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NAUKA O MEDICINSKOJ MARIHUANI I IZAZOVI U ISTRAŽIVANJU

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SAŽETAK

Endokanabinoidi su retrogradni neurotransmiteri na bazi lipida koji se vežu za kanabinoidne receptore, od kojih su trenutno dva opisana: CB1 i CB2. Dve glavne aktivne komponente kanabisa su tetrahidrokanabinol (THC) i kanabidiol (CBD), koji se na različite načine vežu za receptore, time omogućavajući različite sistemske efekte, kao i modifikaciju sopstvenih efekata. Zbog ovih različitih osobina, terapijski efekat marihuane direktno zavisi od srazmere THC: CBD u određenoj formulaciji. Trenutno se sintetički i proizvodi nastali iz kanabisa koje je odobrila Uprava za hranu i lekove Sjedinjenih Američkih Država koriste za lečenje epileptičnih napada, mučnine izazvane hemoterapijom, i anoreksije kod pacijenata sa HIV infekcijom. Istraživanja su pružila dokaze niskog do srednjeg kvaliteta o koristima kanabinoida koji se koriste za lečenje hroničnog neuropatskog bola i bola izazvanog kancerom. Međutim, veliki su izgledi da će se oni koristiti kao alternativa opiodima. Ostaju izazovi u medicinskim istraživanjima kanabisa, naročito u smislu nekonzistentnog hemijskog sastava i izvora, malih uzoraka, slabih kontrola, i kratkog kliničkog istraživanja. Najveće medicinske ustanove pozivaju na rigorozna istraživanja da bi se dalje istražila bezbednost i efikasnost marihuane.

Ključne reči: medicinska marihuana, mehanizmi delovanja, indikacije, bezbednost, efikasnost

Uvod

Korišćenje kanabisa u medicinske svrhe se prvi put pominje u drevnoj kineskoj farmakopeji napisanoj u prvom veku pre nove ere, koja opisuje lekove koji su se koristili tokom prethodna dva milenijuma (1). Reumatski bol, konstipacija, malarija i ginekološki poremećaji bili su navedeni u medicinskoj upotrebi kanabisa. U drevnoj Indiji, kanabis se brzo širio zbog svoje sposobnosti da izazove sreću. Takođe je korišćen za lečenje nesanice, gastrointestinalnih poremećaja i različitih vrsta bolova. Antički Grci i Arapi su koristili kanabis za slične medicinske svrhe, i naglašavali su njegovu efikasnost u borbi protiv upala, edema i reumatizma. Kanabis su u Novi svet doneli robovi iz Južne Amerike u 16. veku, uglavnom zbog njegovih psihoaktivnih efekata. Ubrzo je uvedena upotreba u medicinske svrhe i biljka je korišćena da izazove san i leči napade, reumatizam i urinarne probleme (1,2). Interesovanje za marihuanu u medicinske i rekreativne svrhe je poraslo tokom prethodnih godina, naročito nakon njene legalizacije u 36 država Sjedinjenih Američkih Država, Kanadi i nekoliko zemalja Evrope. U ovom radu su prikazani mehanizmi delovanja, trenutne indikacije i budući pravac istraživanja medicinske marihuane.

Kanabinoidni receptori

Endokanabinoidi su retrogradni neurotransmiteri na bazi lipida koji se vežu za kanabinoidne receptore, od koji su do sada dva opisana: CB1 i CB2 (3). CB1 receptori se nalaze u centralnom nervnom sistemu (CNS): naročito u hipokampusu (koji je odgovoran za kratkoročno pamćenje), korteksu, bazalnim ganglijama (motoričke sposobnosti), malom mozgu (motorička koordinacija), hipotalamusu, limbičkom sistemu, kičmenoj moždini. U mozgu, kanabinoidi utiču na funkcije poput kognitivne, na pamćenje, motoriku i percepciju

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THE SCIENCE BEHIND MEDICAL MARIJUANA AND RESEARCH CHALLENGES

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SUMMARY

Endocannabinoids are lipid-based retrograde neurotransmitters that bind to cannabinoid receptors, two of which are currently described: CB1 and CB2. The two main active components of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD), have differing binding affinities to the receptors, allowing them to mediate different systemic effects as well as modulate each other's effects. Due to these varied properties, the therapeutic effect of marijuana is directly correlated with the THC:CBD ratio in a particular formulation. Current FDA-approved synthetic and cannabis-derived products are indicated for the treatment of nausea induced by chemotherapy, seizure disorders, and anorexia in AIDS patients. Regarding the treatment of chronic neuropathic pain and cancer pain, research has shown a low-to-moderate quality evidence for use of cannabinoids, but greatly promising in providing alternatives to opioids. Challenges in medical research on cannabis remain, particularly in terms of inconsistent chemical composition and sourcing, small sample sizes, poor controls, and short duration of trials. Major medical institutions call for more thorough research and further investigation of marijuana safety and efficacy.

Keywords: medical marijuana, mechanisms of action, indications, safety, efficacy

Introduction

The first reference to a cannabis product use for medicinal purposes was found in ancient Chinese pharmacopoeia, in 1. BC, which describes remedies used over the previous two millennia (1). Among the reported medical uses of cannabis were constipation, rheumatic pain, gynecological disorders, and malaria. In ancient India, cannabis spread rapidly for its ability to elicit happiness. It was also used to treat insomnia, gastrointestinal disorders, and different forms of pain. The ancient Greeks and Arabs used cannabis for similar medicinal purposes, and highlighted its efficacy at fighting inflammation, edema, and rheumatisms. Cannabis was brought into the New World through South America in the 16th century by African slaves, largely for its psychoactive effects. Medicinal uses were soon introduced and the plant was used to induce sleep and treat seizures, rheumatisms, and urinary afflictions (1,2). Interest in marijuana use for both medicinal and recreational purposes has increased in recent years, especially following its legalization in 36 U.S.A. states, Canada, and several European countries. Here, we provide an outline of the mechanisms of action, indications, and future directions of study for medical marijuana.

Cannabinoid receptors

Endocannabinoids are lipid-based neurotransmitters that bind to cannabinoid receptors retrogradely, of which two are currently described: CB1 and CB2 (3). CB1 receptors are present throughout the central nervous system (CNS): particularly in the hippocampus (responsible for short-term memory), cortex, basal ganglia (motor activity), cerebellum (motor coordination), hypothalamus, limbic system, and spinal cord. In the brain, cannabinoids affect cognition, memory, motor movement, and the perception of pain. This is due to the inhibitory-mediated action of the CB1 receptor's continuous release of many excitatory and inhibitory neurotransmitter systems at the terminals of central and peripheral neurons (4). CB2

bola. Ovo je posledica inhibitorne aktivnosti CB1 receptora koji utiču na dalje oslobađanje jednog broja ekscitatornih i inhibitornih sistema neurotransmitera na vrhovima centralnih i perifernih neurona (4). CB2 receptori su najviše izraženi u imunskim ćelijama: CB2A u B limfocitima, NK ćelijama, monocitima, testisima; CB2B u slezini i gastrointestinalnom sistemu. Ovo ukazuje da kanabinoidi posredstvom receptora imaju specifičan uticaj na imunski sistem, posebno putem CB2 receptora (5).

Kanabidiol i THC

Dve glavne komponente kanabisa su tetrahidrokanabinol (THC) i kanabidiol (CBD). Oni imaju slične efekte u određenim domenima, ali potpuno suprotne u drugim. THC deluje kao delimični agonist CB1 i CB2 receptora. S obzirom da ima osobinu vezivanja sličnu CB1 receptorima, THC se pripisuju psihoaktivne osobine, koje uključuju prolazne psihotičke simptome, kao i povišeni nivo uznemirenosti, intoksikaciju i sedaciju. Takođe, utvrđeno je da THC proizvodi, u zavisnosti od doze, hipoaktivnost, hipotermiju, narušenu prostornu i verbalnu kratkoročnu memoriju (6,7). Analgetsko dejstvo THC-a je dokazano u stanjima poput fibromialgije i reumatoidnog artritisa. Takođe, može da pojača analgetska svojstva opioida (8).

Pokazano je da je CBD efikasan u blokiranju većine efekata THC-a, kada se oba leka daju istovremeno. CBD nije imao značajnog uticaja na ponašanje, ali kada su primenjivani zajedno sprečavao je privremene psihotičke simptome koje je izazvao THC. Anksiolitičko dejstvo CBD-a nastaje zbog njegovog uticaja na limbički i paralimbički sistem (9). Takođe, smatra se da CBD ima antipsihotički efekat, s obzirom da je to potencijalno antipsihotički lek, ali i da je to mogući lek za druga stanja poput inflamacije, dijabetesa, kancera, i neurodegenerativnih bolesti (10). CBD se ne dovodi u vezu sa analgezijom, u stvari, on je u negativnoj korelaciji sa oslobađanjem od nekih oblika bola (11).

Zbog ovih raznolikih svojstava THC-a i CBD-a, terapeutsko dejstvo marihuane je u direktnoj vezi sa sadržajem THC-a u određenoj formulaciji, kao i sa odnosom THC:CBD. Potrebna su dodatna istraživanja da bi se odredio terapijski indeks u smislu doziranja i srazmere THC:CBD. Na primer, u reklamama za većinu proizvoda dostupnih na tržištu se navodi da imaju >15% THC-a, što može biti neodgovarajuće za lečenje neuropatskog bola (12).

S obzirom da je marihuana legalizovana zakonima nekih država u Sjedinjenim Američkim Državama, na tržištu se pojavilo mnoštvo CBD proizvoda izvedenih od marihuane poput CBD ulja u kapima, kapsulama, prehrambenim proizvodima, topikalnim losionima i dijetetskim suplementima. Tvrdnje o dobrobitima ovih proizvoda često su preterane i neosnovane, a variraju od lečenja anksioznosti i nesanice do lečenja demencije i kancera. Uprava za hranu i lekove Sjedinjenih Američkih Država (eng. *FDA*) je osudila dodavanje lekova u prehrambene proizvode za ljude i životinje. FDA je odobrila *Epidiolex* (kanabidiol), CBD lek izveden iz kanabisa za lečenje napada koji se povezuju sa *Lennox-Gastaut* sindromom ili Dravet sindromom kod pacijenata starih dve godine ili više. Takođe, odobrena su još tri sintetička THC leka: *Marinol* (dronabinol), *Syndros* (dronabinol) i *Cesamet* (nabilone). Oni su dostupni uz recept i koriste se za mučninu koja je povezana sa hemioterapijom i za lečenje anoreksije koja se povezuje sa gubitkom težine kod pacijenata koji imaju sidu.

Indikacije i neželjena dejstva

Dokazi srednjeg kvaliteta podržavaju korišćenje kanabinoida za lečenje hroničnog bola i mišićnog spasticiteta, dok je kvalitet dokaza bio nizak za rezultate koji se povezuju sa kanabinoidima u slučaju mučnine i povraćanja u hemoterapiji, dobijanja težine kod HIV infekcije, poremećaja sna i Turetovog sindroma.

Sistematski pregled i meta-analiza medicinske upotrebe kanabisa dati su u studiji koju su sproveli Vajting i saradnici, a koja je uključila 79 kliničkih istraživanja. Većina njih je pokazala poboljšanje simptoma koje se povezuje sa kanabinoidima, ali ova veza nije dostigla statističku značajnost u svim istraživanjima. Najčešće kratkoročne nus pojave kanabinoida bile su vrtoglavica, suva usta, mučnina, zamor, pospanost, euforija, povraćanje, dezorijentisanost, konfuzija, gubitak ravnoteže i halucinacije (13). U Tabeli 1 su sažeto prikazana poznata neželjena dejstva marihuane.

Još jedna negativna posledica marihuane je njeno dejstvo na mlađu populaciju. Dugoročna upotreba kanabisa predstavlja predispoziciju za promene u beloj masi mozga u razvoju. Narušene veze u mozgu kod korisnika kanabisa mogu da

receptors are mostly expressed in immune cells: CB2A in B lymphocytes, NK cells, monocytes, testes; CB2B in the spleen and gastrointestinal system. This suggests that cannabinoids act on the immune system specifically through CB2 receptors (5).

Cannabidiol and THC

The two main components of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). They have similar effects on certain areas while having almost opposite effects in others. THC acts as a partial agonist to both CB1 and CB2 receptors. As a result of its high binding affinity with CB1 receptors, THC is attributed psychoactive properties, which may include transient psychotic symptoms as well as increased levels of anxiety, intoxication, and sedation. THC was also found to produce hypoactivity, hypothermia, spatial and verbal short-term memory impairment depending on the dose (6,7). Analgesic effects of THC have been shown in conditions including fibromyalgia and rheumatoid arthritis. It may also enhance the analgesic properties of opioids (8).

CBD was shown to be efficient in blocking most of the effects of THC, when both drugs were administered together. CBD had no significant effect on behavior, and when administered together it could prevent the temporary psychotic symptoms caused by THC. CBD's anxiolytic effect is produced through its activity on limbic and paralimbic system (9). CBD is also considered to have antipsychotic properties, being considered as a potential antipsychotic medicine, and a possible remedy for other conditions such as diabetes, neurodegenerative diseases, cancer, and inflammation (10). CBD is not associated with analgesia, in fact it has a negative correlation with relief from certain forms of pain (11).

Due to these varied properties of THC and CBD, the therapeutic effect of marijuana is directly correlated with the THC content in a particular formulation, as well as the THC:CBD ratio. More research is needed to determine the safe therapeutic index in terms of dosing and THC:CBD ratio. For example, the majority of products available on the market are advertised as >15% THC, which could be unsuitable for treating neuropathic pain (12).

Since the legalization of marijuana under some USA state laws, markets have seen an expanse of marijuana-derived CBD products such as CBD oil in drops, capsules, food products, topical lotions, and dietary supplements. Claims about the benefits of these products are often exaggerated and unfounded, varying from the treatment of anxiety and insomnia to the treatment of dementia and cancer. The addition of drug products to human and animal food products based on insufficient scientific evidence was condemned by the US Food and Drug Administration (FDA). The FDA approved Epidiolex (cannabidiol), a cannabis-derived CBD drug product for treating seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years and older. Three synthetic THC drug products have also been approved: Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone). The products are available with a prescription for use in nausea associated with chemotherapy side effects and for the treatment of anorexia correlated with weight loss in AIDS patients.

Indications and side effects

There is moderate-quality evidence that supports the use of cannabinoids for treating spasticity and chronic pain, and low-quality evidence supported cannabinoid-associated improvement in chemotherapy induced nausea, increase of appetite in HIV, Tourette's and some sleep disorders.

A systematic review and meta-analysis for the medical use of cannabis performed by Whiting PF et al. included 79 trials. Most of them showed positive progress in symptoms associated with cannabinoids, however, without reaching statistical significance in all included trials. The most common short-term adverse effects with cannabinoids included drowsiness, dizziness, euphoria, fatigue, somnolence, nausea, vomiting, dry mouth, confusion, disorientation, and hallucination(13). Table 1 summarizes the known systemic side effects of marijuana.

Another negative consequence of marijuana is its effect on the younger population. Long-term cannabis use predisposes white matter alterations in the brain as it develops. Cognitive impairment and susceptibility to anxiety, depression, and psychosis may be due to disturbed brain connectivity in chronic users of marijuana (14). Cannabis utilization during imperative phrases of

Tabela 1. Sistemski neželjeni efekti inhalacije marihuane

Kardiovaskularni	Povećana stopa infarkta miokarda; Povezanost sa povećanim kardiovaskularnim mortalitetom (18).
Cerebrovaskularni	Moždani udar (19); Prolazni ishemijski napad.
Gastrointestinalni	Kada se marihuana koristi na dnevnoj osnovi to je faktor rizika za razvoj fibroze jetre kod pacijenata sa virusnim hepatitisom C, uprkos činjenici da se marihuana nekada preporučuje pacijentima sa virusnim hepatitisom C (20,21).
Respiratorni	Hronični kašalj i bronhitis; Inhalacija pirolitičkih nus proizvoda; Povećani rizik za pneumoniju kod imunokompromitovanih pacijenata (22).
Reproduktivni	Sprečava oogenezu; Povezuje se sa atrofijom testisa; Povezuje se sa abnormalnom pokretljivošću spermatozoida; Delta-9-THC blokira oslobađanje LHRH iz hipotalamusa, i proizvodnju LH iz adenohipofize (23). THC prolazi kroz placentu. Prenatalna izloženost kanabisu se povezuje sa redukcijom rasta fetusa (24).

budu osnova za kognitivna oštećenja i osetljivost na psihoze, depresiju i poremećaje anksioznosti (14). Upotreba kanabisa tokom kritičnih faza u razvoju mozga može ozbiljno da naruši endokanabinoidni sistem i na kraju bazične funkcije mozga. Na PET skeneru je pokazano da ispitanici koji su počeli da koriste marihuanu pre sedamnaeste godine imaju manju moždanu masu, kao i manji procenat centralne sive mase u poređenju sa pojedincima koji su počeli da je koriste nakon tog uzrasta (15). Nasuprot tome, magnetna rezonanca kod mlađih ljudi koji često koriste marihuanu nije pokazala atrofiju ili opštu promenu zapremine tkiva (16). Strukturalne promene mozga na jedrima akumbensu i amigdale su pokazane na magnetnoj rezonanci visoke rezolucije kod mladih koji rekreativno koriste marihuanu u poređenju sa onima koji je ne koriste (17).

Hemijski sastav i kontrola kvaliteta

Kanabis je složena biljka sa više od 400 sastojaka od kojih su više od 60 kanabinoidna jedinjenja. Smatra se da je THC glavni psihoaktivni sastojak, dok je pokazano da kanabidiol ima anksiolitička i antipsihotička svojstva, narušavajući efekte THC-a (10). Velika većina proizvoda od marihuane ne ispunjava osnovne standarde za farmaceutske proizvode. Sadržaj THC-a ili CBD-a u testiranim proizvodima je često značajno manji nego što je navedeno. Takvi proizvodi ne obezbeđuju željeni medicinski benefit ili stavljaju pacijente u povećani rizik od neželjenih dejstava. CBD je na osnovu informacija o proizvodu manje štetan zbog manje mogućnosti za zloupotrebu ili za ozbiljna neželjena dejstva, dok THC s druge strane, može da izazove intoksikaciju ili oštećenje, naročito ako nema suprotnog dejstva CBD-a (25,26).

Primena kanabisa raste širom sveta u zadnje vreme (27). Povećana primena THC-a tokom vremena izaziva zabrinutost po pitanju pouzdanosti i primenjivosti benefita i neželjenih dejstava marihuane koji su dokazani u starijim istraživanjima, naročito u studijama koje su procenjivale dugoročne ishode (28). Potreban je regulatorni sistem, na koji bi zdravstveni stručnjaci mogli da se oslone kako bi uverili pacijente i javnost generalno da je kanabis bezbedan i efikasan. Možda je marihuana manje štetna od drugih supstanci koje imaju potencijal za zloupotrebu, ali je potrebno istraživanje podataka o hroničnoj toksičnosti u proceni rizika, koji može biti potcenjen u složenim jedinjenjima sa niskom akutnom toksičnosti poput kanabisa. Ovaj zadatak predstavlja izazov zbog velikih varijacija THC-a u svakom proizvodu, što ga čini teškim za praćenje (29). Jedan od potrebnih koraka u obezbeđivanju bezbednosti marihuane je standardizacija i kontrole kvaliteta kulture. Biljka bi trebalo da bude gajena organski, bez genetskih modifikacija, na osnovu dobre poljoprivredne prakse i prerađena na osnovu Vodiča za dobru proizvođačku praksu. Ovaj proizvod takođe treba da ima sertifikat da je bez pesticida, da nije kontaminiran mikrobima i teškim metalima (30).

Tabela 1. Systemic side effects of marijuana inhalation

Cardiovascular	Increased rates of acute MI; Association with increased cardiovascular mortality (18).
Cerebrovascular	Stroke(19); Transient ischemic attack.
Gastrointestinal	Daily smoked marijuana is a risk factor for progression of liver fibrosis in Hepatitis C patients, despite the fact that marijuana is sometimes recommended in Hepatitis C patients (20,21).
Respiratory	Chronic cough and bronchitis; Inhalation of pyrolytic by-products; Increased risk of pneumonia in immunocompromised patients (22).
Reproductive	Suppresses oogenesis; Associated with testicular atrophy; Associated with abnormal sperm motility; Delta-9-THC blocks the release of LHRH from the hypothalamus, and LH production by the adenohypophysis (23). THC crosses the placenta barrier. Prenatal cannabis exposure was associated with fetal growth reduction (24).

brain growth can lead to a strong disturbance of the endocannabinoid system and cause inappropriate hardwiring in the brain. People who consumed marijuana at a young age (<17) have a grossly smaller brain, as well as the percent of central gray matter compared to individuals who began using it after the age of 17, as shown on a PET scan (15). In contrast, Block et al. showed that young, frequent cannabis users had no significant changes in tissue volume or atrophy on MRI images (16). A more recent study showed structural brain changes on high-resolution MRI in young recreational cannabis users when compared to non-users, particularly in the nucleus accumbens and the amygdala (17).

Chemical composition and quality control

Cannabis has over 400 active chemical substances and more than 60 of them are cannabinoids, increasing the complexity of the plant. THC is perceived as the main psychoactive ingredient, while cannabidiol has been shown to have anxiolytic and antipsychotic properties, antagonizing the effects of THC (10). The big majority of marijuana products are far from meeting the basic label accuracy standards for pharmaceuticals. The THC or CBD content in the tested products is often found to be significantly less than the labeled dose. Those products may not assure the anticipated medical benefit, or place patients at increased risk for side effects. CBD under labeling is less concerning due to low abuse liability or serious adverse events, while THC on the other hand, can produce intoxication or impairment, especially in the absence of antagonizing effects of CBD (25,26).

Recently, there has been an increase in marijuana potency throughout the world (27). The THC potency increase over time raises concerns about the reliability and applicability of the benefits and side effects of marijuana use discovered in older studies, especially studies that assessed long-term outcomes (28). A regulatory system is needed upon which health care professionals can rely on to assure the patients, and the public in general, that cannabis itself is safe and effective. Perhaps marijuana is less harmful than other substances with potential for abuse, but nevertheless, the investigation of chronic-toxicity data is necessary in estimating the risk, which may be underestimated in compounds with low acute toxicity such as cannabis. This task is also challenging to perform because of the wide variations of THC in every product, making it difficult to be monitored (29). One of the required steps in assuring safety of marijuana products is the standardization and quality control of culture. The plant should be cultivated organically, without genetic modification, following Good Agricultural Practice, and processed by following guidelines of Good Manufacturing Practice. The product should also be accompanied by certification that it has no pesticides, microbial or heavy metal contamination (30).

Novi naučni dokazi: stanje bola

Medicinska marihuana je sve više popularna kao alternativa tradicionalnim lekovima protiv bolova. Dokazi ukazuju na malo analgetičko dejstvo u lečenju hroničnog neuropatskog bola (31,32). Jedno randomizirano kliničko istraživanje je pokazalo da medicinska marihuana, naročito THC, izaziva značajno povećanje praga bola (33). Kao alternativa, CBD može imati sinergističke farmakokinetičke interakcije, povećavajući koncentracije THC u plazmi, ali i antagonističke farmakokinetičke interakcije, smanjujući analgeziju izazvanu THC-om (33). U jednom sistematskom pregledu, u kome su istraživani specifični mehanizmi kojima kanabinoidi moduliraju bol, pokazano je kako kanabinoidi povećavaju prag bola, povećavaju toleranciju bola, i smanjuju neprijatnost koju izaziva eksperimentalni bol. Međutim, kanabinoidi nisu smanjili intenzitet eksperimentalnog bola ili mehaničku hiperalgeziju (34).

Kod pacijenata sa hroničnim bolom, kojima je prepisano da puše medicinsku marihuanu, doziranje je bilo u visokoj pozitivnoj korelaciji sa incidencijom depresije. Međutim, srednji nivo bola i stepen anksioznosti nisu bili u korelaciji sa dozom (35).

U lečenju bola koji izaziva kancer, dokazi iz sistematskih pregleda nisu bili ubedljivi, verovatno zbog niskog kvaliteta dostupnih dokaza. Randomizirana klinička istraživanja koja se tiču ove teme nisu pokazala razliku između kanabinoida i placeba po pitanju smanjenja bola, problema sa nesanicom, doziranja opioida i učestalosti kombinovanog odgovora, ozbiljnih neželjenih dejstava, i psihijatrijskih poremećaja. Treba istaći da su studije imale ograničenja u smislu loših kontrola i pristrasnosti u objavljenim istraživanjima (36,37).

Izazovi koji se tiču legalizacije marihuane uključuju rizik od zloupotrebe, fizičke i mentalne zavisnosti koje se povezuju sa dugoročnim korišćenjem, i potencijal za neželjena dejstva. Marihuana se povezuje sa neželjenim efektima koji imaju veze sa centralnim nervnim sistemom (psihoza, kognitivno oštećenje) i neželjena dejstva povezana sa gastrointestinalnim sistemom (suva usta, mučnina, sindrom kanabinoidne hiperemeze). Dugotrajno korišćenje se povezuje sa fizičkom i mentalnom zavisnošću (31). Međutim, pokazano je da su ozbiljna neželjena dejstva bila slična između grupa kod kojih je korišćen kanabinoid i placebo grupa (32).

Novi naučni dokazi: zamena za opioide

Pronalaženje alternative opioidima u lečenju hroničnog bola bi predstavljalo najveći napredak u borbi protiv opioidne krize. Na primer, nakon što je Kolorado legalizovao marihuanu, oni su bili svedoci značajnog pada u distribuciji opioida, što je bio veći pad nego u državama bez zakona o rekreativnom korišćenju marihuane (38). Među korisnicima opioida koji su patili od hroničnog bola, korišćenje marihuane na dnevnoj bazi povezivano je sa značajno nižom upotrebom nelegalnih opioida na dnevnoj bazi (39). Istraživanje među ljudima koji su koristili i opioide i marihuanu u proteklih godinu dana pokazalo je da je 41% njih prijavilo smanjenje ili prestanak korišćenja opioida zbog upotrebe marihuane (40). Postoji nekoliko drugih istraživanja koje prijavljuju da konzumiranje marihuane dovodi do značajnog smanjenja korišćenja opioida (41,42). Ono što obećava je činjenica da korišćenje marihuane nije povezivano sa dozom opioida ili zloupotrebom opioida (43). U stvari, emotivni simptomi su se poboljšali kod pacijenata koji su koristili medicinsku marihuanu (44). Međutim, dokazi ne podržavaju uvek korišćenje kanabinoida kao zamenu za opioide. Jedno randomizirano kliničko istraživanje na malom broju ispitanika pokazalo je da dronabiol nije umanjio ili nije promenio analgeziju koju je izazvao oksikodon, već da je povećao zloupotrebu ili subjektivne efekte povezane sa oštećenjem koji se pripisuju oksikodonu (45).

Metodologija i izazovi u istraživanju

Ima mnogo razlika u metodologiji istraživanja marihuane kojima se treba baviti kako bi se poboljšao kvalitet dokaza i omogućilo donošenje boljih zaključaka. Jedan sistematski pregled pokazao je da su rezultati studija generalno pozitivniji u studijama bez kontrolnih grupa, i da je 15 od 21 primarne studije o marihuani bilo bez kontrolnih grupa. Pored toga, oni su pronašli da su studije koje su koristile više doze marihuane vodile ka zaključku da je marihuana efikasna, što predstavlja jedno od pitanja zato što su se lekovi i protokoli primene u velikoj meri razlikovali u studijama (46).

Česta nedoslednost u istraživanju medicinske marihuane se tiče srazmere THC: CBD i doziranja. Generalno, <10% THC imalo je najvišu efikasnost u lečenju neuropatskog bola, pa ipak, velika većina dostupnih proizvoda kanabisa imaju >15% THC, na-

New scientific evidence: pain conditions

Medical marijuana is gradually becoming a popular alternative to traditional pain-relieving medications. Evidence points to a small analgesic effect in the treatment of chronic neuropathic pain (31,32). One randomized controlled trial has found that medical marijuana, THC in particular, causes a noteworthy increase in the pressure pain threshold (33). Alternatively, CBD may have synergistic pharmacokinetic interactions, by increasing THC plasma concentrations, but antagonistic pharmacodynamic interactions, by decreasing THC-induced analgesia (33). A systematic review also investigating the specific mechanisms by which cannabinoids modulate pain has found that cannabinoids increase pain thresholds, increase pain tolerance, and reduce the unpleasantness of ongoing experimental pain. However, cannabinoids didn't decrease experimental pain intensity or mechanical hyperalgesia (34).

In patients prescribed smoked medical marijuana for chronic pain, the dosage was found to be highly positively correlated with the incidence of depression. Mean level of pain and severity of anxiety, however, were not correlated to the dosage (35).

In cancer pain treatment, evidence from systematic reviews has been inconclusive, most likely due to the very low quality of evidence available. RCTs on the topic have typically found no difference between placebo and cannabinoids in reducing pain, dose of opioids, sleep issues, as well as serious adverse events, or other side effects such as psychiatric-like disorders. Most notably, studies carried design limitations, such as poor controls, and publication bias (36,37).

Challenges when it comes to legalizing marijuana include the risk of misuse, dependence, and addiction which have been associated with long-term duration of use, and the potential for adverse effects. Marijuana has been associated with psychiatric disorder like side effects (psychosis, cognitive impairment) and GI-related adverse effects (dry mouth, nausea, vomiting). Long-term duration of use has been associated with dependence and addiction (31). Severe adverse effects, however, were found to be similar between cannabinoid and placebo treatment groups (32).

New scientific evidence: opioid replacement

Finding an opioid alternative to treating chronic pain would constitute major progress in the battle against the opioid crisis. For instance, in the years after Colorado legalized marijuana, they witnessed a significant drop in opioid distribution, a larger decrease than seen in states without recreational marijuana policies (38). Among chronic pain sufferers using opioids, daily marijuana use was linked with significantly lower odds of daily illicit opioid use(39). A survey among people who used both opioids and marijuana in the past year showed that 41% reported a reduction of opioid dose or completely stopping use as a result of marijuana use(40). There are several other new reports of marijuana consumption leading to a significant reduction in opioid consumption (41,42). Promisingly, marijuana use was not associated with opioid dose or opioid misuse behavior (43). In fact, emotional symptoms improved in patients taking medical marijuana (44). Nonetheless, the evidence does not always align in using cannabinoids as an opioid adjuvant. A small RCT found that dronabinol decreased or did not change oxycodone-induced analgesia, rather, it augmented oxycodone related side effects(45).

Methodology and challenges in research

There is much variability in marijuana research methodology which needs to be addressed in order to improve the quality of evidence and enable better informed conclusions to be drawn. A systematic review into the topic found that study deductions were generally more positive in non-controlled studies, and that 15 of 21 primary studies on marijuana were noncontrolled. Additionally, they found that studies using greater doses concluded that marijuana was effective, which is an issue because drugs and protocols of administrations ranged greatly across studies (46).

A common inconsistency in research on medical marijuana revolves around the THC:CBD ratio and dosing. Overall, <10% THC has demonstrated the highest efficacy in treating of neuropathic pain, yet the great majority of cannabis products available are >15% THC, most likely to appeal to the recreational use realm (12). Currently, none of the states with legalized medical or recreational marijuana deliberate the THC:CBD

jverovatnije da bi bili privlačni u domenu upotrebe u rekreativne svrhe (12). Trenutno se nijedna od država sa legalizovanom medicinskom ili rekreativnom marihuanom ne bavi odnosom THC:CBD u regulativama. Uz to, u objavljenim studijama, ta srazmera često nije navedena ili je trivijalizovana zbog dostupnosti (47).

Takođe, postoji velika potreba za dodatnim istraživanjem upotrebe marihuane u populacijama specifičnih pacijenata uključujući trudnoću, gerijatrijsku i pedijatrijsku poplaciju. Kada je u pitanju pedijatriska populacija, trenutno postoje samo dve objavljene studije o medicinskoj marihuani koja se koristi za lečenje bola u pedijatriji, od kojih je jedna studija slučaja (48).

Postoji i velika potreba za dugoročnim studijama koje bi se bavile procenom rizika i benefita koji su povezani sa dugoročnim korišćenjem. Do sada, dugoročno, hronično korišćenje kod ljudi mlađih od 25 godina se povezuje sa gubitkom pamćenja, kognitivnom disfunkcijom, psihozom koja rano počinje ili šizofrenijom (49).

Zaključak

Medicinska marihuana ima brojne potencijalne medicinske efekte, kao i moguće rizike po zdravlje ljudi. Vodiči koje izdaju institucije poput Uprave za hranu i lekove (eng. *Food and Drug Administration*, FDA), Američkog lekarskog društva (eng. *American Medical Association*, AMA), Svetskog lekarskog udruženja (eng. *World Medical Association*, WMA) i Društva za kancer Sjedinjenih Država podržavaju rigoroznija istraživanja. Dokazi o benefitima kanabinoida u poremećajima koji izazivaju bolna stanja su niskog do srednjeg kvaliteta, ali ima izgleda da će obezbediti alternativu opioidima. Većina studija je uključivala mali broj ispitanika, neadekvatne kontrole i bile su kratkotrajne, tako da je potrebno dalje istraživanje kako bi se ispitala bezbednost i efikasnost marihuane. Važno je istaći da se postojeći dokazi baziraju na evaluaciji upotrebe sintetičkih kanabinoida, ili nekomercijalno dostupnih proizvoda koji imaju kontrolisane i regulisane sastojke. Nažalost, proizvodi koji su dostupni na tržištu ne mogu biti uključeni u istu kategoriju kontrolisanih i regulisanih komponenti, stoga lekari koji se bave bolnim stanjima moraju biti oprezni kada preporučuju medicinsku marihuanu pacijentima.

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ratio in protocols. Moreover, in published studies, the ratio is often not listed or trivialized based on availability (47).

There is also a need of additional research into marijuana use in specific patient populations including pregnancy, geriatric, and pediatric populations. Concerning the latter, for instance, there are currently only two published studies on medical marijuana on pediatric pain, of which one is a case report (48).

There is also a great need of more long-term studies to assess the risks and benefits associated with long-term use. To date, long-term chronic use in the younger population was associated with serious cognitive impairment, memory loss, and early onset of psychotic symptoms(49).

Conclusions

Medical marijuana has many potential medical benefits, as well as possible health risks. Emerging guidelines from institutions such as the FDA, AMA, WMA, and the American Cancer Society encourage more rigorous research. The evidence of cannabinoids' benefit in pain disorders is of low-to-moderate quality, but greatly promising in providing alternatives to opioids. Most studies were comprised of small populations, poor controls and short duration, and further research is necessary to examine marijuana safety and efficacy. Of note, the existing evidence is based on the evaluation of synthetic cannabinoids' use, or non-commercially available products that have controlled and regulated components. Unfortunately, the products available on the market cannot be included in the same category of controlled and regulated components, therefore pain medicine physicians must be cautious when suggesting medical marijuana to patients.

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