Forensic Science International 298 (2019) 298–306

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Cannabis as a cause of death: A review

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ARTICLE INFO

Article history:
Received 28 November 2018
Received in revised form 4 March 2019
Accepted 7 March 2019
Available online 14 March 2019

Keywords:
Arrhythmias
Cardiovascular disease
Forensic
Heart disease
Myocardial infarction
Stroke

ABSTRACT

Synthetic cannabinoids have caused a large number of emergency presentations to hospitals for adverse cardiovascular events including numerous deaths, particularly for the more potent analogs acting on the CB_1 receptor. While smoked cannabis use is often associated with significant changes in heart rate and cardiac output, amongst other physiological changes, it has been rarely considered in the forensic literature as a significant contributory or causal factor in sudden unexpected death. A review of case reports of admissions to hospitals for cardiovascular events was undertaken together with a review of epidemiological studies, and case reports of sudden death attributed, at least in part, to use of this drug. These publications show that use of cannabis is not without its risks of occasional serious medical emergencies and sudden death, with reports of at least 35 persons presenting with significant cardiovascular emergencies who had recently smoked a cannabis preparation. At least 13 deaths from a cardiovascular mechanism have been reported from use of this drug which is very likely to be an under-estimate of the true incidence of its contribution to sudden death. In addition, many cases of stroke and vascular arteritis have also been reported with the latter often involving a limb amputation. While it is a drug with widespread usage among the community with relatively few deaths when faced with a circumstance of very recent use (within a few hours), a positive blood concentration of THC and a possible cardiac-related or cerebrovascular cause of death this drug should be considered, at least, a contributory cause of death in cases of sudden or unexpected death.

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1. Introduction

Marijuana (cannabis) is a widely used recreational substance with over 190 million users world wide and lifetime use in much of the world is well over 20% of the population, with a significant number of regular users [1]. In the USA and Europe the prevalence of daily or nearly daily use was about 3.5% and 1%, respectively in 2015 [2]. In Australia about 10% have used cannabis in the last year and over 35% of persons over the age of 14 years admit to use at least once in their life [3].

The main active substance in the cannabis plant is Δ^9-tetrahydrocannabinol (THC) with some contribution from other cannabinoids. When smoked, THC concentrations appear within

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https://doi.org/10.1016/j.forsciint.2019.03.007
0379-0738/

seconds in blood but dissipate rapidly on cessation as the drug is distributed into tissues. Within one hour less than 10% of the peak blood THC concentration is present dropping to less than 5 ng/mL within a few hours [4]. Any acute effects of smoked cannabis would be expected to occur relatively rapidly but these effects should also dissipate rapidly [5]. Oral use of cannabis products e.g. cookies or brownies) produces much lower peak concentrations of THC (usually less than 5 ng/mL), however significant amounts of 11-hydroxy-THC is formed through first-pass metabolism. This metabolite has similar pharmacological activity to THC and contributes to the physiological effects of cannabis when consumed orally.

In some regular but heavy users cannabis causes drug dependency and is associated with psychoses and longer-term changes in mental health [6]. Use can also likely worsen psychomotor skills and cognitive performance that have become issues of concern in drivers of motorized vehicles and those persons engaged in safety-critical occupations [7,8]. These adverse effects tend to be concentration related although the magnitude of effect is also dependent on developed tolerance to the drug; how timely the sampling is able to be undertaken in relation to the incident (from pharmacokinetic loss of THC with time), and involvement of other CNS-active drugs [9–11].

THC primarily acts on two cannabinoid receptors which are a G-protein-coupled with two subtypes known: CB_1 (brain, peripheral sensory and autonomic nervous systems) and CB_2 (largely associated with immune function) [12–14]. THC use is often associated with cardiovascular changes including acute increases in heart rate, various types of arrhythmias, coronary vasospasm and acute myocardial infarction [15–18].

Over the last decade numerous synthetic cannabinoids have been detected, some of which are even more potent than THC itself on the cannabinoid receptors, particularly those acting on the CB_1 sub-type. These include generic names such as Spice and K2, but also named drugs including the large JWH series, and the newer analogs PB-22, 5F-AMB, MDMB-Chmica, UR-144 etc. [1]. Moreover, there have been numerous reports of these novel psychoactive drugs causing presentations to emergency departments for psychoses, agitation, confusion and a variety of cardiovascular effects including arrhythmias and myocardial infarction [19–21]. In recent years a number of deaths have been attributed to the use of synthetic cannabinoids [19,22–25].

While synthetic cannabinoids are increasingly been given as the cause of death there are relatively few deaths attributed to cannabis itself [23,24,26,27] since it is often regarded as a relatively safe recreational drug and now has an increasing medical use for defined conditions [28].

However, there have been numerous reports that link cannabis use to presentations to emergency centers at hospitals for cardiovascular-related medical events [15,29,30]. This publication reviews reports of published presentations to hospitals with a focus on cardiovascular events, and reviews published reports of deaths attributed to use of cannabis in an attempt to understand what, if any, role cannabis has on contributing or causing serious cardiac dysfunction and sudden death.

2. Methods

All publications in the English language that reported fatalities attributed to the use of cannabis or marijuana, but not involving any synthetic cannabinoid, were searched in PubMed as well as Scopus. Key words included: marijuana or cannabis, plus (and) fatality, death, poisoning, arrhythmias, heart, myocardial infarction. Publications not captured in the initial searches but cited in publications were also retrieved and included, where relevant.

Publications were included where cannabis was believed to have contributed to an admission to an emergency department at a hospital for a cardiovascular or related medical event, or was believed to have contributed to, or caused, the death. In addition, epidemiology studies were included if they were designed to investigate if any link exists for cannabis use and cardiovascular disease.

3. Pharmacology of Δ^9-tetrahydrocannabinol

The principal active component of cannabis is Δ^9-tetrahydrocannabinol (THC), a substance that has high binding affinity to the CB_1 and CB_2 receptors, although it only appears to act as a partial agonist compared to many of the synthetic cannabinoids. For THC the Inhibitory Constant (Ki) on these receptors varies from 5 to 80 nM and 1.7 to 75 nM, respectively, depending on the conditions and source of receptors with an average around 20–40 nM for both receptor subtypes [12,13]. CB_1 receptors are found in pre- and post-synaptic neurons of the central nervous system (CNS) such as motor systems, motor cortex, basal ganglia, cerebellum, hypothalamus and spinal cord as well as heart, lungs, liver and kidneys, and are involved in modulating appetite, mood, sedation, spasticity and the sensation to pain, whereas the CB_2 receptor is mainly localized in cells associated with the immune system and respond to inflammatory conditions [12].

The effects on the heart and wider cardiovascular system are complex. CB_1 activation leads to centrally-mediated sympathetic stimulation often causing marked increases in heart rate and cardiac output. The smoking of one to three cannabis joints led to significant increases in heart rate, sometimes up to 50% increase, and a modest increase in cardiac output, although this diminished with repeated use as a result of tolerance becoming established [31]. The effect of cannabis on blood pressure is less predictable with some persons showing increases and others show small decreases possibly since it is known to lower peripheral resistance. Recently it has been shown that there is a modest association between recent cannabis use and systolic blood pressure [32]. THC is well known to cause postural hypotension manifesting in syncope or near-syncope [33].

THC can cause sinus tachycardia and premature ventricular beats; it lowers the threshold for angina, induces others of arrhythmias and is believed to be associated with some acute myocardial infarcts [15].

THC also causes vasoconstriction of cerebral vessels and has been associated with ischemic stroke [34,35] as well as arteritis associated with regular use of high doses of cannabis and progressive ischemia of the limbs [36,37]. A host of other effects to THC is also known to cause bronchodilatation and as an antipruritic and antioxidant, amongst others [12].

4. Pharmacology of other cannabinoids, and phytochemicals

The cannabis plant contains a host of other active compounds that modify the effects of the plant extract and include other cannabinoids, terpenes and terpenoids.

While a number of cannabinoids have been identified the main one that is known to modify the response to THC is cannabidiol (CBD) whose content varies substantially from one variety to another (chemovars) [38]. While CBD has low affinity for CB receptors it appears to antagonize CB_1 at low concentrations in the presence of THC by acting as a non-competitive negative allosteric modulator at CB_1 receptors [39]. It is also possesses anti-anxiety actions, anti-psychotic effects, and even modulates metabolism of THC by blocking its conversion to the more psychoactive 11-hydroxy-THC [40,41]. Indeed, CBD is also a potent inhibitor of

Table 1
Summary of selected publications associated with non-fatal medical presentations with cardiovascular dysfunction following cannabis use.

No.	Reference	Age/sex	Drug history/toxicology	Medical presentation, and/or diagnosis
1	Charles et al. [29]	25 y.o. male	Healthy, occasional user, similar previous episodes	AMI and pulmonary edema following a cannabis cigarette; coronary arteries normal.
2	Akins & Awdeh [86]	21 y.o. male	User of cannabis, last used previous evening	Admitted to ED for syncope, severe sinus bradycardia, 2nd degree AV block, HR 48, BP 135/100 (supine), BP 128/100 (standing)
3	Collins et al. [30]	33 y.o. female	Cannabinoids screen positive (urine)	Admitted for severe chest pain; started whilst smoking cannabis at a party; only used cannabis 3 times in 3 years, but smoked tobacco regularly; HR 96, ST elevation and ventricular fibrillation followed by heart block and mild AMI; normal coronary arteries.
4	Kosior et al. [87]	24 y.o. female	Collapsed several minutes after smoking cannabis	Admitted for first ever paroxysmal atrial fibrillation, vomiting, nausea and brief loss of consciousness, HR 140; K 3.4 mM, no structural defects or disease in heart
5	Mouzak et al. [88]	3 male cases (ages 18, 26, 30 years)	All heavy cannabis smokers	All presented with transient ischemic attacks — 2 at least shortly after cannabis use; no heart disease detected.
6	Caldicott et al. [89]	21 y.o. male	No history of drug use; had drunk excessive alcohol and had one cone cannabis night before; urine cannabinoids positive	Admitted to hospital feeling unwell with nausea and vomiting and chest discomfort with left shoulder pain; two clots detected in his left anterior descending coronary artery and delayed raised CK. Diagnosis thrombus formation
7	Fisher et al. [90]	35 y.o. female	Infrequent use of cannabis; urine positive for cannabinoids	While in hospital to treat headaches and hypertension smoked cannabis and 20-30 min later developed palpitations, chest pain and shortness of breath; very high BP and HR — atrial flutter with 2:1 atrioventricular block.
8	Lindsay et al. [91]	Case 1: 48 y.o. male	Case 1: Cannabis user	Case 1: developed chest pain often after smoking cannabis; most recent cardiac arrest requiring insertion of stent to previous coronary grafts.
		Case 2: 22 y.o. male	Case 2: recent high dose Skunk	Case 2: central chest pain and shortness of breath immediately after smoking cannabis; ST elevation, AMI confirmed by raised CK, troponins; atheromatous plaque.
9	Sürder et al. [92]	26 y.o. male	Cannabis user	Presented with acute ST-segment elevation MI; large thrombus in LAD artery, but no atherosclerosis
10	Kotsalou et al. [93]	53 y.o. male	Cannabis use for 35 years	Presented with angina, AMI confirmed but no coronary artery disease.
11	Dwivedi et al. [94]	Case 1: 23 y.o. male	Case 1: cannabis smoker, not tobacco currently.	Case 1: left-sided chest pain for 3 days treated hypertensive; ST segment flattening/depression and T-wave inversion; acute coronary syndrome.
		Case 2: 50 y.o. male	Case 2: regular cannabis and tobacco smoker. No cannabinoid tests.	Case 2: acute onset severe retrosternal chest pain, sweating, vomiting on admission; ST segment elevation, raised CK; AMI diagnosed.
12	Sattout & Nicol [95]	15 y.o. male	Drug use; urine screen positive for cannabinoids	Witnessed cardiac arrest following use of cannabis and alcohol; initially asystole then ventricular fibrillation and GCS 4; no sequelae after drug cleared body.
13	Bailly et al. [96]	36 y.o. female	Heavy cannabis user, 10 joints daily for 20 years but changed dealer – stronger cannabis? no toxicology performed	Admitted for severe central chest pain radiating to jaw and both arms; HR 66, BP 119/75; elevated CK, Troponin levels; massive occlusion of anterior interventricular artery, major anterograde dissection left main artery and left circumflex artery; no other heart disease; possible vasospasm
14	Duchene et al. [97]	45 y.o. female	Heavy cannabis use	Right carotid and middle cerebral artery thrombosis and stroke, and AMI, linked to cannabis use.
15	Leblanc et al. [98]	26 y.o. male	Cannabis and tobacco use; urine cannabinoids 168 ng/mL	Minor recurrent stroke following AMI and left ventricular thrombus and no coronary artery disease and recent cannabis use
16	Arora et al. [99]	37. y.o. male	Cannabis user, urine cannabinoids positive	Chest pain and sweating developed immediately after cannabis joint; HR 102, elevated CK, troponin, AMI but no coronary artery disease; non-smoker but had used Viagra 36 h earlier.
17	Yurtdaş & Aydin [100]	26 y.o. male	Used 2 h previously; cannabis twice-weekly 8 years;	Admitted for chest pain (2 h); total occlusion of proximal portion of RCA with large thrombus elevated creatine kinase & troponin T.
18	Pratap et al. [101]	19 y.o. male	Cannabis user; urine positive to cannabinoids only	Admitted to ED after a 5 min episode of syncope, 1 h after a large measure of cannabis inhalation; HR 96, BP 110/70, incomplete right bundle block with 3 mm elevation in leads V1, V2; Brugada syndrome
19	Renard et al. [102]	33 y.o. male	Heavy cannabis user for 15 y; recently 20-25 joints daily; also tobacco smoker; urine positive	AMI causing cardioembolic stroke; presented with hemiparesis and dysarthria with earlier chest pain; elevated troponin.
20	Romero-Puche et al. [103]	42 y.o. male	Regular cannabis user	Three ED presentations for palpitations shortly after using cannabis; frequent premature ventricular beats; diagnosed with Brugada syndrome following cannabis use.
21	Safaa et al. [104]	40(s) y.o. male	Cannabis user; frequency unknown; no toxicology testing	Chest pain within 1 h of smoking cannabis; HR 78, BP 110/69, treated hypertensive with Hashimoto disease; normal coronary arteries and normal heart function, mild ventricular hypertrophy, small elevation in troponin; presented with same symptoms one month later shortly after smoking cannabis, new ST/T wave changes in V3/V4 leads, rise in troponin; possible vasospasm
22	Deharo et al. [105]	24 y.o. male	Massive cannabis user (10 sticks daily) over 12 y; with tobacco	Chest pain for 4 h during football match; thrombotic occlusion of right coronary artery but no atherosclerosis; aspiration treatment with antithrombotic drugs.
23	Menahem [106]	21 y.o. male	25–35 bongs daily mixed with tobacco	Regular dizzy spells during periods of inhalation and occasional brief loss of consciousness; Holter monitoring showed sinus or sinus arrhythmia with regular cardiac asytole and absence of P-waves which stopped when cannabis use stopped.
24	Casier et al. [51]	Case 2: 23 y.o. male	Chronic cannabis user; urine screen positive	Collapsed at home; admission led to diagnosis of total occlusion of both ostial LAD and proximal RCA, high troponin levels — 2 months after discharge had heart transplant.
25	Hodcroft et al. [107]	21 y.o. male	Regular cannabis smoker, tobacco	Left-sided chest pain after a soccer game; attributed to recurrent cannabis-associated MI without coronary artery disease.

Table 1 (*Continued*)

No.	Reference	Age/sex	Drug history/toxicology	Medical presentation, and/or diagnosis
26	Gunawardena et al. [108]	29 y.o. male	Smoked potent form cannabis 4 h earlier; LSD 2 days earlier; smoked tobacco	Admitted to ED with retrosternal chest pain; ST segment elevation and mild increase in Troponin; diagnosed with acute coronary syndrome.
27	Velibey et al. [109]	27 y.o. male	heavy cannabis use (4 times a week)	Presented with chest pain for 5 h; sinus bradycardia with poor R-wave progression, serum markers elevated, total occlusion of LMCA with retrograde perfusion of left ventricle requiring bypass graft surgery.
28	Alonso & Teo [110]	19 y.o. male	Cannabis user	Hx palpitations and dizzy after cannabis; ECG changes consistent with Brugada syndrome.
29	Shah et al. [111]	24 y.o. male	Regular marijuana use and recently use of synthetic cannabinoid within past week	Presented to ED with nocturnal sub-sternal chest pain; 70% calcified lesion in proximal LAD artery, thrombus formation and MI
30	Tournebize et al. [112]	15. y.o. male	Started use of cannabis 8 months previously	Admitted to ED with severe chest pain; diagnosis of acute myocarditis attributed to cannabis use; viral etiology excluded.
31	Brancheau et al. [113]	28 y.o. male	Self-reported cannabis use; frequency unknown	Syncope regularly associated with use of cannabis; diagnosed as vasovagal syncope following admission to hospital after a minor traffic crash caused by an episode of syncope.

Publications are ordered by publication date. AMI = acute myocardial infarction, B = blood, BP = blood pressure, CK = creatine kinase, COD = cause of death, CPR = cardiopulmonary resuscitation, ECG = electrocardiograph, ED = emergency departments (hospitals), GCS = Glasgow Coma Scale, CPR = cardiopulmonary resuscitation, HR = heart rate, Hx = history, LAD = left anterior descending (artery); LMCA = left main coronary artery, RCA = right coronary artery, y.o. = year old.

many of the CYP450 isozymes, more so than THC itself, and when present in sufficient amounts could influence clearance of not only cannabinoids, but also other co-administered drugs metabolized by this pathway. CBD also reduces the effect of THC on a number of cytokines that are involved in inflammatory responses [42].

When CBD is present with THC it reduces some of the adverse effects of cannabis such as anxiety, sedation and tachycardia and is beneficial for the treatment of at least some forms of epilepsy and pain [42–44]. This has led to the use of Sativex® (Nabiximols), which is a 1:1 combination of THC and CBD, a pharmaceutical used to treat neuropathic pain, spasticity, overactive bladder, and other symptoms of multiple sclerosis [43,44].

CBD does reach measurable concentrations in humans if present in cannabis preparations, hence, if present, it is likely to modify the effects of THC. As for THC, blood concentrations following oral use of CBD are also very low and usually below 5 ng/mL [45]. When CBD (20 mg) was taken by volunteers in a deuterated form the Cmax following smoked or intravenous administrations were 110 and 686 ng/mL, respectively, with apparent half-lives of 31 and 24 h and a bioavailability of about 30% [46]. In another study involving one person (37 y.o. female) who had smoked 47 mg CBD in a joint gave peak blood concentrations of about 50 ng/mL, which then reduced quickly as seen previously for THC and showed no accumulation after 10 days of twice-daily use [47]. High dose Sativex only produced peak plasma concentrations of 2–20 ng/mL (mean 6.7) after 15 mg CBD following oromucosal use in volunteers [48].

In addition a number of terpenes and terpenoids are present in the cannabis plant that are active biologically and in combination with the cannabinoids appear to modify the overall physiological responses to marijuana [49]. The most abundant and active biologically are the caryophyllenes, D-limonene, linalool, myrcene, and α-pinene, although these and many others are also present in varying quantities and proportions [12,38]. Sativex one of the formulations available for oromucosal use also contains 6–7% terpenes and terpenoids [40].

5. Cannabis associated hospital admissions: case reports

There are numerous reports outlining admissions to hospital emergency departments (ED) associated with some form of cardiovascular crisis associated temporally with cannabis use. Thirty-one of these case reports are summarized in Table 1. In most cases there was only a limited history of prior cannabis use available but all had cardiovascular episodes during or not long after use of cannabis. Not all had their cannabis use confirmed by a drug test and when this was done it was usually based on urinary cannabinoids. Other drugs were excluded as best as possible either from their history or from a drug test. Conditions and diseases not mentioned were generally excluded as part of the clinical management in hospitals.

These reports comprised 35 individuals with ages ranging from 15 to 53 years old and with a median age of 25 years. Five of these were female whose ages ranged from 24 to 45 years old and median of 33 years.

Most of these had one or more symptoms of chest pain associated with angina, arrhythmias, thrombus in a coronary artery and even diagnosed acute myocardial infarction (AMI), and some even had minor strokes. However, 24 of the cases had no evidence of coronary artery disease; rather they experienced a vasospasm and/or arrhythmia seemingly triggered by recent use of cannabis. Eighteen had an AMI confirmed by a rise in creatine kinase and/or troponins. No other drugs were implicated as a cause of the admission.

There were 5 cases of stroke or transient ischemic attack secondary to a cardiovascular event, three cases of possible Brugada's syndrome and one of myocarditis linked to recent cannabis use.

6. Cannabis associated fatalities: case reports

Six case reports have been published linking recent use of cannabis with sudden death [50–55]. These reports are summarized in Table 2.

The reports relate to 13 individuals with ages ranging from 17 to 52 years (median 37, all male) presented in 6 publications. In eight of these cases some degree of significant coronary atherosclerosis was noted and/or other pathology, three with superimposed thrombus and two with enlarged hearts and at least three were diagnosed as suffering from an AMI.

Five of these cases (all males) had little or obvious pathology with ages ranging from 17 to 42 years old (mean 31). Two had mild narrowing of a coronary artery, one had slight enlargement of the heart, one with histological evidence of single cell necrosis, and one had mild to moderate evidence of a fatty liver with an organizing thrombus that might be secondary to cannabis associated toxicity. One of these had a prior history of epilepsy but no evidence of recent seizures but had collapsed after smoking a cannabis joint. In this case rhythm disturbance was suggested but not confirmed and if it occurred it may have been secondary to cannabis associated toxicity. In all of these cases the authors believed cannabis use was a significant contributor to their deaths.

Table 2
Summary of selected publications relating to deaths associated with cannabis use.

Reference	Age/sex	Drug history/toxicology results	Brief circumstances, autopsy results (if conducted) and/or cause of death/finding
Bachs & Morland [50]	Six deaths attributed to cannabis (males, aged 17-43 years)	Case 1: THC (B) 22 ng/mL	Case 1: 39 y.o. found dead in living room; Hx recent shoulder pain; autopsy recent MI, heart hypertrophy, widespread coronary artery disease.
		Case 2: THC (B) 4 ng/mL	Case 2: 40 y.o. dead in car following minor crash, mild narrowing of left coronary artery.
		Case 3: THC (B) 2 ng/mL	Case 3: 43 y.o. Hx of MI but not drug use; widespread coronary artery disease and earlier MI.
		Case 4: THC (B) 5 ng/ml (BAC 0.04%)	Case 4: 37 y.o. found dead; widespread coronary artery disease and emphysema.
		Case 5: THC (B) 3 ng/mL	Case 5: 17 y.o. found dead in bed. Hx drug use. Slight enlargement of heart only.
		Case 6: THC (B) 7 ng/mL	Case 6: 42 y.o. died suddenly in hotel. CPR unsuccessful. Mild coronary artery disease
Tormey [55]	37 y.o. male	Cannabis user for pain; urine cannabinoid positive, no THC in B	Chest pains, dizziness and immediately collapsed and died at home; Autopsy showed fresh organizing thrombus in LAD artery and mild chronic inflammation, mild to moderate steatosis in liver and chronic inactive gastritis. Coroner found that cannabis was a secondary COD.
Casier et al. [51]	Case 1: 52 y.o. male	Case 1: Hx alcohol abuse and cannabis user;	Case 1: Collapsed 2 h after a joint; admission with asystole and poor left ventricular function and vasospasm; 3 days later developed fatal ventricular tachycardia.
	Case 3: 28 y.o. male	Case 3: occasional cannabis	Case 3: Athletic man collapsed at home; admission led to diagnosis of occlusion of proximal LAD and intermediary artery and RCA stenosis; high Troponin. Patient died few days alter from multiple organ failure
		Urine screens positive for cannabinoids	
Hartung et al. [52]	1: 23 y.o. male	1: THC (B) 5.2 ng/mL	Case 1: apparent healthy and suddenly collapsed using public transport and died 40 min later despite attempts at resuscitation; autopsy showed congestion of organs, mild atherosclerosis, cardiac hypertrophy and thrombus formation in a small vessel; marijuana in his pockets.
	2: 28 y.o. male	2: Hx substance abuse 2 years earlier, recent use of cannabis THC (B) 1.9 ng/mL	Case 2: found dead at home with recent evidence of cannabis use; internal organs congested, histopathological signs of single cell necrosis in the heart and negative immunohistochemical reaction with C5b-9 antibody, but there here were no signs of an infectious disease; death attributed to cannabis inducing acute ischemia in heart.
Dines et al. [53]	18 y.o. male	Self-reported cannabis use	Death with one-year history of epilepsy but seizure free without medication and recent migraine and collapsed while smoking cannabis; on admission high BP, HR, respiratory rate with asytole; urine confirmed cannabis use; possible death from rhythm disturbance. No autopsy was performed.
Orsini et al. [54]	40 y.o. male	Use of recreational drugs; urine screen only positive for cannabinoids; BAC 0.119%	Admission to ED following a cardiac arrest and defibrillation; eventually brain dead and autopsy showed acute anterior, lateral, septal, and posterior wall MI with a mural thrombus in the left ventricle as well as hypertensive and atherosclerotic heart disease; authors suggested possible link to cannabis use.

Publications are ordered by publication date. *Abbreviations*: MI = myocardial infarction, B = blood, COD = cause of death, CPR = cardiopulmonary resuscitation, HR = heart rate, Hx = history, LAD = left anterior descending (artery); RCA = right coronary artery, THC = Δ^9-tetrahydrocannabinol, y.o. = year old.

One case (a 28 y.o. male) had no atherosclerosis or cardiomegaly but appeared to have died from an acute ischemic event [52] as there was no histopathological evidence of cellular necrosis in the heart.

Eight of these deaths had a positive THC concentration in blood ranging from 2 to 22 ng/mL (median 4 ng/mL); four were positive to urinary cannabinoids and in only one case no measurement for cannabinoids was conducted. However, in all cases recent use of cannabis was regarded as the trigger for the heart failure and no other drugs were implicated.

7. Wider-scale clinical and/or epidemiological studies

Twelve epidemiological studies were located that investigated possible links of cannabis use and various forms of cardiovascular disease [53,56–66]. These are summarized in Table 3.

Eleven of these either described trends to increased mortality or showed significant associations to increased risk.

Interestingly, but not surprising given the short duration of action of smoked cannabis the risk of myocardial infarction (MI) in cannabis users was 4.8 times (95% CI 2.9–9.5) greater than baseline in the hour after use of cannabis in patients [57]. In the second hour after smoking the risk decreased to 1.7 times. Obvious confounding variables and risks, including tobacco and some other illicit drugs were excluded, however toxicological analysis was not conducted on these patients to definitively prove that the blood was positive for THC at the time of MI [57].

However a review of over 2 million hospitalized patients with acute myocardial infarction in the USA found no increase in overall mortality with cannabis use but found significant increases in prevalence of respiratory failure, cerebrovascular disease, cardiogenic shock, septicemia and dysrhythmia. The prevalence of mortality from AMI in cannabis users had risen to 63 per 100,000 in 2014 with an annual prevalence of AMI of 1650 in that year [63].

A systematic review of published literature found an association between exposure to cannabis-based products and cardiovascular disease, with the evidence stronger for ischemic strokes than for any other cardiovascular diseases [67]. The review included 81 case reports (involving 116 mostly male persons with a mean age range of 31 years), 29 observational studies, 3 clinical trials, and 2 experimental studies.

In contrast, another systematic review of clinical studies investigating cardiovascular risk factors and their possible association with use of cannabis found no compelling evidence to link use of this drug with any mortality, including AMI or other forms of cardiovascular disease [68]. While some studies did find an increased risk [58,59] this could not replicated [64]. According to the authors, these three studies and others had significant limitations that could have affected any conclusions made.

8. Discussion

Cannabis is a complex mixture of a variety of cannabinoids in which THC and CBD appear to be the main active components, although in variable amounts and proportions from one variety to another with essentially no consistency over content, other than a few limited medicinal products. The activity of cannabis products is also likely to be further influenced by the presence of various

Table 3
Summary of epidemiology studies examining cannabis use and any associations with cardiovascular disease.

Reference	Study design and summary	Results	Comments
Petronis & Anthony [56]	Results of interviews to 6702 household residents in National Institute of Mental Health epidemiological catchment area, aged 18-44 y.o., soon after sampling and 1 year later; occurrence of palpitations and any drug use was questioned.	Estimated adjusted relative risk for daily cannabis users was 2.24 (95% CI 1555-3.25, P < 0.0001). RR for cocaine users was highest at 3.4.	Unknown if drug use preceded palpitations or not; other confounders were possible.
Mittleman et al. [57]	Case-crossover study design. Results of interview of 3882 patients (1258 women) within 4 days of admission to hospital across 64 centers for AMI (August 1989-September 1996); use of smoked cannabis in hour preceding infarction, medial Hx including medications and obvious possible risk factors such as obesity, tobacco smoking, hypertension.	Risk of AMI within 1 and 2 h of smoking cannabis was 4.8 fold (95% CI 2.9-9.5) and 1.7 (95% CI 0.6-5.1), respectively.	Limitations included self-reported use of cannabis, AMI caused by other factors including co-morbid heart disease or other triggers.
Mukamal et al. [58]	Inception cohort study of mortality of 1913 patients hospitalized for MI across 45 centers (1989-1994) for self-reported cannabis use in year prior to death.	Hazard ratio for weekly use of cannabis was 4.2 (95%CI 1.2-14) compared to 2.5 (95%CI 0.9-7.3) for use less than weekly suggesting increased mortality in patients with prior myocardial infarction.	Limitations included self-reported use of cannabis; presence of other risks predisposing to death.
Frost et al. [59]	Multicenter "Determinants of MI Onset Study" utilizing data from 64 centers in USA involving follow-up interview of hospitalized MI patients enrolled in 1989-1996 using National Death Index.	3886 patients were followed up for 18 years with 519 deaths of whom 22 reported cannabis use in year prior to their death. Mortality rate was 29% higher in cannabis users, but this was not significant.	A detail of cannabis use was not able to be determined. Study cannot rule out unmeasured or residual confounding including details of treatments and any secondary prevention measures that changed over time. Insufficient power.
Jouanjus et al. [60]	Assessment of reports to French Addictovigilance Network (2006-10) for cardiovascular complications associated with hospital admissions and recent cannabis use.	35 (1.8%) of all cannabis-related notifications were cardiovascular in nature; 20 were acute coronary syndromes, 10 had peripheral complications, 3 cerebral and 9 died.	Reliability of reporting possible drug-induced admissions let alone cause and presence of other morbidities.
Dines et al. [53]	356 of cannabis-related presentations of 2198 admissions to 14 European hospital networks in 10 countries (Euro-DEN) from October 2013 to March 2014.[a]	16.2% involved cannabis (alone or with other drugs); 36 cannabis alone, of which 35 presented with agitation/aggression (23%), psychoses (20%), anxiety (20%) & vomiting (17%). Three had chest pain & 3 had palpitations. One death occurred from asystolic cardiac arrest.	
Rumalla et al. [61]	Nationwide Inpatient Sample database (2004-11) queried for all admissions (ages 15-54) with AIS and if cannabis had been used recently.	Adjusted RR 1.17 (95%CI 1.15-1.20) for cannabis users compared to non-users; adjusted for confounders (age, sex, race, tobacco, other drugs).	Doses and frequency of drug use could not be determined; not able to assess if a temporal relationship existed.
Draz et al. [62]	Cross-sectional study on 138 hospital admissions (aged <41 y.o.) with AMI. All had Hx taken, clinical examination, ECG, and urine testing conducted for cannabis use and other drugs.	Cannabis-only patients (Group 1) showed high incidence of cardiac diseases including evidence of infarction compared to patients negative for drug use.	Tobacco smoking had a high incidence in this cohort; reliance on urine cannabinoids.
Desai et al. [63]	Use of National Inpatient Sample database of 11-70 y.o. AMI patients (USA) for any association between use of cannabis and AMI.	Multivariable analysis of 2.45 million admissions showed cannabis use a significant risk factor for AMI when adjusted for age, sex, race and other drug use. A number of co-morbidities were associated with cannabis use, incl. cardiomyopathy, previous myocardial infarction, CAD, chronic pulmonary disease etc.	Neither recent nor amount of cannabis use was able to be determined, only lifetime use of cannabis and other drugs.
Reis et al. [64]	Adults (aged 18 to 30 y.o.) were followed for more than 25 years as part of a coronary artery risk development study in young adults (CARDIA study). Cumulative lifetime exposure to marijuana was evaluated using repeated assessments collected at examinations every 2 to 5 years. The primary outcome was incident CVD. Alcohol, tobacco and other drug use was assessed.	84% of 5113 adults reported cannabis use of which there 104 CAD and 50 CVD deaths; compared with no marijuana use, cumulative lifetime and recent marijuana use showed no association with CVD mortality when stratified by age, gender, race, or family history.	Reliance on self-reports of cannabis use and adverse medical outcomes; few recent cannabis users.
Lee et al. [65]	Prospective chart review of patients with ST-elevation AMI that are non-users and users of cannabis at a single, urban hospital.	Cannabis users tended to have less angiographic evidence atherosclerosis and lesser number of cardiovascular risk factors than non-users and tended to be younger in age.	Only 10 cannabis users in study. Urine toxicology used to determine cannabis use.
DeFilippis et al. [66]	Retrospective study of patients that presented with type 1 MI at <51 y.o. from 2000-16 in 2 centers in Boston, MA; medical Hx assessed from electronic patient records and death certificates; tobacco and drug use included including toxicology screen in some cases. Focus was on cannabis and cocaine use.	Cannabis use was identified in 6.0% of 2097 cases and was associated with higher cardiovascular mortality (adjusted hazard ratio 2.22, 90%CI 1.27-3.70).	Retrospective study design and degree of substance use including other drugs and lifestyle differences with control group.

AIS = acute ischemic stroke; AMI = acute myocardial infarction; CAD coronary artery disease; CVD = cardiovascular disease; h = hours; Hx = history; y.o. year old; 95%CI 95% confidence intervals; MI = myocardial infarction; RR = relative risk.

[a] Euro-DEN = European drug emergencies network.

terpenes and the related terpenoids, which vary significantly in content and type from one product to another.

Nevertheless, THC exerts significant effects which are often manifested as significant increases in heart rate and cardiac output, particularly in novice or occasional users who have not developed significant tolerance to the drug. This is believed to occur primarily by activation of the CB_1 receptor resulting in an increased sympathetic tone and reduced parasympathetic activity. This in turn can lead to sinus tachycardia and others forms of arrhythmias, thrombosis and even myocardial infarctions. While these outcomes may be more likely in persons with preexisting compromised cardiovascular function case reports summarized here outline numerous instances of cases admitted to emergency departments, or of those who have even died, without evidence of significant heart disease.

This is further exemplified by a study of 10 non-cannabis users who had stable exercise-induced angina who smoked one cannabis joint and had significantly decreased exercise performance associated with earlier onset angina [69]. A decrease in exercise performance as a consequence of cannabis use occurs in otherwise fit and healthy persons [70].

Cerebrovascular events have also been linked to cannabis use [35,71,72]. Some of these are included in this publication (see Table 1) particularly where a thrombus that has originated from the heart has led to a stroke.

Furthermore, well over 50 reports of arteritis associated with long-term heavy cannabis consumption have been published, with many victims requiring amputation of one or more limbs and many quite young without other likely causes of this disease [37,73,74].

In addition, some deaths have been also attributed to cannabinoid hyperemesis syndrome [75–78].

However, as seen in the larger scale retrospective studies and the systematic reviews the evidence for a link between cannabis use and increased risk of cardiovascular death is not clear. Anyone of the symptoms and cardiovascular diseases mentioned earlier could have arisen for other reasons including in the setting of rhythm disturbance and arrest, and previous undiagnosed channelopathies. People have arrhythmias and heart attacks that do not use cannabis, or indeed other drugs, and most cannabis users are likely also to have smoked tobacco for much of their lives, which is another significant risk factor for premature cardiovascular disease [79]. Nevertheless, the absence of significant associations or significant causal links from retrospective epidemiological studies could still be explained by an adverse effect caused by cannabis use in a relatively small number of persons, acting in concert with other morbidities. Clearly, given the widespread use of the drug by tens of thousands of users worldwide the risk of these forms of adverse medical outcomes is probably rare, but nevertheless at least in theory, it can occur. Ideally the presence of cannabis in these cases (as THC) should be recorded in death statistics such as not to underestimate cannabis-associated mortality.

There are many other corollaries in forensic medicine where a cause of death from a drug is inferred based on exclusion of other likely and relevant causes. In most cases of a death caused by a drug where there is no clear evidence from the scene of drug misuse or drug-related self-harm pathologists need to ensure that there is no other reasonable or competing explanations for the death (e. significant natural disease, injuries etc.), and that (1) the drug(s) is capable of causing death (that is to say the mechanism for its potential toxicity is understood), (2) the drug(s) is present at a concentration capable of doing so, and (3) it is not inconsistent with the context (circumstances, medical history etc.) of the case.

In the case of a sudden or unexpected death and the absence of significant injuries where toxicology confirms presence of THC in blood it may not be unreasonable to include cannabis in the cause (or part cause), particularly if no other significant drugs that can cause death are present and given the understanding of the physiological effects of the drug and the particular distribution of cannabinoid receptors.

Tormey discusses the attribution to cannabis and some cases of sudden death associated with natural disease of the heart in Northern Ireland but advised that while cannabis could be contributory it can only be seen to contribute to death providing it was used within 2 h of the cardiorespiratory arrest and ideally with confirmation of THC in blood [80]. This is consistent with most of the case reports where cannabis was used quite recently. It even applies to the increasing number of deaths from synthetic cannabinoids.

Most of the cases and series reporting a possible link between cannabis use and a cardiovascular event have not had a blood measurement positive for THC, let alone other cannabinoids, largely because this resource may not have been available in hospitals. This would not normally be an issue for deaths reported to coroners and similar death investigation systems where post-mortem toxicology is available. Clearly, if a death is to be associated with the recent use of cannabis a blood test for THC is required to establish this, rather than reliance on the presence of urine cannabinoids, or information from the history alone.

Given the inevitable delays from death to sampling on admission to a mortuary or at autopsy it may not be possible to provide minimum concentrations of THC in blood that might be regarded as being a cause. Many if not most forensic toxicology laboratories can detect 1–2 ng/mL of THC in post-mortem blood, and indeed anything lower could most likely represent use from days earlier. If THC quantification has occurred and the case fits into the criteria outlined earlier then this could arguably be sufficient to include THC (cannabis) as a causal or contributory factor in the death. Circumstances that indicate recent use of cannabis and collapse would greatly assist in making this link.

It is also conceivable that any toxicity associated with cannabis will be affected by other cannabinoids present, such as in particular CBD which can antagonize CB_1 receptors at low concentration and in the presence of THC [12]. The measurement of blood CBD concentrations in conjunction with THC may provide further insights into the degree of cannabis use and any associated toxicity.

The CBD content of street cannabis is generally quite low when it is measured. For Example, in Australia an analysis of over 200 confiscated cannabis samples and an analysis of 26 samples of known provenance showed THC and CBD contents (with their respective acid precursors) averaging at 15% and 0.14%, respectively [81]. In the UK most of the cannabis contains little CBD, particularly sinsemilla [82], while in the USA content of chemotype I is similar although chemotypes II and III flowers do contain significant CBD [83]. It is entirely possible that street-sourced cannabis that contains higher relative amounts of CDB to THC may be safer than those products that have a zero or low CBD relative content, however this is yet to be determined since few forensic laboratories also measure CBD in blood toxicology. Oral use of cannabis products are also likely to be safer given the much lower blood concentrations of THC that are obtained due to the low oral bioavailability.

Of course in any assessment of a possible drug caused death the involvement of other possible co-morbidities is required, including use of alcohol, amphetamines and cocaine [84].

In conclusion, evidence is presented that use of cannabis can lead to serious adverse health outcomes, other than drug dependency, drug-impaired driving and acute psychoses, and even has the potential to contribute or cause sudden death. It is argued that the inclusion of cannabis as a cause or contributor to death in appropriate cases is to be encouraged and will allow estimates of the global burden of disease from drugs to more accurately reflect harm associated with this drug [85].

Declaration

The authors declare that this manuscript has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Acknowledgments

The author would like to acknowledge the Victorian Institute of Forensic Medicine and the Department of Forensic Medicine at Monash University for their support, in particular Professor Stephen Cordner for his helpful advice.

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