Supplementary 1. Effects of Cannabis on Systemic Health

Cannabis-Based Medications: Between Relief and Risk

Historical records from traditional Chinese medicine write down that cannabis has been used for pain management since approximately 2700–2900 B.C. (1,2). A systematic review and meta-analysis conducted by Whiting et al. (30) reported that, while cannabinoids offer therapeutic potential in managing pain, their use is often accompanied by short-term adverse effects. These include dizziness, xerostomia (dry mouth), nausea, fatigue, somnolence, euphoria, vomiting, disorientation, lethargy, confusion, loss of balance, and hallucinations (3).

On the other hand, a review by McDonagh et al. (4) that evaluated the benefits and risks of cannabinoid-based products—primarily for chronic neuropathic pain—suggested that many adverse effects may be closely related to the route of administration (4). Their findings shown that oral synthetic cannabis formulations with high THC/CBD ratios, as well as sublingual cannabis extracts, were more likely to cause dizziness and sedation (4). Despite the growing use of these substances, the authors emphasized a lack of robust evidence supporting the efficacy of many cannabinoid products for pain management (4), thereby highlighting the urgent need for more comprehensive and long-term clinical trials.

Parmar et al. (5) also examined various routes of medicinal cannabis administration, finding a broad spectrum of clinical applications depending on the formulation and method of delivery (5). Smoked marijuana, for example, has been used in the treatment of neuropathic

pain and glaucoma (5). Dronabinol, a synthetic analog of THC, has been commonly prescribed for weight gain in patients with AIDS, as well as for chemotherapy-induced nausea and vomiting (5). It has also been employed for pain relief in multiple sclerosis—indications for which nabilone, another synthetic cannabinoid, is similarly used (5). Nabiximols, a natural cannabis extract delivered via oromucosal spray, is primarily prescribed for spasticity associated with multiple sclerosis and for moderate to severe cancer-related pain (5).

However, the pharmacological effects and adverse profiles of these products vary significantly depending on their route of administration. These differences are largely attributable to factors such as bioavailability, time to peak plasma concentration, onset of action, half-life, and hepatic metabolism (5). Notably, the metabolism of oral THC leads to the formation of 11-hydroxy-THC, a potent psychoactive compound (5). The inhalation of cannabis, particularly through smoking, has been associated with a range of side effects including cough, chronic bronchitis symptoms, dizziness, numbness, tachycardia, nightmares, visual disturbances, headaches, intoxication, dry mouth, drowsiness, anxiety, emotional lability, cognitive impairment, mental slowness, delayed reaction times, and burning sensations at neuropathic pain sites (5). Additionally, more severe effects such as hyperemesis, syncope, orthostatic hypotension, hypertension, palpitations, paroxysmal atrial fibrillation, and peripheral vasodilation have been reported (5).

Age is a critical factor influencing the safety and efficacy of cannabinoid-based therapies. Physiological and metabolic changes associated with aging may increase susceptibility to adverse reactions. Scott et al. (6) found a higher prevalence of arrhythmia, cognitive

dysfunction, dizziness, sedation, confusion, and psychosis in older adults undergoing cannabinoid treatment (6). Given these findings, it is essential to consider age, duration of use, and route of administration when evaluating the pharmacokinetics, pharmacodynamics, and therapeutic effectiveness of these substances. Long-term, multicenter clinical trials that incorporate a variety of cannabinoid formulations and delivery methods—including both synthetic and plant-derived compounds—are necessary to assess their true therapeutic potential and associated risks across different age groups.

This approach is especially relevant considering the widespread belief of cannabis products as inherently safe due to their natural origin. However, many of the adverse effects associated with medicinal cannabis are likely underreported (6). This underscores the pressing need to prioritize patient safety and promote evidence-based research that moves beyond cultural stigma and anecdotal use.

Cardiovascular, Cerebrovascular and Coagulation Effects

Cannabis use has been linked to a variety of systemic health risks, including stroke, cardiovascular events, respiratory dysfunction, drug interactions, immune dysregulation, and behavioral disorders (7–14, 15). A study by Wolff and Jouanjus (9), involving ninety-eight young cannabis and synthetic cannabinoid users, found a temporal correlation between cannabis use and stroke (9). These events were hypothesized to result from reversible cerebral vasoconstriction (9). Similarly, Mittleman et al. (10) reported that cannabis consumption increased the risk of acute myocardial infarction by 4.8-fold during the first hour following use, particularly in younger individuals. Regular consumption of Δ9-

tetrahydrocannabinol (Δ9-THC) exceeding 10 mg per day has been associated with a higher risk of dependence, and this compound may persist in the body for up to ten days (10). In fact, studies such as those by Rumalla et al. (16) and Hemachandra et al. (17) have reported an incidence of cerebrovascular ischemia ranging from 2.3 to 2.9-fold in young cannabis users, particularly when compared to tobacco smokers (16,17).

Many cerebrovascular events have been associated with increased cerebral blood flow, a phenomenon linked to the activation of cannabinoid receptor type 1 (CB1), which stimulates the synthesis of vasodilatory agents (18). This effect is particularly plausible given that the cells involved in cerebrovascular regulation are known to produce endocannabinoid ligands, such as anandamide, and express cannabinoid receptors, including CB1 (18). However, the onset and severity of physiological responses are often dose- and time-dependent (18).

The impact of cannabis on coagulation is still a subject of ongoing debate, as some studies have reported both procoagulant and anticoagulant effects of cannabinoids (18). To date, cannabinoid receptors have not been found in platelets or their associated RNA, which has led to alternative hypotheses regarding cannabinoid-mediated modulation of hemostasis. One such theory posits that Δ9-THC may function as a cyclooxygenase-2 (COX-2) inhibitor, thereby reducing oxylipin levels in platelets and eliciting effects comparable to those of aspirin (19). While these findings are intriguing, they should be interpreted with caution and not generalized across all patient populations. Nevertheless, they provide important insights for clinicians—particularly in surgical and dental contexts—where bleeding and clotting risks must be carefully managed.

Respiratory effects

Smoking is the most widely used method of cannabis administration worldwide, particularly among young adults (20), and it has even come to be considered the second most smoked psychoactive substance after tobacco (20). This increase over the past decade has been largely attributed to a lack of awareness about the associated adverse effects and health risks (20). The respiratory adverse effects of cannabis use are primarily related to combustion (20). Smoked cannabis can be consumed through various methods, including joints, blunts, and spliffs—conventional hand-rolled cigarettes that are typically unfiltered and rudimentary in preparation. Some have only cannabis, while others include added tobacco (20). Other more elaborate methods include vaporization through devices such as bongs, hookahs, e-cigarettes, and vapes (20).

Smoking cannabis eases the inhalation of numerous irritant and carcinogenic agents (18), many of which are also found in tobacco smoke, except for nicotine (18). Common components include carbon monoxide, ammonia, hydrogen cyanide, isoprene, acetaldehyde, formaldehyde, acrolein, phenols, polycyclic aromatic hydrocarbons such as benzopyrene, and heavy metals such as cadmium, mercury, and lead (20).

Respiratory effects associated with smoked cannabis largely depend on the method of inhalation, the depth and duration of smoke retention in the lungs before exhalation (18), the temperature, and the chemical composition of the smoke (18,20). These factors contribute to a range of respiratory alterations, including irritation of the bronchial tree (20), development of chronic bronchitis, bronchial inflammation, bronchodilation, airway remodeling,

pharyngeal and uvular edema (18), and increased susceptibility to infections due to impaired alveolar macrophage function (20). Other factors such as frequency and duration of exposure, as well as whether the individual is a cannabis-only user or also smokes tobacco, must also be considered. However, compared to tobacco smoke, cannabis smoke has been shown to be more irritating and hotter to the bronchial tissues (20), leading to certain types of pulmonary tissue damage that have not yet been seen in tobacco smokers (20). It is important to clarify that we do not take a stance either for or against tobacco when compared to smoked cannabis, as there is substantial evidence documenting the systemic and oral cavity-related harm associated with the habit of smoking.

At this point, it is worth making a final remark about the use of vaporizers as a method of cannabis administration (20). The association between vaping and the development of lung disease, such as EVALI (e-cigarette or vaping-associated lung injury), is well known (20). Although many studies show that cannabis alone does not directly cause EVALI, most of these devices have flavoring agents, vitamin E acetate, and cannabis (20). Therefore, future research should rigorously investigate the effects of these vapor-based electronic combustion devices and their derivates on various systems of the human body.

Pharmacological Considerations

Cannabinoids are known to interact with the hepatic cytochrome P450 enzyme system, which plays a critical role in the metabolism of numerous pharmaceutical agents (5). One clinically relevant interaction involves the anticoagulant warfarin, whose efficacy may be potentiated by either Δ^9-THC or cannabidiol (CBD), potentially leading to elevated international

normalized ratio (INR) values in patients using both agents concurrently (11). This interaction is thought to result from cannabinoid-mediated inhibition or modulation of cytochrome P450 enzymes (12), which can increase warfarin bioavailability and its anticoagulant effect.

Despite growing awareness of these interactions, current evidence is still limited and largely speculative. Most reports are based on case studies or theoretical models rather than large-scale pharmacokinetic trials. Nonetheless, several clinically significant interactions have been proposed. Co-administration of cannabinoids with central nervous system depressants—including alcohol, benzodiazepines, muscle relaxants, and opioids—may potentiate sedative effects and lead to cross-tolerance. Additionally, concurrent use of cannabis with systemic corticosteroids may worsen immunosuppression (5). There is also evidence suggesting that cannabinoids may reduce the therapeutic efficacy of certain protease inhibitors and antipsychotic medications (5).

It is important for clinicians to consider these types of interactions before prescribing cannabinoid-based medications at their professional discretion, especially in patients who may be susceptible to adverse effects. Furthermore, caution should be exercised when prescribing added medications or administering treatment as required by the patient's condition, whether the individual is a medical or recreational cannabis user.

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