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Managing Cannabis Use in Patients with Cardiovascular Disease

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In the context of widespread legalization of cannabis use for both medical and recreational purposes, health care providers need to understand and manage cannabis use and its complications in older patients, particularly in those with cardiovascular disease (CVD). The report by Drs. Saunders and Stevenson[1] illustrates some of the cardiovascular (CV) problems that may occur with cannabis use in such patients.

The relevant clinical features of this case include an older man with stable coronary artery disease (CAD), taking appropriate cardiac medications, who consumed a large dose of delta-9-tetrahydrocannabinol (THC) orally for treatment of pain and to aid sleep. The patient had smoked marijuana in his youth, but had not used since then. The ingestion resulted in extreme discomfort, which included anxiety and fearful hallucinations, associated with intense sympathetic neural stimulation and a non- ST segment elevation myocardial infarction. Initial vital signs included tachycardia and hypertension, despite taking substantial doses of metoprolol and a calcium channel blocker. After resolution of the hallucinations, the chest pain resolved. A number of prior case reports, as well as epidemiological studies, have described the association between cannabis use and acute CV adverse events, including myocardial infarction, stroke, arrhythmias and sudden death.[2-4]

In considering the toxicity of medical cannabis use broadly, one needs to appreciate the main cannabinoid constituents. Cannabis products may contain THC, the main psychoactive and cardioactive chemical, and/or cannabidiol (CBD), a cannabinoid with minimal psychoactivity and no cardioactivity. The latter is widely used for relief of pain and anxiety and to aid sleep. Products may contain mostly THC, mostly or only CBD, or varying proportions of the two. Thus, an important question the provider needs to address is what constituents are being consumed by the patient. For the remainder of this editorial, the focus will be primarily on THC-containing cannabis products.

Cardiovascular toxicity of marijuana can be viewed as a consequence of one or more the following 1) inhalation of combustion products of marijuana; 2) direct CV effects of THC; and 3) indirect effects of THC related to acute anxiety, hallucination and/or psychosis.

Aside from one containing THC and the other nicotine, the composition and toxicity of marijuana smoke is qualitatively similar to that of cigarette smoke. Marijuana smoke exposes the smoker to even more of some toxicants such as ammonia and cyanide than cigarette smoking.[5]

Smoke exposes the smoker to high levels of oxidants, particulates, numerous toxic volatile organic chemicals and carbon monoxide. Adverse cardiovascular effects of smoke include oxidant damage, inflammation, endothelial dysfunction, induction of a prothrombotic state and reduction of oxygen carrying capacity of red blood cells. These toxic effects can translate into plaque rupture, acute thrombosis and/or vasoconstriction with reduced coronary blood flow, resulting in an increased risk of acute coronary syndrome, stroke, and sudden cardiac death [Figure]. While these mechanisms and adverse events are most extensively described in active regular cigarette smokers, the same acute cardiovascular effects are also seen acutely in people who smoke only occasionally and in the context of secondhand cigarette smoke exposure. A case-crossover study supports the idea that smoking a single marijuana cigarette can acutely trigger myocardial infarction.[6]

THC, acting on the cannabinoid receptor 1 (CB1R), primarily via central nervous system pathways, increases sympathetic nervous system activity, resulting in a dose-related tachycardia, (20-100%), increased myocardial contractility, supine hypertension and systemic catecholamine release.[7] Coronary blood flow may be reduced due to catecholamine effects to constrict coronary vessels and/or activate platelets. The net effect is a substantial increase in myocardial work and oxygen demand combined with an impairment in the expected and necessary compensatory increase in coronary blood flow. Marijuana was shown many years ago to markedly reduce exercise tolerance in patients with stable angina pectoris, a consequence of increased myocardial work and reduced coronary blood supply.[8] Increases in sympathetic tone can trigger supraventricular or ventricular arrhythmias and increase ventricular response rate in atrial fibrillation. Paradoxically, THC can also cause orthostatic hypotension, believed to be due to impaired venoconstriction, which may aggravate myocardial ischemia in the context of CAD or precipitate stroke. In the elderly, orthostatic hypotension also increases the risks of syncope or falls with concomitant injury.

Another aspect of THC toxicity, as seen in the patient described in this issue's case report, is the onset of acute anxiety, paranoia, hallucination and panic. Such effects are typically seen with high doses of THC and with the use of synthetic cannabinoids, but are also observed with smaller therapeutic doses in older people, such as in cancer patients taking THC to manage nausea and vomiting and for appetite stimulation. Many such individuals who are THC-naïve and are not used to taking any mind-altering drugs can become highly distressed by impaired

cognition and feelings of loss of control produced by THC. In the case of the patient in the case report, the dose of THC consumed was approximately 70 mg, an extremely large dose for a THC-naïve person. This compares to the recommended starting dose of dronabinol (Marinol), a synthetic THC marketed for nausea and vomiting and appetite stimulation in patients undergoing cancer chemotherapy or with AIDS, of 2.5 mg for an older patient. The maximal recommended dose for any patient is 20 mg per day. Extreme emotional responses in the context of THC psychiatric toxicity are associated with surges of catecholamines, which can have adverse acute cardiovascular effects.

Important considerations with respect to cannabis toxicity are the pattern of use, dose, route of administration and degree of tolerance. Some people take a couple of puffs of marijuana before bedtime for sleep, in which case toxicity is likely to be low. Others use cannabis products all day. Smoking or vaping cannabis results in a rapid increase in arterial blood THC levels, which peak soon after inhalation; and inhaled THC has a duration of action for 4-6 hours.[9] Inhaled doses can be relatively small since the rapid absorption of small doses delivers high concentrations to the brain, facilitating titration of dosing to desired effect. On the other hand, oral ingestion of cannabis results in slow and erratic absorption with blood THC levels peaking at 4 hours or longer, and with a duration of action that can be 24 hours or more.[10] Due to slow absorption, the psychoactive effects or oral THC are delayed, leading to consumption of large doses before effects are felt, which may then lead to protracted exposure to high levels and toxicity. While the oral bioavailability of THC is relatively low (10-20%), THC is metabolized to 11-hydroxy-THC, which is also highly psychoactive.

Tolerance is an important determinant of toxicity. With regular use, a high degree of tolerance can develop to both psychological and cardiovascular effects. Conversely, as discussed above, even a moderate dose of THC in a naïve user, particularly in older adults, can produce significant toxicity.

How should health care providers should manage patients with CVD who are using or would like to use cannabis products? Many patients would like to use or are using cannabis to manage anxiety, chronic pain and/or to aid sleep, as was the case for the patient described in the case report.[1] Particularly vulnerable to the adverse effects of cannabis are patients with coronary artery or cerebrovascular disease, heart failure and arrhythmias, including atrial fibrillation,

paroxysmal supraventricular arrhythmias and ventricular tachycardia.

No empirical evidence is available to guide management of cannabis use in older patients and/or patients with cardiovascular disease. I suggest an approach as follows: For the cardiovascular patient at high risk, the use of THC should be discouraged. The concern about THC is greater for those who use THC throughout the day as opposed to those who use small doses prior to sleep. For patients who want to use cannabis, one can recommend the use of CBD rather than THC for relief of pain and to aid sleep. For patients who are smoking marijuana for the effects of THC and who are unwilling to stop, it is advisable to switch to a non-combusted delivery system, such as vaporizer. This will at least avoid the harmful effects of marijuana smoke. Since the toxic effects of THC are dose-related, patients should be advised to use the smallest doses that provide the desired beneficial effects. THC is often packaged and sold in a way that is difficult for the consumer to evaluate an appropriate dose. Some edible products, such as brownies for example, may contain several 'servings" of THC, but the patient may not know that. In the case of a 90 mg THC lollipop, such as was purchased by the patient in this case report, an appropriate starting dose might be a few licks or a small piece. Understanding appropriate dosing would likely have prevented the toxicity suffered by the patient. Patients may need counseling as to what constitutes a low dose, and how that compares to the amount of THC in products they may have purchased; and the health care providers may be called upon to provide guidance.

Another management question relates to the selection of medications in cardiovascular patients using THC-containing cannabis products. Again, there are no empirical data, and the following represents my approach: Selection of medications will depend on a number of factors, including the dosing pattern, coexisting medical conditions and medications. The logical target of medication in THC users is control of tachycardia, which can aggravate CAD and arrhythmias. Patients on beta-blockers may need higher doses. Others may need to have beta-blockers started. With co-existing hypertension, which may be aggravated by the effects of THC, a beta-blocker with alpha-blocking activity such as carvedilol, or a beta-blocker and calcium-blocker combination are reasonable options. At the same time, the likelihood of orthostatic hypotension needs to be considered. Patients should be warned that the consumption of THC, especially at bedtime, may result in dizziness with standing with an increased risk of falling at night, and this risk would be expected to be even higher in a patient taking alpha-blockers for prostate disease. Counseling may include sitting on the side of the bed for a minute or two until dizziness

resolves, and avoidance of prolonged standing.

The legalization of cannabis has considerable public support, but also raises public health concerns. Some users may benefit from the social and medical effects, but others will be at risk for adverse health outcomes. Little information has been disseminated to patients or health care providers about cannabis use in older patients, and in particular those with cardiovascular disease. For better or worse, providing advice and care to such patients who are using cannabis is now necessary for the provision of optimal medical care to such patients.

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Figure 1: Overview of mechanisms by which marijuiana smoke might cause acute cardiovascular events