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Cannabis & Anaesthesia

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INTRODUCTION

Cannabis sativa is amongst the oldest cultivated plants. Evidence of its use dates back 4000 BC for therapeutic, spiritual, and recreational purposes[1,2]. History of cannabis use spans across different cultures[1]. In the Chinese pharmacopeia it was used for the treatment of joint pain, muscle spasm, and malaria[1], whilst in India, cannabis was used to remedy a multitude of medical disorders such as infections, pain disorders, inflammation, seizures, and anorexia[3]. Anaesthetic use of cannabis date back to the second century by Hau Tou, a Chinese surgeon who made use of cannabis boiling powder 110 – 207 AD to facilitate analgesia and anaesthesia during his surgical procedures[1,3].

Cannabis is a voguish pharmacological agent with recreational and medical use, perceived widely by recreational users and some leading medical journals as being harmless[4]. The preceding two decades displayed an increased prevalence and interest in recreational use of cannabis, resulting in a dynamic legal landscape internationally and domestically[5].

South Africa(RSA) is the third largest producer of cannabis, due to optimal cultivation conditions in the dagga belt which includes Eastern cape and kwa-Zulu Natal[6]. Cannabis is the most common illicit substance in RSA after alcohol[6]. The prevalence of cannabis use in RSA ranges between 5-10% among adolescents, 2% among adults, 29 -50% of trauma patients and with 39% being associated with crime[6]. Men and urban areas dwellers (particularly Western Cape and Gauteng) have been associated with increased use of cannabis[6].

Recent legalisation and increased prevalence of cannabis use in our setting necessitate education for all physicians in managing “cannabis users”. Only a fraction of medical schools & residency programs covers cannabis and the endocannabinoid system as part of their curriculums. Thus, profound deficiencies in knowledge and confidence exist when engaging with cannabis users in different clinical settings especially in the perioperative period[2,7]. No global consensus governs the use of cannabis and related products.

This document will highlight essential physiological plus pharmacological effects of cannabis, and the key perioperative anaesthetic consideration for the “cannabis user”.

CANNABIS

A plethora of colloquial names have been used to describe cannabis. The commonly used English names include: dagga, cannabis, marijuana, skunk, Hashish, bud herb, resin, weed, ganja, purple haze, northern lights, charis, Thai sticks, grass, and pot[8]. In RSA cannabis is mostly referred to as dagga. However; in this document the term Cannabis will be used as it represents the Genus of the plant.

The single convention on Narcotic Drugs, define cannabis as a flowering or fruiting top of the cannabis plant from which the resin has not been extracted thus excluding the seeds and leaves when not accompanied by the tops[8]. It is an annual, dioecious flowering herb, with the flowering staminate (male) plants being tall and less robust compared to seed bearing pistillate (female) plants[8]. The plant belongs to Genus Cannabis, Family Cannabaceae, Order Urticales which has three genetically, morphologically and chemically distinct variant cannabis species: *Sativa*, *Indica*, and *Ruderalis*[8].

Over 100 cannabinoids have been identified in *Cannabis sativa*[9]. Delta 9-tetrahydrocannabinol (Δ^9-THC), and cannabidiol (CBD) are the two most studied cannabinoids of therapeutic value[5]. Natural cannabis plant contain 5 to 15% of Δ^9-THC, the psychoactive cannabinoid (high concentration in *Cannabis Sativa*) producing euphoria, altered sense of time, analgesia, increased appetite, and impaired memory[10]. CBD is a nonpsychoactive cannabinoid (high in *Cannabis Indica*) with anti-inflammatory and neuroprotective effects[5,10].

All cannabinoids are present as carboxylic acids and require thermal decarboxylation to form active cannabinoids[8]. Cannabinoids differ in pharmacological properties with some displaying agonists, partial agonist, and antagonist effect on the various cannabinoid like receptors[8]. The cannabis and resin are strictly regulated due to their high Δ^9 -THC content as compared to the root and stem of the plant[8].

LEGAL LANDSCAPE

Legal restriction of cannabis in RSA occurred under the Medical, Dental, and pharmacy act no. 13 of 1928[11]. The South African health product regulatory authority (SAHPRA) formally known as, the Medical control council (MCC), classifies cannabis as a schedule 7 substance, placing cannabis as a substance of no medical value, illegal to cultivation, analysis, possession, research, use, sell, and supply without authorisation from the Department of health. Possession of over 115 grams was presumed as guilty of dealing under the Drugs and Drug Trafficking act of 1992.

In the USA cannabis was widely used until 1937[12]. Adverse public health effects and increased crime rates lead congress to propose federal restriction[12]. Cannabis was declared illegal and removed from the United States pharmacopeia in 1942[5,12]. These legal restrictions hindered research on therapeutic efficiency of cannabis resulting in questionable scientific legitimacy[1,5,12].

In 2016 the SAHPRA published regulations providing for medical use of cannabis, and expressed a desire to reclassify cannabinoid medication to schedule 6, making it available for medicinal use with special authorisation to the physician prior to

prescription[13]. The scheduling of cannabis is widely debated with many clinicians and experts in the field who argue that the use of cannabis is not addictive[5], while other experts are of the opinion that cannabis is a “gate-way” drug with the potential to pave the way for use of stronger drugs such as cocaine or heroin, especially in the adolescent population[2].

The access to cannabis and related products varies geographically. Major health stake holders are inconsistent in their approach and recommendations for medical cannabis use[2]. The World Health Organisation (WHO) expert committee on drug dependence recommended the rescheduling within the international Drug Control Conventions occurs for cannabis, cannabis resin, Dronabinol, Δ^9-THC, extracts and tinctures of cannabis, and with removal of CBD preparations with less than 0.2% Δ^9-THC from the international drug control conventions[2].

A trend of legalisation for cannabis is apparent internationally, with consequent increase in cannabis and related product availability[2,5]. Recreational cannabis is legal in Uruguay, Canada, and parts of USA[5]. Medical use of Cannabis is currently legal in 23 states and in the District of Columbia but it remains a federal offence to grow, sell, or purchase cannabis in some states[5].

In South Africa cannabis was legalised in 2018, following two landmark court rulings[2,14].

High court ruling by Judge Dennis Davis in 31 March 2017[14]:

- Any law disallowing the use and cultivation of cannabis by an adult in a private dwelling is unconstitutional and therefore invalid, and on these grounds such infringement of the constitutional right to privacy could not be justified[14].
- Due to appeals from the state the decision needed to be confirmed by the constitutional court before taking full effect[14].

Constitutional court ruling by Deputy Chief Justice R. Zondo in 18 September 2018[14]:

- An adult person may, use or be in possession of cannabis for personal consumption in private[14].
- The use, including smoking, of cannabis in public or in the presence of children or in the presence of non-consenting adult person is not permitted[14].
- The use or possession of cannabis in private other than by an adult for his or her personal consumption is not permitted[14].
- The cultivation of cannabis by an adult in a private place for his or her personal consumption in private is no longer a criminal offence[14].
- The judgment does not define a limit an adult person may cultivate or possess, leaving this up to the parliament of South Africa[14].
- The constitutional court ordered Parliament to bring the laws in line with their judgment within 24 months[14].

A summary of current legal status of cannabis and cannabinoids can be found in the review by Patrick Tapley et al[2].

PHYSIOLOGY

The endocannabinoid system is a ubiquitous signalling system involved in a myriad of physiological functions vital for homeostasis[15]. Its functions are depicted by the phrase “Relax, eat, sleep, protect, and forget”[16]. The components of the system consist of receptors, endocannabinoids, and enzymes which regulate its function[15].

Endocannabinoid receptors

In 1992 neuronal cannabinoid-1 receptor was discovered and subsequently peripheral cannabinoid-2 receptor was identified[15]. Recently a cannabinoid-3 has been identified in the liver and brain[15]. These cannabinoid receptors are members of the rhodopsin-like G-protein($G_{i/o}$) coupled receptor family, which when activated lead to the suppression of adenylyl cyclase, reduced formation of cyclic adenosine monophosphate (cAMP) and reduction in calcium influx with inhibition of neurotransmitter release[15].

Cannabinoid receptor distribution

Cannabinoid-1 receptor distribution includes neuronal and peripheral tissue, where high concentrations are expressed in presynaptic terminals for retrograde signalling of endocannabinoids, and also postsynaptic sites for self inhibition[15].

Nervous system distribution of Cannabinoid-1 receptor includes[15]:

Central nervous system[15]

- High levels: Olfactory bulb, hippocampus, Basal ganglia, Cerebellum[15].
- Moderate levels: Cerebral cortex, septum, amygdala, hypothalamus, part of the brainstem, dorsal horn of spinal cord[15].
- Low levels: Thalamus, Brainstem, ventral horn of spinal cord (explaining lack of respiratory depression with cannabis overdose)[15].

Peripheral nervous system[15]

- Sympathetic nerve terminal, trigeminal ganglion, dorsal root ganglion, and dermal nerve endings of pain sensory neurons[15].

Peripheral tissue distribution includes[15]

- Cardiovascular system: upregulated in pathological conditions and can lead to myocardial oxidative stress, inflammation, fibrosis and cardiac dysfunction[15].
- Gastrointestinal system: enteric nervous system, enterocytes, enteroendocrine cells, immune cells, and mucosa where it modulates mobility, secretion of fluid, hormones and neurotransmitters, as well as epithelial permeability[15]. Thus, controlling appetite in the hypothalamus and regulates food intake plus energy balance[15].
- Hepatic: regulates energy balance and metabolism[15]. Expression is increased in pathological conditions leading to insulin resistance, fibrosis, and lipogenesis[15].
- Respiratory, adipose tissue, reproductive system, adrenal, skin, muscular-skeletal, and eyes[15].

Cannabinoid-2 receptor shares 44% sequence homology with Cannabinoid-1 receptor[15]. Two Isoforms have been described of which one is expressed in lymphoid hematopoietic tissue such as spleen and in lower levels of the brain, whereas the other is expressed in testes and reward regions of the brain[15].

Cannabinoid receptor ligands

These are specific ligands which specifically bind and activate the cannabinoid receptors[15]. Three categories exist: Endocannabinoids which are endogenous to the body, Phytocannabinoids from plants, and Synthetic cannabinoids manufactures in a laboratory[15]. Table 1 below outlines commonly described cannabinoids[2].

Table 1: Classification cannabinoids

Endocannabinoids	Phytocannabinoids	Synthetic
• N-Arachidonoy-l ethanolamide (Anandamide)[2] • 2-arachidonylgylcerol (2-AG)[2] • Docosatetraenoyl-ethanolamide (DEA)[2] • N-arachidonyldopamine (NADA)[2] • Virodhamine[2] • 2-arachidonylglyceryl[2] • Noladin ether[2] • Dihomo-gamma-linolenoylethanolamide (HEA)[2]	Δ^9-THC 1-22% with CBD 0.05-9% • Inhalational (Marijuana)[2] • Oral (Hashish)[2] Pure Cannabidiol (CBD) • Capsule[2] • Oromucosal spray[2] • Oil (Epidiolex)[2] Δ^9-THC and CBD • Nabiximol (Sativex) 2.7mg Δ^9-THC: 2.5mg CBD oromucosal spray[2] • Cannador 2.5mg Δ^9-THC: 1.25mg CBD oral capsule[2]	Synthetic Δ^9-THC • Dronabinol (Mirinol) oral capsule[2] • Syndros Liquid [2] Synthetic THC analogue • Nabilone (Cesamet) oral capsule[2] Other derivatives: • Spice K2 Eclipse Jwh-018, Ur-144, Pb-22 (oral/ smoked)[2]

N-arachidonoyl-ethanolamine (AEA)/ (anandamide) and 2-arachidonoylglycerol (2-AG) are the two extensively studied endocannabinoids[15]. These endocannabinoids are synthesised from cell membrane phospholipids on demand following physiological or pathological stimuli[15].

AEA is synthesised from N-acyl-phosphatidylethanolamine (NAPE) by NAPE-specific phospholipase D (NAPE-PLD) in the post synaptic terminal[15]. It activates presynaptic and intracellular cannabinoid -1 receptor and other none cannabinoid receptor targets, such as the inhibition of L-type calcium channels, activation of transient receptor potential cation channel subfamily V member 1 (TRPV1)[15]. Fatty acid amide hydrolase (FAAH) in postsynaptic terminals degrade AEA to arachidonic acid and ethanolamine[15]. AEA has high-affinity, and is a partial agonist of cannabinoid-1 receptor and inactive on the cannabinoid-2 receptors[15].

The biosynthesis of 2-AG is from postsynaptic terminals from diacylglycerol (DAG) by diacylglycerol lipase-alpha (DAGL-alpha); it activate the presynaptic cannabinoid-1 receptor suppressing calcium influx and neurotransmitter release[15]. In astrocytes, activation of cannabinoid-1 receptor by 2-AG leads to glutamate release[15]. The excess 2-AG is taken up into the presynaptic terminal where it is degraded by monoacylglycerol lipase (MAGL) into arachidonic acid and glycerol[15]. 2-AG is a full agonist at both cannabinoid receptors with moderate to low affinity[15]. The baseline level of 2-AG is 1000 times higher than AEA in the brain[15]. Based on this it is postulated that 2-AG is the primary endogenous ligands for the cannabinoid receptors in the central nervous system[15].

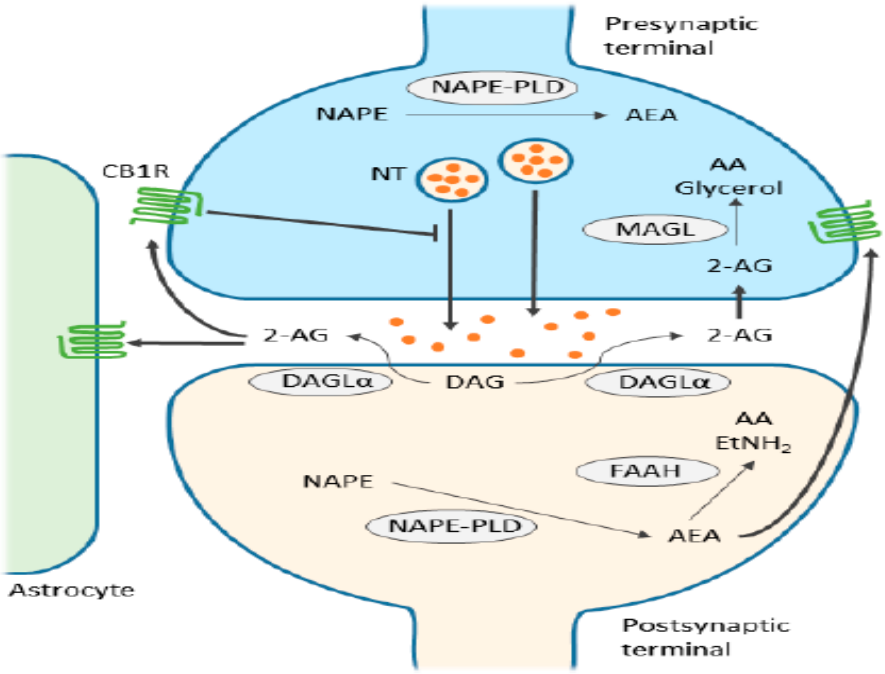

Figure 1: Is a schematic summary of these endocannabinoids described[15].

PHARMACOLOGY

Naturally cannabis contains 5 to 15% of the active ingredients Δ^9-THC and CBD[5]. Different plants vary in THC-to-CBD ratio, making dosage standardisation challenging[2]. THC-to-CBD ratio with optimal therapeutic effect and minimal adverse effects has been shown to be 1:1. Widespread inaccuracy in labelling of Δ^9-THC content of cannabis products contributed to inaccuracies when prescribing a dosage[2,5].

Pharmacokinetics

The pharmacokinetics of cannabinoids are difficult to predict due to several variables that dictate the Δ^9-THC concentration in a delivered dose such as the product's Δ^9-THC concentration, route of delivery, metabolism, and elimination of the cannabinoids[7,17]. Table 2 below outlines the different administration routes with their advantages and disadvantages[7,17].

Absorption

Absorption rate of cannabis varies with product lipid solubility, organ tissue differences, and Δ^9-THC concentration[2]. Bioavailability varies with route of administration and as such the onset of effect[7]. Inhalational route result in 10-60% bioavailability with a rapid onset of action within seconds to minutes while oral administration result in a lower bioavailability of 20-30% due to extensive first pass metabolism and has a delayed onset of action of 1-2 hours[7].

Distribution

The volume of distribution is 32 l/kg for CBD and 3.4l/kg for Δ^9-THC[2].Cannabinoids follows a three compartment model, and are rapidly distributed to vessel rich organs, placenta, and breast milk[18]. Cannabinoids undergo significant redistribution and accumulation due to their liposolubility[9,18]. The plasma half-life for Δ^9-THC ranges

from 20 to 30 hours, with tissue half life of 30 days depending on the frequency and duration of use[7,19].

Table2: Different routes of cannabis administration and their characteristics[7,17].

Smoking	Vaporisation	Oral ingestion	Other
Commonest route (Joints, bongs, pipes etc.) Combustion at 600 – 900 ^{O}C produce Tar, PAC, CO, NH_3	Heating cannabis at 160 – 230 ^{O}C reduces CO, but not PAH.	Includes oils, capsules, edibles, prays, lozenges juicing and teas.	Topical is ideal for local symptoms, but limited research. Variable OOA, DOA. Less systemic effects, good local symptom effect.
OOA 5-10min DOA 120-240hr	OOA 5-10min DOA120-240hr	OOA 60-180min DOA 120-240min	
Advantages: • Rapid OOA • For acute pain • Treats episodic N&V	Advantages: • Rapid OOA • For acute pain • Treats episodic N&V • Less harmful biproducts vs. Inhalation • Less pulmonary symptoms vs. Inhalation	Advantages: • Oils, Capsules offer convenience and accuracy of dosing. • Less odour • Discrete • For chronic symptoms	Suppository for specific population (cancer, GI symptoms, young, elderly etc.) Highest bioavailability 80%. Recreational routes: "shatter", "dabs" deliver high dose Δ^9-THC leading to side effects and are inappropriate for medical use.
Disadvantages: • Dexterity required • Chronic use leads to respiratory (Bronchitis, Cough, Phlegm) • 30 to 50% of cannabis is lost in the side stream • Mixing cannabis with tobacco increase respiratory and cancer risk.	Disadvantages: • Dexterity required • Vaporisers expensive, and not always potable	Disadvantages: • Titration challenge due to delayed OOA • Edibles(brownies/cookie) is more difficult to dose • Juicing and Tea's does not allow for adequate decarboxylation of the plant. • Spray (Nabiximol) standard dose 1:1 Δ^9-THC: CBD expensive and spotty availability. • Tinctures and lozenges have intermediate onset, but limited research.	

NH_3 – Ammonia, CO – Carbon monoxide, PAH – polycyclic aromatic hydrocarbons, OOA – Onset of action, DOA – Duration of action[7]

Metabolism

Is mainly by hydroxylation and glucuronidation in the liver by the cytochrome P450 isoenzyme system [19]. Δ^9-THC is metabolised to over 80 metabolites, and result in the inhibition of CYP3A4 which leads to significant drug interactions with warfarin and oxycodone[2]. CBD is metabolised to over 100 metabolites and inhibits CYP2D6 and CYP3A4 resulting in significant drug interaction with benzodiazepines, haloperidol, and oxycodone[2,19].

Elimination/Excretion

Clearance of cannabinoids is 38.8l/hr to 53L/hr[2]. Casual users have a prolonged elimination half-life of 56hours, and only 28hours for chronic users [2]. Excretion of Δ^9-THC and its metabolites is via faeces (65 to 80%) and urine (20-35%)[2]. CBD and its metabolites are excreted in the urine with an elimination half life of 2-5 days[2]. 15% of metabolites undergo entero-hepatic recycling thus leading to prolonged clinical effect[2].

PHARMACODYNAMICS

Cardiovascular effects

Effects are mediated by agonist action at the cannabinoid-1 receptor in cardiac myocytes and suppressed by cannabinoid-1 receptor antagonist[17]. Intensity of response depends on the dose and patient tolerance to cannabinoids[17]. Sympathetic effects are more pronounced in naive users, and parasympathetic activation predominates in chronic or heavy (Δ^9-THC≥10mg) cannabinoid users[17,20].

Naive users experience a dose dependent increase in inotropy, chronotropy resulting in an increased blood pressure which correlates with peak Δ^9-THC plasma levels and is sustained for up to 60 minutes post cessation of inhalational cannabis intake[17]. This is due to an increase in catecholamine concentration following sympathetic activation and parasympathetic inhibition[17]. Cannabis users have a fivefold increased risk of myocardial infarction attributed to an increase in myocardial oxygen consumption (VO2), high carbon monoxide level, and coronary thrombosis[17,19]. The sympathetic effects can be blunted by pre-treatment with propranolol[17].

Echocardiogram studies show an increase in cardiac output and in the velocity of circumferential myocardial fibre shortening[17]. There is a common occurrence of premature ventricular contractions[17]. Noradrenalin levels rise gradually and reach a peak at 30 minutes which is sustained for 120 minutes post cannabis exposure[17]. Δ^9-THC may potentially have Anticholinergic effects through depletion of acetylcholine stores[17].

Chronic or heavy users (≥ 10mg) have a dominant parasympathetic response accompanied by baroreceptor dysregulation leading to a negative chronotropy response and postural hypotension, not compensated for by sympathetic activation[17]. Malignant arrhythmias and sudden death occur frequently in chronic cannabinoid use[17]. The risk of arrhythmia doubles in hospitalised male patients between the ages 45-64 years, with atrial fibrillation being the most common arrhythmia[17,19]. Other conduction abnormalities and arrhythmias associated with cannabis include 2nd degree heart block, ventricular tachycardia, ventricular fibrillation, Brugada pattern and asystole[17]. Coronary spasm leads to myocardial infarction especially in individuals with coronary artery disease[17,19].

Due to the long half life of cannabinoids and the significant cardiovascular consequences that result; anaesthesia should be avoided for a minimum of 72 hours post exposure[17,19]. An enquiry of angina-free functional capacity before and after cannabis use is vital during the preoperative visit, and a delay of an hour may be required to mitigate the risk of perioperative myocardial infarction[19].

Respiratory effects

Cannabis inhalational intake increases perioperative pulmonary complications[2,17]. Vaping and smoking unfiltered cannabis preparations facilitate inhalation of irritants and carcinogenic chemicals[17,19]. Radiological imaging demonstrated extensive airway opacification in a centri-lobular pattern “tree in bloom”[17]. An FDA warning has been issued following multiple reports of severe pulmonary disease associated with

vaping Δ^9-THC products[2]. Cannabinoid-1 receptor activation mediated by the endocannabinoid anandamide leads to bronchodilation during smoking[17].

Long term cannabis smoking results in an increased bronchial tone and airway hyperreactivity which may impact on anaesthetic airway management[17]. Chronic cough, bronchitis and emphysema similar to cigarette smoking have been documented in cannabis users[19]. Post operative airway obstruction due to pharyngeal and uvula edema has been reported in chronic cannabis users[17]. Postponement of elective surgery is therefore recommended for patients that have recently consumed cannabis[2,17,20]. Some practitioners administer steroids to minimise uvular edema or uvulitis[17]. Diffuse alveolar haemorrhage and necrotizing bronchiolitis occurs with high dose Δ^9-THC use[17]. Synthetic cannabinoids are associated with pulmonary embolism[17].

Thermoregulation

Cannabinoid -1 receptor activation alters central thermoregulation, leading to perioperative hypothermia and post-operative shivering, thus predisposing patients to hypoxemia, increased heart rate, increased oxygen consumption, myocardial ischemia and acidosis[17.] The above effects are reversed by administration of cannabinoid-1 receptor antagonist[17]. Anaesthetist need to take this into consideration as concomitant use of inhalational agents following cannabis exposure may potentiate vasodilatation, exacerbate hypothermia and lead to post-operative shivering[17].

Coagulation

Both pro-coagulation and anticoagulation effects have been demonstrated with cannabis use[17]. High dose Δ^9-THC is associated with ADP-induced platelet aggregation and thrombocytopenia[17]. Cannabinoids may reduce nitric oxide availability leading to endothelial dysfunction and platelet activation[17]. Concomitant use of cannabis with warfarin results in a clinically significant coagulopathy due to the inhibition of CYP3A4 and CYP2D6, thus increasing the risk of haemorrhage[17]. Chronic cannabis users have showed increased bleeding times[17].

Cerebrovascular system

Ischemic stroke is common in cannabis users with an incidence 4.7 times higher than non-smokers[17]. Younger cannabis users have a 2.3 to 2.9 increased risk of cerebrovascular ischemia when compared to tobacco smokers[17]. Ischemic stroke and Transient ischemic attacks are more common than haemorrhagic stroke, with the posterior circulation being mostly affected in up to 53% of the cases[17]. The main risk factors for cannabis related cerebrovascular disease include: male gender with a male to female ratio of 3.7:1, age 30-35 years and chronic cannabis use[17].

ANAESTHESIA INTERACTION WITH CANNABIS

Intravenous and inhalational induction agents

Evidence of cannabis and anaesthetic agent interactions in humans is limited. Cannabis shares mechanism of action with general anaesthetic induction agents on modulating the ϒ- aminobutyric acid receptor (GABA), and this may result in cross tolerance[17]. Cannabis smokers require a significantly higher dose of propofol and volatile anaesthesia when compared to non-cannabis users[21,2,17].
The psychomotor effects of Ketamine are also enhanced with cannabis use[2].
The antiemetic properties of propofol may be mediated by the endocannabinoid[22].

Acute pain management

Cannabis is comparable to placebo in analgesic efficacy for acute pain management[23]. The effect of cannabis interaction with opiods remains controversial. Several studies have shown a greater incidence of opiod misuse with concomitant use of cannabis and opiods for acute pain[17]. Holdcroft A et al evaluated a cannabis extract with 10mg and 15mg of Δ^9-THC for efficacy in post-operative pain reduction, also showed a number needed to treat of 2 and 1.3 respectively, however a serious vasovagal adverse events was documented[3,24].
Ketamine induces endogenous cannabinoid release similar to paracetamol, and this contributes to its analgesic effect[2,25].

Neuromuscular blockers

Canabinoid-1 receptors are also located in the neuromuscular junction. No published reports describe the interaction between cannabinoids and nondepolarizing muscle relaxants in humans[17].

Adjuncts

Activation of the cannabinoid receptors lead to increased activity of the α 2 subunits on voltage gated calcium channels and reduction in neuronal transmission[2].
High dose gabapentin for management of cannabis tolerance produce Δ^9-THC like effects [2]. A synergistic effect with co administration of Δ^9-THC and gabapentin occurs, however more Δ^9-THC side effects result suggesting overlapping pharmacological effect [2].

Ketamine induces endogenous cannabinoid release leading to anti-nociception, and its psychomotor side effects are enhanced with CBD administration[2].

A limited amount of studies evaluates the interaction of cannabis and α2 agonist in humans[2.] Synergistic effects have been postulated to be the result of similar intercellular signalling mechanism plus close locality of the target receptors in the periaquiductal grey matter and substantia gelatinosa[2].

USES OF CANNABIS RELEVANT TO ANAESTHESIA

Chronic pain

Chronic pain conditions where cannabis and cannabinoids have been reported to have analgesic efficacy include: neuropathic pain management from multiple causes including HIV-neuropathy, diabetic neuropathy, spinal cord injury, peripheral nerve injury, spasticity in multiple sclerosis patients[2]. Randomised clinical trials which evaluate cannabis use for the treatment of chronic pain have various limitations which make conclusions on efficacy difficult[26]. Limitations are due to short duration of exposure to cannabis, small sample size, heterogeneity in definition of chronic pain, high withdrawal rates in the treatment arms due to adverse effects and lack of benefit[26-28].

Reviews vary in their findings and recommendation on the beneficial effect of cannabis for chronic pain, and there remain a lack of consensus in many regulatory authorities[2,29,12,30]. Stockings E et al showed that the number needed to harm(NNTH) is 6 for cannabis which is above that of opiods NNTH of 5[28]. The number needed to treat(NNT) is 24 for a 30% pain reduction thus compares unfavourable with opiods NNT 4.3, pregabalin NNT 7.7, tricyclic NNT 3.6[28]. Several studies report moderate evidence for analgesic efficacy when compared to placebo, however there is a high likelihood of adverse effects such as drowsiness, hallucination , confusion, dizziness, dry mouth, nausea and vomiting, diarrhea, somnolence, fatigue and loss of balance[26,28,31]. These studies also had a high drop out rates ranging from 15-20% due to poor tolarance of adverse effects[26,28,31].

Nausea and vomiting secondary to chemotherapy

Cannabis is a broad-spectrum antiemetic, through the activation of cannabinoid-1 receptor in the brainstem and enteric nervous system[17]. Cannabinoids have been shown to be superior to placebo with similar or better efficacy than antiemetics (dopamine antagonists) in the treatment of chemotherapy associated nausea and vomiting[32]. Nabilone and Dronabinol are the two synthetic Δ^9-THC approved for the treatment of intractable post-chemotherapy nausea and vomiting[26,32]. Although cannabinoids had more side effects; they were better tolerated and preferred by patients[32]. Meiri E et al compared Dronabinol and Ondansetron, and showed similar efficacy[33]. Efficacy in the peadiatric population is less conclusive and no clinical trial has evaluated CBD for this benefit[26].

Post operative nausea and vomiting (PONV)

Limited evidence exist on the beneficial effect of cannabis for prevention and treatment of PONV[2]. Intravenous administration of Δ^9-THC is ineffective for PONV and may be associated with intolerable adverse effects[34]. Prophylactic treatment with Nabilone has no benefit for PONV prevention[35,36]. Some beneficial effects have been demonstrated when cannabis is used as part of a multimodal strategy in PONV prophylaxis[2].

ADVERSE EFFECTS

Cannabinoid hyperemesis syndrome

This is a paradoxical hyperemetic condition which occurs in chronic cannabis users. It is charectarised by: cyclic nausea and vomiting, abdominal pain refractory to standard antiemetics and analgesics[17]. These symptoms rapidly improve after cannabis cessation[17]. The pathophysiology remains ambiguous; postulated to result from medicated activity in the gastrointestinal tract & enteric nervous system, and desensitization of cannabinoid -1 receptor in the brain[17]. Complete symptom relief has been obtained with butyrophenones[17]. There is no association between this syndrome and PONV[17].

Acute intoxication

Intoxication from cannabis is extremely rare in adults, however a few cases have been documented after accidental ingestion in children[4,37]. Clinical manifestation vary according to age, with neurological manifestations (ataxia, purposeless movements, lethargy, coma) being prominent in children[37]. In adolescence and adult presentation: acute intoxication is due to the physiological effects of cannabis[19]. Neuropsychiatric features such as psychosis, psychomotor, mood, perception, thought content impairment may be witnessed, and features associated with complications secondary to inhalation when smoking route is used[37].This is relevant in the perioperative period as these individuals have a high tendency for violent emergence from anaesthesia[19].

Symptoms of intoxication can be similar to other perioperative presentations such as malignant hyperthermia, serotonin syndrome, neuroleptic malignant syndrome, and thyrotoxicosis which have a high mortality if not promptly addressed[19].

Obtaining consent may not be possible due to memory and perception impairment[19]. Drug testing has no value in the perioperative setting as it only provide qualitative assesment, and this is due to the long half life of cannabis[19].Treatment for acute intoxication is supportive[37].

Tolerance

Repeated exposure to cannabis leads to tolerance that develops within weeks, due to down regulation of the cannabinoid -1 receptor and endocannabinoid levels[19].

Withdrawal

Withdrawal develops within days of high dose cannabis cessation[19]. Severe and rapid withdrawal symptoms occur in females[19]. The Diagnostic and statistical manual of mental disorders (DSM-5) define cannabis withdrawal syndrome by the presence of three or more of the following: irritability, anger or aggression, nervousness or anxiety, sleep difficulty, decreased appetite or weight loss, restlessness, and depressed mood[17].

This DSM-5 criteria also includes at least one of the following physical symptoms causing discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, and/or headache[17].

No treatment guideline is available to managing cannabis withdrawal, however benzodiazepines and synthetic Δ^9-THC improves symptoms[19].

Addiction

This occurs in 9% of users, with an increased risk in teenagers[38]. Teenage use is of concern as it is during this phase where brain development occurs[38]. Impairment in neural connectivity has been reported in the precuneus, fimbria, frontal and subcortical network[38]. These areas perform executive functions and activities that require a higher degree of integration, learning and memory[38].

Summary of anaesthetic considerations in cannabis users	
Drug history	• History of indication, duration, frequency, route, last intake • Other illicit drug use
Acute intoxication	• Signs may be similar to perioperative emergencies i.e. malignant hyperthermia, serotonin syndrome. • Violent emergence
Airway	• Upper airway obstruction due to oedema
Respiratory	• Bronchial hyperreactivity • Pulmonary edema • Pulmonary emboli
Cardiovascular: Naive users Chronic users	• Increased: Heart Rate, Left Ventricular contractility, Cardiac Output & Systolic Blood Pressure. • Increased risk of myocardial infarction • ↓HR, postural hypotension, cardiac arrest, myocardial infarction, malignant arrhythmias, coronary spasm
Nervous system: Naive users Chronic users	• Increased Cerebral Blood Flow, Ischemic stroke • Increased anaesthetic requirement (induction and maintenance)
Thermoregulation	• Intraoperative hypothermia • Postoperative shivering
Coagulation	• Increased clotting time • Thrombocytopenia • Prolonged INR if on Warfarin
Analgesic requirements	• Synergistic effect with chronic opiod, α2 agonist, gabapentin • Anti-analgesic in opiod naive, requiring more rescue analgesia
Adverse effects	• Withdrawal • Acute intoxication • Addiction

CONCLUSION

More research is still required on the clinical effects of Δ^9-THC and CBD cannabinoids. Studies relevant to anaesthesia are required for anaesthetic interactions with cannabinoids. Consensus statements and guidelines are needed for the perioperative physician for managing the cannabis user. As a result of these findings, caution must be exercised when providing care to the cannabis user.

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