European Journal of Internal Medicine 61 (2019) e14–e15

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Letter to the Editor

Recommending marijuana use: Violation of the Hippocratic aphorism of "do good or do no harm"

Legalization of medical or recreational use of marijuana presupposes that all drug-formulations have been tested and proven safe. However, this has not been the case with this substance, and to be fair, with other substances (e.g. tobacco) or drugs as well, which are plagued by various adverse effects. At least, when the medicinal use of cannabis is considered, its adverse events should be weighed against the adverse events of the currently available medicines. Unfortunately, regarding cannabis, accumulated evidence to-date converges to a rather dismal outlook [1]. Cannabis use has been charged with addiction and mental-health disorders, traffic injuries, respiratory adverse-effects, serious and life-threatening cardiovascular (CV) complications, or even a carcinogenic potential [1]. Regulatory authorities have only recently started taking a stance about the medical use of marijuana suggesting a limited use as a third-line option for chronic neuropathic pain alone and "under close clinical surveillance" [2]. Even the proponents of its medical use admit to its potential harm and propose "more research into the efficacy and side-effects" [3].

Cannabis use can lead to acute and life-threatening CV problems and sudden cardiac death, not only in individuals at increased CV risk, but also in young people without any history of CV disease or risk factors, with the only apparent trigger being use of marijuana [1,4]. Myocardial infarctions, life-threatening arrhythmias, and ischemic strokes have been consistently reported in the literature, particularly with use of large doses. Unfortunately, the number of cannabis users is increasing in the adolescent population where cannabis confers neurotoxic effects on their brain, in addition to its detrimental CV and other adverse-effects [1].

According to an analysis of the National Inpatient Sample (NIS) 2009–2010 database, cannabis use in > 300,000 individuals aged 18–55 years old was associated with a higher prevalence of heart failure, stroke, coronary artery disease, and sudden cardiac death compared with > 20 million non-users [5]. After multivariate regression analysis, cannabis use remained an independent predictor of both heart failure and stroke. Another NIS analysis showed that between 2010 and 2014, 2.7% of hospitalized marijuana users developed arrhythmias with a consistently increasing trend (nearly two-fold) of all-cause arrhythmia; with atrial fibrillation being the most common arrhythmia [6]. The all-cause inpatient mortality in hospitalized marijuana users with arrhythmias increased from 3.7% in 2010 to 4.4% in 2014. The World Health Organization (2016) emphasizes that cannabis use follows risky patterns with persistent use, early onset and progression to dependence, with negative health and psychological outcomes that include mental, respiratory, CV and other adverse effects (www.who.int/substance_abuse/publications/msbcannabis.pdf).

A population-based cohort study examining men (n = 49,321) aged 18–20 years old assessed for cannabis use found that "heavy" cannabis smoking was significantly associated with more than a twofold risk (hazard ratio 2.12) of developing lung cancer over the 40-year follow-up period, even after adjustment for baseline tobacco use, alcohol use, respiratory conditions, and socioeconomic status [7].

A likeness of the deleterious effects of cannabis to those of tobacco has been suggested (Fig. 1) and despite some differences in mechanisms, the outcome may be similar, or even worse, as the effects may appear at a younger age [1]. These differences may relate to the acuteness of the CV effects of cannabis, emerging as acute coronary events, arrhythmias, sudden death, and ischemic strokes, rather than an initial insidious progression of the atherosclerotic process conferred by tobacco with subsequent later development of acute CV syndromes. Thus, both these substances, tobacco and cannabis, constitute public health-hazards, and this will only be getting worse with the spreading of cannabis-use legalization across the globe. When one considers the mental-health problem closely linked to cannabis use, one can only anticipate a grisly future, rather than a hopeful perspective paved by the medicinal uses of cannabis. Legalization has already led to a substantial increase in the content of tetrahydrocannabinol, the major psychoactive constituent of cannabis, from 5% to > 15% with potentially unpredictable complications [8]. Second-hand marijuana smoking is another emerging potential risk, particularly for children and young individuals [1].

A recent analysis of cardiac-related mortality data from the U.S. National Vital Statistics System for 1990–2014, indicated increased rates of cardiac-related mortality following passage of medical-cannabis laws [9]. Significant increases (2.3% for men and 1.3% for women) in the rate of cardiac death were observed following passage of such laws. For both genders, the effects increase with age and are also stronger in States with more a lax approach to cannabis dispensing.

Cannabis-associated emergency department visits per 100,000 emergency department discharges were recently reported as steadily increasing annually by 7% in the U.S., with the highest risk at the younger age group (12 to 17 years) [10]. There are also increasing numbers of hospital admissions for acute myocardial infarction among cannabis users, with younger age groups most commonly afflicted who may have no other major CV risk factors [1]. Other worrisome concerns relate to an increase of cannabis use in pregnancy predominantly noted among women of younger ages and those of lower socioeconomic status.

A disconcerting spread of cannabis use is occurring at a fast pace after its recent legalization in several countries around the globe despite that many authorities recognize the fact that it constitutes a public health hazard with alarming preponderance in the younger age groups. Based on compelling evidence of a plethora of adverse-effects of marijuana use that cannot be appeased by the prospect of a controlled medicinal use of this potentially deleterious substance, it appears that recommending marijuana use obviously violates the ancient Greek

https://doi.org/10.1016/j.ejim.2019.01.009
Received 2 December 2018; Received in revised form 10 January 2019; Accepted 20 January 2019
Available online 24 January 2019

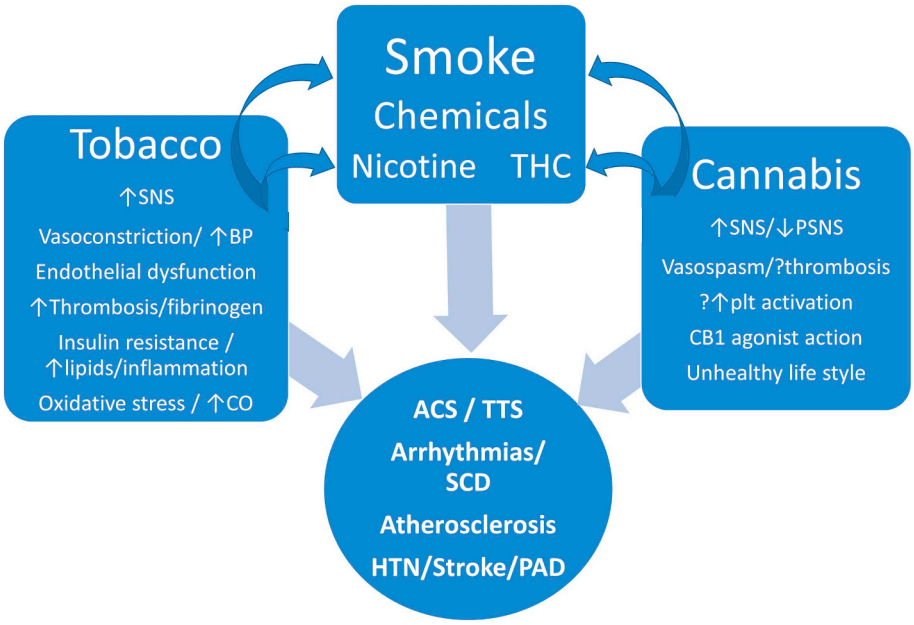

Fig. 1. The schema illustrates the mechanisms by which the two substances, tobacco and cannabis produce deleterious cardiovascular (CV) effects. Although the active ingredients of the cannabis plant differ from those of the tobacco plant, each one produces ~4000 chemicals when smoked and these are grossly similar; however, due to different modes of smoking, cannabis chemicals are retained in the body for a longer time. The CV effects of tobacco have been more or less well-known. The CV effects of cannabis are slowly emerging, including alterations of the autonomic nervous system (sympathetic activation), adverse vascular effects (vasospasm, arterial stiffness), prothrombotic effects (?platelet activation and/or pro-inflammatory action of THC on the arterial wall and endothelium), sluggish coronary flow, pro-atherogenic effects (via activation of CB1 receptors; increase in apolipoprotein C-III levels by THC). Arrhythmias comprise both atrial (atrial fibrillation) and ventricular arrhythmias with the latter leading even to cardiac arrest. ACS = acute coronary syndrome(s); BP = blood pressure; CO = carbon monoxide; HTN = hypertension; PAD = peripheral arterial disease; plt = platelet(s); PSNS = parasympathetic nervous system; SCD = sudden cardiac death; SNS = sympathetic nervous system; THC = tetrahydrocannabinol; TTS = Takotsubo syndrome.

adage, known as the Hippocratic aphorism of "*Do Good or Do No Harm*".

Nevertheless, the issue may remain unsettled until *the evidence-based medicine paradigm* can be applied to the field of medical cannabis with the completion of adequately powered prospective studies to more definitively determine the CV, mental and other health effects of marijuana use. Until then, the clinicians should apprise themselves of currently available information regarding the potential risks and benefits of cannabis use that may allow them to engage in shared decision-making discussions with their patients, and hopefully guide them to safer alternatives [11].

Conflict of interest

None to be declared.

References

[1] Manolis TA, Manolis AA, Manolis AS. Cannabis associated "high" cardiovascular morbidity and mortality: marijuana smoke like tobacco smoke? A Déjà Vu/Déjà Vécu Story? Mini Rev Med Chem 2018 Nov 13. https://doi.org/10.2174/1389557518666181114113947. [Epub ahead of print].

[2] Hauser W, Finn DP, Kalso E, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain 2018;22:1547–64.

[3] Barnes MP. The case for medical cannabis-an essay by M P Barnes. BMJ 2018;362:k3230.

[4] Rezkalla S, Kloner RA. Cardiovascular effects of marijuana. Trends Cardiovasc Med 2018 Nov 10. https://doi.org/10.1016/j.tcm.2018.11.004. [pii: S1050-1738(18)30141-5]. [Epub ahead of print].

[5] Kalla A, Krishnamoorthy PM, Gopalakrishnan A, Figueredo VM. Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the National Inpatient Sample. J Cardiovasc Med (Hagerstown) 2018;19:480–4.

[6] Desai R, Patel U, Deshmukh A, Sachdeva R, Kumar G. Burden of arrhythmia in recreational marijuana users. Int J Cardiol 2018;264:91–2.

[7] Callaghan RC, Allebeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control 2013;24:1811–20.

[8] Kilmer B. Recreational cannabis - minimizing the health risks from legalization. N Engl J Med 2017;376:705–7.

[9] Abouk R, Adams S. Examining the relationship between medical cannabis laws and cardiovascular deaths in the US. Int J Drug Policy 2018;53:1–7.

[10] Shen JJ, Shan G, Kim PC, et al. Trends and related factors of cannabis-associated emergency department visits in the United States: 2006–2014. J Addict Med 2018 Nov 9. https://doi.org/10.1097/ADM.0000000000000479. [Epub ahead of print].

[11] Kaufman TM, Fazio S, Shapiro MD. Brief commentary: marijuana and cardiovascular disease-what should we tell patients? Ann Intern Med 2019 Jan 8. https://doi.org/10.7326/M18-3009. [Epub ahead of print].

Antonis S. Manolis[a,*], Theodora A. Manolis[b]

[a] *Third Department of Cardiology, Athens University School of Medicine, Greece*

[b] *Red Cross Hospital, Athens, Greece*

E-mail address: asm@otenet.gr (A.S. Manolis).

* Corresponding author at: Third Department of Cardiology, Vas. Sofias 114, Athens 115 27, Greece.