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Synthetic cannabinoid drug use as a cause or contributory cause of death

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ABSTRACT

Adverse effects associated with synthetic cannabinoid use include agitation, psychosis, seizures and cardiovascular effects, all which may result in a lethal outcome. We report the collection of data from 25 medical examiner and coroner cases where the presence of synthetic cannabinoids was analytically determined. Participating offices provided case history, investigative and relevant autopsy findings and toxicology results along with the cause and manner of death determination. This information, with the agency and cause and manner of death determinations blinded, was sent to participants. Participants offered their opinions regarding the likely contribution of the toxicology findings to cause and manner of death. The results show that some deaths are being attributed to synthetic cannabinoids, with the highest risk areas being behavioral toxicity resulting in excited delirium, trauma or accidents and as contributing factors in subjects with pre-existing cardiopulmonary disease. While insufficient information exists to correlate blood synthetic cannabinoid concentrations to effect, in the absence of other reasonable causes, the drugs should be considered as a cause or contributory cause of death based on history and circumstances with supporting toxicological data.

1. Introduction

Synthetic cannabinoid CB_1 and CB_2 receptor agonists were developed in an attempt to provide the therapeutic benefits claimed for botanical cannabis, such as appetite stimulation, anti-nausea properties, and pain relief, while limiting the psychoactive effects [1]. The number of synthetic cannabinoids and their potencies has dramatically increased within the last decade. As such, toxicology laboratories have made concerted efforts to keep pace with the rate that at which these drugs are being designed and introduced into the user markets [2]. Only limited data from controlled studies exist however, to evaluate pharmacokinetic parameters [3]. The correlation between concentration and effect therefore is not clearly defined, and the interpretation of postmortem findings is further complicated by the lack of data examining influences from postmortem redistribution. In lieu of this information, pathologists, clinicians and toxicologists have relied upon case studies involving self-reported use where toxicology testing may not have been performed. In one study that surveyed 518 patients from 60 emergency facilities in Japan, 86% claimed to have inhaled synthetic chemicals contained in herbal products. Other than neuropsychiatric behaviors, 10% of patients had physical complications such as rhabdomyolysis [4]. The signs and symptoms that have been associated with synthetic

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cannabinoid use do include central nervous system effects (e.g., agitation, confusion, sedation and psychosis), cardiovascular effects (e.g., arrhythmia, bradycardia and tachycardia) and gastrointestinal effects (nausea and vomiting) [5–7]. For some cases, cause of death has been directly attributed to synthetic cannabinoid use [8–11]. In one case, the 59-year-old male decedent was found with three herbal blend sachets at his residence. MAM-2201 was analytically determined to be present in several of his biological specimens and as no evidence of endogenous disease or external injuries were noted, his death was attributed to the use of this drug. Another case describes a 36-year old man who collapsed at home and experienced seizures after smoking an herbal blend called "Mary Joy Annihilation". Toxicology testing showed the presence of five different synthetic cannabinoids in peripheral blood in addition to 250 ng/mL amphetamine. The synthetic cannabinoids were included as a contributory factor in his death due to drug intoxication. This study aims to evaluate how this toxicological information is used in cause and manner of death determinations in cases where the presence of at least one synthetic cannabinoid was analytically confirmed.

2. Methods

2.1. Case identification and inclusion criteria

The primary inclusion criterion was that the presence of one or more synthetic cannabinoids had to be proven in a postmortem case through toxicology testing. The deaths occurred between November 2010 and May 2014. It should be noted that due to the rapid turnover in the specific synthetic cannabinoids in circulation at any given time, the scope of testing changed over the period during which these cases were analyzed. Therefore, while each case had confirmed toxicology findings, not every case was subjected to the same scope of analysis, but to a scope relevant at the time of the investigation. All testing was performed by Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS) based on previously published methods [11,12], and updated and validated as the scope changed. Analytes were quantified when appropriate deuterated internal standards were available; otherwise the analytes were qualitatively reported. Cases were included in the series irrespective of the initially determined cause and manner of death, and whether or not other drugs were detected. Participating offices were recruited via the National Association of Medical Examiners LISTSERV®. All of the reported cases came from offices represented by the co-authors of this manuscript. Respondents completed a form with two main sections, Section A: Case Background and Investigation and Section B: Pathology and Toxicology Findings. Requested information for each section is shown in Table 1. In total, 25 cases were submitted in which there was adequate information for review as determined by the authors.

2.2. Data processing and review

After the information received for each case was compiled, a second spreadsheet blinded to the office of origin was generated and electronically sent to all respondents who was comprised of medical examiners, coroners and toxicologists. Specifically for each case, each respondent was asked to review the case information and provide an opinion, referring to the categories listed in Table 2, regarding the likely contribution of the synthetic cannabinoid to the cause of death from a toxicological point of view. When this interpretive information was received back from the respondents, the results were tabulated and are shown in Table 3, along with the information on which the opinions were based.

Table 1
Requested information for each case submitted by a participating office.

Section A Case background and investigation	Section B Pathology and toxicology findings
• Case identifier • Age • Gender • Date of death • City and State of death • Brief history of events surrounding death • Drug use history • Photographs of any drug packets, products or paraphernalia • Any lab reports of analysis of seized drug material found at the scene of determined to be related to the case • Other relevant information	• Determinative pathology findings • Toxicology findings • Cause and manner of death per death certificate • Other relevant information

Table 2
Contribution categories with explanation of synthetic cannabinoid deaths.

Contribution Category	Explanation
Behavioral and physical contribution	Psychotic and/or excited delirium resulting in restraint followed by death.
Behavioral contribution	Behavior resulting in trauma or injury leading to death.
Combined drug intoxication	Mixed drug intoxication including synthetic cannabinoids.
Mono intoxication	Synthetic cannabinoid(s) only relevant drug class identified that contributed to death.
Contribution unknown/natural	Not clear if/how the presence of synthetic cannabinoid(s) contributed to death.

3. Results

3.1. Initial determination of role of synthetic cannabinoid in cause and manner of death

In total 25 cases met the criteria for inclusion. The cases with the brief history provided, determinative pathology findings, toxicology and initial cause and manner of death information are summarized in Table 3. The subjects (6 female and 19 male) had an age range of 15–61 years for the females and 15–58 years for the males with one male age unspecified. In total, eight different synthetic cannabinoids were identified across all cases, with 16 cases being positive for only one. AM-2201 was the most frequently encountered drug followed by XLR-11, and various JWH compounds. When quantified, concentrations for all the synthetic cannabinoids in blood ranged from 0.11 ng/mL to 105 ng/mL. The synthetic cannabinoid, the frequency found, and the associated concentration range, if analytically determined, are shown in Table 4. The concomitant use of illicit drugs was noted in nine cases. Illicit drugs identified or implicated were cannabis ($n = 6$), heroin ($n = 1$), methamphetamine ($n = 1$) and MDEA and MDA ($n = 1$). The original cause of death determinations show that the term synthetic cannabinoid(s), synthetic marijuana or a listing of specific synthetic cannabinoids are solely used in 13 cases and included as part of mixed drug intoxication in an additional 2 cases. Two of the deaths (Case 1 and Case 2) are attributed to agitated or