The Prevalence of Cannabis-related Arrhythmias in Patients with Cancer: Real-world Data Evidence of Patient-reported Outcomes

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ABSTRACT **Background:** Cannabis consumption is suspected of causing arrhythmias and potentially sudden death.

Objectives: To investigate prevalence and temporal relationships between cannabis use and onset of symptomatic arrhythmias among cancer patients using Belong.life, a digital patient powered network application.

Methods: Real-world data (RWD) were obtained through Belong.Life, a mobile application for cancer patients who use cannabis routinely. Patients replied anonymously and voluntarily to a survey describing their demographics, medical history, and cannabis use.

Results: In total, 354 cancer patients (77% female, 71% 50–69 years of age) replied: 33% were smokers and 49% had no co-morbidities. Fifteen had history of arrhythmias and two had a pacemaker; 64% started cannabis before or during chemotherapy and 18% had no chemotherapy. Cannabis indication was symptom relief in most patients. The mode of administration included oil, smoking, or edibles; only 35% were prescribed by a doctor. Cannabis type was delta 9-tetrahydrocannabinol > 15% in 43% and cannabidiol in 31%. After starting cannabis, 24 patients (7%) experienced palpitations; 13 received anti-arrhythmic drugs and 6 received anticoagulation. Eleven needed further medical investigation. Three were hospitalized. One had an ablation after starting cannabis and one stopped cannabis due to palpitations. Seven patients (2%) reported brady-arrhythmias after starting cannabis, but none needed pacemaker implantation.

Conclusions: RWD showed that in cancer patients using cannabis, the rate of reported symptomatic tachy- and brady-arrhythmias was significant (9%) but rarely led to invasive treatments. Although direct causality cannot be proven, temporal relationship between drug use and onset of symptoms suggests a strong association.

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The use of cannabis is increasing worldwide. In recent years there have been concerted efforts in many countries to campaign for its legalization. However, there is rising concern regarding cannabis-related adverse effects. Cannabis consumption has been shown to cause arrhythmia, including ventricular tachycardia and potentially sudden death, and to increase the risk of myocardial infarction (MI) [1]. These effects appear to be compounded by cigarette smoking and precipitated by excessive physical activity, especially during the first few hours after consumption.

In younger patients, without a history of acute coronary syndrome, cannabis use was shown to be associated with an increased risk of ventricular fibrillation (VF), atrial fibrillation (AF), atrial flutter, pre-excited syndromes, and long-QT syndrome [2]. Multiple isolated cases of arrhythmias associated with cannabis use have been published [1-6]. A recent study [3] found 27 cases of arrhythmia associated with cannabis. Most cases were reported in young males (81%) with a mean age of 28 ± 10.6 years. AF (26%) and VF (22%) were the most common arrhythmias reported. Brugada pattern was reported in 19% of the patients. Cannabis-associated arrhythmia resulted in a high mortality rate of 11%. Our group also published a case series of patients with structurally normal hearts and cannabis-related arrhythmias that tended to be multiform regarding their presentation [4]. Although causality concerning cannabis use could not be proven in these cases, the temporal relationship between drug use and the onset of symptoms suggested a strong association.

The American Heart Association stated that cannabis use may be linked to an increased risk of heart attacks, AF, and heart failure. Cannabis use showed substantial risks with no benefits for cardiovascular health. More research is needed [7].

There are multiple cannabis species, each with a differing amount of the two major active ingredients, delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [8]. THC is responsible for the euphoric effects of cannabis, while CBD is often marketed for its anti-inflammatory actions. The synthetic, THC-like dronabinol and nabilone are used as treatments for nausea and vomiting [9] and epilepsy [10]. Medical marijuana has also

been used for the treatment of neuropathic pain associated with cancers and neurological disorders [8].

We investigated the real-world data and patient-reported outcomes regarding the prevalence, temporal relationship between drug use and the onset of symptoms, and type of arrhythmias in cannabis users among Belong.life cancer patients. Belong.life is a digital patient powered network (PPN). We tried to show a causality between the drug and the onset of cardiac arrhythmias.

PATIENTS AND METHODS

Real-world data were obtained through technology paired with mobile devices on worldwide cancer patients who used cannabis routinely. To the best of our knowledge, this application is the world's largest social network for managing and navigating treatments for cancer patients and their caregivers.

The patient population was cancer patients who used cannabis and subscribers of the Belong.life mobile application who were willing to complete a survey and share their information regarding their cannabis use and medical status. Via the Belong.life application (https://web-cancer.belong.life) [11], cancer patients receiving cannabis received a 17-questions-survey. In total, 354 patients replied anonymously to this survey describing their demographics, medical history, and cannabis use. Categorial data were reported as number and percentage of patients.

The study was approved by the investigational review board (ethics committee) of our institution. The review board prohibited uploading patient medical records and electrocardiograms due to data security policies and patient anonymity; thus, the focus of the study was symptoms and patient-reported outcomes.

RESULTS

BASELINE CHARACTERISTICS

The cohort included 354 patients with a diagnosis of cancer who completed the questionnaire. Baseline characteristics are presented in Table 1.

In total, 274 patients (77.4%) were female; 250 were 50–69 years old (70.6%) and 13.3% were 40–49 years; 281 (80.1%) lived in the United States and 50 (14.2%) lived in Israel. Cancer types were mostly breast (35.03%) and lung (9.32%).

In 202 patients, the only reported medical condition was cancer (49.2%). Only 118 patients (33%) were smokers or former smokers. Most smokers (96.6%) smoked for more than 3 years, and 41% smoked more than 20 cigarettes per day. Hypertension was diagnosed in 28%, 16.7% were obese, 13% had diabetes, and 5% had hyperlipidemia.

A background of heart disease was reported in 48 patients (13.6%), 148 (41.7%) reported coronary heart disease, 15 (33.3%) had a background of arrhythmia, 2 (0.6) had a pacemaker, 52 (14.6%) had valvular heart disease, and 44 (12.5%) had a family history of heart disease.

CANNABIS USAGE

In the cohort, 291 patients (82.2%) were treated with chemotherapy. Among them 32.3% used cannabis prior to chemotherapy, 45% during the treatment, and 20.27% post-chemotherapy.

The indication for cannabis was symptom relief in most patients: relief of pain (67%), sleep deprivation (59.8%), anxiety (58.1%), nausea (50.4%), and lack of appetite (43%). Some patients used it for mood changes (27.4%) and others as an anti-cancer drug (4.8%). Respondents indicated other indications as well, such as neuropathy, seizures, weight gain, attention deficit hyperactivity disorder, and fun. Only 35% of patients had cannabis prescribed by a doctor.

Table 1. Baseline characteristics

	Cohort patients, n=354 (%)
Sex (female)	274 (77.4)
Age in years	
30–39	18 (5.1)
40–49	47 (13.3)
50–69	250 (70.6)
≥ 70	39 (11)
Country	
United States	281 (80.1)
Israel	50 (14.2)
United Kingdom	8 (2.3)
Canada	7 (2)
Other	8 (2.3)
Cancer types	
Breast	124 (35)
Lung	33 (9.3)
Ovarian	24 (6.8)
Colon / colorectal	34 (9.6)
Multiple primary	18 (5)
Prostate	17 (4.8)
Multiple myeloma	16 (4.5)
Pancreatic	12 (3.4)
Non-Hodgkin lymphoma	8 (2.3)
Other	68 (19.2)
Co-morbidities	
Smokers/past smokers	118 (33)
Hypertension	100 (28.2)
Obesity	59 (16.7)
Diabetes	47 (13.3)
Hyperlipidemia	18 (5.1)

There were different ways of cannabis usage, and some patients used more than one: oil (52.3%), inhaling smoke (45.8%), edibles (29.1%), vaping (21.2%), pills (5.1%), topicals (2.5%), and suppositories (1.1%).

Cannabis types and concentrations included: THC > 15% in 42.7% of patients, cannabidiol (CBD) in 30.8%, THC < 15% in 23.4%, and various concentrations in 9%; 31.1% did not know the concentration and some used a variety of types and concentrations.

The length of cannabis usage was variable: 36.7% used it for more than 2 years, 19.5% for 1–2 years, 17.5% for 0.5-1 year; and 26.3% used it for less than 6 months.

The most common frequency of use varied; 37.3% took cannabis more than once a day, 37.9% once a day, 10.7% a few times a week, 3.4% once a week, and 10.7% used cannabis less often.

PALPITATIONS AND TACHYARRHYTHMIAS

After beginning cannabis use, 24 patients (6.8% of cannabis users) experienced palpitations. For16 patients, this phenomenon was new. Eight patients (33.3%) had a background of heart disease; 11 (45.8%) needed medical care due to these palpitations. Care included cardiology examination (54.5%), electrocardiography (ECG, 63.6%), 24–48-hour ECG-Holter monitor (72.7%) echocardiography (54.5%), or cardiac MRI (18.2%).

This investigation resulted in further hospitalization of three patients (27.3%) [Table 2]. Of the entire cohort, 22 patients (6.2%) were prescribed medications due to palpitations and/or arrhythmia (4 experienced before). Among them, 12 received rate-control medications, 1 received anti-arrhythmic drugs, 6 received anti-coagulant medications, and 2 patients received treatment for heart failure.

Five patients had an ablation due to arrhythmia [Table 3]. Four of them had the ablation prior to cannabis use and had no palpitations after. However, one patient had arrhythmia after she started cannabis and was referred for ablation treatment.

Only one patient had to stop cannabis use due to palpitations. This female patient was 40–50 years of age with stage 4 glioblastoma. She had started cannabis during chemotherapy for pain, sleep deprivation, and anxiety control. She used cannabis in a vaping form in an unknown concentration, a few times a week for 1 to 2 years. She experienced palpitations after she started cannabis use and was hospitalized for cardiac investigations. She stopped cannabis use and no antiarrhythmic drugs were needed.

SLOW HEART RHYTHM AND CONDUCTION BLOCKS

Of the cohort of 354 patients with cancer who used cannabis, 7 (2%) reported slow heart rhythm and conduction blocks [Table 4]. All were in the age range of 50–69 years and were taking cannabis in a concentration of THC > 15%. However, only three had to undergo further non-invasive examinations. No one was hospitalized due to the slow rhythm, nor had to stop cannabis use, nor to undergo pacemaker implantation.

DISCUSSION

Previous isolated cases of arrhythmias associated with cannabis use have been published [1-6], including a case series of patients with structurally normal hearts and cannabis-related tachy- and brady-arrhythmias that tended to be multiform regarding their presentation [4]. Although causality concerning cannabis use could not be proven in these cases, the temporal relationship between drug use and onset of symptoms suggested a strong association.

In the current study, real-world data and patient reported outcomes were obtained from 354 cancer patients who used cannabis and were members of Belong.life mobile application.

Table 2. Patients with cancer who were hospitalized for palpitations/arrhythmia while using cannabis

	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Female
Age range, years	40–49	50–59	60–69
Cancer type	Glioblastoma	Breast	Multiple myeloma
Background heart disease	No	No	CHF
Background risk factors	DM	No	HTN DM
Relation of cannabis to starting chemotherapy	During chemotherapy	During chemotherapy	During chemotherapy
Palpitations started simultaneously when starting cannabis	Yes	Yes	Yes
Mode of cannabis use	Vaping	Smoking and edibles (gummies)	Smoking
Concentration of cannabis	Unknown	Unknown	Unknown
Frequency of cannabis use	Few times a week for 1–2 years	Once a week for 0.5–1 year	Few times a day for more than 2 years
Cause of hospitalization	To investigate palpitations (including cMRI)	To investigate palpitations (including cMRI)	To investigate palpitations
AAD/rate controls	No	No	No

AAD = antiarrhythmic drugs, CHF = congestive heart failure, cMRI = cardiac magnetic resonance imaging, DM = diabetes mellitus, HTN = hypertension

Table 3. Patients with cancer who used cannabis and underwent ablation for arrhythmias

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Female	Female	Female	Female	Female
Age range, in years	50–59	60–69	60–69	60–69	⩾ 70
Cancer type	Breast	Breast	CLL	Ovarian	Lymphoma, colorectal
Background heart disease	s/p MV repair and PPM	No	No	No	AF, CHF
Background of arrhythmia	Yes	No	Yes	Yes	Yes
Relation of cannabis to starting chemotherapy	No chemotherapy	Started cannabis post-chemotherapy	No chemotherapy	During chemotherapy	During chemotherapy
Relation of palpitations to cannabis start	None*	Palpitations started simultaneously with cannabis use	None*	None*	None*
Mode of cannabis use	Oil	Vaping	Oil and smoking	Smoking	Smoking, vaping and edibles
Concentration of cannabis	Unknown	Unknown	THC > 15%, CBD	Unknown	THC > 15%
Frequency of cannabis use	Once a week for less than 6 months	Few times a day for 1–2 years	Once in 2 weeks for 0.5–1 year	Once daily for less than 6 months	Few times a week for more than 2 years
Type of ablation	For atrial arrhythmia	N/A	N/A	N/A	AF ablation
AAD/rate controls	No	No	BB	No	yes

AAD = antiarrhythmic drugs AF = atrial fibrillation, BB = beta-blockers, CBD = cannabidiol, CHF = congestive heart failure, CLL = chronic lymphocytic leukemia, MV = mitral valve, PPM = permanent pacemaker, THC = tetrahydrocannabinol-Δ9-trans

*Had ablation prior to cannabis use. No palpitations since.

We found that 24 patients (6.8% of cannabis users) experienced palpitations after they began to use cannabis. For 16 this phenomenon was new. Thirteen were treated with rate controls or anti-arrhythmic drugs and 6 received anticoagulation. Eleven (3% of the whole cohort) needed further medical investigation, three (0.8%) were hospitalized due to arrhythmia, and one had to undergo ablation (0.3%). Only one patient (0.3%) had to stop cannabis use due to palpitations. The mode of cannabis use, its concentration, the frequency of use, and the length of use were variable among the group that reported palpitations.

More patients had ablation before the initiation of cannabis (4 of 5), thus providing evidence that cannabis use rarely leads to significant symptomatic arrhythmias that necessitate ablation. Alternatively, it is possible that patients were treated more conservatively due to their basic illness.

Seven patients (2.0%) reported brady-arrhythmias after starting cannabis use; most of them used THC > 15% and at least once daily, but only 3 (0.8% of the whole cohort) had to undergo further non-invasive examinations. No one was hospitalized due to the slow rhythm and none had to stop cannabis use or to undergo pacemaker implantation.

At the time of our research, the usage of cannabis as a recreational drug was increasing worldwide. In recent years there have been concerted efforts in many countries to campaign for its legalization (in our study of cancer patients, only 35% had their cannabis prescribed by a doctor). Cannabis is also prevalent for other medical conditions due to its anti-inflammatory actions, as a treatment for nausea and vomiting [9], for epilepsy [10], and for the treatment of neuropathic pain associated with cancers and neurological disorders [8,12,13]. We showed that despite increasing use of cannabis and complaints of palpitations/arrhythmias/slow rhythm, 9% in our cohort of cancer patients who used the Belong. Life application rarely needed invasive interventions. Perhaps avoiding THC > 15% and decreasing the frequency of use to less than once daily would help. Previous studies reported cardiac arrythmias and palpitations in cannabis use, with the incidence of arrythmias increasing by twofold in users [9]. Heavy cannabis users have a greater risk of developing palpitations compared to lighter users, with daily users having a relative risk of 2.2 (95% confidence interval [95%CI] 1.6–3.3, *P*-value < 0.0001) compared to a relative risk of 1.4 (95%CI 1.1–1.9, *P*-value < 0.006) in occasional users [14]. A retrospective review of almost 2.5 million patients in the National Inpatient Sample database found that 2.7% of cannabis users experienced arrythmias, with atrial fibrillation being the most common subtype [15]. A recent Mendelian randomization study estimated the effects of genetically determined cannabis

Table 4. Patients with cancer who reported slow heart rates while using cannabis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Female	Male	Female	Female	Male	Male	Male
Age range in years	50–59	60–69	50–59	60–69	50–59	60–69	60–69
Cancer type	Breast	Prostate	SCLC	Lung	Colorectal	Multiple myeloma	Prostate
Background heart disease / arrhythmia	Arrhythmia(rare)	Aortic aneurysm and IHD	No	No	No	No	No
Use of chemotherapy	Cannabis post-chemotherapy	No chemotherapy	Cannabis before chemotherapy	No chemotherapy	Simultaneously	Cannabis post-chemotherapy	simultaneously
Relation of palpitations to cannabis start	simultaneously	No palpitations	No palpitations	simultaneously	No palpitations	No palpitations	No palpitations
Mode of cannabis use	Oil	Smoking, oil, and vaping	Oil	Vaping	Oil	Smoking	Oil
Concentration of cannabis	THC > 15%	THC > 15%	THC > 15%	N/A	THC<15%	THC > 15%	THC > 15% and CBD
Frequency of cannabis use	Few times a day for less than 6 months	Few times a day for more than 2 years	Once daily for less than a year	Once daily for less than a year	Once daily for 1–2 years	Once daily for less than a year	Once daily for 1–2 years
Symptoms	Aggravation of palpitations	No	No	Yes	No	Yes	Yes
Need for further investigation, hospitalization, PPM, or discontinue cannabis	No	No	No	Further investigation	No	Further investigation	Further investigation

IHD = ischemic heart disease, SCLC = squamous cell lung cancer, PPM = permanent pacemaker, THC = tetrahydrocannabinol-Δ9-trans, CBD = cannabidiol

use on risk of cardiovascular diseases, using 10 single-nucleotide polymorphisms related to cannabis. After adjusting for tobacco use and body mass index, the multivariate Mendelian randomization analysis suggested a causal effect of cannabis use on the risk of small vessel stroke and atrial fibrillation [16]. Another recent study provided prevalence trends of arrhythmia associated with cannabis use among hospitalized teenagers in the United States from 2003–2016. Prevalence trends of arrhythmias increased six-fold during this period, and there was a significant risk of mortality when cannabis use was associated with arrhythmia [17].

In our cohort, chemotherapy was one of the confounders that induced arrhythmia by itself [18,19]. However, among the patients hospitalized for arrhythmia, despite being treated with chemotherapy when developing palpitations, they all reported that the palpitations started simultaneously when starting cannabis [Table 1]. Similarly, among those with slow heart rates, there was no consistent temporal relationship with chemotherapy use [Table 4].

The arrhythmias reported with cannabis use included sinus tachycardia, ectopic atrial or ventricular rhythm, atrial fibrillation, and ventricular fibrillation. While the exact mechanisms of arrhythmias associated with cannabis are not clear, several hypotheses were introduced, including the effect of cannabis on cardiac ion channels as well as its effects on the central nervous system [1]. Most authors attribute the tachyarrhythmias to a hyperadrenergic state after cannabis use [8,20], through either a direct sympathetic stimulation or as a direct consequence of parasympathetic vasodilatation, also induced by THC [20,21]. It has been reported that cannabis might be the sole precipitating factor for atrial fibrillation in individuals younger than 45 years of age with a recurrence of atrial fibrillation occurring repeatedly after every exposure [8]. Adrenergic stimulation causes a reduction in action potential duration and results in a micro-reentrant tachycardia [22]. Different doses of cannabis affect different cannabinoids receptors. Delta-9-tetrahydrocannabinol (THC) is the active psychotropic component of cannabis, which acts mainly via G-protein and cannabinoid receptors CB1 and CB2. Animal models have shown that activation of CB1 receptors lead to sympathetic inhibition and enhanced vagal tone, bradycardia, and hypotension [23]. Cannabis use has also been implicated in premature ventricular contractions (PVCs), *p-wave and T-wave* changes, and reversible ST-segment changes [21,22,24].

THC was shown to decrease atrial refractory period, the sinoatrial conduction time and atrioventricular conduction time, and it also causes a decrease in the atrioventricular nodal refractory period [17,24]. Others have postulated that PVCs could be related to a slow coronary flow phenomenon in a cannabis user [25].

LIMITATIONS

Our study has several limitations. First, its design as a patient report outcome study has an inherent selection bias by the group of people that chose to answer the questionnaire. However, the real-world data have its strength in being international; in including many types of background cancers and chemotherapies; and in including different types, concentrations, and frequencies of cannabis use; thus, reflecting real-life evidence of the frequency of palpitations/arrhythmias among cannabis users.

A second limitation was the absence of reports regarding ablations and hospital-discharge, as well as the lack of electrocardiogram documentation of arrhythmias (e.g., the three patients from Table 1) due to concerns of patient anonymity. Thus, the study is based on patient reports of symptoms and/or the perception of a medical condition. Feelings of palpitation are not equal to arrhythmia. However, patient reports of real-life consequences of those tachy- and brady-arrhythmias (e.g., hospitalization, ablation, pacemaker implantation) enrich our knowledge regarding the possible effects for cancer patients who use cannabis. The method of using a digital patient powered research network to identify outcomes was used in previous studies and yielded valuable data [11]. Third, it is possible that medical surveillance was tighter after cannabis initiation, thus resulting in higher usage of medical surveillance (e.g., Holters). This care may have led to incidental findings of arrhythmias and may have resulted in higher patient awareness of symptoms. However, only 35% of our study cohort had their cannabis prescribed by a doctor; thus, this concern is relevant to this group only.

CONCLUSIONS

Real-world data from the Belong.life app shows that in cancer patients using cannabis, the rate of patient reported tachy- and brady-arrhythmias was significant (9%) but rarely led to invasive treatments. Patients should avoid THC > 15% and decrease the frequency of use to less than once daily. Although direct causality to cannabis use cannot be proven definitively, the temporal relationship between drug use and onset of symptoms suggests a strong association.

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