Letter by Brown Regarding Article, "Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association"

Joshua D. Brown, PharmD, PhD

1Consortium for Medical Marijuana Clinical Outcomes Research, University of Florida, Gainesville, FL

2Center for Drug Evaluation & Safety, Department of Pharmaceutical Outcomes & Policy, University of Florida College of Pharmacy, Gainesville, FL

Corresponding author:

Joshua Brown, PharmD, PhD

1225 Center Drive HPNP 3320

Gainesville, FL 32610

E: joshua.brown@ufl.edu

P: 352-294-8593

Words: 468

The American Heart Association Scientific Statement and review article on medical and recreational marijuana and cardiovascular health is a comprehensive resource.[1] The article fills a critical gap in assessing the interaction between cannabis and cardiovascular health which continues to grow in importance as more and more people have access to cannabinoids for complex medical use. The authors thoroughly covered suspected cardiovascular side effects and concerns related to those with pre-existing heart disease as well as theoretical drug-drug interaction potential. However, there are additional points that should be considered prior to using cannabis in patients with cardiovascular disease.

First, while the authors review and the existing literature on cardiovascular side effects, the conclusions on these effects remained unclear to this reader. Cardiovascular side effects such as palpitations, tachycardia, and hypotension were reported in clinical trial for tetrahydrocannabinol containing products (e.g. dronabinol and nabiximols) more frequently than in controls though incidence remains small (~1%).[2, 3] It should be emphasized, however, that in countries other than the United States where Sativex® has been approved, those products carry contraindications in those with cardiovascular disease, specifically, ischemic heart disease, arrhythmias, uncontrolled hypertension, or heart failure. [2, 3] Thus, recommendations in those with heart disease should likely be strengthened to be in line with these other federal guidelines. In addition, cardiovascular side effects should not be considered in a vacuum. Co-occurrence of tachycardia or hypotension along with other cannabinoid effects such as somnolence, sedation, and dizziness can increase the risk of falls, fractures, or other accidents especially in older adults who may also take other potentiating medications.[2, 3]

In addition, while drug-drug interaction pathways such as the Cytochrome P450 enzymes are covered, there is growing evidence of the importance of carboxylesterases (i.e. CES1 and CES2) in drug metabolism and clear inhibitory activity on carboxylesterases by cannabinoids at clinically relevant concentrations.[4] Carboxylesterases are commonly implicated in the metabolism of medications for cardiovascular disease that are pro-drugs such as angiotensin-converting enzyme inhibitors as well as clopidogrel and dabigatran etexilate. For the latter examples, these indicate situations where cannabinoids could prevent conversion to the active form leading to lack of efficacy and severe patient outcomes. In addition, cannabinoids are highly protein bound[1] and can displace medications such as warfarin and digoxin and should be used with caution in these patient populations. For example, an interaction between warfarin and cannabis has been previously reported in a case series leading to severe bleeding outcomes.[5]

The disease and drug interaction potential of cannabis and cannabinoids is of growing interest to clinicians and patients. Efforts such as those by the AHA committees go a long way to provide up to date evidence on emerging issues. Needs for future research must move the needle from theoretical and hypothetical drug and disease interactions to concrete evidence to ensure patient safety with cannabis use.

Acknowledgments: None

Sources of Funding: None

Disclosures: Dr. Brown receives support from the Consortium for Medical Marijuana Clinical Outcomes Research from State of Florida appropriations.

REFERENCES

1. Page RL, Allen LA, Kloner RA, Carriker CR, Martel C, Morris AA, Piano MR, Rana JS and Saucedo JF. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation*. 0:CIR.0000000000000883.

2. Brown JD. Potential Adverse Drug Events with Tetrahydrocannabinol (THC) Due to Drug–Drug Interactions. *Journal of Clinical Medicine*. 2020;9:919.

3. Brown JD and Winterstein AG. Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use. *J Clin Med*. 2019;8.

4. Qian Y, Wang X and Markowitz JS. In Vitro Inhibition of Carboxylesterase 1 by Major Cannabinoids and Selected Metabolites. *Drug Metab Dispos*. 2019;47:465-472.

5. Damkier P, Lassen D, Christensen MMH, Madsen KG, Hellfritzsch M and Pottegård A. Interaction between warfarin and cannabis. *Basic Clin Pharmacol Toxicol*. 2019;124:28-31.

Response to Letter from Dr Brown

We would like to thank Dr. Brown for his insightful, salient comments regarding the recent American Heart Association Scientific Statement on Medical Marijuana, Recreational Cannabis, and Cardiovascular Health.[1] Dr. Brown brings attention to two very important clinical and pharmacokinetic concerns. First, while not approved in the United States, Sativex, which is a combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administered as an oral buccal spray for spasticity in patients with multiple sclerosis, is contraindicated in patients with cardiovascular diseases, such as ischemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure based on the observed adverse events within clinical trials. [2] If we can apply these findings to orally consumed cannabis, these findings add to the paucity of literature surrounding the potential for cardiovascular concerns for edible cannabis products, where research is desperately needed.

Second, Dr. Brown also sheds light on the potential for CBD and THC to inhibit carboxylesterases (CES). [3] The CES are a well conserved multi-gene family of α,β-hydrolase-fold proteins that are highly expressed in the liver and play a role in catalyzing hydrolysis of esters, amides, carbamates and thioesters, as well as bioconverting prodrugs.[4] In distinct contrast to our understanding of the importance of cytochrome P450 enzymes in drug disposition, the key role of CES in the metabolism of substrate drugs has been largely overlooked and continues to emerge as a potential source for drug-drug interactions. If the *in vitro* data correlates to the clinical setting, then administration of a CBD and/or THC containing product could impact the

metabolism of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, antiplatelets, statins, antivirals, and central nervous system medications.[3,4,5]

Again, we thank Dr. Brown for his comments and insights as they emphasize the important need for research and science in the cannabis arena in the context of cardiovascular health.

Robert L Page II, PharmD, MSPH, FAHA
Professor, Department of Clinical Pharmacy
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences

References:

1. Page RL 2nd, Allen LA, Kloner RA, Carriker CR, Martel C, Morris AA, Piano MR, Rana JS, Saucedo JF; on behalf of the American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e000–e000. doi: 10.1161/CIR.0000000000000883.
2. Sativex. Delta-9-tetrahydrocannabinol and cannabidiol Product Monograph. GW Pharma Ltd. Histon, Cambridge UK. December 11, 2019. Available at:

https://www.bayer.ca/omr/online/sativex-pm-en.pdf. Accessed September 19, 2020.

3. Qian Y, Wang X , Markowitz JS. In vitro inhibition of carboxylesterase 1 by major cannabinoids and selected Metabolites. *Drug Metab Dispos*. 2019;47:465-472.
4. Di L. The impact of carboxylesterases in drug metabolism and pharmacokinetics. *Curr Drug Metab*. 2018; 19(14): 91–102.
5. Brown JD. Potential adverse drug events with tetrahydrocannabinol (THC) due to drug–drug interactions *J Clin Med*. 2020 Apr; 9(4): 919.