

# Synthetic and natural cannabinoids: the cardiovascular risk

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## Key words

cannabis, cannabinoids,  
myocardial infarction,  
preconditioning

doi: 10.5837/bjc.2015.006

*Br J Cardiol* 2015;22:7–9

Cannabis has been employed medicinally and recreationally for thousands of years,<sup>1,2</sup> but it was not until the 1960s that the structure and pharmacology of its primary phytocannabinoid components, cannabidiol (CBD)<sup>3</sup> and tetrahydrocannabinol (THC)<sup>4</sup> were identified, and another generation before the nature and function of the endocannabinoid system (ECS) were elucidated (see reference 5 for a comprehensive review). The ECS consists of endogenous cannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), their biosynthetic and catabolic enzymes, and their receptors: CB<sub>1</sub>, which is psychoactive, analgesic, neuromodulatory and the most abundant G-protein coupled receptor in the brain, and CB<sub>2</sub>, which is non-psychoactive, immunomodulatory and anti-inflammatory. The ECS may be thought of as a grand homeostatic regulator of chordate physiological functions, whose roles have been summarised as: “relax, eat, sleep, forget and protect”.<sup>6</sup> Those actions closely describe the effects of THC and AEA, which are both weak partial agonists at CB<sub>1</sub> and CB<sub>2</sub>.

The positive chronotropic and other cardiac effects of cannabis and THC were confirmed in the first modern experiments,<sup>7</sup> but are highly species- and state-specific and dose dependent.<sup>8</sup> CB<sub>1</sub> stimulation, particularly in the novice cannabis-smoker, produces increased heart rate and variable blood pressure. At low doses, THC stimulates the sympathetic system and inhibits the parasympathetic, but typical of phytocannabinoids, displays prominent biphasic tendencies, such that at high doses, opposite effects occur, and orthostatic hypotension and bradycardia may result. THC can produce vasoconstriction in a CB<sub>1</sub>- and endothelial-dependent manner.<sup>8</sup> The acute effects of THC including intoxication and tachycardia are quite subject to tachyphylaxis, and will often diminish with chronic administration.<sup>9</sup> Cannabidiol is an anti-inflammatory antioxidant<sup>10</sup> that tends to counter to the anxiety and tachycardia of THC,<sup>11</sup>

and appears to be broadly cardioprotective,<sup>12,13</sup> as is CB<sub>2</sub> stimulation.<sup>8</sup>

## Morbidity and cannabinoids

Cardiovascular morbidity secondary to cannabis has been reported: THC metabolites in unexplained cardiac deaths in young people,<sup>14</sup> and a claim of a 4.8 times increased risk of myocardial infarction (MI) in the first hour after cannabis smoking,<sup>15</sup> but given the meteoric increase in cannabis usage over the past five decades, one might expect a commensurate public health signal, which has been quite unapparent in epidemiological studies.<sup>16,17</sup> Cannabis smoking did decrease exercise tolerance in angina.<sup>18</sup> While increased all-causation death rates after first MI in cannabis smokers were initially claimed,<sup>19</sup> this study did not examine subsequent cannabis use patterns, and no significant differences in cardiac mortality were observed on 18-year follow-up of the same cohort.<sup>20</sup> More recent epidemiological investigation places cannabis MI risk at 0.8%, with a significantly lower population attributable fraction than air pollution.<sup>21</sup> Earlier claims of “cannabis arteritis”<sup>22</sup> or precipitant of thromboangiitis obliterans have been largely debunked due to a lack of distinctive pathology and failure to control for concomitant tobacco usage.<sup>23</sup>

Cardiovascular side effects are distinctly more common with THC concentrates (“dabs”, butane hash oil)<sup>24</sup> and these are perceived to produce greater tolerance and withdrawal by their users.<sup>25</sup> In formal studies of therapeutic administration of nabimixols (Sativex®, GW Pharmaceuticals), a cannabis-based extract oromucosal spray containing equal measures of THC and CBD, cardiovascular adverse events were seen occasionally in early studies in which rapid titration and high doses (up to 130 mg of THC/day) were allowed. These have become quite rare with conventional dosing (to 32.4 mg/day) and slower escalation: tachycardia, hypertension, both well under 2% incidence;

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and orthostatic hypotension 0.1–0.2% (personal communication, 2014, Tilden Etges, GW Pharmaceuticals). At doses up to 97.2 mg THC/day, nabimixols spray produced no QTc or other cardiac conduction abnormalities.<sup>26</sup>

Recently, ultra-low THC doses proved cardioprotective via preconditioning effects.<sup>27</sup> THC 0.002 mg/kg *ip* given 2 h or 48 h before experimental MI in mice produced echocardiographic benefits on physiological measures, fractional shortening elevation, smaller infarct size, decrease in serum troponin and neutrophil infiltration to highly statistically significant degrees. Ultra-low doses of CBD have produced similar benefit as well as neuroprotective effects, and the combination is additive/synergistic, suggesting possible utility as protective agents prior to cardiopulmonary bypass.

## Mis-use

Contemporaneously, synthetic cannabinoids developed as pharmacological tools have appeared on the black market.<sup>28</sup> Certain of these designer drugs with colourful nicknames contrast with THC and anandamide as potent selective full

agonists at CB<sub>1</sub>, and display quite distinct pharmacology. I first heard of human use in 1999, when a young scientist related a harrowing experience after ingesting HU-210, a dimethylheptyl analogue of THC that rendered him prostrate, mute, tachycardic, panicked and hallucinating for 48 hours. These agents have become popular as black market alternatives to cannabis because they were previously legal in many locales, and have been undetectable in urine drug screens where THC metabolites may remain for weeks.<sup>29</sup> As clandestine products, their provenance and actual content are never guaranteed.

An article in this issue (see page 40)<sup>30</sup> portrays a young man using enormous chronic doses of 5F-AKB48 and sustaining embolic-type coronary occlusions. The authors put forward a possible promotion of platelet aggregation due to fluoridation of this molecule, which contrasts to reported antiplatelet effects of smoked cannabis<sup>31</sup> or THC.<sup>32</sup> This pattern is distinct from that of a case series<sup>33</sup> with 'K2', an agent often containing the analgesic JWH-018 and others, wherein three adolescents suffered ST and troponin elevation, two with normal coronaries, while another patient suffered

similar derangements with persistent chest pain.<sup>34</sup> Many synthetic cannabinoid victims have suffered additional morbidities such as seizures, nausea, etc. that support excessive CB<sub>1</sub>-stimulation as the culprit, but seemingly, various cardiac pathologies may be operative, perhaps endothelial damage<sup>35</sup> analogous to that seen in the nephrotoxicity in fatal cases of designer cannabinoid intoxication (personal communication, Pal Pacher, 2014). Clearly, additional investigation is necessary to understand the operative mechanisms.

To date, it appears that ultra-low THC and therapeutic phytocannabinoid dosing are cardioprotective, while supra-therapeutic recreational doses pose cardiovascular risks, and hyper-CB<sub>1</sub> stimulation by potent full agonists is distinctly dangerous to the heart. It remains for society to ascertain how science-based education may lower such risks and help potential consumers avoid a perilous misadventure in pharmacological roulette ●

## Conflict of interest

None declared.

## Editors' note

See also the article by Walsh *et al.* on page 40 of this issue.

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