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# An outbreak of deaths associated with AMB-FUBINACA in Auckland NZ

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ABSTRACT

*Background:* AMB-FUBINACA is a synthetic cannabinoid that has been associated with periodic outbreaks of acute poisonings, but few fatalities. In late May, June and July 2017 Auckland, New Zealand, experienced an outbreak of deaths associated with AMB-FUBINACA that continued at a rate of about 2−3 per month through February 2019. The aim of this study was to define the demographic, circumstantial, pathological and toxicological characteristics of this outbreak.

*Methods:* All records of the Northern Forensic Pathology Service, Auckland Hospital, were reviewed in which the word "AMB-FUBINACA" was referenced, including initial police reports, autopsy reports and toxicology reports. Recorded data included age, sex, race/ethnicity, times and locations, cause of death, autopsy and toxicology findings, and a brief summary of the circumstances of death. Descriptive statistics were performed using IBM® SPSS® Statistics Version 24 and Microsoft® Excel® Version 14.7.2.

*Findings:* Sixty-four cases were identified. One sudden infant death and five cases where cause of death was due to trauma were excluded. Of the remaining 58 cases, 88% were male. Mean age was 42 years. In 95% of the deaths, AMB-FUBINACA alone or in combination with alcohol or another drug was listed as the primary or contributory cause of death. In 41 cases postmortem blood concentrations of AMB-FUBINACA acid were available, ranging from <45 ng/mL to >1000 ng/mL, mean 229 ng/mL, median 140 ng/mL. Comorbidities identified included mixed intoxications (29%), heart disease (47%) and obesity (16%). A mental health diagnosis was reported in 50%, and 40% were on antipsychotic medications.

*Interpretation:* This study presents characteristics, comorbidities and toxicological findings in a unique outbreak of deaths associated with the synthetic cannabinoid AMB-FUBINACA in Auckland, NZ.

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## 1. Introduction

Synthetic cannabinoids are a chemically diverse group of substances active at CB1 and CB2 cannabinoid receptors, designed to mimic the effects of cannabis [1−3]. They are a major category of new psychoactive substances (NPS) monitored by the United Nations Office of Drugs and Crime (UNODC) since 2009 [2]. In a survey of American medical examiner/coroner offices between 2010 and 2014, 25 deaths were reported in which synthetic cannabinoids were toxicologically confirmed and may have contributed to death [4]. Since 2014 an increasing number of deaths associated with a variety of synthetic cannabinoids has been reported [5−15]. A recent review of Australian coronial deaths between 2000 and 2017 revealed 55 cases in which synthetic cannabinoid use was considered a contributory mechanism to death [16].

AMB-FUBINACA is a synthetic cannabinoid that has caused outbreaks of poisonings in New York [3] and Connecticut [17], USA, in July 2016 and Aug 2018, respectively. Although no deaths were reported in these outbreaks, AMB-FUBINACA in combination with other synthetic cannabinoids (EMB-FUBINACA and 5F-ADB) has been implicated in at least two fatalities [13,14]. In late May, June and July 2017, 17 deaths associated with AMB-FUBINACA were observed in Auckland, New Zealand [18]. Since then, the Northern Forensic Pathology Service of New Zealand (NFPS) has encountered periodic deaths associated with this drug. Analysis of plant material suspected

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**Research in context**

*Evidence before this study*

Synthetic cannabinoids are a significant class of new psychoactive substances of public health concern. A survey of American medical examiner/coroners offices between 2010 and 2014 reported 25 deaths in which synthetic cannabinoids were detected. Since 2014 an increasing number of fatalities associated with these substances have been reported. A recent review of Australian coronial deaths between 2000 and 2017 revealed 55 cases in which synthetic cannabinoid use was considered a contributory mechanism to death. AMB-FUBINACA is a synthetic cannabinoid that has been associated with outbreaks of bizarre behaviour and emergency room visits in New York and Connecticut, but with no reported fatalities in either instance. The Australian series of deaths lists AMB-FUBINACA in one instance, and there have been two published case reports of fatalities associated with AMB-FUBINACA in combination with another synthetic cannabinoid. In late May - July 2017 Auckland, New Zealand experienced an outbreak of deaths associated with AMB-FUBINACA that continued at a rate of about 2–3 per month through February 2019.

*Added value of this study*

This is the first report of an outbreak of multiple deaths associated with the synthetic cannabinoid AMB-FUBINACA. The demographic features, summary of circumstances of death, pathologically defined cause(s) of death and toxicological findings are presented. Concentrations of AMB-FUBINACA acid in blood appeared high relative to those reported in deaths associated with other synthetic cannabinoids, and are consistent with reported high concentrations of the substance in samples seized by NZ law enforcement during the same period. Significant risk factors identified in the outbreak included mixed intoxications, heart disease, obesity and mental health history of psychosis, notably on the schizophrenic spectrum.

*Implications of all the available evidence*

The contribution of synthetic cannabinoids to drug mortality may not be fully appreciated, especially the potential for significant mortality associated with toxicity due to the introduction of a new synthetic cannabinoid into a community. This study confirms a number of features associated with synthetic cannabinoid deaths reported in earlier studies including age, male predominance, mixed intoxications and history of heart disease in a significant number of cases. Obesity may be an unreported medical risk factor identified in our study, perhaps mediated through heart disease. A high prevalence of psychosis noted in this series has not been previously reported. Whether it is a risk factor for death specifically, or a feature of the population of users of synthetic cannabinoids is not clear. Further research into this emerging public problem is indicated.

to contain synthetic cannabinoids seized in New Zealand between January and December 2107 revealed AMB-FUBINACA in 157 samples (64%) [19]. In 55 of these 157 samples, para-fluorophenylpiperazine (pFPP) was also detected, although it was not found in plant material with other synthetic cannabinoids. In the past, pFPP has been marketed as a "party pill" in NZ [19]. Subsequently, pFPP was detected in several blood samples from persons in NZ who had died and tested positive for AMB-FUBINACA. The contribution to drug mortality of synthetic cannabinoids, specifically AMB-FUBINACA alone or in combination with other substances such as pFPP, may not be fully appreciated. This outbreak presents a unique opportunity to document the characteristics of a series of deaths associated with the synthetic cannabinoid AMB-FUBINACA.

## 2. Methods

### 2.1. Case identification

A list of all deaths associated with AMB-FUBINACA in the database of the NFPS was obtained by a word search "AMB-FUBINACA." Each electronic record was reviewed including the "POL 47″ (initial intake and history form created by the investigating police officer), the report of autopsy, toxicology report, and medical records available to the pathologist as part of the coronial investigation.

### 2.2. Data gathered

The following data were recorded: date and time of death, date and time of event, age, sex, race/ethnicity, cause of death, autopsy findings, toxicology findings, and a brief summary of the circumstances of death.

*Autopsy findings* included body weight and height (BMI), organ weights (brain, heart, lungs, liver, kidney, spleen), major anatomic diagnoses, vitreous biochemistry (sodium, potassium, chloride, urea, creatinine, glucose, hydroxybutyrate), blood tryptase, and whether a postmortem CT was done.

*Toxicology findings* included the postmortem detection of AMB-FUBINACA and AMB-FUBINACA acid (metabolite) in blood and urine; as well as blood THC, ethanol (blood, urine, and vitreous) and any other drugs detected in blood. Antemortem toxicology findings in blood and urine, if performed, were also included.

A summary of the *circumstances of the death* was made, and specific characteristics were listed, including the date, time, and Auckland suburb of the event, witnesses to the event or who found the body, type of location of the event (home, street, car park, etc.), location of death (scene of event, emergency department, hospital), whether resuscitation was attempted, history of previous drug/alcohol/synthetic cannabinoid abuse, mental health diagnoses, route of ingestion of drug (smoking or no), history of seizure or vomiting, witnessed state of intoxication, behaviour, and any other signs or symptoms that may suggest mechanism of death.

### 2.3. Determination of cause of death

Cause of death was that determined and reported to the coroner by the pathologist who performed the autopsy. In every case a primary cause of death was recorded. Contributory causes, if any, were also recorded. Pathologists did not necessarily report contributory causes in every case.

### 2.4. Toxicology testing

Blood, preferentially from the femoral vessels, was obtained at the time of autopsy in all cases. Samples of postmortem blood were submitted to the Institute of Environmental Science and Research (ESR), Kenepuru, Porirua, New Zealand, for toxicological analysis. Initial screening included headspace gas chromatography with flame ionization detection (GC-FID) for the presence of alcohol (ethanol) and liquid chromatography with time-of-flight mass spectrometric detection (LC-TOFMS) for the presence of a range of antipsychotics, narcotics, antidepressants, antihistamines, sedatives, drugs of abuse, anticonvulsants and cardiac medications, and immunoassay for evidence of recent use of cannabis. Blood was analysed by liquid chromatography with tandem mass spectrometric detection (LC-MSMS) and LC-TOFMS for tetrahydrocannabinol (THC), THC-acid, a range of

synthetic cannabinoids and metabolites (including AMB-FUBINACA and AMB-FUBINACA acid), and pFPP.

*Statistical analyses*, including descriptive statistics (frequency and percentages for categorical variables, means and standard deviations, medians and interquartile ranges for continuous variables) and correlations [heart weight and BMI, mental health diagnoses and antipsychotic medications (Table 6) and blood concentrations of AMB-FUBINACA acid and pFPP], were performed using IBM® SPSS® Statistics Version 24, 2016 and Microsoft® Excel® Version 14.7.2, 2010 (interquartile ranges).

All cases in this series were investigated under authority of the New Zealand Coroner Act of 2006 (Public Act 2006 No. 38), including performance of autopsies and all toxicology tests. The study was approved by the Chief Coroner. An earlier unpublished version of this study involving 58 cases from May 2017 through November 2019 was reviewed and exempted (performed under statutory authority) by the Institutional Review Board of George Washington University as part of the MPH Culminating Experience (master's thesis) of one of the authors (PLM).

### 2.5. Role of funding

All work was performed as part of the usual employment of the authors in their respective institutions during the course of their duties for the NZ coroner system. No special funding sources were reported.

## 3. Results

There were 64 deaths associated with toxicological evidence for the use of AMB-FUBINACA in the 18-month period beginning late May 2017 and continuing through to the end of February 2019 (Fig. 1). Previously the drug had not been reported in New Zealand deaths. The peak incidence occurred in July 2017 (11 cases). By September, following a public health campaign regarding the dangers of synthetic cannabinoids, incidents dropped to a few cases per month (range 0 to 5).

AMB-FUBINACA or its metabolite was detected in four traumatic cases in which it was not a direct cause of death, although it may have contributed in terms of behavioural effects, including two motor vehicle deaths - one in a person driving erratically, and one in a pedestrian witnessed to be crawling on the side of the road before collision - and two suicidal hangings. A fifth case involved an agitated mental health patient who died during restraint in which AMB-FUBINACA acid was identified in antemortem serum. AMB-FUBINACA acid was also detected in the sudden death of an infant who had other illicit drugs detected as well, and the contribution of AMB-FUBINACA to the cause of death is uncertain. The case is noteworthy, however, because the route of ingestion appeared to be breast milk.

The four traumatic deaths, the restraint death, and infant death were excluded from the remainder of the study, yielding a total of 58 cases. Table 1 includes a brief summary of the circumstances of death of each of the 58 cases, including cause of death and toxicological findings for AMB-FUBINACA, AMB-FUBINACA acid, and pFPP.

### 3.1. Patients

Fifty-one (51) of the cases were male (88%). Ages ranged from 17 to 64 years with a mean of 42 years (± 12 std. dev.), and median of 44 years (interquartile range: 20). Thirty-nine (39) cases (67%) of the deaths were reported to be of Māori descent, 10 cases (17%) were reported of European descent, and nine cases (16%) were Pacifica.

Nearly all (90%) had a history of drug or alcohol abuse, including a history of synthetic cannabis specifically (88%). One half of the cases (29) were reported to have a mental health history (other than substance abuse), including 22 cases with psychosis. Twenty (20) cases included a diagnosis of schizophrenia or schizoaffective disorder. Bipolar disorder was reported in five cases (four in combination with schizophrenia or schizoaffective disorder). There was one diagnosis of drug-induced psychosis. Depression was reported in four cases (one in combination with schizophrenia). Other mental health diagnoses included paranoia and aggressive behaviour, Attention Deficit Hyperactivity Disorder (ADHD), "mental health issues," and self-harm (Table 6).

### 3.2. Cause of death/Autopsy findings

Complete autopsy with toxicology was performed in all cases. Twenty-two (22) cases (38%) included a postmortem CT scan. A summary of the causes of death is shown in Table 2. (See Table 1 for cause of death by individual case). In 42 cases (72%), the primary cause of death was attributed to AMB-FUBINACA intoxication alone (20 cases) or in combination with alcohol or another drug (16 cases), or as a direct complication of intoxication (positional asphyxia, hypothermia

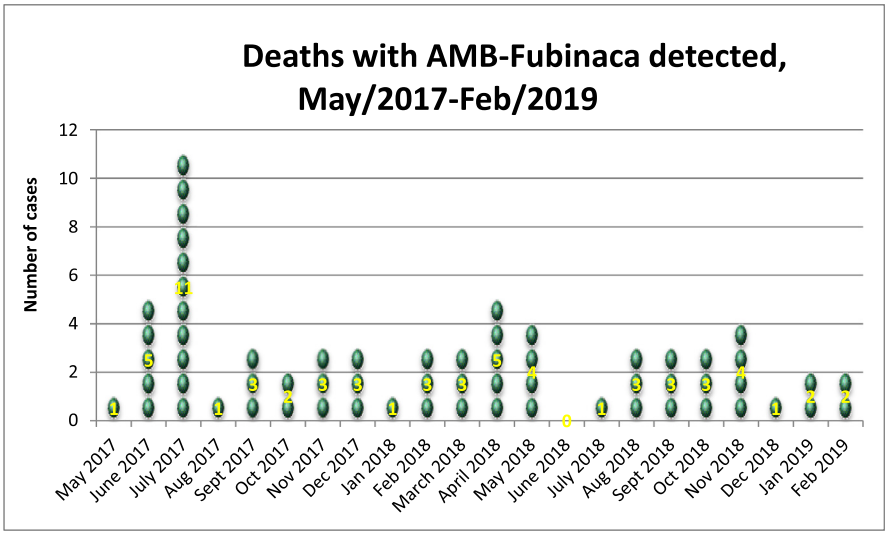


**Fig. 1.** Deaths (all causes) in which AMB-FUBINACA or its metabolite were detected in blood and/or urine at autopsy between May 2017 and February 2019, Northern Forensic Pathology Service, Auckland Hospital, Auckland, NZ.

**Table 1**
History, Cause of Death and Toxicology, 58 Non-Traumatic Deaths Associated with AMB-FUBINACA and pFPP, May 2017- February 2019, Auckland, NZ.

| Brief History of Circumstances of Death | Primary COD[2] at Autopsy | Contributory COD at Autopsy | AMB-FUB[3] | AMB-FUB acid (ng/mL) | pfPP[4] (ng/mL) |
|---|---|---|---|---|---|
| Witnessed sudden collapse. Initially thought to be sleeping. CPR initiated by ambulance. Died in ICU after 2 days. | Hypoxic Encephalopathy (due to AMB-FUB Toxicity) | — | NT[5] | C[6] | NT |
| Found dead in foetal position between bed and bicycle in room. | Positional Asphyxia due to Alcohol and AMB-FUB Toxicity | — | ND[7] | 45 | <4 |
| Found collapsed in car park. | Coronary Artery Atherosclerosis | AMB-FUB Toxicity | C | 680 | 27 |
| Found unresponsive. Intoxicated associate gave history of syn can[8] use prior to collapse. Brain death declared after 2 days in ICU. | Hypoxic Encephalopathy (due to AMB-FUB Toxicity) | Cardiac Hypertrophy | ND | 70 | ND |
| Smoked syn can with family member, who passed out and awoke to find him unresponsive. | AMB-FUB Toxicity | — | ND | 690 | 51 |
| Drinking and smoking syn can in doorway on street, became unresponsive. | Alcohol and AMB-FUB Toxicity | Coronary Artery Atherosclerosis | ND | 48 | ND |
| Found collapsed in bedroom at home. Evidence of sudden fall. | Morbid Obesity | — | ND | 280 | ND |
| Found by police apparently sleeping on steps of church during routine patrol. | HASCVD[9] | AMB-FUB Toxicity | ND | 220 | ND |
| Found dead in bed, lying on face with vomitus. History of nausea and vomiting for several days. | Undetermined | — | ND | 250 | 10 |
| Found slumped on kitchen floor. Noted earlier to be severely intoxicated and vomited in friend's room. | Undetermined | — | ND | 150 | ND |
| Drinking and smoking with friends, passed out on floor. After about 40 min, noted not breathing. CPR initiated by ambulance. Brain dead in ICU after 1 day. | Alcohol and AMB-FUB Toxicity | — | ND | 110 | ND |
| Had been using syn can. Subsequently found "blue," not breathing. CPR initiated by ambulance. Died in ICU. Previous admission for "seizure" due to syn can use. | Hypoxic Encephalopathy (due to AMB-FUB Toxicity) | HASCVD; Morbid Obesity | ND | 160 | ND |
| Smoking syn can with flat mate, both passed out about half hour later. Subsequently found unresponsive after 1−2 h. | AMB-FUB Toxicity | Morbid Obesity | ND | C | ND |
| Found dead on floor of room. Known to smoke syn can. | Alcohol and AMB-FUB Toxicity | — | ND | <45 | ND |
| Smoking syn can on street with girlfriend (GF) who passed out. GF was awakened by ambulance responding to call from bystanders who found both unresponsive. | Drug (Meth[10]), Alcohol, and AMB-FUB Toxicity | — | ND | C | NT |
| Found on bathroom floor after having gone for shower earlier. Earlier in day had apparently smoked syn can. | AMB-FUB Toxicity | Obesity related Heart Disease | ND | 90 | 6 |
| Found collapsed on toilet. | AMB-FUB Toxicity | Obesity related Heart Disease | I | <45 | <4 |
| Found dead on kitchen floor in puddle of water from overflowing sink. Unknown postmortem interval: last seen alive about 2 weeks earlier, but not decomposed. | Hypothermia | Multiple Drug (Morphine, AMB-FUB, Diazepam, Zopiclone, Haloperidol, Citalopram) Toxicity | ND | C | NT |
| Found in crouching position, propped up on knees, creamy substance coming from mouth and nose. | Undetermined | AMB-FUBINACA Toxicity | ND | C | NT |
| Found by flat mates on floor in his own vomitus. | AMB-FUB Toxicity | Cardiomyopathy; Renal Failure | ND | 780 | 44 |
| Smoked syn can with another, both fell asleep. Companion awoke to find victim dead. ED admission for syn can about 7 months earlier. | Alcohol and Drug (AMB-FUB, Zopiclone) Toxicity | — | C | 120 | 5 |
| Found dead by flat mates. | AMB-FUB Toxicity | — | ND | 120 | 4 |
| Family member heard "crash" and came out to find victim collapsed on porch at home. | AMB-FUB Toxicity | — | C | C | NT |
| Had been drinking at home. Joined others outside and collapsed after smoking cone of syn can. Found by police, companions severely intoxicated. | Alcohol and AMB-FUB Toxicity | — | I | 100 | ND |
| Had been drinking and consuming drugs with compatriots throughout the day, found unresponsive on floor. | AMB-FUB Toxicity | — | ND | 150 | 6 |
| Found dead on couch in room where he had been sleeping. | AMB-FUB Toxicity | — | ND | 720 | ND |
| Several years' history of syn can addiction, recent release from rehab. Relapsed the night before found unresponsive at home. | AMB-FUB Toxicity | Obesity related Heart Disease | ND | 430 | 10 |
| Drinking heavily, collapsed onto floor, unresponsive but breathing. Found dead in same position later that day. | AMB-FUB Toxicity | Alcohol Intoxication; Complications of Chronic Alcohol Abuse | ND | C | NT |
| Found dead lying on face in bed in same position as seen about 2 h earlier. Too intoxicated to go to work the day before. | AMB-FUB and Alcohol Toxicity | Coronary Artery Atherosclerosis | ND | 70 | <4 |
| Developed seizure about 2 min after smoking syn can, became unresponsive, snoring. About an hour later found not breathing. | AMB-FUB and Meth Toxicity | — | ND | 140 | ND |
| Found decomposed on bed. Last seen alive about 2 weeks earlier, drug paraphernalia in room. | AMB-FUB Toxicity | — | ND | 110 | ND |
| Found dead and decomposed on bed in barricaded apartment. Had not been seen for 10 days and had not responded to knock on door 2 days earlier. | AMB-FUB Toxicity | Fatty Liver | ND | C | NT |
| Smoked syn can cigarette, started seizing and vomited. Put in recovery position, started snoring, then stopped breathing and turned blue. | Drug (AMB-FUB, Zuclopenthixol) Toxicity | — | ND | 100 | ND |

(*continued*)

**Table 1** (*Continued*)

| Brief History of Circumstances of Death | Primary COD[2] at Autopsy | Contributory COD at Autopsy | AMB-FUB[3] | AMB-FUB acid (ng/mL) | pfPP[4] (ng/mL) |
|---|---|---|---|---|---|
| Began "acting strange" after smoking syn can with friend. Seizure and became unresponsive after a second hit. Subsequently found unresponsive, and friend "asleep". | AMB-FUB Toxicity | — | ND | C | NT |
| Found slumped over the wheel at rural parking spot. Bystanders initiated CPR. | AMB-FUB Toxicity | — | ND | C | NT |
| Found deceased in stairwell of car park. Smoking paraphernalia nearby. | Undetermined | AMB-FUB Toxicity; Dilated Cardiomyopathy | ND | 70 | ND |
| Had been smoking syn can for two days, blacked out and vomited. Brought around and moved to chair where he continued smoking. Subsequently found unresponsive in chair, head over knees. | Undetermined | AMB FUBINACA Toxicity; Atherosclerosis; Dilated Cardiomyopathy | C | 230 | 41 |
| Found dead wrapped in blanket near back stair of unoccupied residence frequented by homeless people. | AMB-FUBINACA Toxicity | — | C | 470 | 30 |
| Bystanders noticed victim lying on sidewalk with two companions standing nearby. Bystanders called ambulance and initiated CPR. | Alcohol and AMB-FUB Toxicity | — | ND | 160 | ND |
| Arrived at friend's house, beer in hand, apparently intoxicated. Smoked syn can with friend who went to sleep. Friend awakened shortly afterwards to find victim unresponsive sitting on floor leaning against refrigerator | AMB-FUB Toxicity | — | I | 140 | ND |
| Found slumped in bedroom in kneeling position, had not been seen for over 24 h. | AMB-FUB Toxicity | — | ND | C | NT |
| Found unresponsive by passers by who called ambulance, CPR for cardiac arrest of no avail. History of ischaemic heart disease. | AMB-FUB Toxicity | Myocarditis; HASCVD | I | 350 | 20 |
| Smoked syn can with friends. All fell asleep. When friends awoke in the am, victim was dead in chair | Obesity related Heart Disease | AMB-FUB Toxicity | ND | 50 | ND |
| Broke into car with mate and forced driver to take them to mini-mart. On return trip decedent started seizing in back seat of car. Subsequently pulled from car. Ambulance called. CPR of no avail. According to driver, had smoked leafy material in car with mate. | AMB-FUB Toxicity | Morbid Obesity; HASCVD | I | 240 | ND |
| Found unresponsive. Had been seen heavily intoxicated in same room earlier, sleeping with others who had been smoking sync can. | AMB-FUB Toxicity | Alcohol Intoxication; HASCVD | ND | C | NT |
| Found dead, partway between bed and a space heater by wall in unusual position. | Positional Asphyxia due to AMB-FUB Toxicity | — | ND | <45 | ND |
| Homeless man found dead on street with his bedding, etc., when checked on by friend. Bottles of alcohol and syn can with body. History of seizures often attributed to alcohol withdrawal. | Alcohol and AMB-FUB Toxicity | Coronary Artery High Takeoff | I | C | NT |
| Found collapsed and unresponsive on wash house floor, after loud banging noise and sounds of vomiting. Initially thought to be asleep, checked periodically and emergency services called when victim felt cold. | Undetermined | — | C | C | NT |
| Found dead. Had been sleeping outside on street and consuming syn can. | Synthetic Cannabinoid Toxicity (AMB-FUB, 5F-ADB, 5F-MDMB PICA acid) | HASCVD | ND | <45 | ND |
| Found dead in bed in am. Had been heard snoring in middle of the night. Had slept most of day before death. | Stroke | HASCVD; AMB-FUB Toxicity | ND | 70 | ND |
| Found collapsed on toilet, evidence of vomiting. | Left Ventricular Hypertrophy (n.o.s.[11]) | AMB-FUB Toxicity | I | 430 | 4 |
| Seemed out of breath when arrived at acquaintance's house. Given some water which he vomited. About 10 min later, went to sleep on couch. When checked about 20 min later, face and fingertips had turned blue. CPR unsuccessful. | Ischaemic Heart Disease | AMB-FUB | ND | 80 | ND |
| Fell asleep in vehicle during visit to family members. Subsequently found unresponsive. | Drug (AMB-FUB, Meth) Toxicity | — | I | >1000 | 7 |
| Found dead outside doorstep where had been "sleeping rough." | Obesity related Heart Disease | AMB-FUB Toxicity | ND | <45 | ND |
| Had been drinking. Arrived at friend's house intoxicated, suddenly collapsed, hitting head. CPR to no avail. | Alcohol and AMB-FUB Toxicity | Left Ventricular Hypertrophy (n.o.s.) | ND | C | NT |
| Found collapsed beside car after dropping off family member at home. | HASCVD | AMB-FUB Toxicity | ND | C | NT |
| Found decomposed at home. | HASCVD | AMB-FUB Toxicity | ND | C | NT |
| Found collapsed in bathroom after housemate heard vomiting. | Synthetic Cannabinoid (5F-MDMB PICA, AMB-FUB), Meth, and pFPP Toxicity | — | I | 100 | 17 |

Notes: [1]M=Male, *F*=Female;.
[2] Cause of Death;.
[3] AMB-FUBINACA;.
[4] Para-fluorophenylpiperazine;.
[5] Not Tested;.
[6] Confirmed;.
[7] Not Detected;.
[8] Synthetic Cannabis;.
[9] Hypertensive Atherosclerotic Cardiovascular Disease;.
[10] Methamphetamine;.
[11] Not Otherwise Specified.

**Table 2**
Cause of death at autopsy: 58 non-traumatic AMB-FUBINACA associated cases.

| | | Primary COD[1] | Contributory COD 1 | Contributory COD 2 | Contributory COD 3 |
|---|---|---|---|---|---|
| Undetermined | | 6 (10%) | – | – | – |
| **AMB-FUBINACA** | 55 cases (95%) | 42 (72%) | 12 (41%) | 1 (14%) | – |
| | Alone | 20 | 11 | 1 | – |
| | Combined with alcohol or other drug | 16 | 1 | – | – |
| | Hypoxic encephalopathy | 3 | – | – | – |
| | Positional asphyxia | 2 | – | – | – |
| | Hypothermia | 1 | – | – | – |
| **Heart disease** | 27 cases (47%) | 8(14%) | 14 (48%) | 4 (57%) | 1 (100%) |
| | HASCVD[2] | 5 | 6 | 3 | – |
| | Obesity related | 2 | 3 | | – |
| **Obesity** | 4 cases (7%) | 1 (2%) | 2 (7%) | 1 (14%) | – |
| **Stroke** | | 1 (2%) | | – | – |
| **Fatty Liver** | | – | 1 (3%) | – | – |
| **Renal failure** | | – | – | 1 (14%) | – |
| **Total** | | 58 (100%) | 29 (99%) | 7 (99%) | 1 (100%) |

Notes:.
[1] Cause of Death;.
[2] Hypertensive and Atherosclerotic Cardiovascular Disease.

or hypoxic encephalopathy) (six cases). Heart disease was listed as the primary cause in eight cases (14%) with morbid obesity and stroke accounting for one case each. The primary cause of death was considered undetermined in six cases (10%); however, in three of these cases contributory causes were listed: AMB-FUBINACA in all three, and heart disease as a second contributor in two. Two of the three remaining undetermined cases occurred within the first month of the outbreak, perhaps reflecting the certifying pathologist's uncertainty of the significance of this newly encountered substance.

A least one additional contributory cause was cited in 29 cases (50%) along with the primary cause. Seven cases listed two contributory causes, and in one case three contributory causes were listed (Table 2). Considering both primary and contributory causes, AMB-FUBINACA contributed directly to death in 54 cases (93%). Heart disease was considered a primary or contributing cause in 27 cases (47%), 14 of which were hypertensive and atherosclerotic disease (HASCVD). Obesity-related heart disease was listed as a contributory cause in five cases. Obesity or morbid obesity was given as a primary or contributory cause in four cases, and when combined with obesity related heart disease, obesity was considered either a primary or contributory cause in 16% of the cases.

Body mass index (BMI) at autopsy ranged from 19 $kg/m^2$ (normal) to 70 $kg/m^2$ (morbidly obese), with a group mean of 33 $kg/m^2$ ($\pm$ 11 std. dev.) and median of 32 $kg/m^2$ (interquartile range: 11·75). Over half (52%) of cases were classified as obese (BMI $\geq$ 30). Eight cases were morbidly obese (Class III, BMI $\geq$ 40), representing 27% of the obese group and 14% overall. Class II obesity (35 $\geq$ BMI $<$ 40) accounted for an additional 10 cases (17% overall).

Mean autopsy heart weight for the group was relatively high at 486 g ($\pm$ 132 std. dev.), median 452·5 g (interquartile range: 133·5), ranging from 294 g (normal) to 900 g (pathologically enlarged). (Reference male heart weight: 233–383 g) [20]. Heart weight is a function of body size to a significant extent. As expected, BMI and heart weight were significantly correlated (Pearson correlation coefficient = 0·734, $p < 0{\cdot}005\%$). However, heart disease including HASCVD and most cardiomyopathies are also associated with increased heart weight. HASCVD was diagnosed at autopsy in 26 instances (45%) and cardiomyopathy in 18 instances (31%), whether considered contributory to death or not. Therefore, elevated heart weight is likely a function of both obesity and heart disease.

Mean combined lung weight was 1461 g ($\pm$ 365 std. dev.), suggesting pulmonary oedema. (Reference weight: 840 g) [21]. Review of autopsy reports indicated no other likely cause for elevated lung weights except in two cases with pneumonia. In both of these, however, pulmonary oedema was also present.

### 3.3. Location

Ninety-five percent of the cases occurred in Auckland with three cases reported elsewhere on the North Island of New Zealand. Auckland is the largest city in New Zealand with a population of 1,415,550 and comprises approximately 33% of the NZ population (2013 census) [22].

Nearly all deaths occurred at the scene of the event (54 deaths, 93%), while only four occurred in hospital: three died of complications as inpatients in intensive care units, and one death occurred in the emergency department. Nevertheless, resuscitation was attempted in 48% (28 cases).

The scene of death (or of the event leading to hospitalization) was most commonly inside a residence (39 cases, 67%). In four cases (7%) it was outside the home. The scene was on the street in 10 cases (17%), in an urban car park in two cases (3%) and in a motor vehicle in three cases (5%).

### 3.4. Witnesses/finding the body

In 19 cases (33%) the event of death was witnessed at the scene. Most common witnesses were family, friends or roommates (14 cases, 74%). Other witnesses included strangers and police. In four cases there were multiple witnesses. A similar spectrum of individuals found the body with unwitnessed cases: family/friends - 28 cases (72%), roommates/land lords - five cases (13%), strangers/passers-by - five cases (13%) and police - one case (2%). Two thirds (67%) of the 39 unwitnessed deaths were discovered the same day as last being seen alive. Seven were found within one day, and two within two days. The remaining four were found 6, 10, 13 and 15 days after last being seen alive. Three of these were decomposed.

### 3.5. Circumstances of event

Route of ingestion in all cases was inhalational (smoking), judged by witness statements or paraphernalia at the scene of death. Thirty-eight per cent were specifically witnessed to smoke synthetic cannabinoids before or during the event, and 40% were witnessed to be intoxicated or to engage in bizarre behaviour before either death or being found dead. In 20 cases the victim was reported to lose consciousness, pass out or "go to sleep" prior to being found dead, while in six instances the victims smoked cannabis with others during which event all passed out or "fell asleep," and subsequently one of the group awoke to find the victim dead. There was a history of seizures in eight cases: four were witnessed to have a seizure before death and four were

**Table 3**
Drugs Detected (Confirmed or Identified) in Blood, 58 Non-traumatic cases.

| Drug | Number of cases | Percent |
|---|---|---|
| AMB-FUBINACA | 15 | 26% |
| AMB-FUBINACA acid (metabolite) | 58 | 100% |
| pFPP (16 cases not tested) | 18 | 31%[1] |
| THC (marijuana) (6 cases not tested) | 23 | 40%[2] |
| Other synthetic cannabinoid | 2 | 3% |
| Alcohol (2 cases not tested) | 23 | 40%[3] |
| Methamphetamine | 6 | 10% |
| Opiates/opioids (morphine, methadone, tramadol, codeine) | 4 | 7% |
| Sedatives (benzodiazepines/zopiclone) | 12 | 21% |
| Psychiatric medications | 28 | 48% |
| Miscellaneous Resuscitative/Therapeutic (amiodarone, ketamine, lignocaine, paracetamol, phenytoin, propranolol, promethazine, rocuronium) | 8 | 14% |
| Caffeine | 51 | 88% |
| Cotinine (tobacco) | 51 | 88% |

Notes:.
[1] 43% of those tested;.
[2] 41% of those tested,.
[3] 42% of those tested.

known to have a history of seizures following synthetic cannabinoid use specifically. In one additional case a medical history of untreated epilepsy was provided (post mortem toxicology revealed no anticonvulsant medications). Vomiting, a recognised sign of synthetic cannabinoid toxicity [23,24], was reported in eight instances. See Table 1 for summary of circumstances by individual case.

### 3.6. Toxicology

Table 3 summarizes the toxicological findings in blood. AMB-FUBINACA acid, a metabolite of AMB-FUBINACA, was confirmed in all 58 cases and in all 17 cases where it was reported as having been tested in urine. AMB-FUBINACA was detected in the blood of only 15 cases (six confirmed, nine identified only), and detected in six of 13 cases (five confirmed, one identified only) where it was reported as being tested in urine. AMB-FUBINACA is rapidly metabolised to its acid metabolite, and finding only the metabolite in blood does not exclude recent use [13,23–25].

Forty-six cases were tested for pFPP (including four cases of death due to traumatic causes), and the drug was detected in 20 cases.

Tetrahydrocannabinol (THC), a major marijuana constituent, was detected in blood of 23 of 52 cases where it was reported as having been tested (22 confirmed, one identified only), suggesting that in the majority of the cases synthetic cannabinoid was specifically smoked, rather than occurring in combination with marijuana, which is consistent with the practice of spraying plant material with a synthetic cannabinoid and marketing it as such [26]. Two cases included other synthetic cannabinoids: 5F-ADB and 5F-ADB acid in blood, 5F-MDMB-PICA acid in urine, in addition to AMB-FUBINACA and THC; and 5F-MDMB PICA, methamphetamine, and pFPP as well as AMB-FUBINACA (see Table 1).

Alcohol (ethanol) was tested for in 56 cases. Blood alcohol concentrations (BAC) ranged from 0 to 361 mg/100 mL with a median BAC of 137 mg/100 mL (interquartile range: 175) of the 23 cases where it was detected. Table 4 shows distribution of alcohol concentration. In 35 cases (62%) BAC was less than 10 mg/100 mL or not detected, while 16 cases showed evidence of intoxication, defined as 50 mg/100 mL or greater. Two cases had BAC greater than 300 mg/100 mL, a level likely to contribute physiologically to death.

Methamphetamine was detected in six cases (five confirmed, one identified only), while opiate/opioid drugs were reported in five instances (four cases): combined methadone and tramadol, tramadol, morphine (likely heroin), and codeine. Fentanyl was reported in one

**Table 4**
Blood Alcohol Concentration (BAC), 56 Non-traumatic cases.

| BAC (mg/100 mL) | Number of cases | Percent |
|---|---|---|
| less than 10 | 35 | 62% |
| 10 to 50 | 6 | 11% |
| 50 to100 | 1 | 2% |
| 100 to 200 | 7 | 12% |
| 200 to 300 | 6 | 11% |
| 300 to 400 | 2 | 4% |
| Total | 56 | 100% |

case, but it was known to have been administered therapeutically and therefore was classified with therapeutic and resuscitative drugs. Sedative drugs were reported in 12 cases: zopiclone and benzodiazepines, six cases each.

One or more psychiatric medications were detected in 28 cases (48%) (Table 5). None were reported as "overdoses." Antidepressant drugs were confirmed in seven cases. In five instances these were detected in combination with an antipsychotic medication. A range of antipsychotics was confirmed in 23 cases (40%) including 20 "atypical" antipsychotics. (See Table 5 for specific drugs). In at least five cases more than one antipsychotic medication was detected (discounting risperidone/9-OH risperidone combination). When mental health history is tabulated with the antipsychotic medication, there is, not surprisingly, a strong correlation (Table 6, $p = 0{\cdot}011$). However, in six individuals with a reported history of psychotic illness no medications were detected, and in five instances antipsychotic medications were confirmed where there was no reported mental health diagnosis, suggesting that the prevalence of psychosis may be even higher than that indicated by either medical history or toxicological detection of medication alone.

A number of resuscitative and therapeutic medications were confirmed in post-mortem toxicological analyses (see Table 3). Nearly all cases showed caffeine and cotinine (a metabolite of nicotine): 51 cases (88%) each.

### 3.7. Quantitative synthetic cannabinoid toxicology

In 41 cases postmortem blood concentrations of AMB-FUBINACA acid were available (see Table 1). In five cases the concentration was below 45 ng/mL, the lower limit of the calibration curve. Of these cases, two were due to mixed intoxications (alcohol, and multiple synthetic cannabinoids with pFPP) and one was due to positional asphyxia. In three of the five, natural disease contributed to death (obesity related heart disease, HASCVD, and cardiomyopathy and renal failure). One case was over the upper limit of the calibration

**Table 5**
Psychiatric Medications, 58 Non-traumatic cases.

| Medication | | Number of cases |
|---|---|---|
| **Antidepressants** | | 7 (12%) |
| | Citalopram (4), Fluoxetine (1), Mirtazapine (1), Sertraline (1) | |
| **Antipsychotics** | | 23 (40%) |
| | Atypical | 20 (34%) |
| | Amisulpride (1) Aripiprazole (1), Olanzapine (6), Clozapine (2), Fluoxetine (1), Flupenthixol (2), Quetiapine (3), Risperidone (2), 9-OH risperidone (9), Zuclopenthixol (3) | |
| | Typical | 3 (5%) |
| | Haloperidol (3) | |
| **Total** | One or more antidepressant or antipsychotic medication | 28[1] (48%) |

Note:.
[1] Five cases with antidepressant and antipsychotic combined.

**Table 6**
Mental Health Diagnoses and Antipsychotic Medications, 58 Non-traumatic cases.

| | | | Antipsychotic medications | | Total |
|---|---|---|---|---|---|
| | | None | Atypical antipsychotic | Typical antipsychotic | |
| **Mental Health Diagnosis** | None known | 24 | 4 | 1 | 29 |
| | Schizophrenia | 4 | 9 | 1 | 14 |
| | Schizophrenia & PTSD[1] | 0 | 1 | 0 | 1 |
| | Schizophrenia & Bipolar | 1 | 1 | 0 | 2 |
| | Schizophrenia & Depression | 0 | 1 | 0 | 1 |
| | Bipolar | 1 | 0 | 0 | 1 |
| | Bipolar & schizoaffective Disorder | 0 | 2 | 0 | 2 |
| | Drug induced psychosis | 0 | 1 | 0 | 1 |
| | Depression | 2 | 1 | 0 | 3 |
| | Paranoia & Aggressive Behaviour | 0 | 0 | 1 | 1 |
| | ADHD[2] | 1 | 0 | 0 | 1 |
| | Mental health issues n.o.s.[3] | 1 | 0 | 0 | 1 |
| | Self Harm | 1 | 0 | 0 | 1 |
| **Total** | | 35 | 20 | 3 | 58 |

[1] Post Traumatic Stress Disorder,.
[2] Attention Deficient Hyperactivity Disorder.
[3] not otherwise specified.

curve (1000 ng/mL). In this case death was attributed to mixed drug intoxication including AMB-FUBINACA, methamphetamine and pFPP. (See Table 1 for details). The concentration of AMB-FUBINACA acid in blood of the remaining 35 cases ranged from 45 ng/mL to 780 ng/mL with a mean of 229 ng/mL and median of 140 ng/mL (interquartile range: 170), indicating a skew (tail) of the curve towards the lower concentrations.

Postmortem blood concentrations of pFPP were reported in 17 cases (including two trauma cases) of the total 46 cases screened. The concentration of in these 17 cases ranged from 4 to 51 ng/mL, mean 18 ng/mL, median 10 ng/mL (interquartile range: 22·5). In addition, there were three cases where the concentration fell below the lower limit of quantitation (4 ng/mL). Blood concentrations of pFPP and AMB-FUBINACA acid showed a positive correlation (Pearson correlation coefficient = 0·717, $p < 0·01$).

In the four excluded trauma cases, the concentrations of AMB-FUBINACA acid were as follows: two hanging cases (>1000 ng/mL, 75 ng/mL), a pedestrian struck by motor vehicle (280 ng/mL) and the driver of an automobile (>1000 ng/mL). The drug pFPP was reported in one case of hanging (5 ng/mL) and the motor vehicle driver (25 ng/mL).

## 4. Discussion

AMB-FUBINACA is a synthetic cannabinoid of the indazole-3-carboxamide class, active at the $CB_1$ and $CB_2$ cannabinoid receptors [23]. Among the Australian coronial deaths associated with synthetic cannabinoids, the indazolecarboxamides were most common (62%) with AB-CHIMACA cited in 38% of cases. AMB-FUBINACA was cited in one instance [16]. Although outbreaks of bizarre behaviour and stupor resulting in increased visits to emergency rooms are well known with AMB-FUBINACA [23,24], we are aware of only two recent case reports of fatalities associated with AMB-FUBINACA, each combined with another synthetic cannabinoid (EMB-FUBINACA and 5F-ADB, respectively) [13,14]. We believe that this series represents the first description of an outbreak of multiple deaths associated with AMB-FUBINACA.

There is relatively little published data on blood concentrations of synthetic cannabinoids, especially in fatalities. "Typical blood concentrations" of synthetic cannabinoids are described as 0·1−10 ng/mL, while autopsy concentrations have been reported as high as 68−200 ng/mL [27]. Reported concentrations in fatalities have varied considerably with different synthetic cannabinoids [15]. In a death associated with AMB-FUBINACA in combination with EMB-FUBINACA, blood concentrations of both compounds were below detection limit (0·1 ng/mL), although various solid tissue concentrations ranged from 0·2 to 0·9 ng/g and 0·2 to 3·5 ng/g, respectively [13]. The blood concentrations encountered in our series were considerably higher than those reported with other synthetic cannabinoids, although our quantitative results were for the metabolite rather than the parent compound. In this context it is noteworthy that the concentrations of AMB-FUBINACA documented in plant material seized by NZ law enforcement during the same period were considerably higher than those reported in other outbreaks [19,26].

Deaths first appeared in late May and June of 2017, peaked in July, and then rapidly fell to a few deaths per month following a public health campaign involving the Chief Coroner and medical authorities (see Fig. 1). During 2017, ten different synthetic cannabinoids were reported in New Zealand border and domestic law enforcement seizures [26]. In the northern part of the North Island (where Auckland is located), 84% of samples were AMB-FUBINACA, compared to 15% in the southern part of the North Island and 42% in the South Island. Furthermore, samples combined with pFPP were only reported in the upper part of the North Island [19]. Thus, the outbreak corresponds with the apparent patterns of synthetic cannabinoid illicit importation, distribution and concentrations seen by New Zealand law enforcement during the same period.

Deaths occurred predominately among males, generally in their early 40′s, but with a wide age range from 17 to 64. The sex and age range are comparable with those reported in America [4] and Australia [16]. As in the Australian experience, deaths most commonly occurred in the home environment and relatively few survived to the hospital [16]. Accidental drug toxicity was the reported the cause of death in 26 of the 55 cases in Australia. Although they did not report specifically how many deaths were considered due to the effects of synthetic cannabinoids alone compared to those in combination with other drugs, they reported other drugs present in 76·4% [16]. Intoxication with AMB-FUBINACA alone was considered the primary cause of death in 34% of our cases, and in combination with another drug or alcohol in an additional 28%. Positional asphyxia due to intoxication was a reported mechanism of death in five Australian cases, comparable to our experience (two cases). Death was attributed to cardiovascular disease, most commonly atherosclerotic disease, in approximately one fifth of the cases in both the American [4] and Australian [16] experience. Giorgetti et al. [15] also noted a significant prevalence of cardiovascular disease in their review of the published literature on deaths involving synthetic cannabinoids. Cardiovascular disease was certified as either the primary or a contributory cause of death in 27 (47%) of our cases, with hypertensive and atherosclerotic disease the most common diagnosis (52%). Obesity related heart disease was cited in five cases (see Table 2).

Witness statements suggest two mechanisms of death: seizures and central nervous system (CNS) depression characterised by passing out and/or "going to sleep." Pulmonary oedema at autopsy in this context suggests three major pathophysiological mechanisms: centrally mediated respiratory depression, neurogenic pulmonary oedema, and acute cardiac (left ventricular) failure. Pulmonary oedema due to CNS/respiratory depression is a well-recognised mechanism of death with many drugs, and the weights of the lungs in this series are compatible with those observed, for example, in opioid deaths [28]. CNS depression due to severe intoxication with AMB-FUBINACA is a likely contributory factor in the two cases due to positional asphyxia and in the case of death due to hypothermia. On the other hand, there were four instances of witnessed seizures upon smoking synthetic cannabinoids before death and a medical history of seizures following the smoking of synthetic cannabinoids in another four individuals. In the case of seizures, neurogenic pulmonary oedema may be an operative mechanism [29]. Sudden arrhythmic cardiac death seems less likely given pulmonary oedema, but one case report suggests that AMB-FUBINACA may be associated with ST elevation and acute myocardial infarction [30]. AMB-FUBINACA has been associated with a number of adverse cardiac reactions [23,24] that may induce acute cardiac failure especially in the context of underlying heart disease. Of course, these various mechanisms need not be mutually exclusive, and different mechanisms may hold in different cases.

Approximately 36% of individuals in this series had a known history of either schizophrenia or another diagnosis on the schizophrenic spectrum, and 23 cases (40%) were on antipsychotic medications at the time of death (see Table 5). Schizophrenics are known to be at increased risk for marijuana abuse [31], and it has been suggested that the endocannabinoid system is deranged in schizophrenia [32]. Furthermore, there is evidence that psychosis and synthetic cannabinoids use may be aetiologically associated [33]. Psychosis, for whatever reason, would appear to be a significant risk factor in this outbreak of deaths.

A limitation of this study is the lack of a well-defined control group. Although we report the characteristics observed in a series of deaths associated with AMB-FUBINACA, we know very little about the population of users of synthetic cannabinoids in New Zealand. There was a corresponding increase of emergency room visits during the early phases of this outbreak, but we have little information on those who survived. How are they different, or the same, as those who succumbed?

Also, the role of competing and contributory causes of death is unclear. Others [15,25] have observed that quantitative toxicology is difficult to interpret in the postmortem context. Although mixed intoxications appeared more commonly at lower concentrations, suggesting a dose-response effect, mixed intoxications and contributory natural disease were noted across the full spectrum, and high blood concentrations were seen in trauma cases where death was not due to direct toxicity, indicating that even the highest levels seen in our series are not necessarily lethal. Furthermore, the pathophysiological effects of the drug after peak blood concentrations and during the course of drug metabolism remain largely unknown. A low concentration of the drug in blood does not necessarily exclude its role in cause of death; any more than a high level necessarily proves lethality. More research on the correlation of blood concentration of the drug and its metabolites and toxicity is needed.

In summary, we have described a recent outbreak of deaths associated with the synthetic cannabinoid AMB-FUBINACA in Auckland, New Zealand. The lethal potential of synthetic cannabinoids may not be fully appreciated, in part because they are not routinely screened for, and in part because their contribution to drug mortality may be obscured by other substances or natural disease. Mechanism of death often appeared to be due to either CNS mediated respiratory depression or seizures. However, several potential medical risk factors were identified, including heart disease, obesity, and combined intoxication, notably with alcohol. The combination of AMB-FUBINACA with pFPP may also have played a role. Other "classic" lethal drugs of abuse, such as opioids and methamphetamine were not prominent, and this group may represent a unique subgroup of drug associated deaths. A high prevalence of psychosis, notably on the schizophrenic spectrum, was identified. Additional study is needed to characterize this subgroup of drug related deaths and its associated risk factors, in order to identify prevention and treatment measures for this evolving public health problem.

## Declaration of Competing Interest

All authors report no conflicts of interest.

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