Cardiovascular Toxicology (2019) 19:191–197
https://doi.org/10.1007/s12012-019-09522-z

Synthetic Cannabinoids and Cardiac Arrhythmia Risk: Review of the Literature

Hayriye Mihrimah Ozturk[1] · Ertan Yetkin[2] · Selcuk Ozturk[3]

Published online: 27 April 2019

Abstract
Synthetic cannabinoids (SCBs) are widely used recreational substances especially among adults. Although they have been considered as safe during the marketing process, our knowledge about their adverse effects has evolved since years. SCBs are associated with various cardiac events including acute myocardial infarction and sudden cardiac death. There is also growing evidence that SCBs are associated with cardiac arrhythmia development both in acute and chronic exposure. SCBs have been shown to be associated with both supraventricular and ventricular arrhythmias. However, the exact mechanism of the SCB related arrhythmia remains unknown. Understanding the exact association and possible mechanisms may help us to identify high risk patients at an early stage and to develop treatment modalities to prevent or reverse the arrhythmic effects of SCBs.

Keywords Synthetic cannabinoid · Arrhythmia · Cardiovascular system · Supraventricular arrhythmia · Ventricular arrhythmia

Introduction

Synthetic cannabinoids (SCBs) were firstly generated in the early 1960s after the discovery of the structure of Delta-9 tetrahydrocannabinol (THC) [1, 2]. Endocannabinoid system (ECS) plays significant roles in many physiological functions such as cognitive processes, memory, motor control, pain sensation, appetite and homeostasis and also in cardiovascular system, gastrointestinal system and immune system regulation. Therefore, cannabinoids have been synthesized for medical researches and therapeutic purposes. SCBs were developed during the researches of the ECS as possible therapeutic agents [3, 4]. They first took place on the markets as herbal blends and presented as 'legal highs' in 2000s [4, 5].

Pharmacologic component of SCBs remains unclear. Delta-9 THC, which is the major psychoactive component of natural cannabis, exposes its effect as a partial agonist at cannabinoid type 1 (CB1) receptors, which are present in the brain and nervous system [3, 6]. SCBs were developed to mimic the effects of THC, and they act as potent cannabinoid receptor agonists. They are full agonists of CB1 and CB2 receptors and reported to be up to 170 times more potent than THC [7]. There are various commercially available SCB types created as JWH-018, JWH-073, JWH-398, JWH-250, HU-210, and CP 59,540, CP-47,497, and their homologous forms; and oleamide [2, 8, 9]. Illustrative molecular structures of delta-9 THC and JWH-018 are represented in Fig. 1. CB1 receptors are located in the nervous system, liver, muscle and fat tissues, while CB2 receptors are located in immune system tissues, spleen and peripheral tissues [3, 4, 6]. CB2 receptors can also be induced in other tissues in pathological conditions. In addition, functional CB1 receptors are also present in the heart and vascular system at low levels [7].

Preclinical and clinical studies have suggested that increased endocannabinoid levels and CB-1 receptor activation may take place in the pathogenesis of hypotension and/or cardiac dysfunction, obesity development and impaired glucose tolerance [10]. In addition, previous findings proposed that CB-1 and CB-2 receptors may play roles in

Handling Editor: Atsushi Sugiyama.

✉ Selcuk Ozturk
selcukozturk85@hotmail.com

[1] Department of Psychiatry, Ufuk University Faculty of Medicine, Ankara, Turkey

[2] Department of Cardiology, Istinye University Liv Hospital, Istanbul, Turkey

[3] Cardiology Clinic, Ankara Education and Research Hospital, Ankara, Turkey

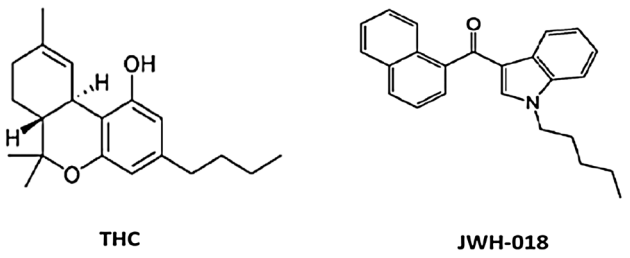

Fig. 1 Molecular structures of delta-9 THC and JWH-018

adjusting cardiometabolic risk, atherogenesis and may also have protective roles in limiting cardiomyocyte damage [7, 11]. In healthy volunteers, CB-1 receptor activation may lead undesirable hemodynamic results such as bradycardia/tachycardia, hypotension and arrhythmias depending on the duration of use [10, 12]. Low but functional CB-1 receptors are expressed in the heart—especially in the myocardium, where they mediate negative inotropy and vasodilatation. CB-1 receptors can also modulate cardiovascular functions by activating vagal afferent neurons [4, 6, 7]. CB-2 receptors are expressed in cardiomyocytes, coronary artery endothelial cells and smooth muscle cells [6]. Based on the current literature, CB-2 receptors may play cardioprotective role by limiting tissue inflammation and injury in various cardiovascular situations [6, 13]. Apart from the cannabinoid receptor activation, THC may cause vasodilatation through transient receptor potential ankyrin type-1 (TRPA-1) channels and NO-mediated or NO-independent mechanisms and also as yet undetected endothelial sites of action [4, 6].

SCBs have been very popular among adults day by day due to the fact that they are very cheap, easy to find, have potent psychoactive effects. In addition, their chemical structure can be changed easily, which makes them hard to detect in routine toxicological tests [14]. Until today, more than 140 SCB products have been identified [2]. At the first years of marketing process, it was considered as an innocent and relatively safe drug compared to other substances. However, it did not look like as demonstrated in several cases of patients and studies. They caused major side effects such as hypertension, hypotension, bradycardia, tachycardia, agitation, psychosis, nausea and vomiting [14–16]. In addition, case reports and clinical studies have suggested a linkage between acute/chronic cannabis and/or SCBs use with serious adverse cardiovascular effects such as stroke, myocardial infarction, cardiomyopathy and cardiac arrest [7]. Although there are some data about the arrhythmic effects of SCBs, there is lack of well-defined clinical studies. Besides, the possible mechanisms of arrhythmic effects of SCBs are not fully known. Accordingly, in this review article we aimed to discuss the effects of SCBs on the electrical conduction system of the heart both at the supraventricular and ventricular level in the light of the previously published reports.

Supraventricular Arrhythmia

Cardiac arrhythmia is defined as deflection of heart rate and/or rhythm from the physiologically normal ranges and divided into two groups according to its origin named as supraventricular and ventricular. Supraventricular arrhythmia is defined as an arrhythmia originating above the bundle of His [17, 18]. It refers to arrhythmias originating from the atrium of the heart [19]. Supraventricular tachycardia (SVT) is the most common type of arrhythmia all over the world and classified in multiple categories. The classification, clinical presentation and pathophysiological mechanisms of SVTs have been discussed in detail in previous review articles [17, 18, 20, 21]. Therefore, we guide readers to these papers for detailed clarification.

SCB-related SVT reports were published in the literature previously. Dogan et al. reported a case of a patient admitting to emergency department with atrial fibrillation (AF) and giant Osborn waves, who stayed outside in extreme cold for extended times, and suffering from hypothermia after SCB consumption [22]. It should be noted that it is not possible to distinguish whether hypothermia or SCB consumption precipitated AF in this patient. Efe et al. reported a patient who used solely SCB for the first time and admitted to emergency department with AF and recovered spontaneously to sinus rhythm [23]. A systematic review, which investigated the admission symptoms of patients suffering from SCB toxicity to emergency departments, found that tachycardia was the most presenting symptom in these patients [16]. However, this study did not aim to describe the type of tachycardia. Orsini and colleagues described a case of a patient presenting to hospital with seizures and acute respiratory failure after K2 consumption, who needed intensive care unit therapy. The patient's rhythm was consistent with sinus tachycardia at admission [24]. There are also cases of SVT patients in the literature, who admitted to emergency departments after consumption of various forms of SCBs and needed hospital stay for recovery [25, 26]. Lam et al. described a case of a patient, who consumed AB-FUBINACA and ADB-FUBINACA and presented a short SVT attack. Toxicological analysis revealed 5.6 ng/mL AB-FUBINACA and 15.6 ng/mL ADB-FUBINACA in the serum sample collected at presentation [26]. In addition to SVT, there are also cases of patients presenting with sinus bradycardia and hypotension after exposure to SCBs [9]. Aksel et al. reported two patients admitting to emergency department with sinus bradycardia and hypotension, which resolved quickly after intravenous lipid emulsion therapy [27]. Westin et al. described a case resulting with death, who was found in cardiac asystole after SCB consumption. Toxicological analysis was performed from the serum sample,

which was obtained 2 h later the victim was found and revealed 1.4 ng/mL MDMB-CHMICA, 1.5 ng/mL THC and mirtazapine at subtherapeutic levels [28].

We have very limited information about whether chronic exposure to SCBs induces cardiac arrhythmia. Sunbul et al. investigated the electrocardiographic parameters in chronic SCB users and found that patients consuming SCB have increased P wave dispersion values compared to control group patients, which is a non-invasive marker of inhomogeneous and discontinuous sinus impulse propagation through the atrium known as the main electrophysiological mechanism for AF development. In addition, they also showed that P wave dispersion values significantly correlated with the addiction severity of the patients [29]. In a recent study published by our study group, we showed significantly higher P wave dispersion values, P wave area in lead two and abnormal P terminal force values in V_1 derivation in chronic SCB users compared to control group patients demonstrating an increased risk of atrial arrhythmia development [30].

Ventricular Arrhythmia

Ventricular conduction system, which consists of 1% of the ventricles' total mass includes His bundle, right and left bundle branches and Purkinje fiber network. QT interval is a measure of ventricular activity on electrocardiography [31]. Ventricular arrhythmias vary from single premature ventricular complexes to sustained ventricular tachycardia and ventricular fibrillation. Sustained ventricular arrhythmias are the most common cause of sudden cardiac death [32].

There are cases of patients in the literature presenting with ventricular arrhythmias including sudden cardiac death after SCB consumption. Von Der Haar et al. reported two cases of patients with SCB abuse with QTc prolongation and second-degree atrioventricular block type 1 [33]. In addition, Nacca and colleagues reported a case of a sinus bradycardia patient, who consumed SCB and progressed to second-degree atrioventricular block type 1 accompanying coma, seizures and hypoglycemia. The patient required intensive care unit stay and surgery in order to treat the toxic effects of the substance. Toxicological analysis at 6th day of hospital stay revealed 34 ng/mL ADB-FUBINACA in the serum of the patient [34]. Although the chemical structure of AB-FUBINACA differs from ADB-FUBINACA by a single methyl group, it was demonstrated to induce bradycardia in a rat model, which could be reversed by CB1 receptor antagonist rimonabant [35]. Left bundle branch block due to SCB consumption was also reported in the literature, which recovered after intravenous lipid emulsion therapy [27]. Davis et al. reported a teenage female patient with ventricular fibrillation after SCB consumption [15]. Yamanoğlu et al. described a patient suffering from recurrent ventricular fibrillation attacks and cardiogenic shock associated with SCB consumption [36]. Similarly, Ibrahim et al. reported a patient, who developed ventricular fibrillation after SCB consumption and treated successfully in the intensive care unit [37]. Effects of SCBs on ventricular arrhythmia development risk have been investigated in previous animal and human studies. Yun et al. investigated the effects of various forms of SCBs including JWH-030, JWH-210, JWH-250 and RCS4. They performed experiments of cytotoxicity, human ether-a-go–go-related (hERG) channel activity, action potential duration (APD) and QT interval duration in vitro, ex vivo and in vivo. All of the SCBs reduced H9c2 cell viability in different doses, while JWH-030 was the most toxic among them by partly inducing apoptosis. The mechanism of JWH-030 induced cytotoxicity was through CB2 receptor activation rather than CB1 receptor activation. JWH-030 also inhibited hERG channel activity in H9c2 cells. To investigate the APD, the authors of the study used rabbit Purkinje fibers and observed that JWH-030 significantly reduced APD; however, JWH-210 had no effect on APD. In addition, JWH-030 reduced left ventricular end diastolic pressure in isolated rat hearts, while JWH-210 had no effect. Intravenous administration of 0.5 mg/kg but not 0.1 mg/kg JWH-030 increased QT parameters on electrocardiogram with no effect on heart rate [38]. In our study group, we also demonstrated significantly higher QT interval levels in chronic SCB users compared to control group patients, although QT levels were within normal levels in both of the groups [30].

Supraventricular and ventricular arrhythmia cases associated with SCB consumption published in the literature are presented in Table 1.

Possible Mechanisms of Arrhythmia

The exact mechanism underlying acute and chronic arrhythmic effects of SCBs is not well known. Understanding this mechanism both at the molecular and cellular levels may help to achieve new treatment modalities to prevent SCB-induced arrhythmic events. However, it should be noted that there may be more than one mechanism and the emerging effects may be case dependent. In addition, studies aiming to explain the relationship mostly originate from animal model studies or in vitro studies.

THC, which is the main psychoactive molecule of SCBs, activates sympathetic nervous system at low or moderate doses causing tachycardia and cardiac output increase, which is partly mediated by catecholamines. This process increases myocardial oxygen demand and tachycardia response of the heart may contribute to arrhythmia development. On the contrary, high dosage consumption of THC activates parasympathetic nervous system resulting with bradycardia

Table 1 Clinical arrhythmias associated with synthetic cannabinoid consumption

Supraventricular arrhythmias	Age	Gender	Type of SCB	Type of toxicity	Therapy	References
– Sinus tachycardia	24	M	N/A	Acute	ILE therapy	[51]
	28	M	N/A	Acute	ILE therapy	[51]
	41	M	K2	Acute	ICU stay	[24]
– Atrial fibrillation	22	M	N/A	Acute	Follow-up in ED	[22]
	23	M	N/A	Acute	ICU stay	[23]
– Sinus bradycardia	19	M	Bonzai	Acute	ILE therapy	[27]
	15	M	Bonzai	Acute	ILE therapy	[27]
	41	M	K2	Acute	IVF therapy in ED	[9]
	35	M	K2	Acute	IVF therapy in ED	[9]
	53	M	K2	Acute	IVF therapy in ED	[9]
– Supraventricular tachycardia	48	M	JWH-018	Acute	Hospital stay	[25]
	24	M	AB-/ADB-FUBINACA	Acute	IVF therapy in ED	[26]
– Asystole	22	M	MDMB-CHMICA	Acute	Death	[28]
Ventricular arrhythmias						
– Left bundle branch block	35	M	Bonzai	Acute	Death	[27]
– QT prolongation	29	M	K2	Acute	Follow-up in ED	[33]
– Atrioventricular block	45	M	K2	Acute	Follow-up in ED	[33]
	38	M	ADB-FUBINACA	Acute	ICU stay and surgery	[34]
– Ventricular fibrillation	16	F	N/A	Acute	ICU stay	[15]
	26	M	N/A	Acute	ICU stay	[36]
	56	M	K2	Acute	ICU stay	[37]

ED emergency department, *F* female, *ICU* intensive care unit, *ILE* intravenous lipid emulsion, *IVF* intravenous fluid, *M* male

and hypotension [7, 39, 40]. Therefore, it is reasonable to speculate that altered autonomic nervous system control by consumption of SCBs may disrupt conduction system of the heart subsequently causing arrhythmia both at the supraventricular and ventricular level.

It is known that myocardial tissues, vascular endothelial and smooth muscle cells express cannabinoid receptors in the heart [7]. The role of cannabinoid receptors in physiological and pathological conditions of the heart has been discussed in detail in previous review articles [41] and briefly in previous sections of this paper. In the light of the available literature, it is reasonable to remark that interaction between cardiac contractility and CB receptors is complex and includes contribution of the nervous system and local physiological and pathological cardiac mechanisms. Although it is unclear that CB receptors residing in the heart directly contribute to supraventricular and/or ventricular arrhythmia development, we need future studies to identify which receptor at which degree contributes to these processes.

SCBs were demonstrated to inhibit Na^+ channels and Na^+/Ca^+ exchanger in rat myocytes, which could contribute to arrhythmia development [42]. Ajulemic acid, which is a form of SCB, was shown to inhibit voltage-gated sodium channels in human embryonic kidney 293t cells [43]. In addition, it was shown that intravenous administration of CB receptor agonists such as HU-210, ACPA, methanandamide and anandamide caused bradycardia in rats. In this study, methanandamide, HU-210 and ACPA did not alter electrophysiological activity in the heart, while anandamide increased QRS duration. HU-210 induced negative chronotropy by CB1 receptor activation in rats, and chronotropic effects observed in this study were free from autonomic nervous system activation [44]. In another study published by Li et al. anandamide was demonstrated to decrease APD and block L-type Ca^+ channels through CB1 receptors in rat cardiac myocytes in a dose-dependent manner [45]. Endocannabinoids and cannabinoid analogues were also shown to inhibit human cardiac Kv1.5 channels [46]. In a previous experimental study published by Yun and colleagues, a type of SCB, JWH-030, was demonstrated to prolong QT interval in rats. Although hERG channel inhibition is known to be associated with APD prolongation, in this study JWH-030 shortened APD, while blocking hERG channels. This conflicting result may be due to contribution of other ion channels such as K^+, Na^+ and Ca^+ related to action potential (AP) induction as discussed by the authors [38]. There are also complicated study results about the effects of THC. For example, THC at various doses exerted no effects on AP parameters in sheep cardiac purkinje fibers. As distinct, 0.1 μM THC increased APD significantly in this study [47]. In this context, it is reasonable to speculate that molecular

and cellular basis of SCB-induced cardiac arrhythmias may be more complex than thought and involve various ionic currents. Diverse effects of various SCB forms at different doses demonstrated in previous studies may be an explanation of various case presentations at the clinical level [38, 48].

In a recent study, higher inflammatory system cell counts were demonstrated in chronic SCB users [49]. In addition, SCB consumption is associated with electrolyte imbalances such as hypokalemia [50]. However, the hypothesis that whether inflammatory system activation and/or electrolyte imbalance plays role in arrhythmia mechanism needs to be tested in further studies. It should also be noted that primary cardiac diseases such as cardiomyopathy, valvular diseases, sudden cardiac death or myocardial infarction either associated with SCB consumption or independently may cause cardiac arrhythmias, which is not in the scope of this review.

Future Perspectives

SCBs have been attracting as recreational substances all over the world since years. However, they are associated with serious adverse cardiac events including acute myocardial infarction and sudden cardiac death. They are also associated with arrhythmic events as evidenced by case reports, preclinical and clinical studies in the literature. However, there are crucial issues need to be clarified in this era. Firstly, there is not much clinical study in the literature to make a direct conclusion whether SCBs are associated with cardiac arrhythmia or not. Higher P wave dispersion was demonstrated in patients consuming SCBs, which was associated with the patients' addiction severity [29]. In another study published by our group, higher P wave dispersion and QT interval levels were demonstrated in SCB consuming patients compared to control group patients [30]. However, several limitations of these papers such as lack of arrhythmia documentation, depending patients' self-reports, limited patient numbers, lack of female gender, investigating chronic consumption instead of acute toxicity etc. should be kept in mind and these limitations hampers to make a direct conclusion. Although there are case reports demonstrating a direct relationship, it is clear that we need stronger, well-designed clinical studies. The second issue is about whether all types of SCBs induce cardiac arrhythmia. The answer of this question mostly comes from experimental studies with varying results. It is not possible to detect SCBs in routine drug screening tests in humans. Although they can be detected from body fluids by complex spectrometric analyses, these tests are performed in specialized clinical laboratories with high costs and time, which limits their clinical adaptability. Besides, the chemical structure of these agents can be changed easily, which limits their detectability in the tests [1]. Therefore, agent-specific analyses can be investigated in animal models or in vitro studies rather than human studies. However, translation of these bench study results to a clinical degree is another problematic issue. The third question is about whether these arrhythmic effects can be reversed by a specific treatment. At present, there is not a clinically available antidote of SCBs. Cannabinoid system receptor antagonists are under investigation for this purpose. Intravenous lipid emulsion therapy has been demonstrated to reverse arrhythmic episodes in acute SCB toxicity in case reports [27, 51]; however, it should be investigated in future studies.

Conclusion

SCB-related cardiac toxicity either presenting with acute or chronic arrhythmic conditions is a significant problem in the cardiovascular era. In the light of the previously published reports and studies, it is reasonable to speculate that arrhythmic effects of SCBs are mainly related to acute consumption and vary from non-lethal arrhythmias to sudden cardiac death. From a pathophysiological point of view, this effect may be more complex than thought at cellular and molecular level, due to the contribution of various receptors, ion channels and diversity of agents and their contents. In addition, chronic exposure to SCBs is also related with electrocardiographic abnormalities, which may be a sign of arrhythmia development in the long term. As our clinical experience develops with new reports and studies, we get one step closer for the solution of the matter. However, we need future studies in a multidisciplinary approach including basic scientists, pharmacologists and cardiologists.

Authors Contribution All authors have substantial contributions to conception and design, or acquisition of data, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Compliance with Ethical Standards

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

References

1. Mills, B., Yepes, A., & Nugent, K. (2015). Synthetic cannabinoids. *The American Journal of the Medical Sciences, 350,* 59–62.
2. Cohen, K., & Weinstein, A. (2018). The effects of cannabinoids on executive functions: Evidence from cannabis and synthetic cannabinoids—a systematic review. *Brain Sciences, 8,* 40.

3. Freund, S. A., & Banning, A. S. (2017). Synthetic cannabinoids: A review of the clinical implications of a new drug of choice. *Journal of the American Academy of PAs, 30,* 1–4.
4. Le Boisselier, R., Alexandre, J., Lelong-Boulouard, V., & Debruyne, D. (2017). Focus on cannabinoids and synthetic cannabinoids. *Clinical Pharmacology and Therapeutics, 101,* 220–229.
5. Zanda, M. T., & Fattore, L. (2018). Old and new synthetic cannabinoids: lessons from animal models. *Drug Metabolism Reviews, 50,* 54–64.
6. Goyal, H., Awad, H. H., & Ghali, J. K. (2017). Role of cannabis in cardiovascular disorders. *Journal of Thoracic Disease, 9,* 2079.
7. Pacher, P., Steffens, S., Haskó, G., Schindler, T. H., & Kunos, G. (2018). Cardiovascular effects of marijuana and synthetic cannabinoids: The good, the bad, and the ugly. *Nature Reviews Cardiology, 15,* 151.
8. McKeever, R. G., Vearrier, D., Jacobs, D., LaSala, G., Okaneku, J., & Greenberg, M. I. (2015). K2–not the spice of life; Synthetic cannabinoids and ST elevation myocardial infarction: a case report. *Journal of Medical Toxicology, 11,* 129–131.
9. Andonian, D. O., Seaman, S. R., & Josephson, E. B. (2017). Profound hypotension and bradycardia in the setting of synthetic cannabinoid intoxication—A case series. *The American Journal of Emergency Medicine, 35,* 940-e945–940-e946.
10. Mukhopadhyay, P., Rajesh, M., Batkai, S., Patel, V., Kashiwaya, Y., Liaudet, L., et al. (2009). CB1 cannabinoid receptors promote oxidative stress and cell death in murine models of doxorubicin-induced cardiomyopathy and in human cardiomyocytes. *Cardiovascular Research, 85,* 773–784.
11. Montecucco, F., & Di Marzo, V. (2012). At the heart of the matter: The endocannabinoid system in cardiovascular function and dysfunction. *Trends in Pharmacological Sciences, 33,* 331–340.
12. Pacher, P., Bátkai, S., & Kunos, G. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological Reviews, 58,* 389–462.
13. Steffens, S., & Pacher, P. (2012). Targeting cannabinoid receptor CB2 in cardiovascular disorders: Promises and controversies. *British Journal of Pharmacology, 167,* 313–323.
14. Castaneto, M. S., Gorelick, D. A., Desrosiers, N. A., Hartman, R. L., Pirard, S., & Huestis, M. A. (2014). Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug and Alcohol Dependence, 144,* 12–41.
15. Davis, C., & Boddington, D. (2015). Teenage cardiac arrest following abuse of synthetic cannabis. *Heart, Lung and Circulation, 24,* e162–e163.
16. Courts, J., Maskill, V., Gray, A., & Glue, P. (2016). Signs and symptoms associated with synthetic cannabinoid toxicity: Systematic review. *Australasian Psychiatry, 24,* 598–601.
17. Antzelevitch, C., & Burashnikov, A. (2011). Overview of basic mechanisms of cardiac arrhythmia. *Cardiac Electrophysiology Clinics, 3,* 23–45.
18. Byrnes, T. J., & Costantini, O. (2017). Tachyarrhythmias and bradyarrhythmias: Differential diagnosis and initial management in the primary care office. *Medical Clinics, 101,* 495–506.
19. Dilaveris, P., Batchvarov, V., Gialafos, J., & Malik, M. (1999). Comparison of different methods for manual P wave duration measurement in 12-lead electrocardiograms. *Pacing and Clinical Electrophysiology, 22,* 1532–1538.
20. Yetkin, E. (2018). Diagnostic challenges in supraventricular tachycardia: anticipating value of natriuretic peptides. *Cardiovascular Endocrinology & Metabolism, 7,* 34–36.
21. Yetkin, E. (2016). Symptoms in supraventricular tachycardia: Is it simply a manifestation of increased heart rate? *Medical Hypotheses, 91,* 42–43.
22. Doğan, S., Akman, C., Yılmaz, A., Kalafat, U. M., & Ocak, T. (2016). A hypothermic case with giant Osborn waves and atrial fibrillation after using synthetic cannabinoid. *The Anatolian Journal of Cardiology, 16,* E1.
23. Efe, T. H., Felekoglu, M. A., Cimen, T., & Dogan, M. (2017). Atrial fibrillation following synthetic cannabinoid abuse. *Turk Kardiyol Dern Ars, 45,* 362–364.
24. Orsini, J., Blaak, C., Tam, E., Rajayer, S., Morante, J., Yeh, A., et al. (2015). The wide and unpredictable scope of synthetic cannabinoids toxicity. *Case Reports in Critical Care*. https://doi.org/10.1155/2015/542490.
25. Lapoint, J., James, L., Moran, C., Nelson, L., Hoffman, R., & Moran, J. (2011). Severe toxicity following synthetic cannabinoid ingestion. *Clinical Toxicology, 49,* 760–764.
26. Lam, R. P. K., Tang, M. H. Y., Leung, S. C., Chong, Y. K., Tsui, M. S. H., & Mak, T. W. L. (2017). Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: A case report with quantitative analysis of serum drug concentrations. *Clinical Toxicology, 55,* 662–667.
27. Aksel, G., Güneysel, Ö., Taşyürek, T., Kozan, E., & Çevik, Ş. E. (2015). Intravenous lipid emulsion therapy for acute synthetic cannabinoid intoxication: Clinical experience in four cases. *Case Reports in Emergency Medicine*. https://doi.org/10.1155/2015/180921.
28. Westin, A. A., Frost, J., Brede, W. R., Gundersen, P. O. M., Einvik, S., Aarset, H., et al. (2015). Sudden cardiac death following use of the synthetic cannabinoid MDMB-CHMICA. *Journal of Analytical Toxicology, 40,* 86–87.
29. Sunbul, E. A., Sunbul, M., Terzi, A., Calli, S., Koca, E., Bilici, R., et al. (2016). The effect of synthetic cannabinoids on P-wave dispersion: An observational study. *Medical Principles and Practice, 25,* 483–487.
30. Ozturk, H. M., Erdogan, M., Alsancak, Y., Yarlioglues, M., Duran, M., Boztas, M. H., et al. (2018). Electrocardiographic alterations in patients consuming synthetic cannabinoids. *Journal of Psychopharmacology, 32,* 296–301.
31. van Weerd, J. H., & Christoffels, V. M. (2016). The formation and function of the cardiac conduction system. *Development, 143,* 197–210.
32. Roberts-Thomson, K. C., Lau, D. H., & Sanders, P. (2011). The diagnosis and management of ventricular arrhythmias. *Nature Reviews Cardiology, 8,* 311.
33. Von Der Haar, J., Talebi, S., Ghobadi, F., Singh, S., Chirurgi, R., Rajeswari, P., et al. (2016). Synthetic cannabinoids and their effects on the cardiovascular system. *The Journal of Emergency Medicine, 50,* 258–262.
34. Nacca, N., Schult, R., Loflin, R., Weltler, A., Gorodetsky, R., Kacinko, S., et al. (2018). Coma, Seizures, Atrioventricular Block, and Hypoglycemia in an ADB-FUBINACA Body-Packer. *The Journal of Emergency Medicine, 55,* 788–791.
35. Banister, S. D., Moir, M., Stuart, J., Kevin, R. C., Wood, K. E., Longworth, M., et al. (2015). Pharmacology of indole and indazole synthetic cannabinoid designer drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chemical Neuroscience, 6,* 1546–1559.
36. Yamanoglu, A., Celebi Yamanoglu, N. G., Evran, T., & Sogut, O. (2018). How much can synthetic cannabinoid damage the heart? A case of cardiogenic shock following resistant ventricular fibrillation after synthetic cannabinoid use. *Journal of Clinical Ultrasound, 46,* 605–609.
37. Ibrahim, S., Al-Saffar, F., & Wannenburg, T. (2014). A unique case of cardiac arrest following K2 abuse. *Case Reports in Cardiology*. https://doi.org/10.1155/2014/120607.
38. Yun, J., Yoon, K. S., Lee, T.-H., Lee, H., Gu, S. M., Song, Y. J., et al. (2016). Synthetic cannabinoid, JWH-030, induces

QT prolongation through hERG channel inhibition. *Toxicology Research, 5,* 1663–1671.
39. Lindsay, A. C., Foale, R. A., Warren, O., & Henry, J. A. (2005). Cannabis as a precipitant of cardiovascular emergencies. *International Journal of Cardiology, 104,* 230–232.
40. Ghuran, A., & Nolan, J. (2000). Recreational drug misuse: issues for the cardiologist. *Heart, 83,* 627–633.
41. Kaschina, E. (2016). Cannabinoid CB1/CB2 receptors in the heart: Expression, regulation, and function, in cannabinoids in health and disease. InTech.
42. Al Kury, L. T., Voitychuk, O. I., Yang, K. H. S., Thayyullathil, F. T., Doroshenko, P., Ramez, A. M., et al. (2014). Effects of the endogenous cannabinoid anandamide on voltage-dependent sodium and calcium channels in rat ventricular myocytes. *British Journal of Pharmacology, 171,* 3485–3498.
43. Foadi, N., Berger, C., Pilawski, I., Stoetzer, C., Karst, M., Haeseler, G., et al. (2014). Inhibition of voltage-gated Na + channels by the synthetic cannabinoid ajulemic acid. *Anesthesia and Analgesia, 118,* 1238–1245.
44. Krylatov, A., Maslov, L., Ermakov, S. Y., Lasukova, O., Barzakh, E., Crawford, D., et al. (2007). Significance of cardiac cannabinoid receptors in regulation of cardiac rhythm, myocardial contractility, and electrophysiologic processes in heart. *Biology Bulletin, 34,* 28–35.
45. Li, Q., Ma, H. J., Zhang, H., Qi, Z., Guan, Y., & Zhang, Y. (2009). Electrophysiological effects of anandamide on rat myocardium. *British Journal of Pharmacology, 158,* 2022–2029.
46. Barana, A., Amoros, I., Caballero, R., Gomez, R., Osuna, L., Lillo, M. P., et al. (2009). Endocannabinoids and cannabinoid analogues block cardiac hKv1. 5 channels in a cannabinoid receptor-independent manner. *Cardiovascular Research, 85,* 56–67.
47. Sheridan, R. D., Turner, S. R., Cooper, G. J., & Tattersall, J. E. (2005). Effects of seven drugs of abuse on action potential repolarisation in sheep cardiac Purkinje fibres. *European Journal of Pharmacology, 511,* 99–107.
48. Ford, B. M., Tai, S., Fantegrossi, W. E., & Prather, P. L. (2017). Synthetic pot: Not your grandfather's marijuana. *Trends in Pharmacological Sciences, 38,* 257–276.
49. Guzel, D., Yazici, A. B., Yazici, E., & Erol, A. (2017). Alterations of the hematologic cells in synthetic cannabinoid users. *Journal of Clinical Laboratory Analysis, 31,* e22131.
50. Bilici, R. (2014). Synthetic cannabinoids. *Northern Clinics of Istanbul, 1,* 121.
51. İzci, F., İzci, V., İzci, S., Çiftçi, E., Koç, Mİ., Bilici, R., et al. (2015). Intravenous lipid emulsion as a treatment of sinus tachycardia induced by synthetic cannabinoid intoxication: Two case reports. *Bağımlılık Dergisi-Journal of Dependence, 16,* 210–213.