noxious neurological and psychiatric effects that have been described in people who use MDMA. Accordingly, further preclinical and clinical studies are warranted to thoroughly characterize the neurobehavioral effects caused by the combination of MDMA and other psychoactive substances that may be contained as adulterants in tablets sold as MDMA. These studies will be essential for better understanding the consequences associated with the use of MDMA coming from illicit sources, which often contain diverse adulterants that may vary in qualitative and quantitative terms. Ongoing public health efforts are essential to properly inform people who use these substances, first responders, healthcare professionals, and the general public about the possible detrimental consequences for health associated with the use of MDMA coming from illicit sources. The expansion of drug checking is one mechanism that could support our understanding of the prevalence of psychoactive adulterants and help to prevent harm relating to their unintended consumption.

CRediT author statement

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Figure legend

Figure 1. Synthetic psychoactive adulterants most frequently found in tablets sold as "MDMA" in Europe, UK, Australia and USA. AB-PINACA, N-[1-(aminocarbonyl)-2-methylpropyl]-1-pentyl-1H-indazole-3-carboxamide; 4F-MDMB-BINACA, methyl 2-(1-(4-fluorobutyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate; 2C-B, 4-bromo-2,5-dimethoxyphenethylamine; 3-CMC, 3-chloromethcathinone; 4F-BDMB-BINACA AB-PINACA, 3-FEA, 3-fluoroethamphetamine; 4-CMC, 4-chloromethcathinone; 3-MMC, 3-methylmethcathinone; 4-MMC, 4-methylmethcathinone; PMMA, para-methoxymethamphetamine.