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Review

Potential Implications of Multi-Drug Exposure with Synthetic Cannabinoids: A Scoping Review of Human Case Studies

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Abstract: Synthetic cannabinoids are a rapidly evolving, diverse class of new psychoactive substances. Synthetic cannabinoid use results in a higher likelihood of adverse events and hospitalization when compared to cannabis use. The mechanisms behind synthetic cannabinoid toxicity remain elusive. Furthermore, poly-substance use may be a significant contributing factor in many cases. This scoping review aimed to identify the key characteristics of synthetic cannabinoid co-exposure cases and discuss the potential implications of poly-substance use in humans. There were 278 human cases involving 64 different synthetic cannabinoids extracted from the databases. Cases involved a total of 840 individual co-exposures, with an average of four substances involved in each case. The most common co-exposures were alcohol (11.4%), opioids (11.2%), and cannabis (11.1%). When analyzed by case outcome, co-exposure to either antipsychotics/antidepressants, alcohol, or tobacco were significantly associated with mortality as an outcome ($p < 0.05$). Drug-use history (63.4%), mental illness (23.7%), and hypertensive and atherosclerotic cardiovascular disease (20.1%) were prevalent patient histories in the case cohort. There are several potential pharmacodynamic and pharmacokinetic interactions between co-exposure drugs and synthetic cannabinoids that could worsen clinical presentation and toxicity in synthetic cannabinoid users. Individuals with substance-use disorders or psychiatric illness would be especially vulnerable to these multi-drug interactions. Further research into these complex exposures is needed for the successful prevention and treatment of synthetic cannabinoid-related harms.

Keywords: synthetic cannabinoid; toxicology; poly-drug exposure; human case

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1. Introduction

Synthetic cannabinoids are one of the fastest growing classes of novel psychoactive substances worldwide [1]. The high potency of these compounds means they pose a much greater threat to users when compared to delta-9-tetrahydrocannabinol (Δ-9-THC), the primary phytocannabinoid in the cannabis genus. Correspondingly, the relative risk for needing emergency medical treatment following synthetic cannabinoid use is 30 times greater than the risk associated with cannabis use [2]. One theory supporting the difference in safety profiles between Δ-9-THC and synthetic cannabinoids is explained by pharmacodynamics, i.e., the affinity and efficacy of the cannabinoids at the human cannabinoid receptors [3]. As a partial agonist, Δ-9-THC, has lower intrinsic activity at the cannabinoid CB_1 receptor (CB_1) and therefore partial efficacy [4–6]. In direct contrast, many synthetic cannabinoids are full agonists at CB_1 and the cannabinoid CB_2 receptor (CB_2) and have greater efficacy compared to Δ-9-THC [7–10]. Additionally, Δ-9-THC displays lower affinity for CB_1 (K_i = 16–80 nM) when compared to many synthetic cannabinoid ligands [9,11,12]. The structure of synthetic cannabinoids differ greatly from the classical structure of Δ-9-THC, where common core structural groups include cyclohexylphenols, naphthoylindoles,

benzoylindoles, phenacetylindoles, alkoylindoles, indole carboxylates, indole carboxamides, indazole carboxamides, benzimidazoles, carbazoles, and γ-carbolines [13–15].

Countless cases of adverse events and several hundred mortalities following synthetic cannabinoid use have been reported worldwide [16]. Synthetic cannabinoid intoxication does not present with a consistent toxidrome and can mirror the symptoms seen with other types of recreational drugs [17]. Adverse effects reported range from agitation, hypertension, and hallucination [18,19] to seizures, cardiac arrythmias, respiratory depression, and even death [20]. Due to the broad range of quantified synthetic cannabinoid concentrations found in post-mortem samples [21], the lethal dose threshold for individual synthetic cannabinoids is unknown.

Synthetic cannabinoids are commonly abused alongside other substances. Within a cohort of patients undergoing treatment for substance-use disorder, 32% reported using synthetic cannabinoids to alter the effects of other drugs [22]. Furthermore, among a global population of recent synthetic cannabinoid users, from data gathered with an anonymous online survey, alcohol, cannabis, tobacco, and 3,4-methylenedioxy-methamphetamine (MDMA) were frequently consumed, with use prevalence in the last month of 91%, 88%, 75%, and 26%, respectively [23]. Approximately one-third of these respondents reported use of mushrooms, benzodiazepines, lysergic acid diethylamide, and/or cocaine in the past year [23]. In cases involving poly-drug abuse, it is possible that both pharmacodynamic and pharmacokinetic interactions could impact synthetic cannabinoid toxicity. To date, these interactions remain largely unexplored.

The mechanisms behind the acute toxicities of synthetic cannabinoid use are poorly understood. It is likely that prior medical history and drug co-exposure have a significant impact on the range of adverse effects associated with synthetic cannabinoid abuse. Therefore, this scoping review aimed to highlight the key characteristics of human cases of synthetic cannabinoid intoxication, with a particular focus on cases of multi-drug exposure.

2. Materials and Methods

2.1. Aims and Scope

The main aim of the study was to identify and extract data on human cases involving synthetic cannabinoid intoxication or mortality, including co-exposure to another drug of abuse or medication. The scoping review subsequently aimed to highlight likely poly-substance combinations, provide potential implications, and determine corresponding gaps in the literature.

2.2. Search Strategy

The search strategy was conducted in early July 2024. The search encompassed articles published between the 1 January 2010 until the 1 June 2024 and relied on the key terms "synthetic cannabinoid" and "case" in each database. Case reports needed to be in English and retrievable in their full text. The search was performed in the following electronic databases: Medline (PubMed), Scopus, and Web of Science. This study was not registered in PROSPERO.

After duplicates were removed, titles and abstracts were first screened for exclusion criteria: off-topic articles (e.g., no synthetic cannabinoid involved or lack of analytical confirmation, therapeutic synthetic cannabinoid use, pre-clinical studies, or lack of co-exposure or quantification/method-based studies without associated case reports), reviews or letters to the editor, or cases not involving humans. Further full-text review was conducted if needed, including screening of references cited in selected articles to find additional, relevant case reports. Additionally, co-exposure clearly stated as a result of medical intervention in hospital/emergency care settings was excluded. Co-exposures to the rodenticide brodifacoum, as an adulterant to synthetic cannabinoid products, were outside of the scope of this study and were therefore excluded. In line with current systematic review guidelines [24], the corresponding PRISMA-led flow diagram (Figure 1) outlines the study review process.

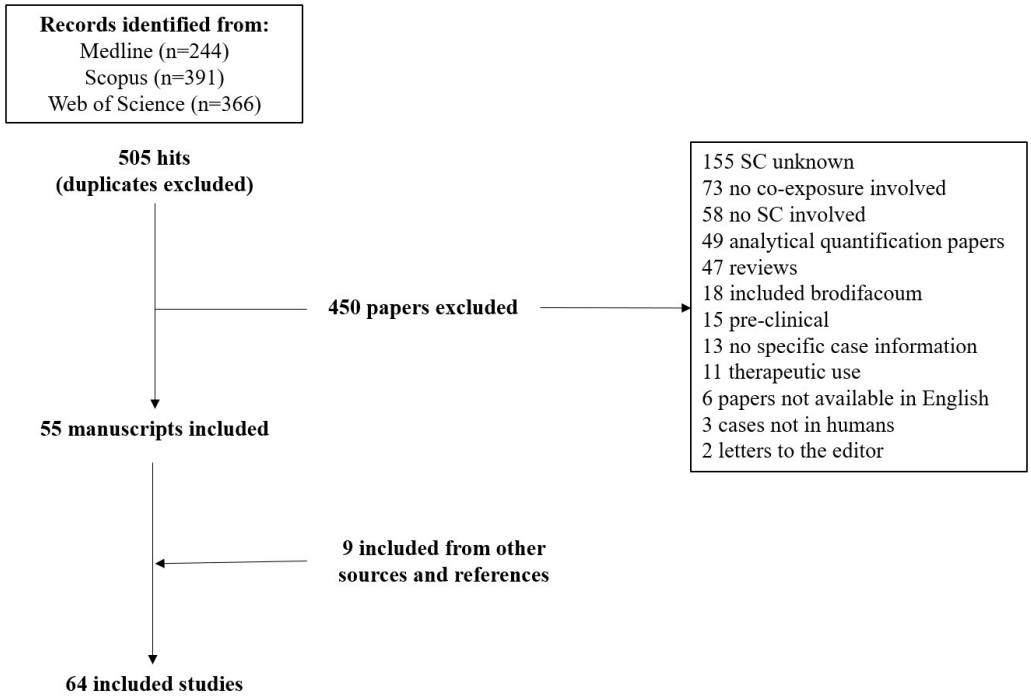

Figure 1. Flowchart of the study screening and selection process.

2.3. Data Extraction

An initial database with broad case information was created in OneNote® (Microsoft 365, version 2206). Specific data extracted from manuscripts were added to a final database constructed in Excel® (Microsoft 365, version 2206). For each manuscript, the following data were collected where present: authors, year published, sex and age of case, synthetic cannabinoids confirmed to be involved in the case, route of synthetic cannabinoid administration, case presentation and outcome, concentration of synthetic cannabinoid parent compound in biological samples (in ng/mL) and corresponding sample type, other substances detected, comorbidities, and medical history.

Synthetic cannabinoids were classified as any synthetically derived compounds known to bind and activate the cannabinoid CB_1 and/or CB_2 receptor. Where more than one name was used across cases for the same synthetic cannabinoid structure, the most prevalent nomenclature was chosen and was used throughout. Quantification of synthetic cannabinoid metabolites within biological samples was not consistently reported, and due to the non-specificity of some synthetic cannabinoid metabolites, parent compound detection was analyzed. Due to the rapid metabolism of synthetic cannabinoids, detection of parent compound may be unobtainable in some cases. Co-exposure included both medications and other drugs of abuse and was confirmed by analytical detection of substances in biological samples from patients. In the context of patient medical history, drug-use history was defined as consistent recreational or problematic drug use, including terms such as "history of illicit drug use" and "drug experience".

2.4. Data Analysis

Quality assessment, risk of bias, and meta-analyses of the included studies were not conducted due to the scoping nature of the review [25]. Descriptive statistics were applied to continuous data gained from the included cases. Categorical data were analyzed for variable frequency. A Fisher's exact test was used to identify significant non-random associations between case outcome and co-exposure. Statistically significant findings required $p < 0.05$. Statistical analyses and data visualization were carried out using GraphPad Prism 8 software.

3. Results

There were 278 cases of human intoxication or mortality with confirmed synthetic cannabinoid involvement and drug co-exposure identified in the literature since 2010 (Table 1) [18,21,26–87].

Table 1. Characteristics of included case reports and case series involving synthetic cannabinoid toxicity and drug co-exposure.

Author	Year	Country	*n*	Sex (M/F)	Mortalities	Non-Fatal Intoxications
Abouchedid et al. [26]	2016	UK	1	F	-	1
Adamowicz et al. [27]	2019	Poland	1	M	1	-
Allibe et al. [28]	2017	France	4	M	-	4
Angerer et al. [29]	2017	Germany	3	M	3	-
Apirakkan et al. [30]	2021	UK	1	M	1	-
Bäckberg et al. [31]	2017	Sweden	8	7M/1F	-	8
Barcelo et al. [32]	2017	Spain	2	1M/1F	-	2
Behonick et al. [33]	2014	USA	2	M	2	-
Bertol et al. [34]	2015	Italy	1	M	-	1
Brandehoff et al. [35]	2018	USA	4	2M/2F	-	4
Chan et al. [36]	2013	UK	1	M	-	1
Chan et al. [37]	2019	Singapore	2	M	2	-
Darke et al. [38]	2020	Australia	42	-	42	-
Elena-González et al. [39]	2020	Spain	1	M	-	1
Engelgardt et al. [40]	2022	Poland	10	9M/1F	-	10
Gaunitz and Andresen-Streichert [41]	2022	Germany	1	M	-	1
Gaunitz et al. [42]	2018	Germany	1	M	1	-
Giorgetti et al. [43]	2020a	Germany	4	3M/1F	4	-
Giorgetti et al. [44]	2024	Germany	1	M	1	-
Goncalves et al. [45]	2022	France	8	7M/1F	-	8
Hamilton et al. [46]	2017	USA	1	M	-	1
Hasegawa et al. [47]	2015	Japan	1	M	1	-
Hasegawa et al. [48]	2018	Japan	1	M	1	-
Hermanns-Clausen et al. [18]	2013a	Germany	7	6M/1F	-	7
Hermanns-Clausen et al. [49]	2013b	Germany	1	M	-	1
Hill et al. [50]	2016	UK	4	M	-	4
Institóris et al. [51]	2022	Hungary	13	12M/1F	-	13
Katz et al. [52]	2016	USA	10	6M/4F	1	9
King et al. [53]	2022	UK	7	6M/1F	-	7
Klavz et al. [54]	2016	Slovenia	1	M	-	1
Kleis et al. [55]	2020	Germany	9	8M/1F	3	6
Kovács et al. [56]	2019	Hungary	1	M	1	-
Kraemer et al. [57]	2019	Germany	3	2M/1F	3	-
Kusano et al. [58]	2018	Japan	1	M	1	-
Labay et al. [59]	2016	USA	19	15M/4F	19	-
Lam et al. [60]	2017	China	1	M	-	1
Langford and Bolton [61]	2018	UK	1	M	1	-
Lapoint et al. [62]	2011	USA	1	M	-	1
Larabi et al. [63]	2019	France	1	M	-	1
Lonati et al. [64]	2014	Italy	1	M	-	1
Morrow et al. [21]	2020	New Zealand	51	-	51	-
Musshoff et al. [65]	2013	Germany	1	M	-	1
Nacca et al. [66]	2018	USA	1	M	-	1
Neukamm et al. [67]	2024	Germany	1	M	1	-
Pant et al. [68]	2012	USA	1	M	-	1
Pieprzyca et al. [69]	2023	Poland	3	3M	3	-
Pucci et al. [70]	2024	UK	6	4M/2F	1	5
Rice et al. [71]	2021	UK	2	1M/1F	2	-
Rojek et al. [72]	2017	Poland	1	M	1	-
Seywright et al. [73]	2022	UK	11	10M/1F	11	-
Shanks et al. [74]	2012	USA	1	M	1	-
Shanks et al. [75]	2015	USA	1	F	1	-
Shanks et al., [76]	2016	USA	1	F	1	-
Simon et al. [77]	2022	Hungary	1	M	1	-
Simon et al. [78]	2023a	Hungary	2	2M	2	-
Simon et al. [79]	2023b	Hungary	1	M	1	-
Soo et al. [80]	2023	Singapore	1	M	-	1
Steele et al. [81]	2022	USA	1	M	1	-
Theofel et al. [82]	2023	Germany	1	M	1	-

Table 1. *Cont.*

Author	Year	Country	*n*	Sex (M/F)	Mortalities	Non-Fatal Intoxications
Tiemensma et al. [83]	2021	Australia	4	M	4	-
Tokarczyk et al. [84]	2022	Poland	1	M	1	-
Van Rafelghem et al. [85]	2021	Belgium	1	M	1	-
Westin et al. [86]	2016	Norway	1	M	1	-
Yamagishi et al. [87]	2018	Japan	1	M	1	-
Total			**278**	**185**	**175**	**103**

Of a total 185 cases with known sex, 159 of these were males (86%). There were 103 non-fatal intoxication cases in the dataset, with the majority (63%) being mortalities. There were 26 case series publications, where the remaining 38 manuscripts were single-case reports.

Of the 181 cases with reported age, the mean age was 32 ±12 years, with a median of 30 years (Table 2). Within this group of human synthetic cannabinoid intoxication cases, the age range spanned 51 years (13–64). The mean number of substances, including synthetic cannabinoids, involved in both mortality and non-fatal intoxication cases was four (Table 2). Notably, a mortality case featured the highest number of involved substances, at 18 substances detected. Of the 224 cases with reported medical history, 63.4% had a history of drug use. History of hypertensive and atherosclerotic cardiovascular disease (HASCVD) (20.1%) and mental illness (23.7%) were also prevalent. The primary causes of death in mortality cases were mixed drug toxicity (29.5%) and synthetic cannabinoid toxicity (25.4%). Heart disease, stroke, and hypoxic brain injury were the next most prevalent causes of death (Table 2). Other less prevalent causes of death included multi-organ failure, polytrauma, and acute respiratory failure. Across biological fluid samples, the overall detected concentration range for parent synthetic cannabinoid compounds was 0.01–230 ng/mL. The most common analytical method for detecting synthetic cannabinoids in biological samples was liquid chromatography coupled with tandem mass spectrometry, followed by liquid chromatography coupled with quadrupole time-of-flight mass spectrometry and liquid chromatography coupled to tandem-mass spectrometry with electrospray ionization.

Overall, 64 different synthetic cannabinoids were detected across the 278 included cases. There were 55 synthetic cannabinoids identified in mortality cases (Figure 2). The primary contributors (combining 43%) within the detected synthetic cannabinoids involved in mortality cases were AMB-FUBINACA; AB-CHMINACA; 5F-MDMB-PINACA, also known as 5F-ADB; and JWH-018 (Figure 2).

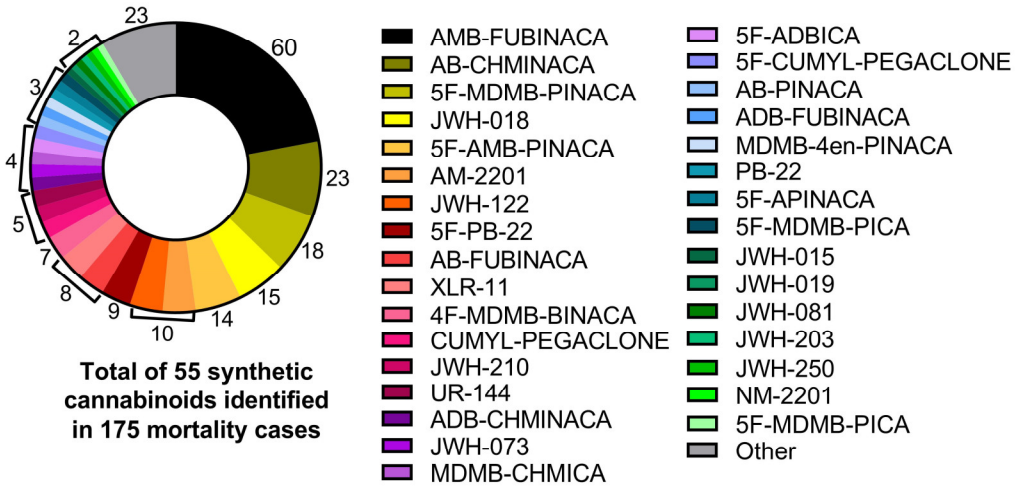

Figure 2. Distribution of synthetic cannabinoids involved in 175 human mortality cases.

Table 2. Study demographics and toxicological findings from included synthetic cannabinoid intoxication cases.

Case Features	Mean	Range
Age	32 years	13–64 years
No. of substances	4	2–18
Route of administration	*n*	%
Inhalation	152	95.6%
Oral	7	4.4%
Comorbidities	*n*	%
Drug-use history	142	63.4%
Mental illness	53	23.7%
HASCVD [1]	45	20.1%
Cause of death	*n*	%
Mixed drug toxicity	36	29.5%
Synthetic cannabinoid toxicity	31	25.4%
Cardiovascular disease	21	17.2%
Stroke, hypoxic brain injury, or encephalopathy	8	6.6%
Asphyxia	5	4.1%
Other	21	17.2%
Synthetic cannabinoid quantification	*n*	Range (ng/mL)
Plasma	6	0.20–44
Serum	29	0.11–230
Urine	7	0.08–24
Whole blood	69	0.01–204

[1] Hypertensive and atherosclerotic cardiovascular disease. n = 181 cases with age reported, n = 278 cases with substance co-exposures, n = 159 cases with route of administration reported, n = 224 cases with comorbidities reported, n = 122 mortality cases with cause of death reported, and n = 111 cases with parent synthetic cannabinoid quantified in biological fluids.

There were 840 substance co-exposures, excluding synthetic cannabinoids, detected across the 278 cases. The substances were classified into broader drug classes, where appropriate, and the percentage of co-exposure incidence was calculated to find the primary contributors. The three most common co-exposures were alcohol (96 instances), opioids (94 instances), and Δ-9-THC (93 instances) (Figure 3). The incidence of antipsychotic/antidepressant and benzodiazepine co-exposure was similar, at 9.6 and 9.4%, respectively. Other frequent co-exposures included "designer" stimulants, such as 18 para-fluorophenylpiperazine (pFPP) exposures and 15 cathinone (e.g., α-PVP, pentedrone, and N-ethyl-hexedrone) exposures.

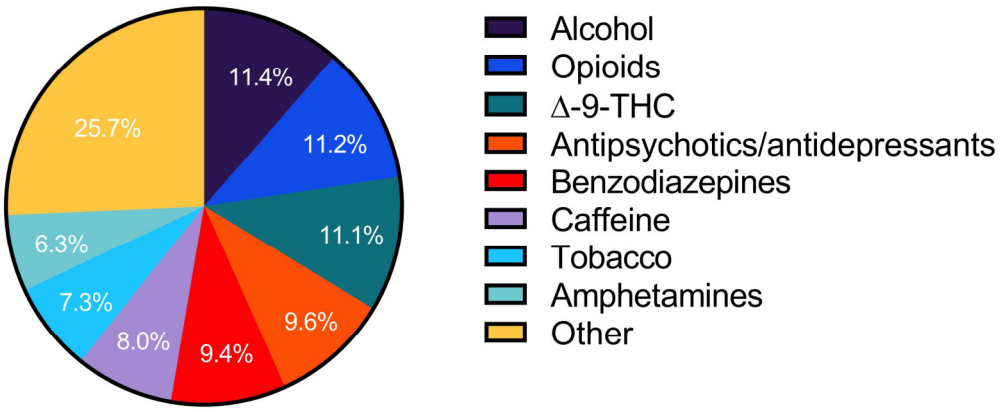

Figure 3. Instances of co-exposure by substance type across 278 human cases.

To further breakdown the substances involved in synthetic cannabinoid poly-pharmacy, the drugs with the greatest prevalence within each drug class were identified (Table 3). Methadone was the most frequent opioid co-exposure, followed by morphine and codeine. The top six most common antipsychotic/antidepressant co-exposures (risperidone, mirtazapine, olanzapine, citalopram, fluoxetine, and haloperidol) accounted for 63% of all antipsychotic/antidepressant co-exposure incidences. Co-exposure to amphetamine or methamphetamine was also high within this case cohort, with 25 and 18 incidences of each, respectively.

Table 3. Most frequent co-exposure drugs in each drug class.

Co-Exposure	Specific Drug	*n*
Opioids	Methadone	24
	Morphine	22
	Codeine	14
	Tramadol	10
	Fentanyl	6
Antipsychotics/antidepressants	Risperidone	13
	Mirtazapine	9
	Olanzapine	8
	Citalopram	7
	Fluoxetine	7
	Haloperidol	7
	Quetiapine	7
Benzodiazepines	Diazepam	9
	Alprazolam	7
	Lorazepam	7
	Midazolam	6
	Nordazepam	6
Amphetamines	Amphetamine	25
	Methamphetamine	18
	MDMA	8
Miscellaneous	pFPP	18
	Cocaine	17
	Pregabalin	14
	Lidocaine	10
	Zopiclone	10
	Diphenhydramine	7

In order to identify any potential associations between co-exposure groups and outcomes in synthetic cannabinoid cases, the percentage of cases from each co-exposure were compared to determine non-random associations. Co-exposure to either antipsychotics/antidepressants, alcohol, or tobacco were significantly associated with mortality from synthetic cannabinoid use (Table 4). Specifically, there was a significant association between the prevalence of antipsychotics/antidepressants, alcohol, and tobacco co-exposure in synthetic cannabinoid mortality cases compared to non-fatal intoxication cases. There was a similar proportion of mortality and non-fatal synthetic cannabinoid intoxication cases that involved Δ-9-THC co-exposure at 30.9% and 35.9%, respectively.

Table 4. Incidence of specific drug co-exposure in synthetic cannabinoid mortality cases versus non-fatal intoxications.

Co-Exposure	Mortalities (n = 175) n (%)	Non-Fatal Intox. (n = 103) n (%)
Antipsychotics/antidepressants	60 (34.3%) *	11 (10.7%)
Alcohol	69 (39.4%) *	26 (25.2%)
Δ-9-THC	54 (30.9%)	37 (35.9%)
Tobacco	57 (32.6%) *	4 (3.9%)
Benzodiazepines	35 (20.0%)	30 (29.1%)
Opioids	32 (18.3%)	27 (26.2%)
Amphetamines	19 (10.9%)	20 (19.4%)

Data all represented as a percentage of the total case outcome. Significant non-random associations between case outcome and co-exposure were analyzed using a two-tailed Fisher's exact test. * significant association between co-exposure and case outcome ($p < 0.05$).

4. Discussion

The case characteristics reported from this series are in line with previous studies. The majority (86%) of cases were male. Earlier studies and case cohorts have reported 88.1% and 74.3% male biases for cases of synthetic cannabinoid-related deaths and synthetic cannabinoid exposures reported to US Poison Centers, respectively [20,88]. This bias does not appear to be linked to increased likelihood of synthetic cannabinoid adverse effects or deaths in males but rather reflects the pre-existing patterns and demographics in synthetic cannabinoid users. In Australia, 77% of reported synthetic cannabinoid users were male [89]. In the Australian cohort, males reported a significantly higher median number of lifetime use occasions when compared to females [89]. In England, from April 2014 to March 2018, 91.2% of the forensic toxicology cases where synthetic cannabinoids were detected were males [90].

The emphasis on co-exposure to both synthetic cannabinoids and other substances in this case series did not impact the age range compared to previous studies. Across a group of deaths associated with synthetic cannabinoids in the USA, the reported age range was 13 to 56 years [18]. In a systematic review of deaths involving synthetic cannabinoids, the mean age in the cohort was 32 years, with a median age of 29 (range 14–61) [20]. These mean and median values are almost identical to those presented in the current study. This is not surprising, as the likelihood of overlap in case inclusion criteria between this study and that conducted by Giorgetti et al. [20] is high.

The diversity in synthetic cannabinoids reported in cases from 2010 to 2024 exhibits the rapid evolution of this class of new psychoactive substances (NPS). The United Nations Office on Drugs and Crime had 899 individual NPS reported to their Early Warning Advisory from 119 countries between 2008 and 2019 [91]. Legislation covering identified synthetic cannabinoid products in the early 2010s was consistently out-competed by the emergence of new, structurally distinct, uncontrolled synthetic cannabinoids [92]. AMB-FUBINACA, AB-CHMINACA, 5F-MDMB-PINACA (or 5F-ADB), and JWH-018 were the most frequent synthetic cannabinoids detected in mortality cases. The dangers associated with these synthetic cannabinoids are well documented. The large number of mortalities associated with AMB-FUBINACA was influenced by the inclusion of the study by Morrow et al. [21] that outlined the outbreak of deaths associated with AMB-FUBINACA in New Zealand. 5F-MDMB-PINACA and AB-CHMINACA were previously associated with fatal synthetic cannabinoid intoxications in Germany [93]. In and around Munich, from 2014 to 2020, the three most commonly detected synthetic cannabinoids in post-mortem cases were 5F-MDMB-PINACA, 5F-MDMB-PICA, and AB-CHMINACA [93]. Additionally, in a recent systematic review of clinical studies and case reports, AB-CHMINACA resulted in the highest frequency of toxicologic effects and was one of the top two synthetic cannabinoids associated with mortality outcomes [94]. As a potential driver of in vivo toxicity, AMB-FUBINACA, 5F-MDMB-PINACA, and AB-CHMINACA are highly potent synthetic cannabinoids, with sub-nanomolar EC_{50} values in vitro [3,10].

The average number of substances, including synthetic cannabinoids, involved in the non-fatal intoxication and mortality cases was four. Based on the required involvement of both a synthetic cannabinoid and co-exposure substance, the minimum number of substances involved in cases was two. As an extreme case of poly-substance use, a 43-year-old female was exposed to 18 substances, with 5 synthetic cannabinoids detected in biological fluids and at least 13 other substances, including drugs of abuse and pharmaceuticals, present [57]. By excluding alternative causes, mixed drug intoxication was determined as the cause of death; however, the contribution of each substance to the resulting toxicity was unable to be distinguished [57]. Mixed drug toxicity was the cause of death in a further 35 cases included in the current review. Frequency of poly-substance use is strongly associated with both morbidity and mortality [95,96]. As an example, the risk of cardiovascular disease increases as the substance-use number increases [97]. Specifically, use of four or more recreational substances, including tobacco, alcohol, and illicit drugs (e.g., amphetamine, cannabis, and cocaine), resulted in a 9-fold greater risk of developing premature heart disease [97]. It is therefore unsurprising that cardiovascular disease was the third most common cause of death in this case cohort behind, and likely linked to, synthetic cannabinoid and mixed drug toxicity.

The four most prevalent co-exposures alongside synthetic cannabinoids in this case cohort were alcohol, opioids, Δ-9-THC, and antipsychotics/antidepressants. An international survey conducted in early 2011 found that alcohol (54%), cannabis (40%), and tobacco (38%) were the most common co-exposures with synthetic cannabinoid use [98]. The emergence of psychiatric medication and synthetic cannabinoid poly-drug use appears to be a more recent trend. The United Nations Office on Drugs and Crime Early Warning Advisory on NPS Toxicology Portal data from 2018 listed antipsychotics and cannabis as the most frequently detected substances in synthetic cannabinoid fatalities [91]. Caffeine detection in the case cohort was likely underreported, as caffeine screening is not routinely performed in emergency medical or forensic settings despite recommendations for its inclusion in toxicology screens [99]. As the world's most widely consumed central nervous system stimulant, sources of caffeine include dietary consumption [100]; herbal supplements, particularly those marketed for weight loss [101]; and as an additive to illicit drugs such as cocaine and MDMA [102].

As a legal substance, it is unsurprising that alcohol is consistently reported as one of the most prevalent co-exposures with both synthetic cannabinoids and cannabis. Interactions between alcohol and cannabinoids have been extensively documented [103–105]. Each substance can alter the pharmacokinetics of the other. Cannabinoids inhibit gastric emptying, which leads to slower absorption of alcohol and lowered bioavailability [106]. Alcohol dilates the microcirculation in the lungs, which can increase cannabinoid concentrations in the blood following inhalation [107]. Use behaviors and consumption are also impacted by co-abuse of alcohol and cannabinoids. Simultaneous use of both alcohol and cannabis is associated with a greater frequency of cannabis and alcohol consumption and quantity of alcohol use [108]. Moreover, users may be less careful with cannabis self-titration after alcohol use [109]. There are also functional and pathological interactions between the two substances, particularly in the liver. The endocannabinoid system and paracrine activation of CB_1 receptors in the liver have been implicated in the development of alcoholic fatty liver disease [110]. Hepatocyte-specific knockout of CB_1 receptors in mice was protective against toxin-induced liver damage, highlighting the role of CB_1 receptors in acute liver pathogenesis [111]. Exposure to the synthetic cannabinoid XLR-11 at 3 mg/kg daily, for five days, caused acute hepatic injury in mice [112]. Acute liver injury was also previously reported in a human case involving synthetic cannabinoid use and a history of binge alcohol intake [113]. Encompassed in the present case cohort, hepatotoxicity in the form of fatty liver disease, along with documented history and detection of alcohol and synthetic cannabinoid use, may have contributed to the death of a 42-year-old female in the case series reported by Labay et al. [59]. Overall, the combination of alcohol and synthetic

cannabinoids may lead to changes in substance pharmacokinetics, detrimental effects on use behaviors, and increased risk of hepatotoxicity.

Cannabis and tobacco are concomitantly used by ~40% of synthetic cannabinoid users [98]. Both of these substances are often smoked, although the prevalence of vaporization is increasing [114,115]. Chronic smoking or vaping of tobacco and cannabis can lead to lung damage, chronic bronchitis, and the development of emphysema [116]. Specifically, computerized tomography scans of 56 cannabis smokers and 33 tobacco smokers revealed that rates of emphysema were 75 and 67% for the respective groups [117]. Furthermore, concurrent use of cannabis and tobacco was associated with a higher odds ratio (OR of 2.59) for respiratory symptoms compared to smoking tobacco alone (OR of 1.50) [118]. People who smoked both tobacco and more than 50 cannabis cigarettes in their lifetime were 2.9 times more likely to develop chronic obstructive pulmonary disease when compared with non-smokers [119]. As newer substances of abuse, there are fewer studies investigating the impact of synthetic cannabinoids on lung function. In C57Bl6/J mice, oropharyngeal administration of the synthetic cannabinoid CP55,940 (2.6 μg/kg) significantly increased lung weight 4 h post administration; induced the expression of inflammatory cytokines including tumor necrosis factor-α, interleukin 1β, and interleukin 6; and increased CB_1 expression in the lung [120]. Currently, studies evaluating the long-term effects of smoking or vaping synthetic cannabinoid products in humans are lacking. However, based on the more severe pulmonary outcomes following combined cannabis and tobacco use [118], the addition of inhaled synthetic cannabinoid products would likely worsen lung inflammation and overall pulmonary function. The association between tobacco use and mortality in the case cohort likely reflects concomitant substance-use tendency. Although the combined use of synthetic cannabinoids and tobacco would increase pulmonary morbidity, this poly-substance exposure is yet to be mechanistically linked to mortality.

Two prevalent patient histories in the current synthetic cannabinoid case cohort were drug-use history (63.4%) and mental illness (23.7%). Similar substance dependence and psychiatric history rates were previously reported in synthetic cannabinoid forensic toxicology cases [90]. The relationship between substance use and psychiatric comorbidity is bidirectional. Psychiatric patients have consistently higher cannabis and synthetic cannabinoid use prevalence compared to the general population [121–123]. Diagnosis of mental disorders, including both mood and anxiety disorders, was associated with an increased risk of developing alcohol- and cannabis-use disorders [124]. Conversely, synthetic cannabinoid use was associated with psychosis, poor outcomes, and increased hospitalization in patients receiving mental health services in the United Kingdom [125]. Synthetic cannabinoids have also caused new-onset psychosis in several cases, induced by either synthetic cannabinoids alone or when combined with cannabis or alcohol [126,127].

To complicate the relationship between substance use and psychiatric comorbidity, patients can be prescribed a wide variety of medications depending on their mental health diagnosis and type of substance-use disorder. The most common psychiatric diagnosis associated with substance-use disorder, at ~50% of all dual diagnoses, is schizophrenia [128]. The first-line pharmacotherapy for the treatment of schizophrenia and comorbid substance abuse is second-generation antipsychotics such as clozapine, risperidone, and olanzapine [129,130]. Individual substance-use disorders are also treated with a range of pharmacotherapies. Tobacco smoking cessation is generally managed with nicotine replacement therapy, bupropion, or a combination of the two [131]. The current FDA-approved treatments for alcohol-use disorder are disulfiram, naltrexone, and acamprosate [132,133]. In reality, patients with alcohol-use disorder are much more likely to be prescribed antidepressants or quetiapine as treatments, with disulfiram and naltrexone being dispensed to only a small minority [134]. Naltrexone is also a pharmacotherapy for opioid-use disorder, as are methadone and buprenorphine [135,136]. The drug-use history, with a prevalence of antipsychotic, antidepressant, and methadone co-exposure in this cohort, may allude to a burden of substance-use disorder and psychiatric comorbidity within the population of synthetic cannabinoid users. The range of prescription medications for dual diagnosis,

including risperidone, olanzapine, methadone, and buprenorphine, features in the synthetic cannabinoid co-exposures of this case cohort. Poly-drug use is of particular concern in relation to synthetic cannabinoid use and mortalities [137]. The potential implications of synthetic cannabinoid use combined with these medications remains largely unexplored.

There are potential pharmacodynamic interactions between antipsychotics and cannabinoids. There is known cross-talk between the CB_1 and dopamine D_2 receptors via heteromerization of these G protein-coupled receptors upon concurrent receptor activation [138–140]. D_2 receptors can modulate the transcription of CB_1 receptor mRNA through the ERK1/2 pathway and the CB_1 receptor promoter [141]. There are further implications for these heteromers with the use of cannabinoids alongside antipsychotics. Haloperidol and a nonselective cannabinoid receptor agonist, CP55,940, had opposing effects on heteromer abundance in the globus pallidus and locomotion as a behavioral measure in C57Bl/6 mice [140]. Many atypical antipsychotics not only block the D_2 receptor but also have affinity for the serotonin 5-$HT_{2A/2C}$ and 5-$HT_{1A/1C}$ receptors [142]. Both D_2 and CB_1 receptors have functional interactions with the 5-HT_{2A} receptor [143,144]. Long-term administration of the synthetic cannabinoid HU-210 (100 µg/kg) up-regulated 5-HT_{2A} receptor activity and down-regulated 5-HT_{1A} in rats [145]. Chronic Δ-9-THC exposure caused functional sensitization to 5-HT_{2A} receptor activation in mice [146]. In humans, both schizophrenic patients treated with antipsychotics and cannabis-use disorder patients have increased 5-HT_{2A} receptor protein expression when compared to matched control subjects [147]. Not only will these pharmacodynamic interactions make it harder to treat schizophrenia and psychoses, but 5-HT_{2A} up-regulation may make cannabis and synthetic cannabinoid users more sensitive to the effects of serotonergic agonists and, consequently, the risk of serotonin syndrome in poly-drug use. Although serotonin syndrome was not reported in the current case cohort, this scenario may go undiagnosed due to the overlap in symptoms between synthetic cannabinoid toxicity and serotonin syndrome [148].

Co-exposure to synthetic cannabinoids and several drugs of abuse or prescription medicines could lead to increased chances of adverse events such as respiratory depression. This is especially relevant due to the prevalence of opioid (11.2%) and benzodiazepine (9.4b) co-exposure in this case cohort. Respiratory depression is not an adverse effect that occurs due to cannabis use but cannot be overlooked in the case of synthetic cannabinoid use. Synthetic cannabinoids can cause respiratory depression on their own both in mice [149] and humans [150,151]. Opioids, alcohol, and benzodiazepines can also cause respiratory depression alone. The combination of methadone or buprenorphine with benzodiazepines is known to worsen respiratory depression and increase overdose risk [152]. In terms of pathophysiology, both synthetic cannabinoids and opioids can reduce respiratory frequency in vivo by inhibiting neurons in the medullary pre-Bötzinger complex [153,154]. The combination of a synthetic CB_1 agonist, AM356 (1 mg/kg), and morphine (10 mg/kg) significantly exacerbated morphine-induced respiratory depression in male CD-1 mice [155]. Pharmacokinetic factors via cytochrome P450 (CYP450) interactions also impact these drug combinations. Along with general CYP2D6 metabolism of opioids in the body, methadone is metabolized primarily by CYP3A4, with minor contributions from CYP2B6, 2C19, and 2C9 [156]. Diazepam can noncompetitively inhibit the metabolism of methadone by CYP450 enzymes, likely because it is a substrate for CYP3A4 [157]. Clozapine, haloperidol, and risperidone are all substrates for CYP3A4 and 2D6 [158]. Fluoxetine and quetiapine inhibit CYP3A4 and the 2D6 metabolism of methadone, increasing plasma concentrations [159–161]. Concurrent benzodiazepine, antidepressant, and antipsychotic use were all moderately strong risk factors for opioid-induced respiratory depression [162]. The combination of opioids, benzodiazepines, and/or alcohol increases the risk of overdose lethality, where combined use of pharmaceutical opioids and benzodiazepines was the leading cause of poly-substance overdose deaths in the USA from 2005–2009 [163]. Given that synthetic cannabinoid-induced respiratory depression is possible, co-exposure to opioids, alcohol, benzodiazepines, and antipsychotics/antidepressants could all worsen this outcome. As potential examples of poly-substance-induced respiratory depression, there

were two cases of mortality, with acute respiratory failure as the cause of death, involving combinations of synthetic cannabinoids, benzodiazepines, antipsychotics, antidepressants, and alcohol in the current case cohort. Adamowicz et al. [27] reported acute respiratory failure in a 27-year-old male with confirmed exposure to two synthetic cannabinoids, alcohol, haloperidol, and lorazepam. Similarly, Angerer et al. [29] presented the case of a 41-year-old male who died of acute respiratory failure, with 5F-MDMB-PINACA, alcohol, trimipramine, and olanzapine all detected in post-mortem samples.

There are numerous limitations of this review. Despite using multiple databases in the search, human cases are often under-reported in the literature, which introduces publication bias to the study. Publication of cases is often biased towards more severe outcomes, such as fatalities, leaving non-fatal intoxications and cases with mild adverse effects under-represented. Hence, this case cohort may not accurately reflect the wider population of synthetic cannabinoid intoxication and mortality cases. The impact of study demographics from particular countries, including the exclusion of articles in languages other than English, may bias the results, particularly for the larger case series included. Due to the scoping nature of the review, no risk-of-bias evaluation or meta-analysis was conducted. Furthermore, the involvement of a synthetic cannabinoid needed to be analytically confirmed in each case for inclusion. This inclusion criterion likely led to loss of data, particularly for earlier synthetic cannabinoid case reporting where analytical techniques and instrumentation were not widely available. Access to analytical methods and variation in analytical reference libraries may have also limited co-exposure substance detection in some cases or biased co-exposure reporting towards traditional drugs of abuse or medications. Lastly, there are a multitude of factors that confound the interpretation of analytical and forensic toxicology cases. The present review focused on outlining potential drug–drug interactions between synthetic cannabinoids and additional co-exposure substances. However, additional factors such as biological fluid sample type and time since last drug exposure, including post-mortem interval for fatalities, the interplay between drug potency and potential development of tolerance in individuals, and pharmacogenomic data, should be considered to fully interpret toxicological reports.

5. Conclusions

In conclusion, the role of drug co-exposure in synthetic cannabinoid intoxication or mortality cases cannot be overlooked. Vulnerable populations are likely to exist, such as those with substance-use disorders, psychiatric illness, or a dual diagnosis of the two. Research aimed at complex, poly-drug exposures with synthetic cannabinoids is needed to fully understand these cases and formulate appropriate overdose treatment strategies.

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