PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

Cannabinoid Clinical Applications

Mark Garofoli, PharmD, MBA, BCGP, CPE

Faculty Disclosure

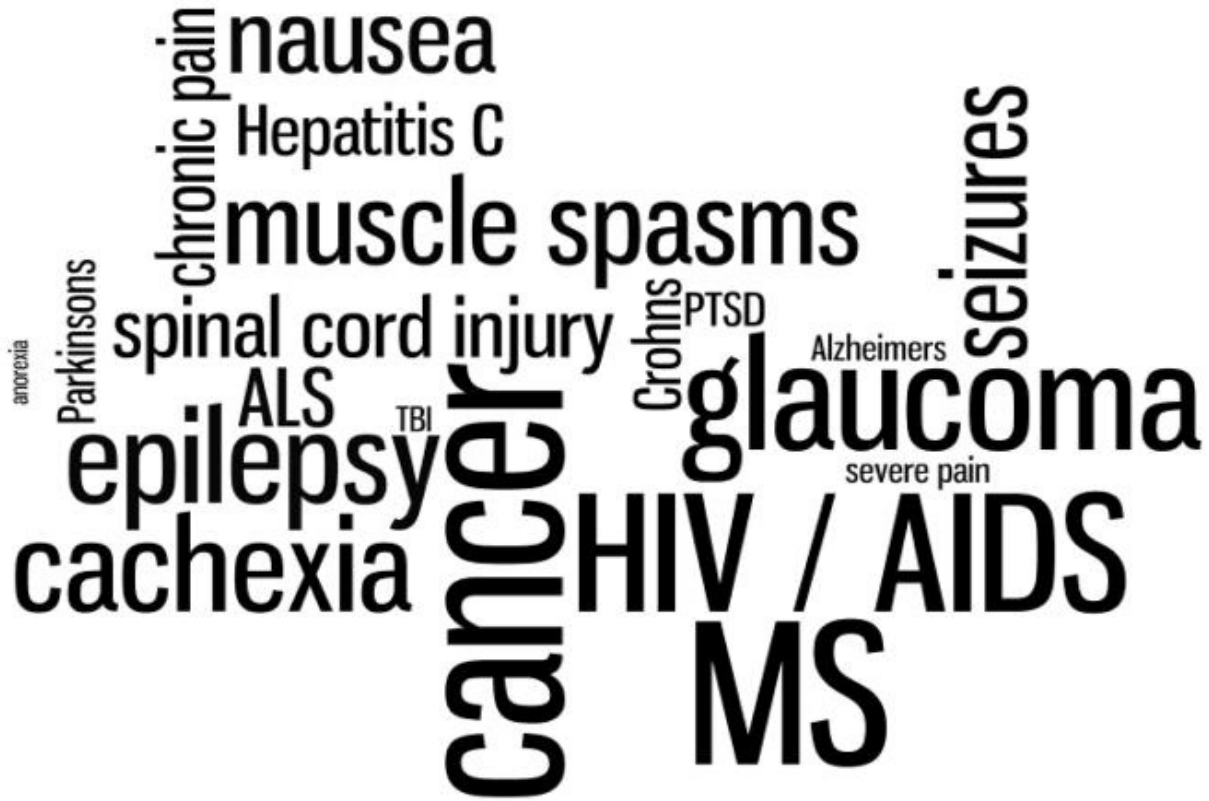
- **Consulting Fee:** HealthXL, Speranza
- **Other**: Expert Witness—Cardinal Health

This presentation was not a part of the presenter's official duties at the WVU and does not represent the opinion of WVU

Learning Objectives

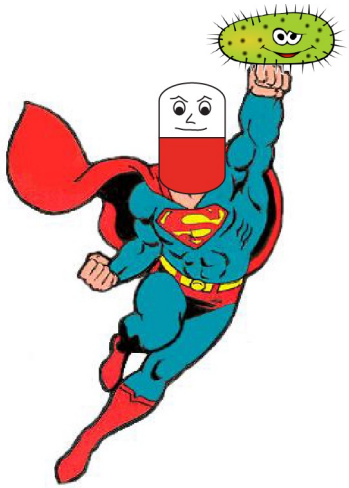
- Recall inconclusive clinical applications for cannabinoids based on multiple reputable recent studies in order to avoid inappropriate treatment selections for patient care.
- Recall cannabinoid clinical applications deemed as “possibly affective” as per multiple reputable recent studies in order to provide appropriate treatment selections and patient education.
- Explain the mechanisms of action for cannabinoid utilization in pain management, cachexia, nausea/vomiting, multiple sclerosis, and epilepsy, referred to as “known to be effective” as per multiple reputable recent studies.

Cannabinoid Possible Utilizations



Bestrashniy. *Psychol Addict Behav*. 2015;29(3):639-6426.

Super Antibiotic?



News > WebMD Health News

CBD as a Superbug Antibiotic?

Kathleen Doheny

July 05, 2019

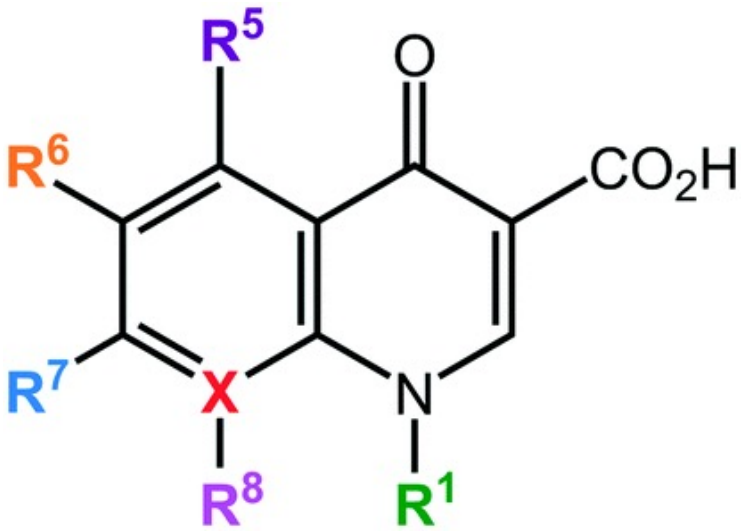
3 Read Comments

WebMD

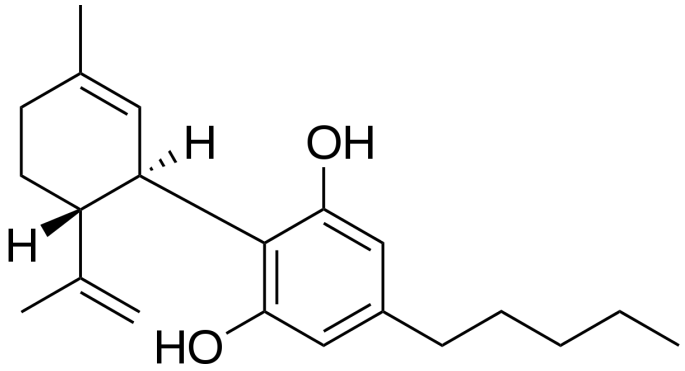
They compared how effective CBD was compared to common antibiotics, such as vancomycin and daptomycin. "We looked at how quickly the CBD killed the bacteria. It's quite fast, within 3 hours, which is pretty good. Vancomycin (*Vancocin*) kills over 6 to 8 hours."

www.medscape.com/viewarticle/915215.

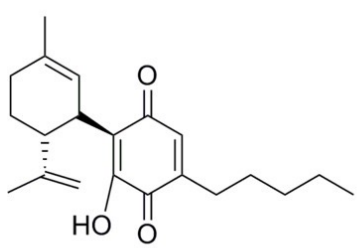
Super Antibiotic?



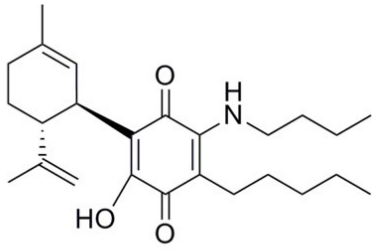
Quinolone



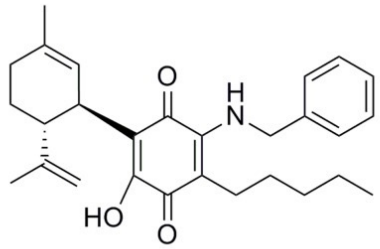
CBD



HU-331



CBD-Q (V)



CBD-Q (VIII)

CBD Quinone Derivatives

Morales. *Front Pharmacol*. 2017;8:422.

Cannabinoids for Cannabis Dependence

JAMA Internal Medicine | Original Investigation

Nabiximols for the Treatment of Cannabis Dependence
A Randomized Clinical Trial

Nicholas Lintzeris, MBBS, PhD; Anjali Bhardwaj, PhD; Llewellyn Mills, PhD; Adrian Dunlop, MBBS, PhD; Jan Copeland, PhD; Iain McGregor, PhD; Raimondo Bruno, PhD; Jessica Gugusheff, PhD; Nghi Phung, MBBS, PhD; Mark Montebello, PhD; Therese Chan, BPharm; Adrienne Kirby, BSc(Hons); Michelle Hall, GradCertHlthSc; Meryem Jefferies, PhD; Jennifer Luksza, PhD; Marian Shanahan, PhD; Richard Kevin, PhD; David Allsop, PhD; for the Agonist Replacement for Cannabis Dependence (ARCD) study group

IMPORTANCE There are no effective medications for treating dependence on cannabis.

OBJECTIVE To examine the safety and efficacy of nabiximols in the treatment of patients with cannabis dependence.

DESIGN, SETTING, AND PARTICIPANTS This parallel double-blind randomized clinical trial comparing nabiximols with placebo in a 12-week, multisite outpatient study recruited participants from February 3, 2016, to June 14, 2017, at 4 outpatient specialist alcohol and drug treatment services in New South Wales, Australia. Participants had cannabis dependence (as defined by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and were seeking treatment, were nonresponsive to prior treatment attempts, were 18 to 64 years of age, had no other substance use disorder, had no severe medical or psychiatric conditions, were not pregnant, were not mandated by a court to undergo treatment, and provided informed consent. Results for primary efficacy measures and all secondary outcomes were obtained using a modified intention-to-treat data set.

INTERVENTIONS Participants received 12-week treatment involving weekly clinical reviews, structured counseling, and flexible medication doses—up to 32 sprays daily (tetrahydrocannabinol, 86.4 mg, and cannabidiol, 80 mg), dispensed weekly.

RESULTS A total of 128 participants (30 women and 98 men; mean [SD] age, 35.0 [10.9] years) were randomized and received at least 1 dose of study medication. Participants had used a mean (SD) of 2.3 (2.1) g of cannabis on a mean (SD) of 25.7 (4.5) days in the past 28 days. Treatment retention was comparable for the 2 groups (placebo, 30 of 67 participants [44.8%]; nabiximols, 30 of 61 participants [49.2%]), and both groups used similar mean (SD) doses (placebo, 18.5 [9.5] sprays daily; nabiximols, 17.6 [9.5] sprays daily, equivalent to a mean [SD] of 47.5 [25.7] mg of tetrahydrocannabinol and 44.0 [23.8] mg of cannabidiol). For the primary end point, the placebo group reported significantly more days using cannabis during the 12 weeks (mean [SD], 53.1 [33.0] days) than the nabiximols group (mean [SD], 35.0 [32.4] days; estimated difference, 18.6 days; 95% CI, 3.5-33.7 days; $P = .02$). Both groups showed comparable improvements in health status, with no substantial changes in other substance use. Medication was well tolerated with few adverse events.

CONCLUSIONS AND RELEVANCE This study demonstrates that cannabinoid agonist treatment, in this case using nabiximols, in combination with psychosocial interventions is a safe approach for reducing cannabis use among individuals with cannabis dependence who are seeking treatment.

Lintzeris. *JAMA Intern Med*. 201915;179(9):1242-1253.

There's No "I" in Pill???

- Opioid addiction → buprenorphine, methadone, and/or naltrexone (HAT?)
- Alcohol addiction → naltrexone, disulfiram, or acamprosate (hospital beer?)
- Cocaine/meth addiction → ? (naltrexone, bupropion, rx amphetamines?)
- Cannabis addiction → ? (more cannabis/cannabinoids, nabiximols?)

➢All of the above → psychological treatment (teamwork)

National Survey on Drug Use. SAMHSA 2019.

Cannabis

Circulation

American Heart Association®

Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association

Robert L. Page II, Larry A. Allen, Robert A. Kloner, Colin R. Carriker, Catherine Martel, Alanna A. Morris, Mariann R. Piano, Jamal S. Rana, Jorge F. Saucedo, ... See all authors

Originally published 5 Aug 2020 | https://doi.org/10.1161/CIR.0000000000000883 | Circulation. 2020;142:e131–e152

Abstract

Cannabis, or marijuana, has potential therapeutic and medicinal properties related to multiple compounds, particularly Δ-9-tetrahydrocannabinol and cannabidiol. Over the past 25 years, attitudes toward cannabis have evolved rapidly, with expanding legalization of medical and recreational use at the state level in the United States and recreational use nationally in Canada and Uruguay. As a result, the consumption of cannabis products is increasing considerably, particularly among youth. Our understanding of the safety and efficacy of cannabis has been limited by decades of worldwide illegality and continues to be limited in the United States by the ongoing classification of cannabis as a Schedule 1 controlled substance. These shifts in cannabis use require clinicians to understand conflicting laws, health implications, and therapeutic possibilities. Cannabis may have therapeutic benefits, but few are cardiovascular in nature. Conversely, many of the concerning health implications of cannabis include cardiovascular diseases, although they may be mediated by mechanisms of delivery. This statement critically reviews the use of medicinal and recreational cannabis from a clinical but also a policy and public health perspective by evaluating its safety and efficacy profile, particularly in relationship to cardiovascular health.

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Inconclusive Evidence (No RCTs)

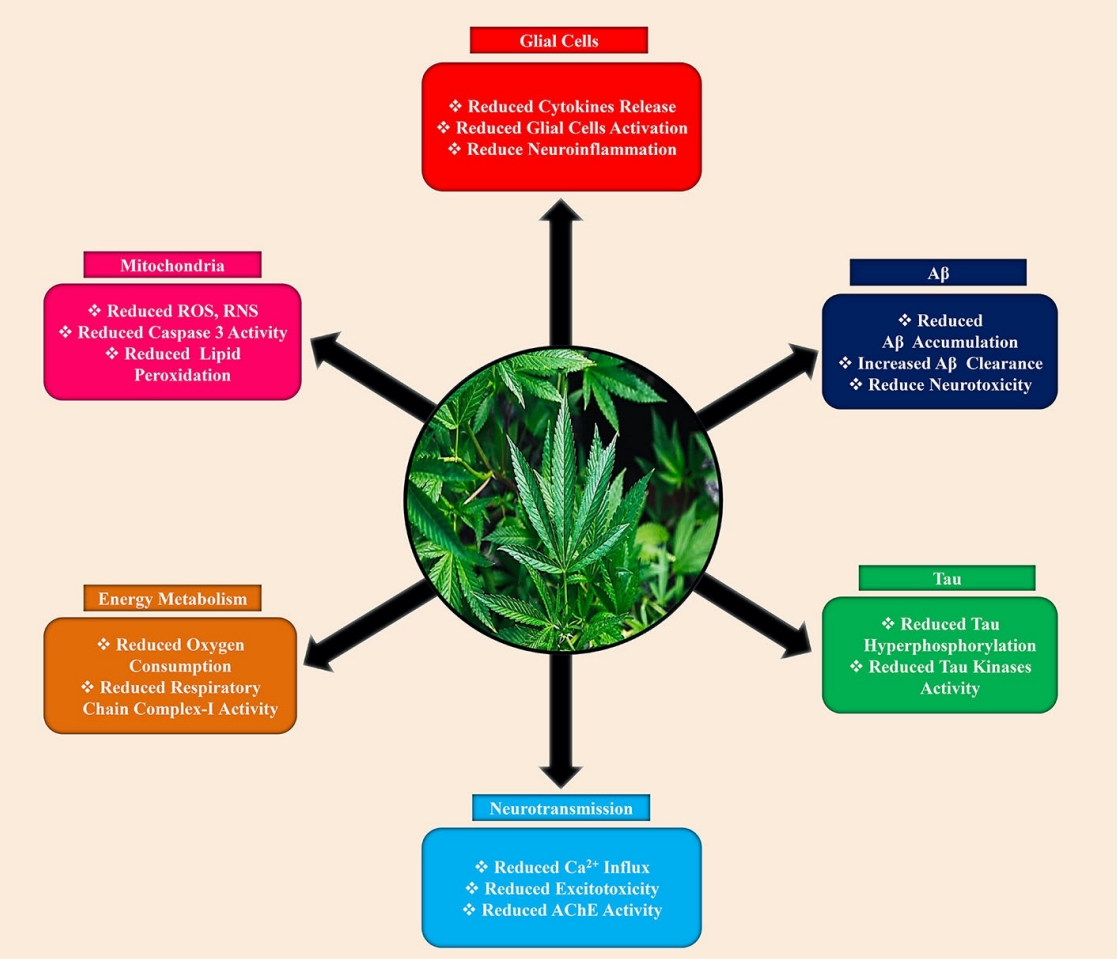
- Alzheimer's disease
- Anxiety and depression
- Tumors
- Irritable bowel diseases (IBDs)
- Heart failure
- Ischemia
- Hepatitis C
- Huntington disease
- Metabolic syndrome, obesity, and diabetes mellitus
- Parkinson's
- Sleep

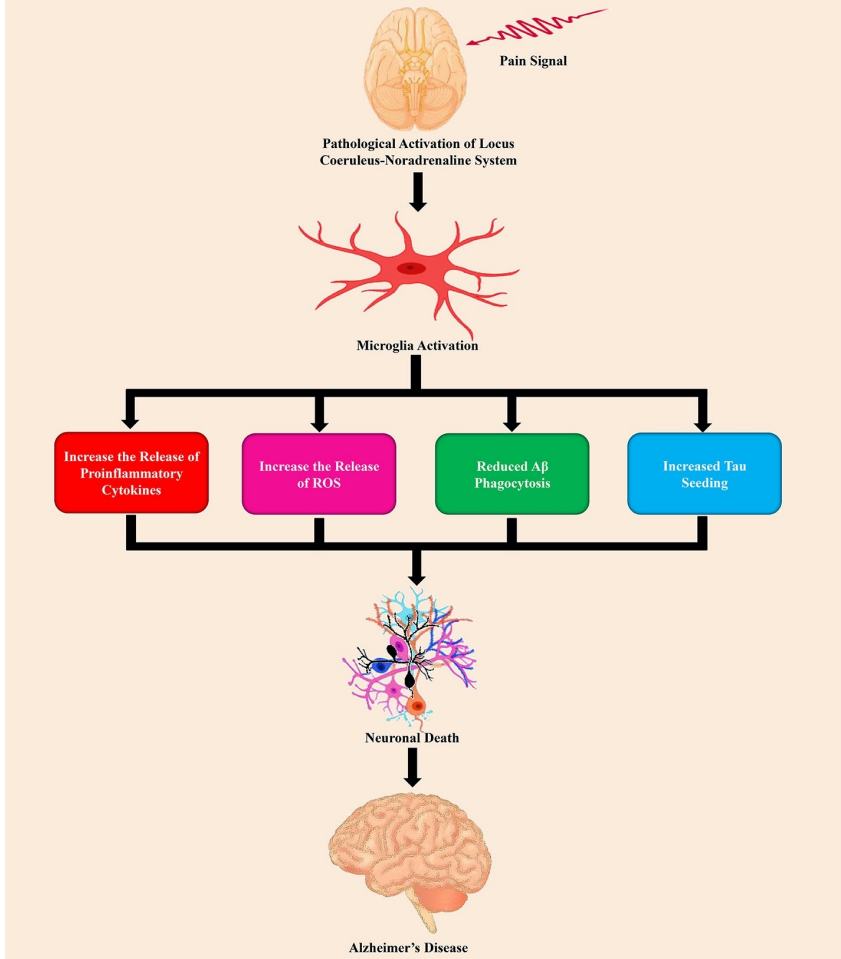
American Heart Association®

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Alzheimer's





Uddin. *Front Pharmacol*. 2020;11:1097.

Cannabinoid Utilizations

Alzheimer's

- 2019 review of 9 studies

- Results implied that the CBD components of cannabis might be useful to treat and prevent Alzheimer's because CBD components could suppress the main causal factors of Alzheimer's

- Moreover, it was suggested that using CBD and THC together could be more useful than using CBD or THC alone

Kim. *J Pharmacopuncture*. 2019;22(4):225-230.

Cannabinoid Utilizations

Alzheimer's

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Preclinical studies suggest that THC and CBD may protect against excitotoxicity, oxidative stress, and inflammation in animal models
  - Limited case, clinical, and observational studies suggest that oral THC and nabilone are associated with improvement in a number of symptoms associated with Alzheimer's disease (e.g., nocturnal motor activity, disturbed behavior, sleep, agitation, and restiveness)

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Anxiety and Depression

THE LANCET Psychiatry

- December 2019 review of over 80 articles
  - Depression (42), anxiety (31), Tourette (8), ADHD (3), PTSD (12), and psychosis (11)
- Scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis
- Very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions
- There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework
- Further high-quality studies (randomized and placebo-controlled) are needed to directly examine the effect of cannabinoids on treating mental disorders

Black. *Lancet Psychiatry*. 2019;6(12):P995-1010.

Cannabinoid Utilizations

Anxiety and Depression

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Small studies with adjunct functional neuroimaging in healthy individuals have demonstrated that CBD and dronabinol reduce anxiety related to its effects on activity in limbic and paralimbic brain areas
  - US adults occasional cannabis use → not associated with social anxiety disorder
  - US adults frequent cannabis use → significantly increased odds of social anxiety disorder

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Tumors

BOSNIAN JOURNAL OF BASIC MEDICAL SCIENCES

TABLE 1. Expression of cannabinoid (CB) receptors in selected human cancer types

Cancer cell type	Regulation of CB_1/CB_2	Mechanisms and other relevant circumstances	Reference
Breast cancer	Elevated CB_2 receptor expression in HER2+breast tumors.	HER2 induces CB_2 expression activating ELK1 (ERK/MAPK cascade); activated pro-oncogenic signaling through tyrosine kinase c-Src.	[28,29]
	Presence of TRPV1 in human breast adenocarcinoma cell line (MCF-7).	TRPV1 agonists/antagonists induce significant inhibition of MCF-7 cell growth.	[30]
	Elevated CB_1 receptor expression.	Activation of Akt signaling pathway was proposed. Increased CB_1 and FAAH levels correlate with severity of the disease.	[31-34] [35,36]
Prostate cancer	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Additionally: Presence of TRPV1 and TRPA1 in all prostate cancer cells (except LNCaP cells), TRPV2 in DU-145 and PC-3 cells only, TRPM8 in AR-dependent prostate cell lines (e.g., LNCaP).	[37-39]
	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Expression of GPR55 in PC-3 and DU-145 cell lines has been reported, mediating effects of LPI.	[40]
Chemically induced hepatocellular carcinoma	Upregulation of CB_1 receptors.	Diethylnitrosamine induced liver cancer.	[41]
Hepatocellular carcinoma	Overexpression of CB_1 and CB_2 receptors.	Overexpression of CB_1 and CB_2 receptors is associated with improved prognosis.	[42]
Non-small cell lung cancer	Overexpression of CB_1 and CB_2 receptors.	Activation of Akt signaling pathway, MMP9 expression and activity.	[43]
Chronic lymphocytic leukemia	Overexpression of CB_1 and CB_2 receptors.	CB_1 receptor expression correlated with high-risk markers.	[44]
Pancreatic cancer	CB1 and CB_2 receptors expressed in normal and pancreatic cancer cells (higher expression of CB_1).	Cannabinoids induced apoptosis via CB_2 receptor (ceramide dependent pathway).	[45-47]
Melanoma	CB_2 is overexpressed in human melanoma tissues and cell lines.	Not reported.	[48]

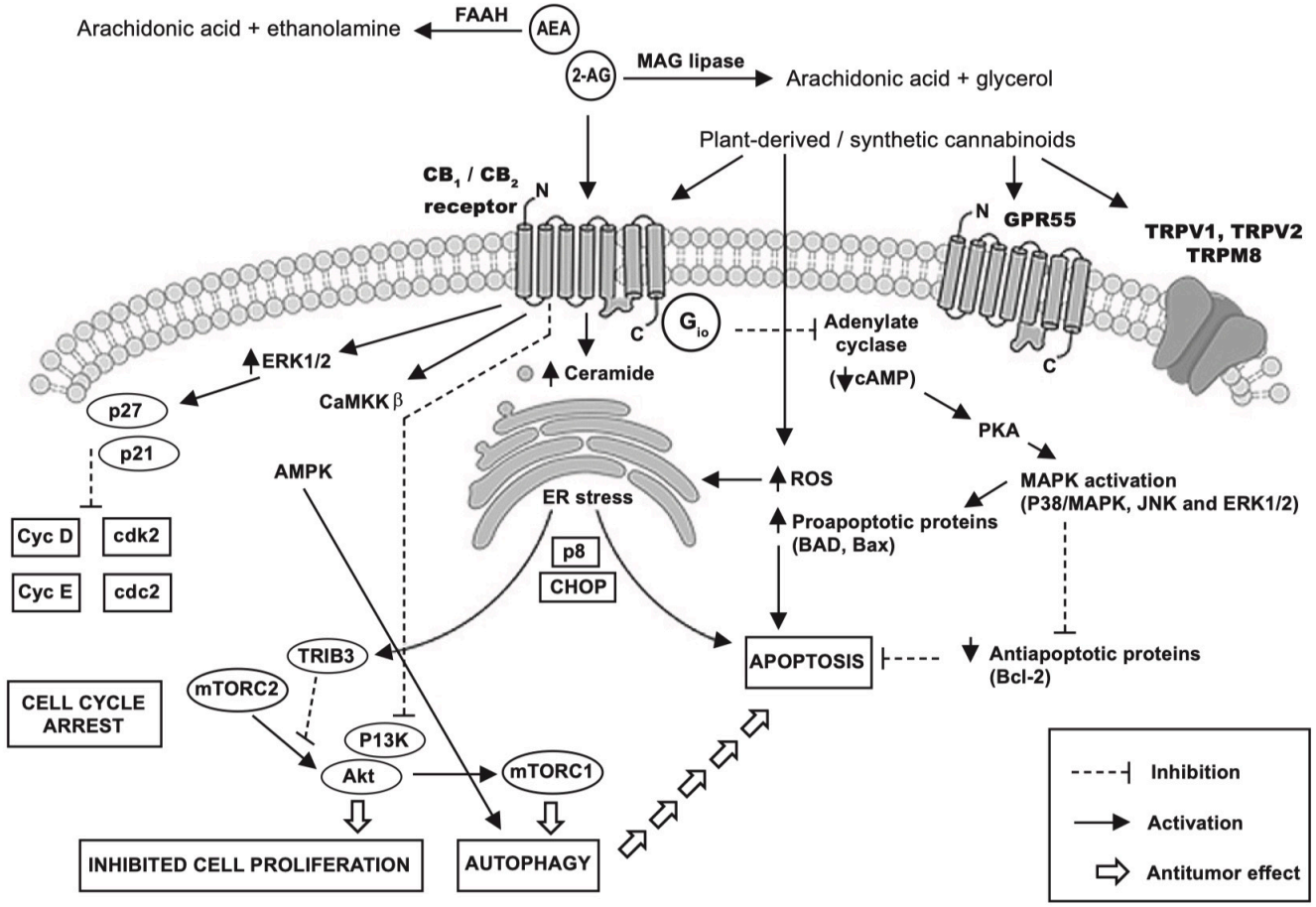
HER2: Human epidermal growth factor receptor 2; ELK1: ETS domain-containing protein; c-Src: Tyrosine-protein kinase Src; ERK: Extracellular-signal-regulated kinase; MAPK: Mitogen-activated protein kinase; TRPV1: Transient receptor potential vanilloid receptor 1; Akt: Protein Kinase B; FAAH: Fatty acid amide hydrolase; TRPA1: Transient receptor potential ankyrin 1; GPR55: Orphan G-protein coupled receptor 55; AR: Androgen receptor; LPI: Lysophosphatidylinositol; MMP9: Matrix metallopeptidase 9

Dariš B. *Bosn J Basic Med Sci*. 2019;19(1):14-23.

Cannabinoid Utilizations

Tumors

BOSNIAN JOURNAL OF BASIC MEDICAL SCIENCES



AEA: Anandamide
2-AG: 2-Arachidonoylglycerol
Akt: Protein Kinase B
AMPK: 5' adenosine monophosphate-activated protein kinase
Bad: Bcl-2-associated death promoter
Bax: Apoptosis regulator
CaMKK: Calcium/calmodulin-dependent protein kinase kinase
Cdk 2: Cyclin-dependent kinase 2
CHOP: C/EBP homologous protein
CycD: Cyclin D
Cyc E: Cyclin E
ELK1: ETS domain-containing protein
ERK: Extracellular-signal-regulated kinase
FAAH: Fatty acid amide hydrolase
GPR55: Orphan G-protein coupled receptor 55
MAG lipase: Monoacylglycerol lipase
MAPK: Mitogen-activated protein kinase
p8: Candidate of metastasis 1
p21: Cyclin-dependent kinase inhibitor 1
p27: Cyclin-dependent kinase inhibitor 1B
PI3K: Phosphoinositide 3-kinase
PKA: Protein kinase A
ROS: Reactive oxygen species;
TRPV1 Transient receptor potential vanilloid receptor
mTORC: Mammalian target of rapamycin complex 1
TRIB3: Tribbles homolog 3

Dariš B. *Bosn J Basic Med Sci*. 2019;19(1):14-23.

Cannabinoid Utilizations

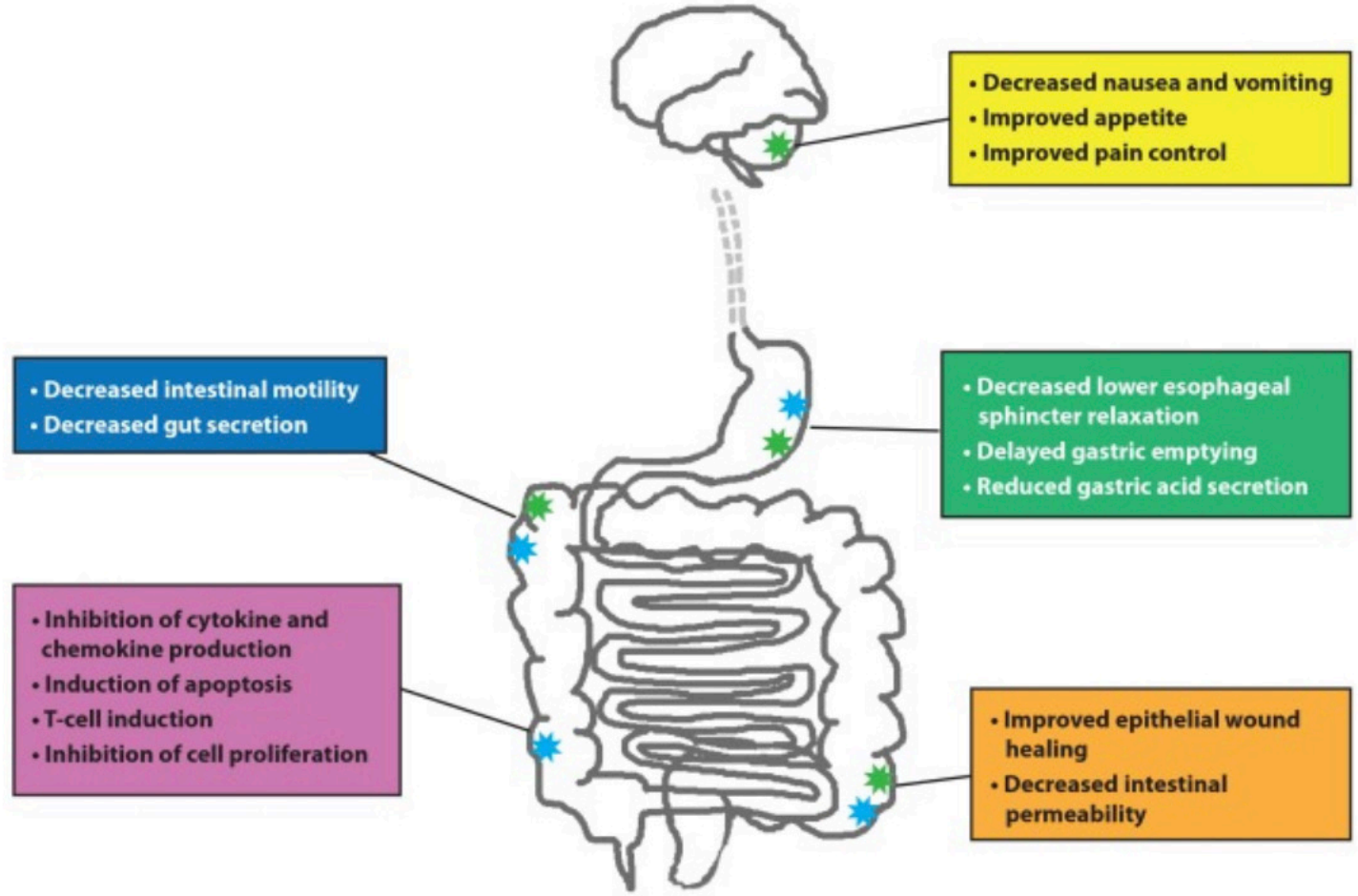
Tumors

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Preclinical studies suggest that very high doses of THC, CBD, CBG, and CBC often, but not always, block the growth of cancer cells in vitro and display a variety of antineoplastic effects in vivo
  - One limited clinical study in patients with glioblastoma multiforme reported that intratumor injection of high doses of THC did not improve patient survival beyond that seen with conventional chemotherapeutic agents

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoids in the GI System



Ahmed. *Gastroenterol Hepatol (N Y)*. 2016;12(11):668-679.

Cannabinoid Utilizations

Irritable Bowel Diseases

Study	Study Design	Subjects	Treatment	Outcomes
Naftali T, et al. Treatment of Crohn's disease with cannabis: an observational study. *Isr Med Assoc J.* 2011;13(8):455–458.	Retrospective, observational	**30 Patients Crohn's disease**	Retrospective inhalational or oral cannabis use	Significant clinical response but need for other drugs and surgery with cannabis
Lahat A, et. al. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. *Digestion.* 2012;85(1):1–8.	Prospective, observational without controls	**13 Patients IBD**	50 g of cannabis cigarette per month (3 months total)	Significant improvement in quality of life, disease activity, and weight gain
Naftali T, et al. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol.* 2013;11(10):1276–1280.e1.	Prospective, randomized, double-blind, placebo-controlled	**21 Patients Crohn's disease**	*Cannabis sativa* cigarette (23% THC, 0.5% cannabidiol)	Significant clinical response with cannabis but no objective decrease in inflammation

Ahmed. *Gastroenterol Hepatol (N Y)*. 2016;12(11):668-679.

Cannabinoid Utilizations

Irritable Bowel Diseases (Crohn's and Ulcerative Colitis)

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Preclinical animal studies suggest that synthetic CB1/2 agonists, THC, CBD, CBG, CBC, and cannabis extract may limit intestinal inflammation
  - Very limited number of small clinical studies of patients with IBD who failed conventional treatments reported improvement with smoked cannabis

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Cardiovascular

- CAD
  - Marijuana use may pose potential cardiovascular risk in patients with atherosclerotic cardiovascular disease, especially early after acute coronary syndromes. In the acute setting, cannabis smoking can lead to increases in heart rate and blood pressure
- Arrythmias
  - A broad range of cardiac electrical effects, including atrial fibrillation/flutter, atrioventricular block/asystole, sick sinus syndrome, and ventricular tachycardia have been described with marijuana use
- Cerebrovascular events
  - Reported in association with marijuana use
- Peripheral artery disease
  - Thrombosis and ischemia of other vascular beds have also been reported
- Cardiomyopathy
  - Cannabis use has been associated with myocardial dysfunction, independent of coronary artery disease

Defilippis. J Am Coll Cardiol. 2020;75(3):320-332.

Cannabinoid Utilizations

Heart Failure

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - In retrospective analysis of 161,000 patients with heart failure, cannabis use was associated with a lower risk for death while the patient was hospitalized with acute heart failure, shorter mean hospital stay, and lower mean hospital costs compared with nonusers

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Ischemia

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Preclinical studies suggest that CBD, THCV, and ultralow doses of THC may have some protective effects against ischemia/reperfusion injury

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Hepatitis C

- CBD decreased HCV replication by 86.4%
  - CBD was discovered to inhibit HCV without eliciting significant damage to the cells used to culture the virus
- CBD was not effective against HBV

JAMAICA OBSERVER

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LATEST NEWS: MoBay Chamber urges more work-from-home arrangements in West 7:58 pm

Dr Wayne McLaughlin

J'can scientists close to creating affordable hepatitis C drug from ganja

Sunday, February 12, 2017

www.jamaicaobserver.com/news/J-can-scientists-close-to-creating-affordable-hepatitis-C-drug-from-ganja_89260.

Cannabinoid Utilizations

Hepatitis C

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Preclinical studies suggest that CB1 receptor activation promotes steatosis and fibrosis, whereas CB2 receptor activation has some beneficial effects
  - Daily cannabis use has been shown to be a predictor of steatosis severity for patients with chronic hepatitis C

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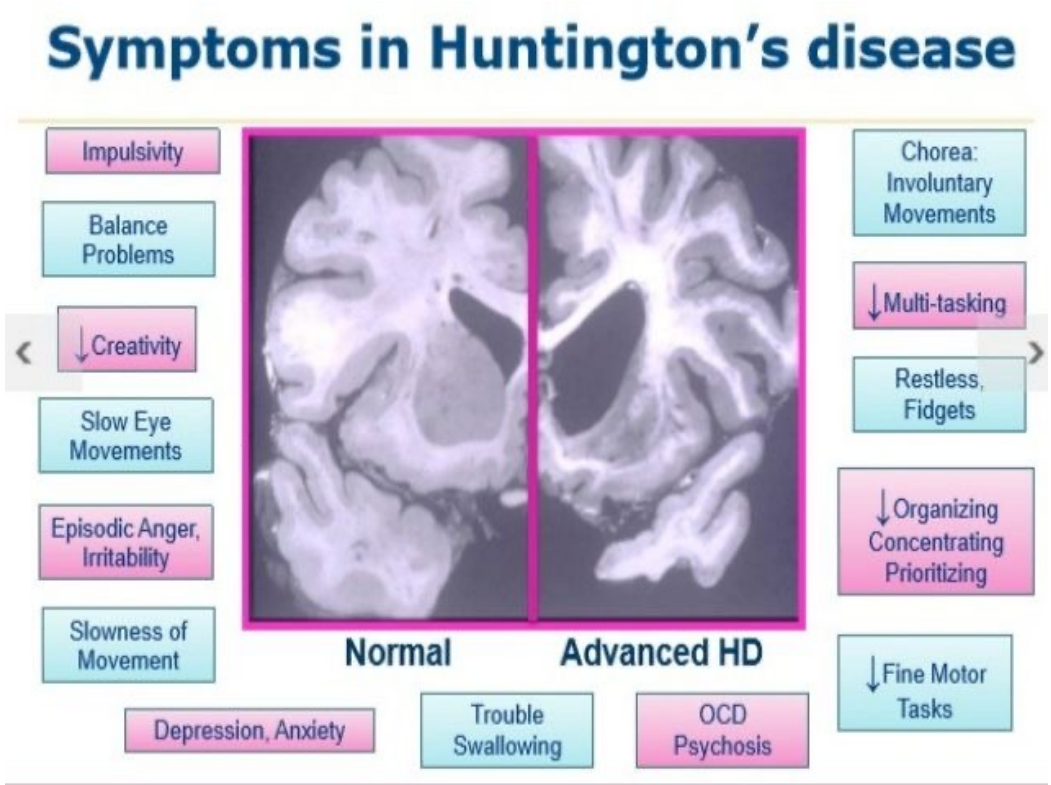
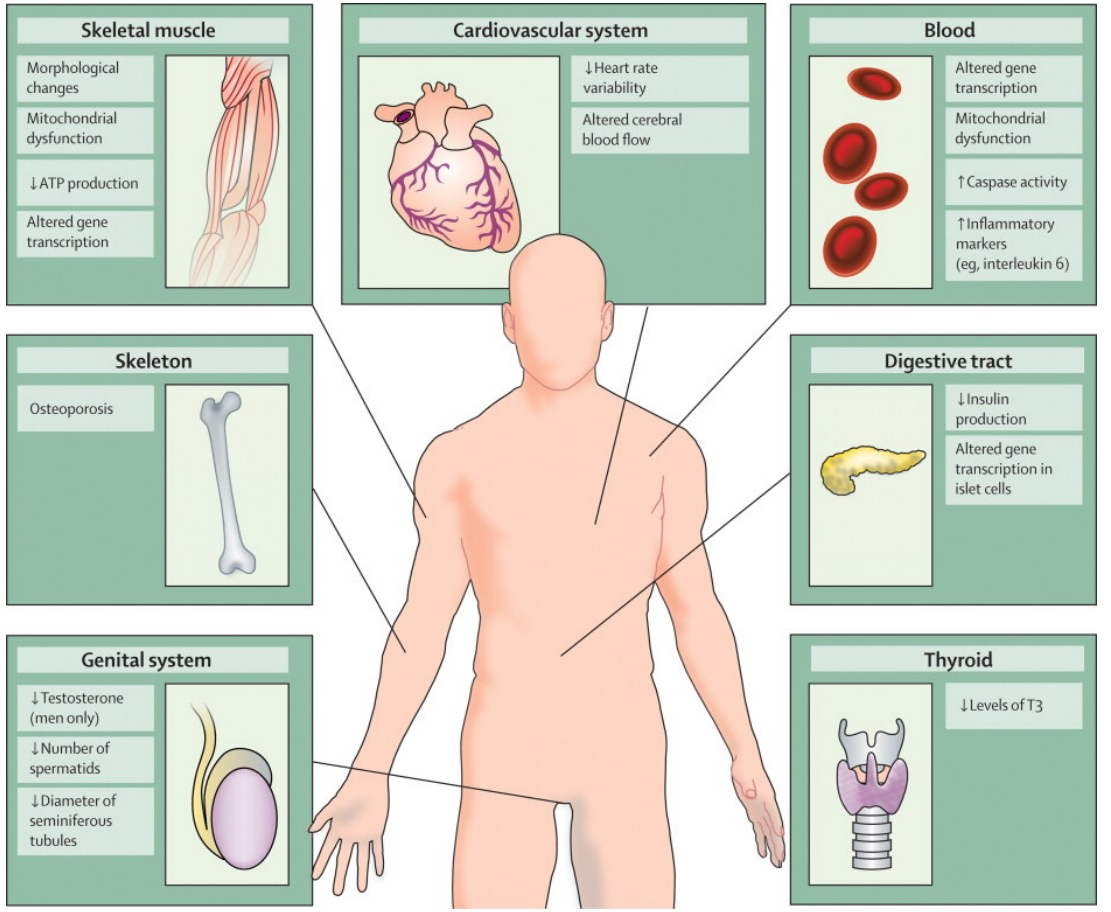
Huntington Disease





www.thelancet.com/journals/lancet/article/PIIS1474-4422(09)70178-4/fulltext.

Cannabinoid Utilizations

Huntington Disease (2016 Study)

- A neurodegenerative disease for which there is no curative treatment available
- A double-blind, randomized, placebo-controlled, cross-over pilot clinical trial with THC/CBD nabiximols oral sprays administered up to 12 sprays/day for 12 weeks
- Primary objectives were safety and no greater deterioration of motor, cognitive, behavioral, and functional scales
- Secondary objective: clinical improvement of Unified Huntington Disease Rating Scale
- 26 patients were randomized and 24 completed the trial
- No differences on motor ($p = 0.286$), cognitive ($p = 0.824$), behavioral ($p = 1.0$) and functional ($p = 0.581$) scores were detected during treatment with nabiximols as compared to placebo [did NOT meet Power]
- Nabiximols was safe and well tolerated in patients with HD, with no clinical worsening

López-Sendón Moreno. *J Neurol*. 2016;263(7):1390-1400.

Cannabinoid Utilizations

Huntington Disease

- 2020 American Heart Association

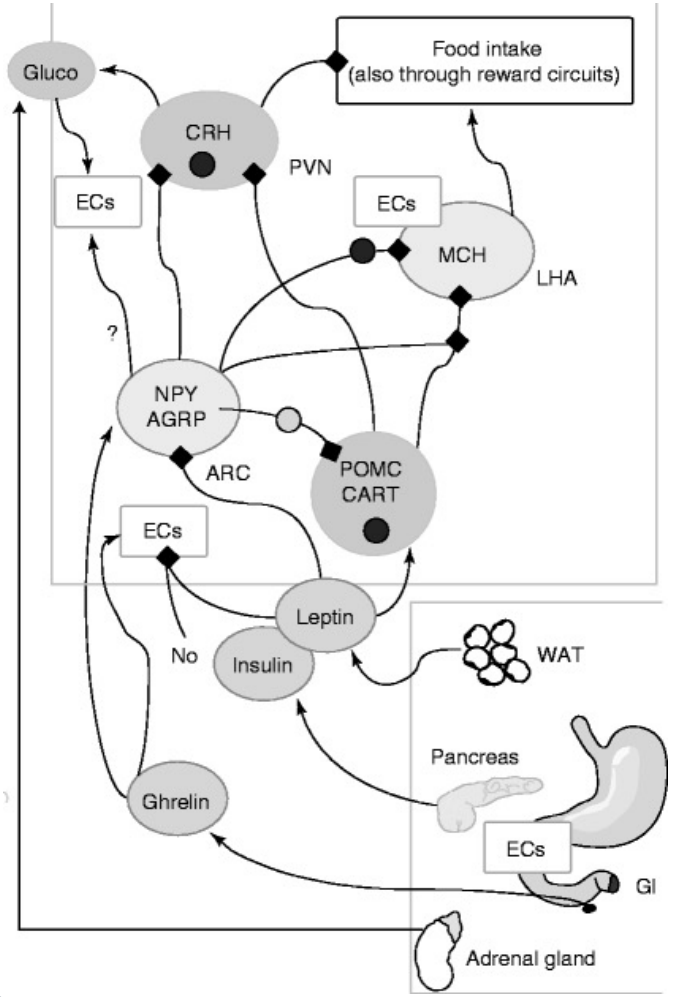
- Inconclusive evidence (no RCTs)
  - Preclinical studies report mixed results with THC on Huntington disease-like symptoms.
  - Limited evidence from case studies and small clinical trials is mixed and suggests a lack of effect with CBD and a limited improvement in Huntington disease symptoms with smoked cannabis

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Metabolic Syndrome, Obesity, and Diabetes Mellitus

- EC: endocannabinoids (ECs)
- Gluco: glucocorticoids in hypothalamus (along with ghrelin)
- CRH: corticotropin-releasing hormone
  - CB_1 receptors negatively control CRH and CART
- CART: cocaine and amphetamine regulated transcript
- PVN: peri ventricular nuclei (PVN)
- ARC: arcuate nucleus
- LHA: lateral hypothalamus
- MCH: melanin-concentrating hormone
- POMC: pro-opiomelanocortin
  - *Dark Circles* denote EC inhibitory actions
  - *Light Circles* denote stimulatory action
  - *Black Diamonds* denote inhibition by non-EC mediators
  - *Black Arrows* denote stimulation/production



Di Marzo. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. In: Schwanstecher (ed). *Diabetes - Perspectives in Drug Therapy. Handbook of Experimental Pharmacology, vol 203*. Springer, Berlin, Heidelberg: 2011.

Cannabinoid Utilizations

Metabolic Syndrome, Obesity, and Diabetes Mellitus

- ECS overactivity
  - Leads to insulin resistance, glucose intolerance, low HDL, high TG, and atherosclerosis
    - Brain → increased desire to consume food
    - Adipocytes → increased abdominal lipogenesis → abdominal obesity
    - Liver → increased fatty acid synthesis
    - Pancreas → dysregulated insulin/glucagon release
    - Skeletal muscle → reduced glucose uptake

Di Marzo. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. In: Schwanstecher (ed). *Diabetes - Perspectives in Drug Therapy. Handbook of Experimental Pharmacology, vol 203*. Springer, Berlin, Heidelberg: 2011.

Cannabinoid Utilizations

Metabolic Syndrome, Obesity, and Diabetes Mellitus

- 2020 American Heart Association

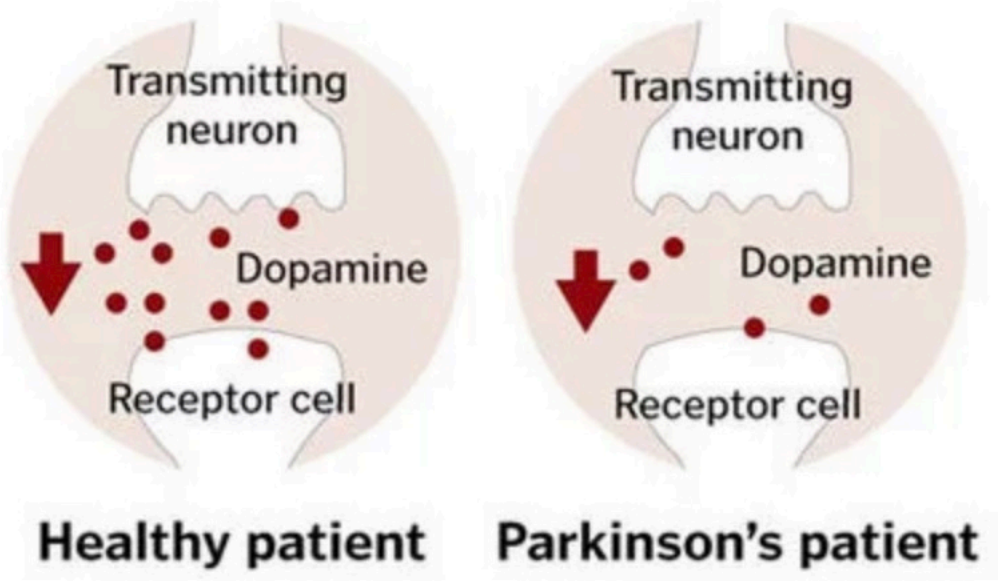
American Heart Association®

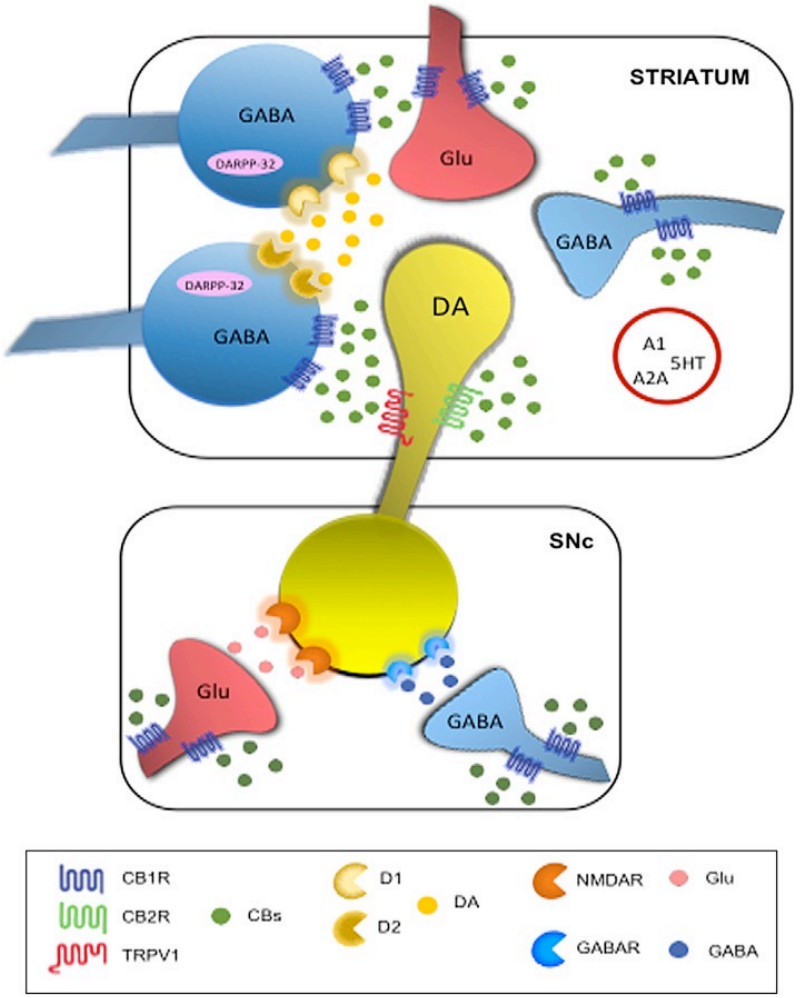
- Inconclusive evidence (no RCTs)
  - Acute CB1 activation → increased fat synthesis and storage
  - Chronic CB1 activation → weight loss and improved metabolic indicators
  - Observational studies suggest an association between long-term cannabis use and an improved metabolic profile
  - Preclinical and very limited clinical evidence suggests a potential beneficial effect of THC on glycemic control (in patients with DM2)

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Parkinson's





- Parkinson's disease results from the death of cells in the substantia nigra region of the midbrain which causes insufficient dopamine production
- Dopamine coordinates smooth and balanced muscle movement
- Cannabinoids increase dopamine release

Stampanoni. *Cannabis Cannabinoid Res*. 2017;2(1):21-29.
chillcryotherapy.net/cryotherapy-potential-prevention-treatment-for-parkinsons-disease/

Cannabinoid Utilizations

Parkinson's

- Stampanoni BM, et. al. Cannabinoids in Parkinson's Disease. *Cannabis Cannabinoid Res*. 2017;2(1):21-29. Published 2017 Feb 1.
- Carroll CB, et. al. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. Neurology. 2004 Oct 12;63(7):1245-50.
- Chagas MH, et. al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacology. 2014 Nov;28(11):1088-98.
- Sieradzan KA, et. al. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study. Neurology Dec 2001, 57 (11) 2108-2111.
- Babayeva M, et. al. "Marijuana Compounds: A Nonconventional Approach to Parkinson's Disease Therapy", *Parkinson's Disease*, vol. 2016, Article ID 1279042, 19 pages, 2016.

- Overall conclusion:
  - PROBABLY INEFFECTIVE for treating levodopa-induced dyskinesias in patients with Parkinson's disease

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Parkinson's

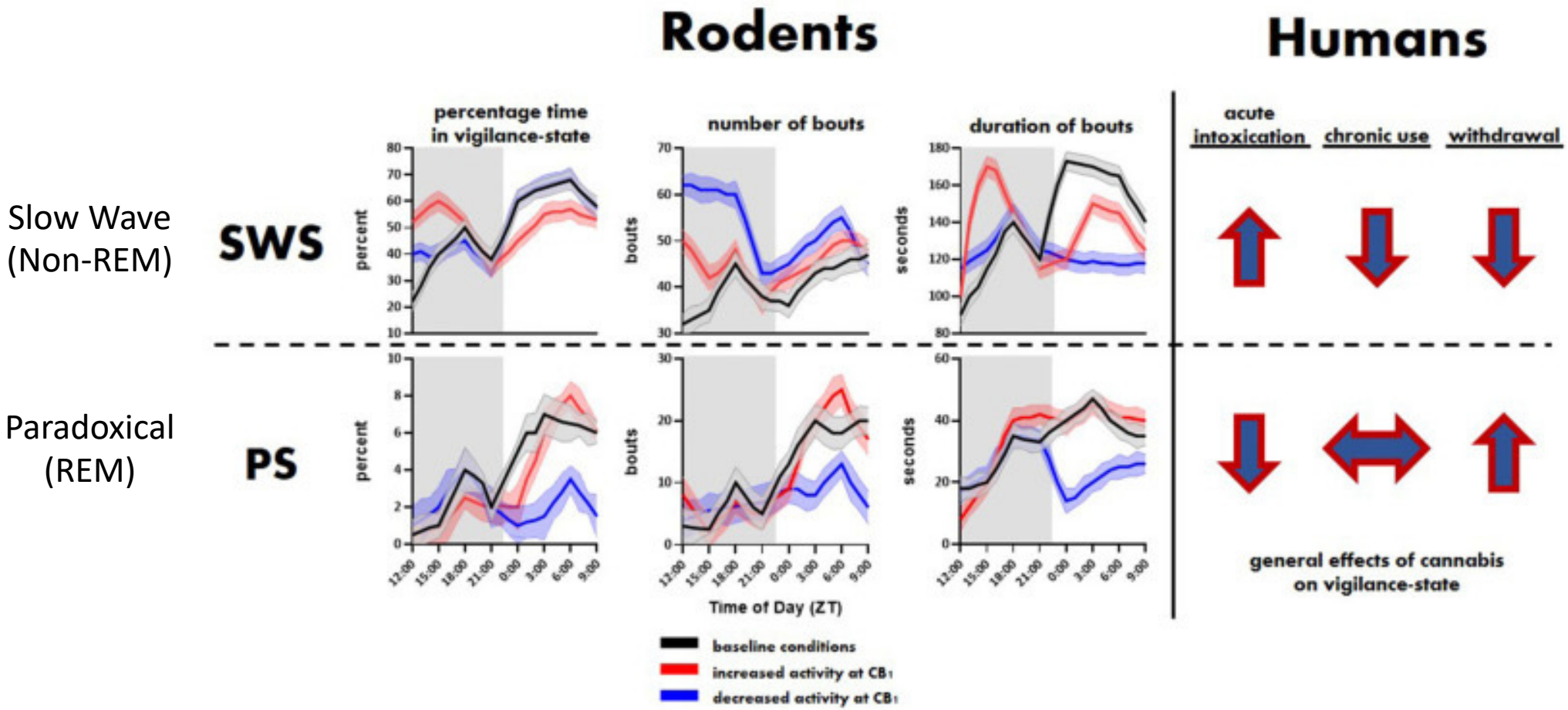
- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Limited preclinical, case, clinical, and observational studies of certain cannabinoids for Parkinson's symptoms are mixed
  - One observational smoked cannabis study suggests improvement in symptoms
  - One clinical THC/CBD extract study and a clinical study of CBD suggest no improvement in symptoms

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Sleep



Kesner. *Front Mol Neurosci*. 2020;13:125.

Cannabinoid Utilizations

Sleep

- 2020 American Heart Association

- Inconclusive evidence (no RCTs)
  - Cannabis and THC have a dose-dependent effect on sleep:
    - Low doses appear to
      - Decrease sleep-onset latency
      - Increase slow-wave sleep and total sleep time
    - High doses appear to cause sleep disturbances
  - Clinical studies suggest that cannabis, nabilone, and dronabinol may improve sleep in patients with sleep disturbances

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Inconclusive

INCONCLUSIVE EVIDENCE (No RCTs)	
Alzheimer's	Preclinical studies suggest that THC and CBD may protect against excitotoxicity, oxidative stress, and inflammation in animal models
	Limited case, clinical, and observational studies suggest that oral THC and nabilone are associated with improvement in a number of symptoms associated with Alzheimer disease (eg, nocturnal motor activity, disturbed behavior, sleep, agitation, and restiveness).
Anxiety and Depression	Small studies with adjunct functional neuroimaging in healthy individuals have demonstrated that CBD and dronabinol reduce anxiety related to its effects on activity in limbic and paralimbic brain areas.
	US adults occasional cannabis use → not associated with social anxiety disorder US adults frequent cannabis use → significantly increased odds of social anxiety disorder
Tumors	Preclinical studies suggest that very high doses of THC, CBD, CBG, and CBC often, but not always, block the growth of cancer cells in vitro and display a variety of antineoplastic effects in vivo.
	One limited clinical study in patients with glioblastoma multiforme reported that intratumor injection of high doses of THC did not improve patient survival beyond that seen with conventional chemotherapeutic agents.
IBDs (Crohn's and UC)	Preclinical animal studies suggest that synthetic CB1/2 agonists, THC, CBD, CBG, CBC, and cannabis extract may limit intestinal inflammation
	Very limited number of small clinical studies of patients with IBD who failed conventional treatments reported improvement with smoked cannabis.
Heart Failure	In retrospective analysis of 161,000 patients with heart failure, cannabis use was associated with a lower risk for death while the patient was hospitalized with acute heart failure, shorter mean hospital stay, and lower mean hospital costs compared with nonusers.
Ischemia	Preclinical studies suggest that CBD, THCV, and ultralow doses of THC may have some protective effects against ischemia/reperfusion injury.

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Inconclusive

INCONCLUSIVE EVIDENCE (no RCTs)	
Hepatitis C	Preclinical studies suggest that CB1 receptor activation promotes steatosis and fibrosis, whereas CB2 receptor activation has some beneficial effects.
	Daily cannabis use has been shown to be a predictor of steatosis severity for patients with Chronic Hepatitis C
Huntington Disease	Preclinical studies report mixed results with THC on Huntington disease–like symptoms.
	Limited evidence from case studies and small clinical trials is mixed and suggests a lack of effect with CBD and a limited improvement in Huntington disease symptoms with smoked cannabis.
Metabolic Syndrome Obesity Diabetes Mellitus	Acute CB1 receptor activation → Increased fat synthesis and storage Chronic CB1 receptor activation → weight loss and improved metabolic indicators
	Observational studies suggest an association between long-term cannabis use and an improved metabolic profile
	Preclinical and very limited clinical evidence suggests a potential beneficial effect of THC on glycemic control (in patients with DM2).
Parkinson's	Limited preclinical, case, clinical, and observational studies of certain cannabinoids for Parkinson's symptoms are mixed.
	One observational smoked cannabis study suggests improvement in symptoms.
	One clinical THC/CBD extract study and a clinical study of CBD suggest no improvement in symptoms.
Sleep	Cannabis and THC have a dose-dependent effect on sleep: • Low doses appear to decrease sleep-onset latency and increase slow-wave sleep and total sleep time • High doses appear to cause sleep disturbances
	Clinical studies suggest that cannabis, nabilone, and dronabinol may improve sleep in patients with sleep disturbances

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

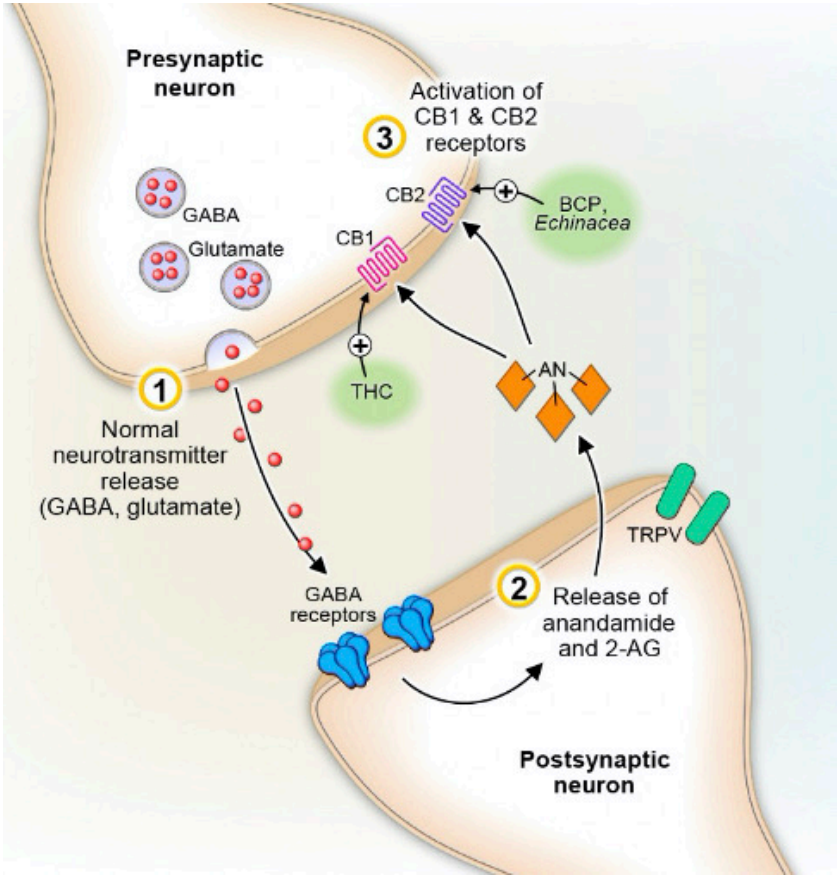
Possible (Moderate Evidence)

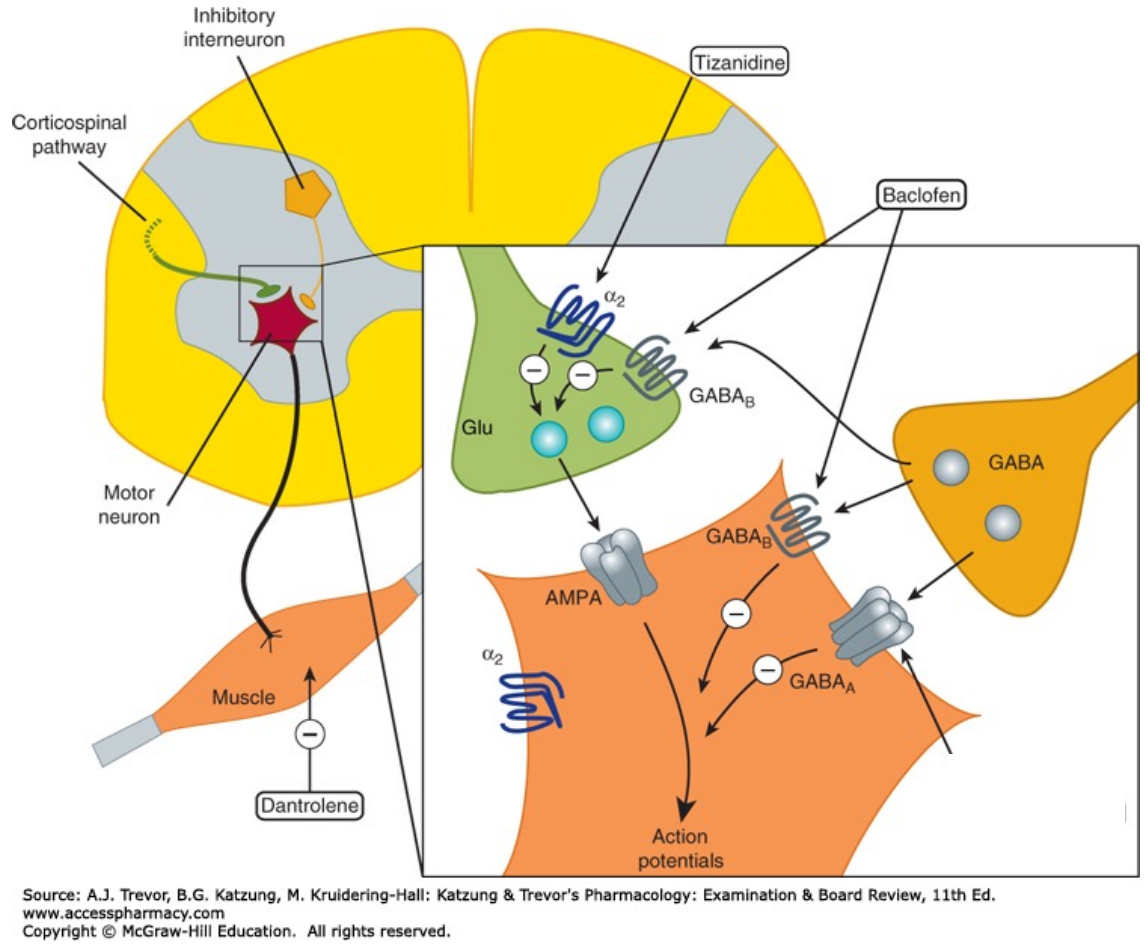
- Long-term opioid use
- Dystonia
- Glaucoma

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Long-Term Opioid Use (GABBA, GABBA, GABBA)





Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

VanDolah. *Mayo Clinic Proceedings.* 2019;94:1840-1851.

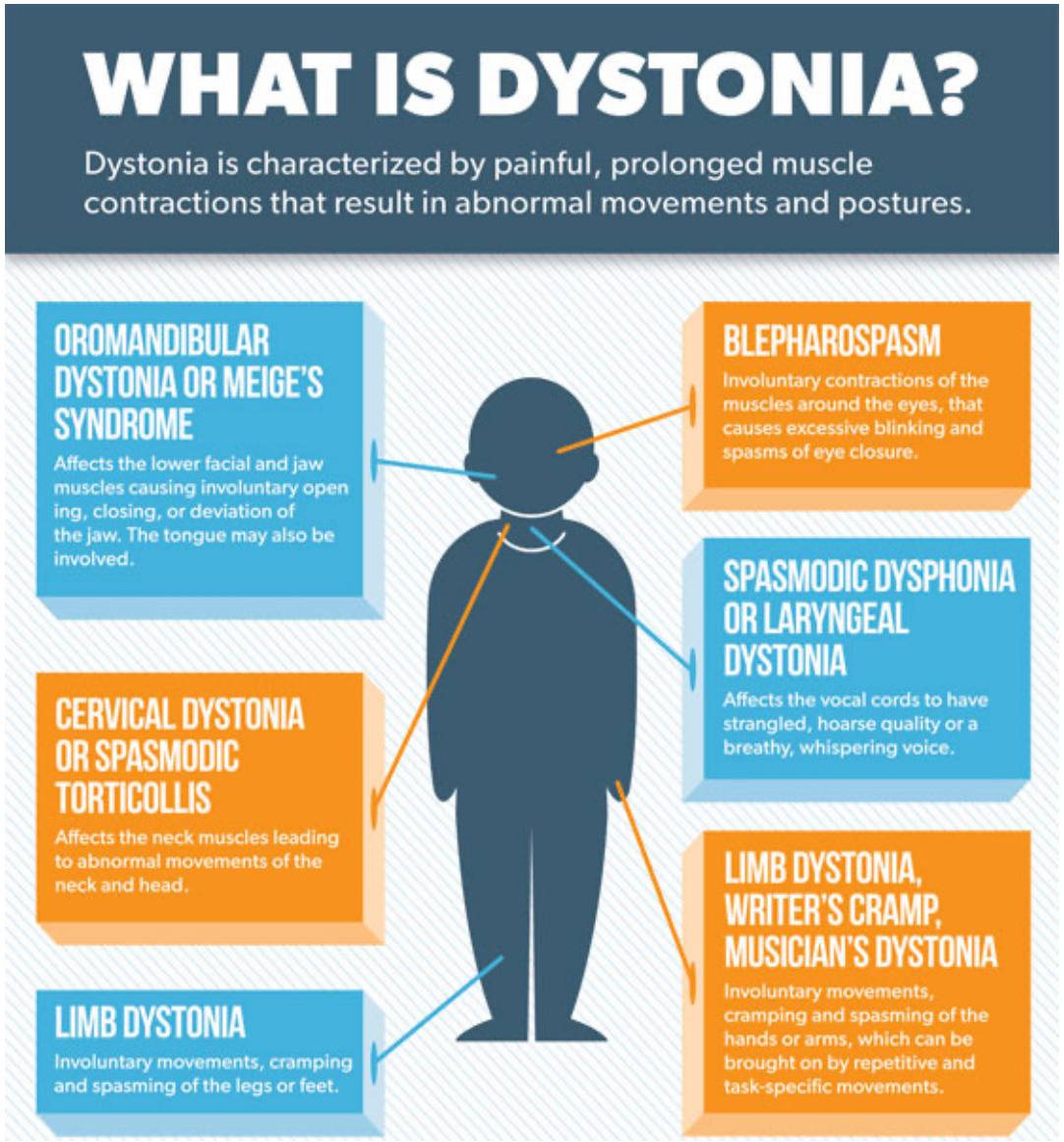
Cannabinoid Utilizations

Long-Term Opioid Use

- 2020 American Heart Association

- Possible (moderate evidence)
  - Preclinical and case studies suggest cannabinoid opioid-sparing effect, however, epidemiological and clinical studies with oral THC are mixed
  - Observational studies suggests cannabis could help alleviate opioid withdrawal symptoms, but insufficient clinical evidence

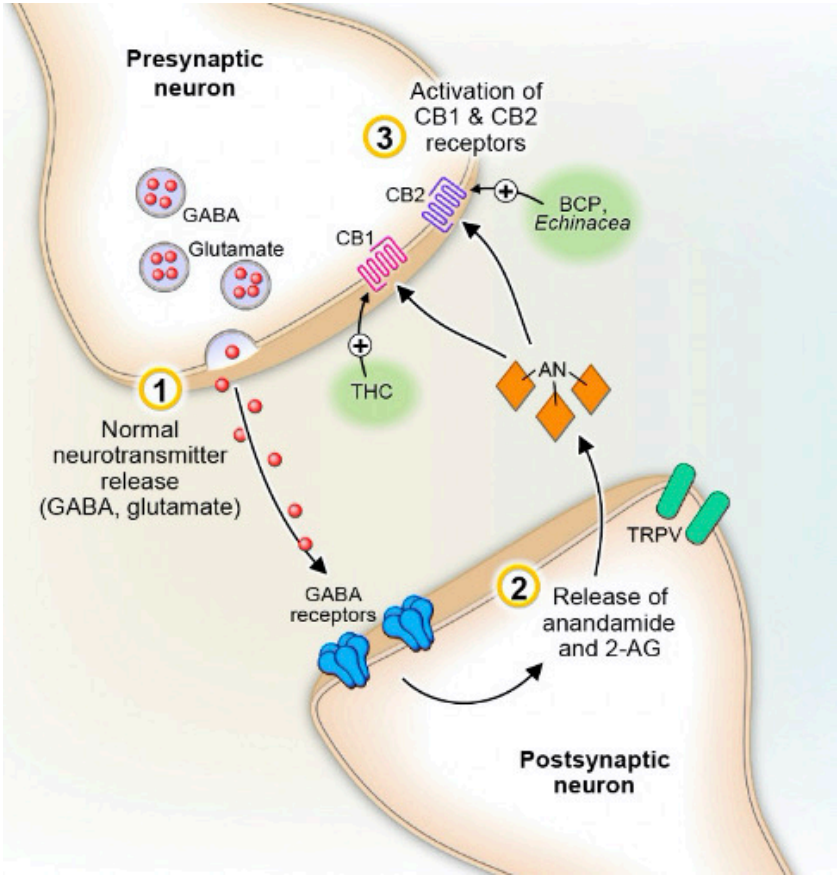
Page. *Circulation*. 2020;142(10):e131-e152.

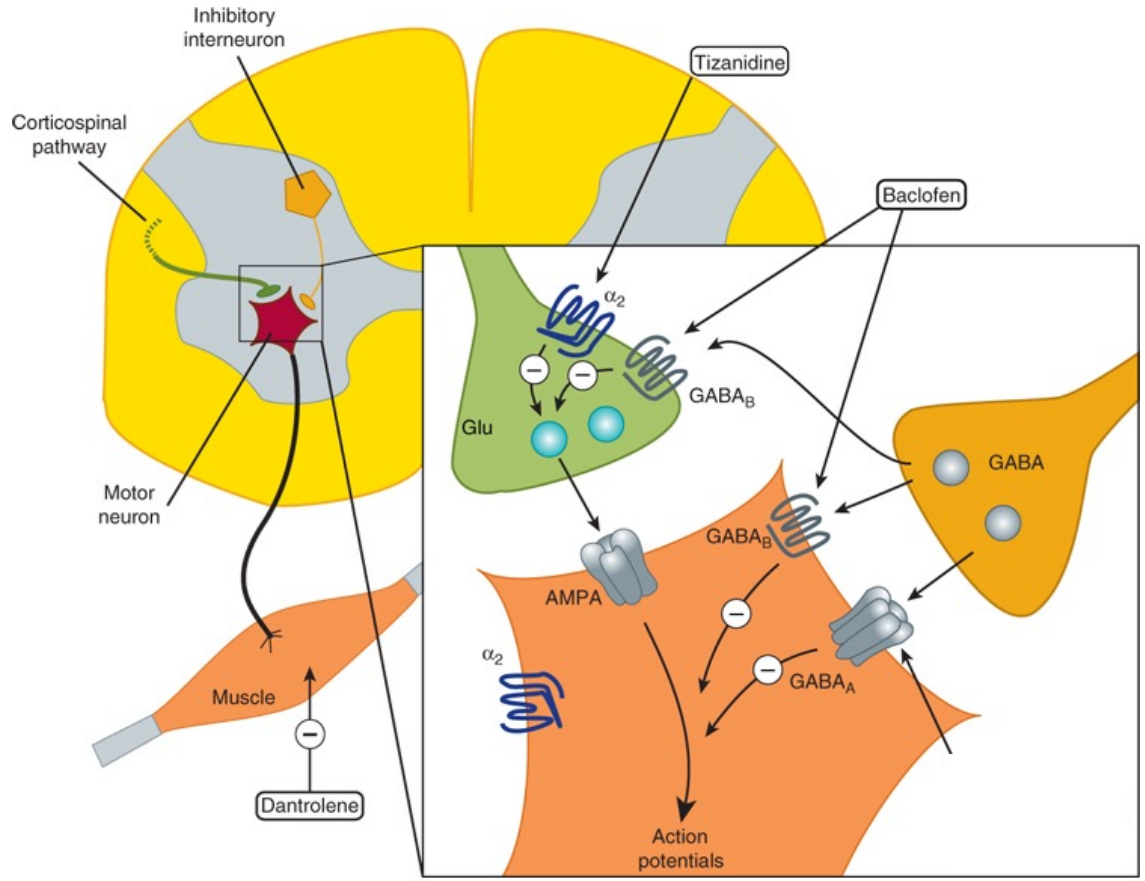


www.invigoratept.com/blog/parkinsons-dystonia-a-bookmarkable-guide.

Cannabinoid Utilizations

Dystonia (GABBA, GABBA, GABBA to calm muscles)





Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

VanDolah. *Mayo Clinic Proceedings.* 2019;94:1840-1851.

Cannabinoid Utilizations

Dystonia

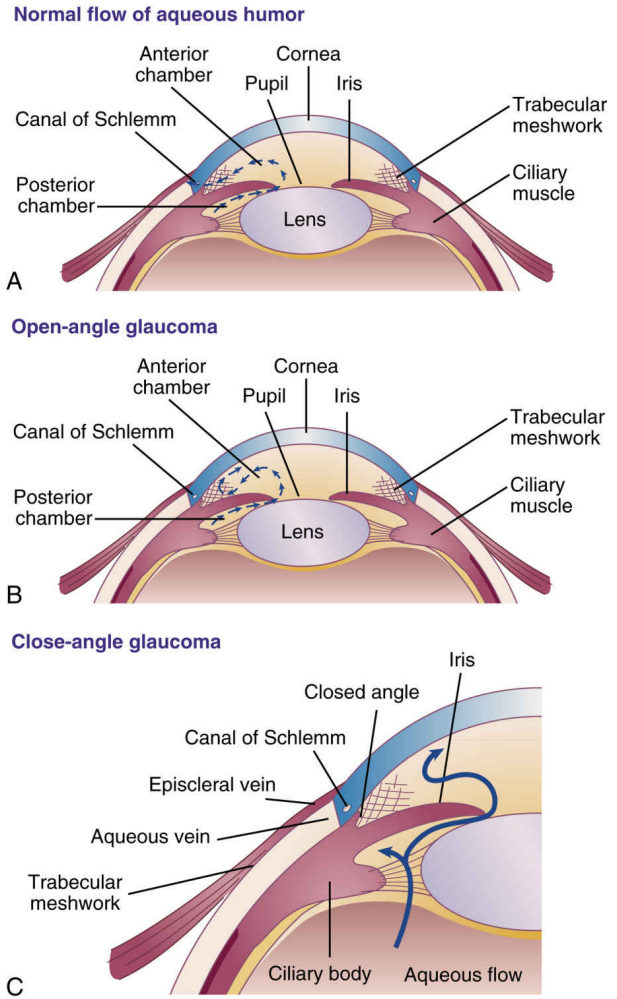
- 2020 American Heart Association

- Possible (moderate evidence)
  - Dystonia-like symptoms and progression
    - Sustained or intermittent muscle contractions causing abnormal movements and postures

Page. *Circulation*. 2020;142(10):e131-e152.

Glaucoma

- Eye drop treatments
  - Beta blockers
  - Carbonic anhydrase inhibitors
  - Prostaglandin Analogues
    - Xalatan® (latanoprost)
    - Lumigan® (bimatoprost)
    - Travatan Z® (travoprost)
    - Zioptan™ (tafluprost)
    - Vyzulta™ (latanoprostene bunod)
  - Combinations

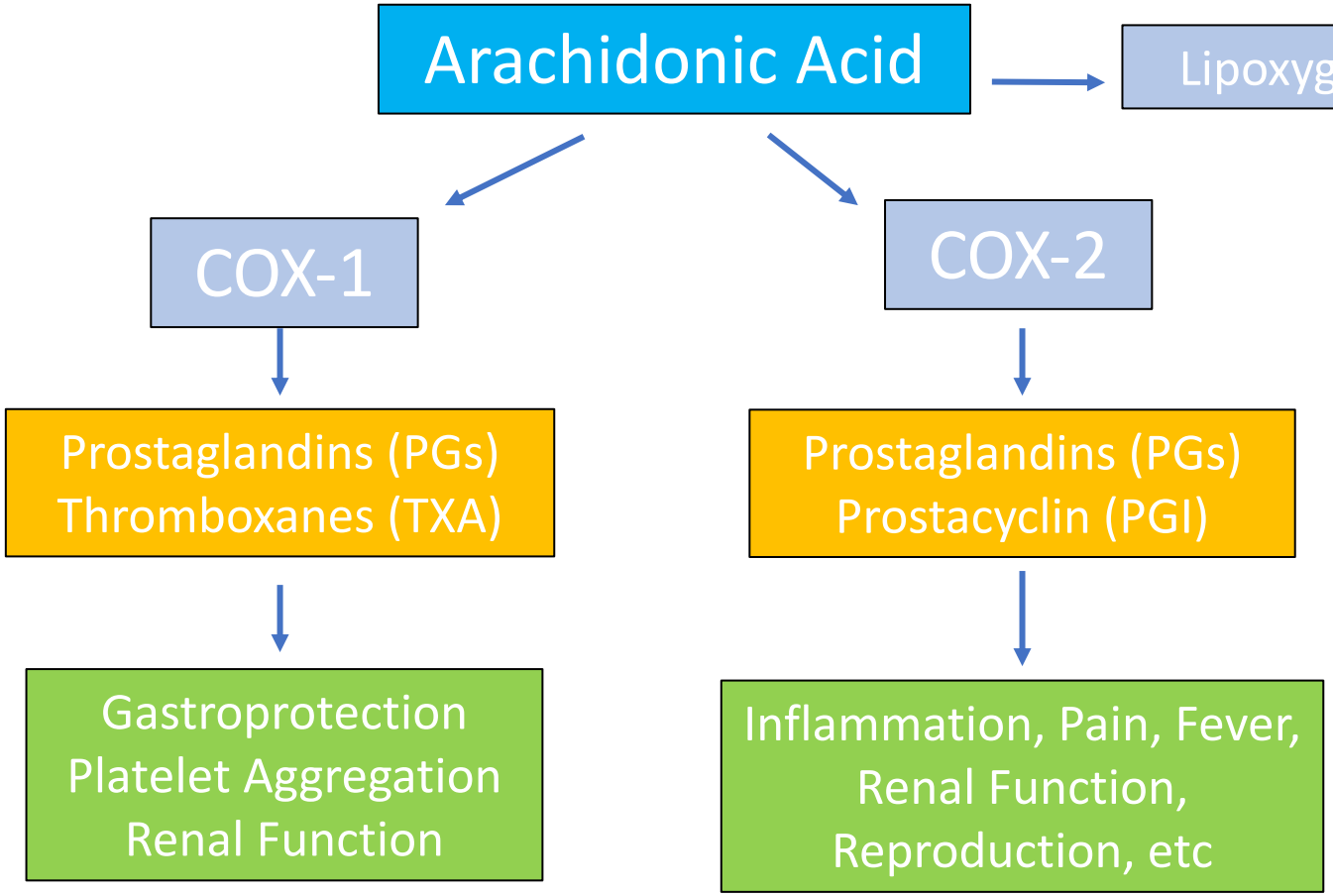


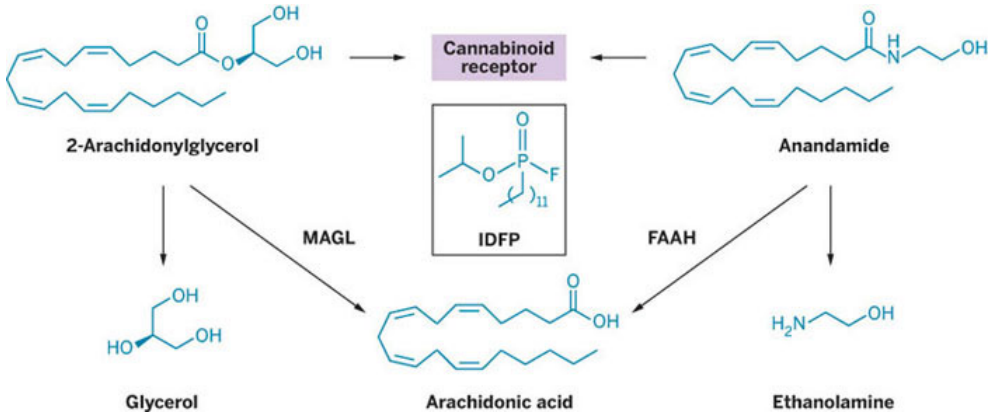
basicmedicalkey.com/eye-and-ear-disorders/.

www.ncbi.nlm.nih.gov/books/NBK543075/figure/diseases_glaucoma.F7B/.

Prostaglandin Mechanisms

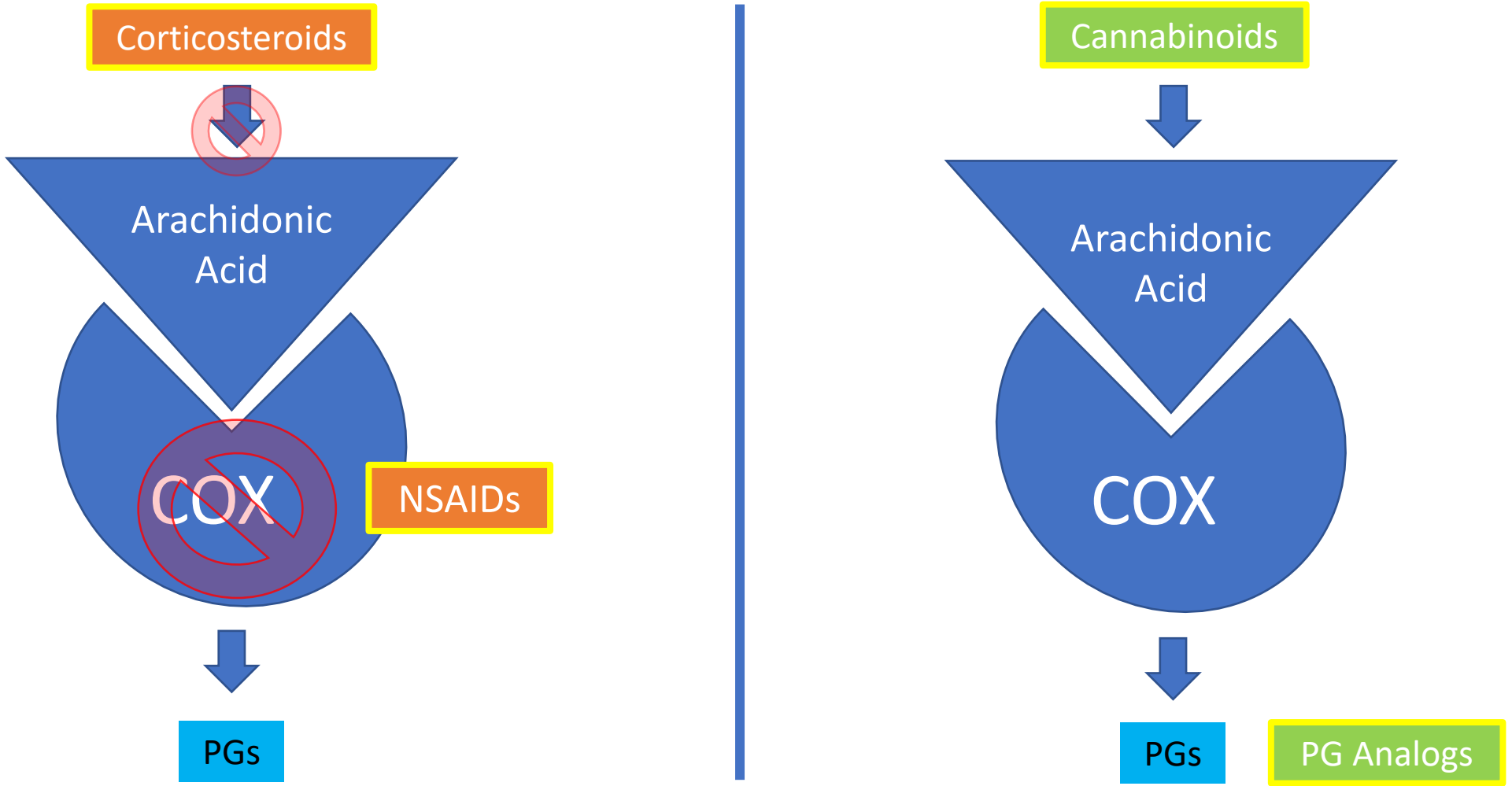
NSAIDs, Corticosteroids, Glaucoma Eye Drops, and Cannabinoids





cen.acs.org/articles/86/web/2008/04/Nerve-Agents-Hit-Cannabinoid-System.html.
tmedweb.tulane.edu/pharmwiki/doku.php/nsaid_side_effects.

NSAIDs, PG Analogs, and Cannabinoids



Cannabinoid Utilizations

Glaucoma

- 2020 American Heart Association

- Possible (moderate evidence)
  - THC → reduction of intraocular pressure
  - CBD → increase of intraocular pressure

➢American Glaucoma Society does not recommend either

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Possible

POSSIBLE (Moderate Evidence)	
Long-Term Opioid Use	Preclinical and case studies suggest cannabinoid opioid-sparing effect, however, epidemiological and clinical studies with oral THC are mixed
	Observational studies suggests cannabis could help alleviate opioid withdrawal symptoms, but insufficient clinical evidence
Dystonia	Dystonia-like symptoms and progression
Glaucoma	THC → reduction of intraocular pressure CBD → increase of intraocular pressure *American Glaucoma Society does not recommend either

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Known (Conclusive/Substantial Evidence)

- Pain
- Cachexia
- Nausea/vomiting
- Multiple sclerosis
- Epilepsy

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Pain

- 2020 American Heart Association

- KNOWN (conclusive/substantial evidence)
  - Neuropathic pain
  - Fibromyalgia
  - Cancer pain

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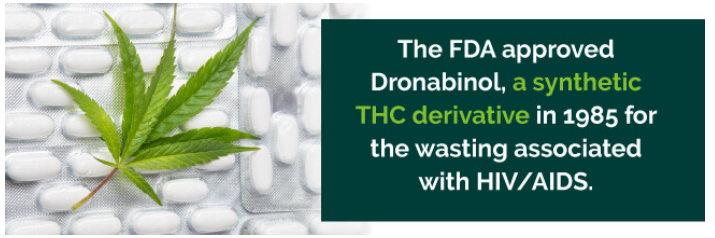
Cannabinoid Utilizations

Cachexia (Kuh Kek See Uh)

- 2020 American Heart Association
- KNOWN (conclusive/substantial evidence)
  - Wasting disorder (extreme weight loss and muscle wasting)
    - HIV-associated anorexia/cachexia
    - Cancer-associated anorexia/cachexia
  - Cannabinoids
    - Stimulate appetite
    - Reduce/eliminate nausea and vomiting

*Caution: cannabis hyperemesis syndrome

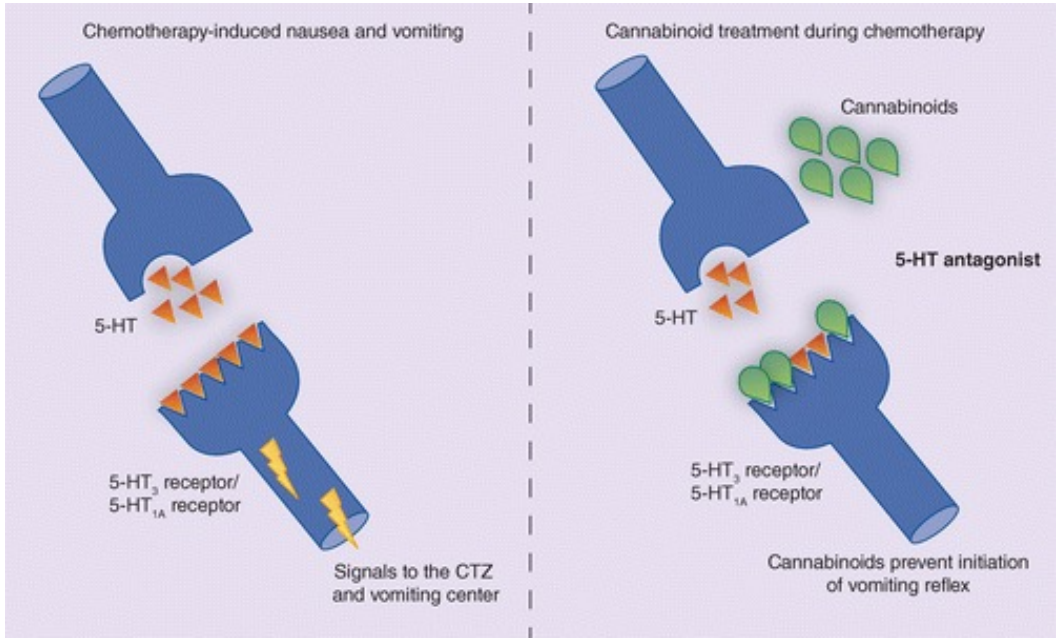


Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Utilizations

Nausea and Vomiting

- Theory: chemotherapy trigger zone (CTZ) effects
  - Triptan cousins???
- Opposite of cannabis hyperemesis syndrome (CHS) involving TRPV



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Cannabinoid Utilizations

Nausea and Vomiting

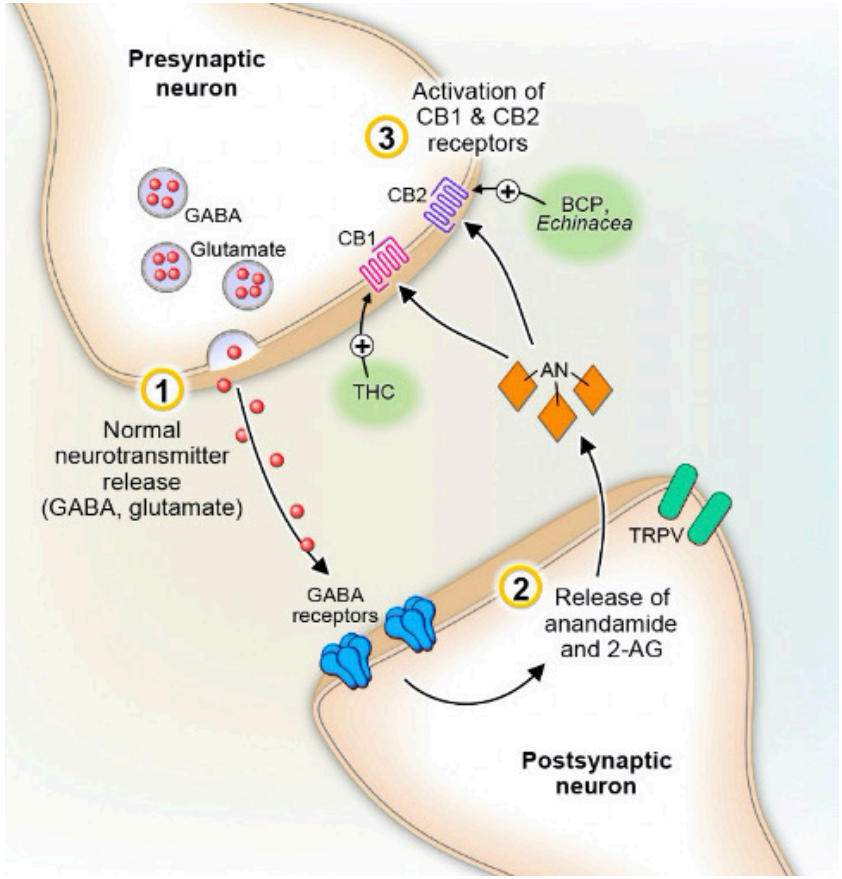
- 2020 American Heart Association
- KNOWN (conclusive/substantial evidence)
  - Chemotherapy-induced N/V

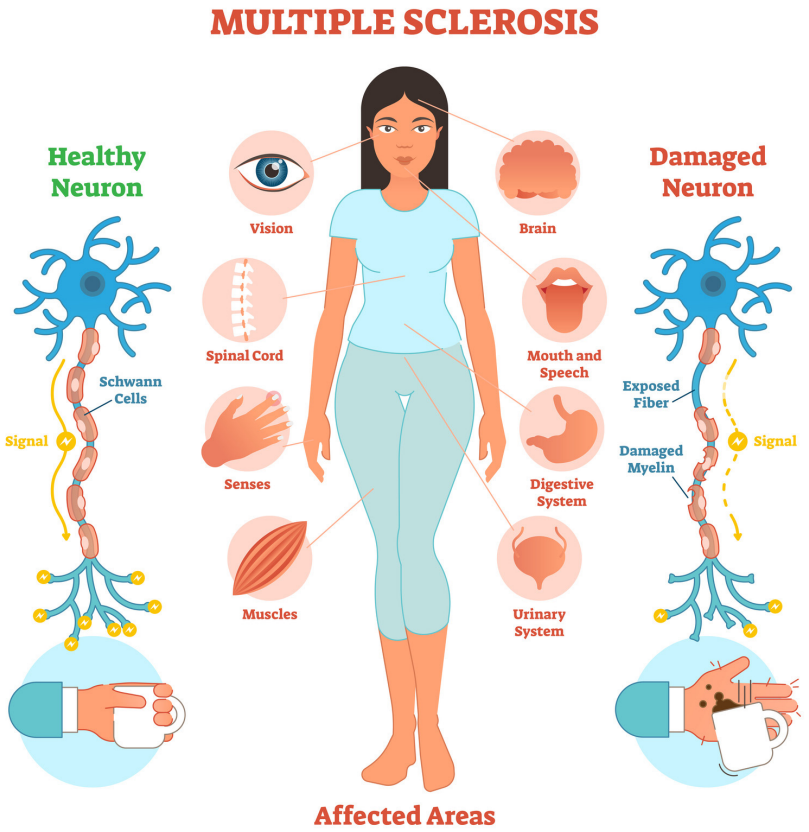
American Heart Association®

*Caution: cannabis hyperemesis syndrome

Page. *Circulation*. 2020;142(10):e131-e152.

Multiple Sclerosis





VanDolah. *Mayo Clinic Proceedings.* 2019;94:1840-1851.

Cannabinoid Utilizations

Multiple Sclerosis (2018 Review of Reviews)

Year	Author	Title	Aim of review
2016	Andrzejewski	Cannabinoids in the treatment of movement disorders: a systematic review of case series and clinical trials	To assess the use of exogenous cannabinoids in the treatment of movement disorders.
2015	Whiting	Cannabinoids for medical use: a systematic review and meta-analysis	To conduct a systematic review of the benefits and adverse events of cannabinoids.
2014	Koppel	Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders	To determine the efficacy of medical marijuana in several neurologic conditions.
2013	Jawahar	A systematic review of pharmacological pain management in MS	To systematically review pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in MS patients.
2012	Zhornitsky	Cannabidiol in humans—the quest for therapeutic targets	To examine the randomised and crossover studies that administered CBD to healthy controls and clinical patients.
2010	Karst	Role of cannabinoids in the treatment of pain and (painful) spasticity	To review the most current and relevant data available on the antinociceptive properties of cannabinoids for their potential or already established use in clinical settings.
2007	Mills	Treatment for ataxia in multiple sclerosis	To assess the efficacy and tolerability of both pharmacological and non-pharmacologic treatments of ataxia and tremor in patients with MS.
2009	Lakhan	Whole plant cannabis extracts in the treatment of spasticity in MS: a systematic review	To systematically evaluate effectiveness of combined THC and CBD extracts on MS-related spasticity in order to increase understanding of the treatment's potential effectiveness, safety and limitations.
2008	Wang	Adverse effects of medical cannabinoids: a systematic review	To create an evidence base for cannabis-related adverse events and to facilitate future cannabis research initiatives.
2006	Ben Amar	Cannabinoids in medicine: a review of their therapeutic potential	To report on the most current data available on the therapeutic potential of cannabinoids.
2003	Shakespeare	Anti-spasticity agents for multiple sclerosis	To assess absolute and comparative efficacy and tolerability of anti-spasticity agents in MS patients.

Nielsen. *Curr Neurol Neurosci Rep.* 2018;18:8.

Cannabinoid Utilizations

Multiple Sclerosis (2018 Review of Reviews)

Product	Reviews	Effect	Conclusions
Cannabis Sativa	1	Positive	Insufficient Evidence
CBD Extract	3	1 Mixed 2 Positive	1 Insufficient Evidence 2 MS Pain Not Reported
Dronabinol	6	1 No Change 5 Positive	3 MS Pain Not Reported 1 More Trials Needed 2 Supportive of Clinical Utilization
Nabilone	2	2 Positive	1 MS Pain Not Reported 1 Mixed Findings
Nabiximols	4	3 Mixed 1 Positive	1 MS Pain Not Reported 1 More Trials Needed 2 Supportive of Clinical Utilization
THC Extract	3	3 Positive	1 MS Pain Not Reported 2 Supportive of Clinical Utilization
THC/CBD Extract	6	4 Mixed 2 Positive	1 Insufficient Evidence 3 MS Pain Not Reported 1 Mixed Findings 1 Supportive of Clinical Utilization

Nielsen. *Curr Neurol Neurosci Rep.* 2018;18:8.

Cannabinoid Utilizations

Multiple Sclerosis (2018 Review of Reviews)

	MS Progression	MS Pain	MS Spasticity	MS Bladder Function	MS Ataxia and Tremor	MS: Sleep	MS Quality of Life	Adverse Events
CANNABIS (SMOKED)	1 study (1 RCT)	1 study (1 RCT)	2 studies (2 RCT)	No studies	No studies	No studies	2 studies (2 RCT)	2 studies (2 RCT)
Findings	No change	Positive effect	Positive effect				Mixed effect	AEs > comparator
Quality of evidence	Low quality	Low quality	Low quality				Low quality	Low quality
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence				Insufficient evidence	Insufficient evidence
DRONABINOL	4 studies (2 RCT)	4 studies (3 RCT)	5 studies (5 RCT)	2 studies (1 RCT)	3 studies (2 RCT)	2 studies (1 RCT)	2 studies (2 RCT)	8 studies (6 RCT)
Findings	No effect	Positive effect	Mixed effect	Mixed effect	No change	Mixed effect (mostly positive)	Mixed effect	AEs > comparator
Quality of evidence	Very low to high	Low to high quality	Low to high quality	High quality	Very low to high quality	Moderate to high quality	Low to high quality	Very low to high quality
Conclusion	Inconsistent evidence	Some evidence of positive effect	Inconsistent evidence	Inconsistent evidence	Unlikely to have an effect	Insufficient evidence	Insufficient evidence	Mild AEs likely
THC EXTRACT	No studies	3 studies (2 RCT)	2 studies (1 RCT)	1 study (No RCT)	No studies	3 studies (2 RCT)	No studies	1 studies (1 RCT)
Findings		Positive effect	Positive effect	Positive effect		Mixed effect		AEs > comparator
Quality of evidence		Very low to low	Very low to low quality	Very low quality		Very low to low quality		Low quality
Conclusion		Some evidence of effect	Insufficient evidence	Insufficient evidence		Insufficient evidence		Mild AEs likely
NABIXIMOLS	2 studies (2 RCT)	8 studies (5 RCT)	7 studies (6 RCT)	2 studies (2 RCT)	2 studies (2 RCT)	1 study (1 RCT)	5 studies (5 RCT)	10 studies (7 RCT)
Findings	No change	Mixed effect	Mixed effect	Mixed effect	No change	Positive effect	Mixed findings	AEs > comparator
Quality of evidence	Moderate quality	Very low to moderate quality	Very low to moderate quality	Moderate quality	Moderate quality	Moderate quality	Moderate quality	Very low to moderate quality
Conclusion	Insufficient evidence	Inconsistent evidence	Inconsistent evidence	Insufficient evidence	Unlikely to have an effect	Insufficient evidence	Some evidence of positive effect	Mild AEs likely
THC:CBD EXTRACTS	6 studies (5 RCT)	7 studies (5 RCT)	6 studies (5 RCT)	4 studies (2 RCT)	4 studies (4 RCT)	4 studies (3 RCT)	3 studies (3 RCT)	8 studies (6 RCT)
Findings	Mixed effect	Mixed findings	Mixed findings	Mixed findings	No change	Mostly positive effect	Mixed findings	AEs > comparator
Quality of evidence	Low to high quality	Very low to high quality	Low to high quality	Very low to high quality	Low to high quality	Low to high quality	Low to high quality	Low to high quality
Conclusion	Inconsistent evidence	Inconsistent evidence	Inconsistent evidence	Inconsistent evidence	Unlikely to have an effect	Some evidence of effect	Inconsistent evidence	Mild AEs likely
NABILONE	No studies	1 study (1 RCT)	2 studies (2 RCT)	1 study (1 RCT)	1 study (1 RCT)	No studies	2 studies (2 RCT)	3 studies (3 RCT)
Findings		Positive effect	Positive effect	Positive effect	No change		Mixed effect	AEs > comparator
Quality of evidence		Very low	Very low to low quality	Very low quality	Low quality		Very low to moderate quality	Very low to low quality
Conclusion		Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence		Insufficient evidence	Mild AEs likely
CBD EXTRACT	No studies	2 studies (2 RCT)	1 study (1 RCT)	No studies	No studies	1 study (1 RCT)	No studies	1 study (1 RCT)
Findings		Mixed effect	Mixed findings			Positive effect		AEs > comparator
Quality of evidence		Low quality	Low quality			Low quality		Low quality
Conclusion		Insufficient evidence	Insufficient evidence			Insufficient evidence		Insufficient evidence

Nielsen. *Curr Neurol Neurosci Rep.* 2018;18:8.

Cannabinoid Utilizations

Multiple Sclerosis

- 2020 American Heart Association
- KNOWN (conclusive/substantial evidence)
  - Central pain
  - Spasticity

Page. *Circulation*. 2020;142(10):e131-e152.

Seizure Medications' Success???

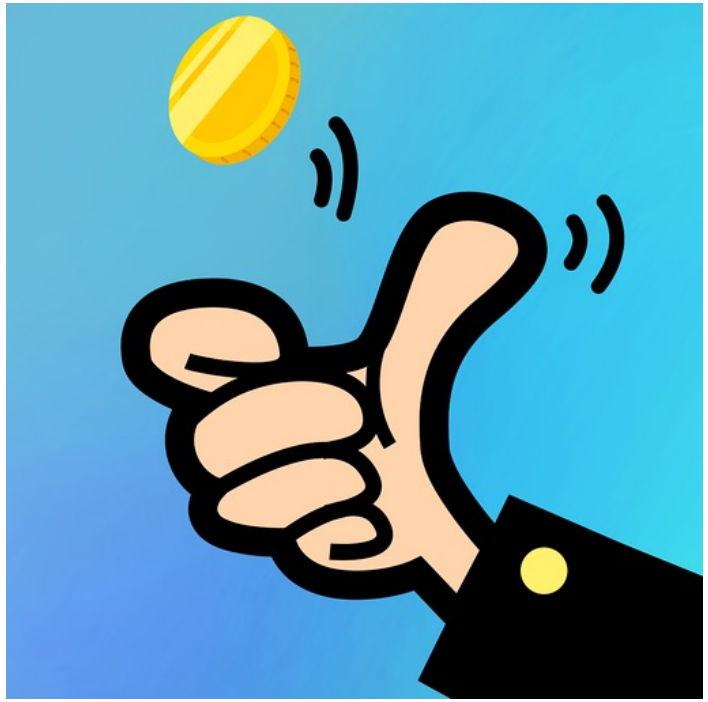
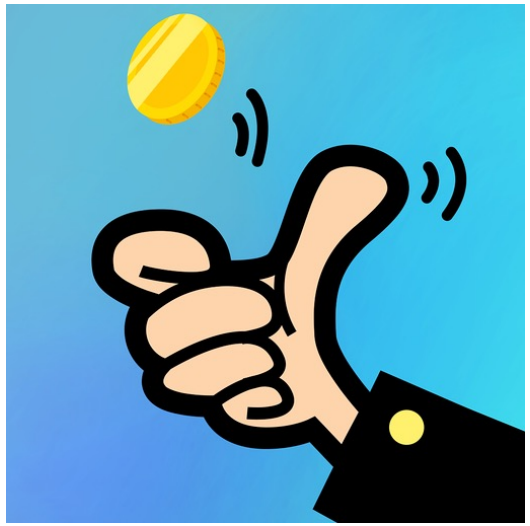


TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	NO. (%)
Response to first drug	222 (47)
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
Response to second drug	61 (13)
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
Response to third drug or multiple drugs	18 (4)
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

Kwan. *N Engl J Med*. 2000;342:314-319.

Cannabinoids in Seizures Success???



	50% reduction in seizures n=19 studies (2 RCTs)	Complete seizure freedom n=17 studies (3 RCTs)	Quality of life n=14 studies (2 RCTs)	Withdrawals n=12 studies (4 RCTs)	Adverse events n=16 studies (4 RCTs)
Cannabis sativa/extract	Two studies (no RCT)	No studies	Two studies (no RCT)	No studies	Two studies (no RCT)
Findings	Positive effect		Positive effect		AEs reported by 13%
Evidence GRADE	⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk		Critical risk		Critical risk
Conclusion	Insufficient evidence		Insufficient evidence		Insufficient evidence
CBD	11 studies (2 RCT)	13 studies (3 RCT)	9 studies (2 RCT)	8 studies (3 RCT)	11 studies (4 RCT)
Findings	Small effect	Positive effect	Positive effect	Patients more likely to withdraw from CBD	AEs reported by 11%–100%
Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk	Low to critical risk	Low to critical risk	Low to critical risk	Low to critical risk
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely
Oral THC	No studies	No studies	No studies	No studies	One study (no RCT)
Findings					AEs reported by 12.5%
Evidence GRADE					⊕◯◯◯ VERY LOW
Risk of bias					No information
Conclusion					Insufficient evidence
CBD:THC	Five studies (no RCTs)	Three studies (no RCTs)	Two studies (no RCT)	Two studies (no RCT)	Two studies (no RCT)
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 14%	AEs reported by 42%
Evidence GRADE	⊕⊕◯◯ LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk	Serious to critical risk	Serious risk	Serious risk	Serious to critical risk
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
Oral cannabis extracts	One study (no RCT)	One study (no RCT)	One study (no RCT)	One study (no RCT)	No studies
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 15%	
Evidence GRADE	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	
Risk of bias	Critical risk	Serious risk	Serious risk	Serious risk	
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	

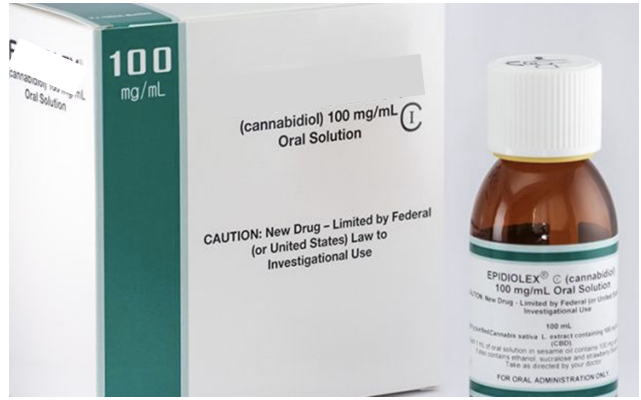
Stockings. *J Neurol Neurosurg Psychiatry.* 2018;89:741-753.

Cannabinoid Utilizations

Epilepsy

- 2020 American Heart Association

- KNOWN[1] (conclusive/substantial evidence)
  - Severe child-onset, drug-resistant epilepsy
  - Treatment-resistant Dravet syndrome
  - Treatment-resistant Lennox-Gastaut syndrome
  - Refractory epilepsy



- Historical record of the CB1 anti-epileptic effects dates back CENTURIES[2]

1. Page. *Circulation*. 2020;142(10):e131-e152.
2. Mechoulam. The Pharmacohistory of Cannabis sativa. In: *Cannabis as Therapeutic Agent.* CRC Press; Boca Raton, FL: 1986.

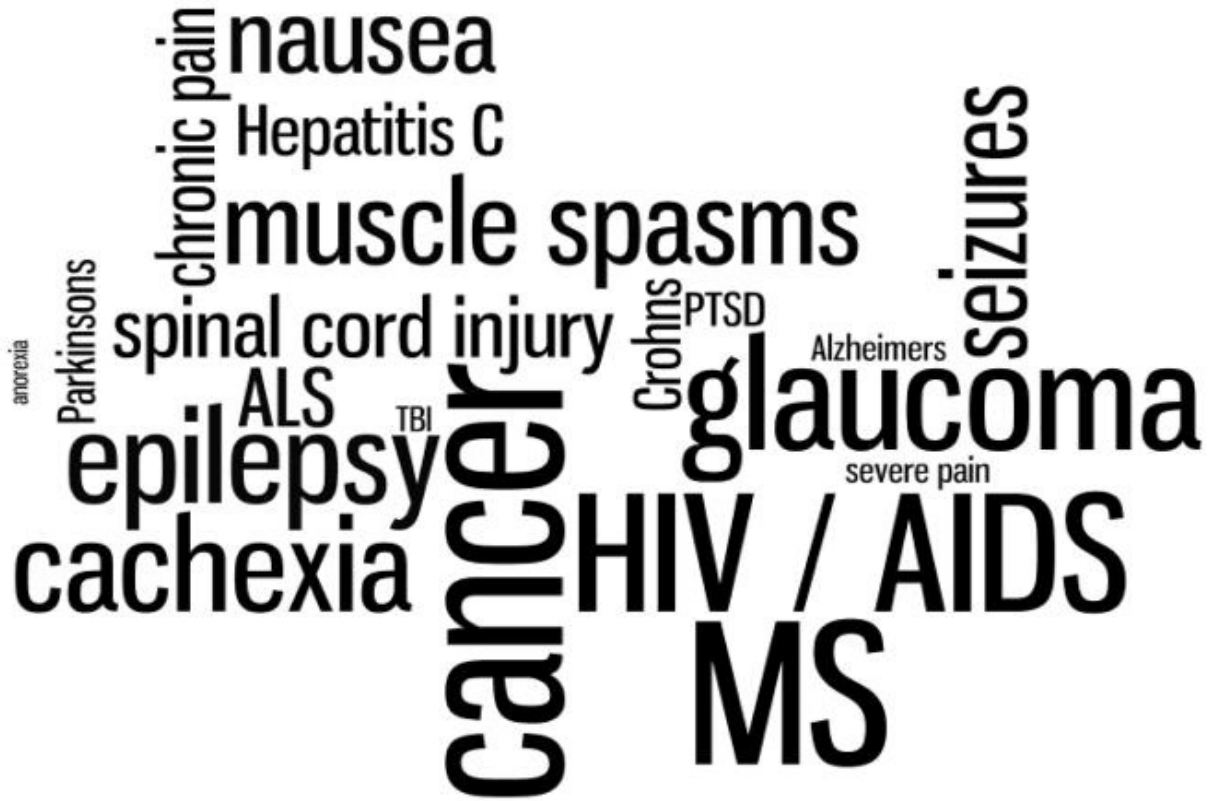
Cannabinoid Utilizations

Known

KNOWN (Conclusive/Substantial Evidence)	
Pain	Neuropathic pain
	Fibromyalgia
	Cancer pain
Cachexia	HIV-associated anorexia/cachexia
	Cancer-associated anorexia/cachexia
Nausea and Vomiting	Chemotherapy-induced N/V *Caution: cannabis hyperemesis syndrome
Multiple Sclerosis	Central pain
	Spasticity
Epilepsy	Severe child-onset, drug-resistant epilepsy
	Treatment-resistant Dravet syndrome
	Treatment-resistant Lennox-Gastaut syndrome
	Refractory epilepsy

Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Possible Utilizations



Bestrashniy. *J Psychol Addict Behav*. 2015;29(3):639-642.

PainWeek

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CANNABINOIDS

Cannabinoid Clinical Applications

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