Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been . . .

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Background.—The use of cannabis, or marijuana, for medicinal purposes is deeply rooted though history, dating back to ancient times. It once held a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases, particularly headache and migraine. Through the decades, this plant has taken a fascinating journey from a legal and frequently prescribed status to illegal, driven by political and social factors rather than by science. However, with an abundance of growing support for its multitude of medicinal uses, the misguided stigma of cannabis is fading, and there has been a dramatic push for legalizing medicinal cannabis and research. Almost half of the United States has now legalized medicinal cannabis, several states have legalized recreational use, and others have legalized cannabidiol-only use, which is one of many therapeutic cannabinoids extracted from cannabis. Physicians need to be educated on the history, pharmacology, clinical indications, and proper clinical use of cannabis, as patients will inevitably inquire about it for many diseases, including chronic pain and headache disorders for which there is some intriguing supportive evidence.

Objective.—To review the history of medicinal cannabis use, discuss the pharmacology and physiology of the endocannabinoid system and cannabis-derived cannabinoids, perform a comprehensive literature review of the clinical uses of medicinal cannabis and cannabinoids with a focus on migraine and other headache disorders, and outline general clinical practice guidelines.

Conclusion.—The literature suggests that the medicinal use of cannabis may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. Supporting literature suggests a role for medicinal cannabis and cannabinoids in several types of headache disorders including migraine and cluster headache, although it is primarily limited to case based, anecdotal, or laboratory-based scientific research. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action, and opiate pathways, suggesting potential synergistic or similar benefits. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation.

Key words: cannabis, hemp, headache, medical marijuana, cannabinoids, cannabidiol, CBD, delta-9-tetrahydrocannabinol, THC

The plant genus *Cannabis* is a member of the plant family Cannabaceae, and there are 3 primary cannabis species which vary in their biochemical constituents: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.[1] In general, cannabis that has high levels of the psychoactive cannabinoid, delta^9-tetrahydrocannabinol (Δ^9-THC), and low levels of the non/anti-psychoactive cannabinoid, cannabidiol (CBD), is referred to as "marijuana." Cannabis that has high levels of CBD, and very low insignificant levels of Δ^9-THC, is referred to as "industrial hemp," or "hemp," and has no psychoactive effects. The botanical origin of cannabis is suspected to be from Western and Central Asia. It has been cultivated since ancient times in Asia and Europe, and spread to the New World in post-Columbian times.[2] Carbon dating has confirmed the use of cannabis fibers in the form of hemp back to 4000 BC.[3,4] Hemp has a long history of many past and current uses including textiles for clothing, industrial products, building materials (such as hempcrete), manufacturing, oil paints, solvents, fuel, paper, soaps, shampoos, cosmetics, food, and medicinal purposes, to name a few.

Historical records reveal that the use of cannabis once held a strong and prominent position in medicine. Various benefits of cannabis have been translated from Sanskrit and Hindi literature under many different names as early as 1400-2000 BC,[5,6] although its medicinal use was more thoroughly described in Indian *Ayurvedic* medicine and the plant cultivated as early as 900 BC.[2] The Greek physicians Claudius Galen (131-201 AD) and Pedanius Dioscorides (40-90 AD) described medicinal indications for cannabis.[7]

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Accepted for publication March 07, 2015.

Headache

Conflict of Interest: Owns stock in CEN-Biotech Inc., a publicly traded company.
Financial Support: None.

In 1839, Dr. William Brooke O'Shaughnessy introduced the Western world to the medicinal uses of *C. indica*, or "Indian hemp," after his time in Calcutta, India. He suggested its use in analgesia and as a muscle relaxant.[8-10] He was a physician and scientist who graduated from the University of Edinburgh, and a professor of chemistry at the Medical College of Calcutta.[11,12] Dr. Clendinning in London was one of the first Western physicians to treat migraine with cannabis in the 1840s,[11,13] and another London physician, Dr. R. Greene, was recommending daily doses of cannabis for the prophylaxis of migraine in 1872.[11,14]

The medicinal use of *C. indica* for both acute and preventive headache treatment was subsequently advocated by many prominent physicians through the 19th and early decades of the 20th centuries, including E.J. Waring, S. Weir Mitchell, Hobart Hare, Sir William Gowers, J.R. Reynolds, J.B. Mattison, and Sir William Osler.[4,8,9,15] Cannabis was included in British and American pharmacopeias for headache treatment during these early years.[4]

In 1887, Dr. S. Mackenzie published an article advocating for the use of marijuana twice daily for chronic daily headache, which was likely chronic migraine by description.[11,16] Dr. J.W. Farlow described the use of marijuana suppositories as having "few equals in its power over nervous headaches" in 1889.[11,17] In 1890, Sir John Russell Reynolds, the president of the British Medical Association and physician to the royal household, wrote a paper in *Lancet* reviewing 30 years of personal experience in prescribing cannabis to advocate for its legitimate medicinal uses for a wide variety of ailments, particularly migraine and neuralgia.[11,18]

In 1915, the father of modern medicine, Sir William Osler, advocated for cannabis use in migraine, which he published in his textbook *The Principles and Practice of Medicine*.[11] He stated that when treating migraine, "*Cannabis indica* is probably the most satisfactory remedy. Seguin recommends a prolonged course."[4,11,15]

Dr. E.C. Seguin, to whom Osler was referring, was a well-known neurologist and president of the New York Neurological Society, and a vocal proponent of cannabis for migraine at that time.[11] In 1916, Dr. Walter Ernest Dixon, who was a well-known professor of pharmacology at Kings' College and the University of Cambridge, described the therapeutic effects of smoked cannabis for headache treatment.[4]

The rising use of medicinal cannabis was eventually derailed by political factors in the United States (US) consisting of propaganda that cannabis was a drug of abuse used by minority and low-income communities, along with a campaign by Harry Anslinger and the Federal Bureau of Narcotics in the 1930s which attempted to associate psychosis, mental deterioration, addiction, and violent crimes to marijuana use. Other historians have stated that the purpose was to also reduce the size of the growing hemp industry, influenced by prominent businesspersons such as Andrew Mellon, and the Du Pont family, who were involved and invested heavily in competing industry including synthetic fibers such as nylon.[11,19-21] These claims and agenda led to the *Marihuana Tax Act of 1937*, despite the American Medical Association's strong opposition to this legislation.[4,22,23] This law imposed a heavy tax on anyone associated with cannabis and hemp for medicinal or industrial uses, with prison and large fines for those failing to comply.[11] In response to this ruling, Dr. Robert Walton published a comprehensive review of cannabis in 1938, and stated that legislation should not prohibit medicinal use and scientific investigation, referencing 12 significant authorities on its efficacy for migraine.[4]

The protest from the medical community could not overcome the political powers pushing for banning cannabis and associating it as a drug of abuse. In 1941, cannabis preparations were taken off the *United States Pharmacopoeia and National Formulary*.[4] Despite this removal, Dr. M. Fishbein, the editor of the *Journal of the American Medical Association*, still recommended oral preparations of cannabis over ergotamine tartrate for menstrual migraine in 1942.[4,24] A resurgence of recreational marijuana use occurred during the anti-establishment cultural phenomenon that developed in the US between the early 1960s and the early 1970s. This counterculture and time period left a lasting impression in many aspects. Unfortunately, one of those lasting impressions and stigma has been the association between the psychedelic hippie counterculture movement of that era and recreational marijuana use, rather than the longer and deeper history of medicinal use that existed long prior to that time period.

In August 1970, the Assistant Secretary of Health, Dr. Roger O. Egeberg, wrote a letter recommending that marijuana be classified as a Schedule 1 substance, the same as heroin and lysergic acid diethylamide (LSD), and it has remained so since the passage of the Controlled Substances Act of 1970. His stated reasoning for this decision was:

> "Since there is still a considerable void in our knowledge of the plant and effects of the active drug contained in it, our recommendation is that marijuana be retained within Schedule 1 at least until the completion of certain studies now underway to resolve the issue."[25]

Therefore, marijuana was classified as a Schedule 1 substance, not because of scientific evidence, but due to a lack of existing scientific knowledge at that time.[25] The consequence of the Schedule 1 classification of cannabis has been detrimental to researching its benefits. This is because research on cannabis in the US remains illegal as a consequence of this classification. This has senselessly left the potential therapeutic applications of cannabis at a standstill for decades, despite possible benefits described through history with extensive anecdotal descriptions and scientific research, the fact that cannabis remained in the Western pharmacopoeia until 1941, and was prescribed for a multitude of symptoms including headache by many of the most prestigious physicians of those times.

The Drug Enforcement Agency (DEA) continues to refuse to take marijuana off the restricted "most dangerous" Schedule 1 classification, claiming it has "no accepted medicinal use," a statement that has no evidence-based medicine to support it. More evidence exists disproving and refuting those claims. The Schedule 1 classification impedes US federal funding for research, or even the legal ability to proceed with research. This has been the primary hurdle in conducting the large-scale medical research that is needed to obtain that necessary evidence-based medicine on the potential benefits, or lack thereof, of cannabis.

Hypocritically, despite the insistence of the Schedule 1 classification, the US Government, as represented by the Department of Health and Human Services, in 2001 filed a patent (US Patent #6,630,507) for cannabinoids that was awarded in 2003 for "cannabinoids as antioxidants and neuroprotectants."[26] This patent is a clear contradiction of the US Government's own definition for classification of a Schedule 1 drug having no medicinal benefit.

Another glaring contradiction to the Schedule 1 status of marijuana is the fact that the US Federal Drug Administration (FDA) has approved synthetic versions of the cannabinoid Δ^9-THC in the form of Dronabinol (Marinol®) and Nabilone (Cesamet®) for medicinal purposes. These observations further confirm that the cannabinoids found in cannabis are recognized by the government to be therapeutic with valid medicinal uses. However, the Schedule 1 status remains intact, stating that there is no accepted medical use of cannabis. Clearly, this Schedule 1 status needs to be reviewed and reclassified.

An attempt to reclassify marijuana to Schedule 2 failed in 1988, despite the DEA administrative law judge, Francis Young's, recommendation that marijuana be removed from Schedule 1 and made available for physicians to prescribe.[27-30] He reviewed evidence and testimonies from the scientific community and stated, "By any measure of rational analysis, marijuana can be safely used within a supervised routine of medical care," and its use was suggested for spasticity, paraplegia, and multiple sclerosis (MS), and as an anti-emetic, while its use for glaucoma was considered "reasonable."[4,28] The FDA reviewed the scheduling of marijuana in both 2001 and 2006, both times recommending that it should remain in Schedule 1. A federal judge is again reviewing whether reclassification is warranted at the time of this writing.

The only access to legal marijuana has been through the FDA's Investigational New Drug Program, which was closed by the Secretary of Health and Human Services in 1992, although the 13 patients in the program at that time were allowed to continue.[31,32] The only federally approved source of research-grade cannabis for that program, and still remaining, has been from a farm at the University of Mississippi. It has had contracts with the federal government since 1968, and has provided medicinal marijuana to a few patients. The program initially started in 1976 when a glaucoma patient sued the government on grounds that the cannabis was preventing his vision loss, and won.[32] Currently there are still 2 patients who receive monthly government supplied marijuana, one for multiple hereditary exostoses, a painful bone tumor disorder, and the other for glaucoma.[32] The program is still controlled by the National Institute on Drug Abuse (NIDA).

In 1995, Richard Smith, the editor of *British Medical Journal*, called for some marijuana legalization and decriminalization,[33] and the *Journal of the American Medical Association* also published a commentary in support of medical marijuana.[34] In November 1995, the *American Journal of Public Health*, the journal for the oldest and largest organization of healthcare professionals in the world, issued a resolution urging lawmakers to make medical marijuana accessible for research as an investigational new drug, and to make marijuana a legally available medicine to ill patients.[27] They further stated that, "cannabis/marijuana was wrongfully placed on the Schedule 1 of the Controlled Substances depriving patients of its therapeutic potential," and concluded that, "greater harm is caused by the legal consequences of its prohibition than possible risks of medicinal use."[27] In 1997, the British Medical Association published a book called *Therapeutic Uses of Cannabis* describing the many potential medical benefits of cannabinoids, and also concluded that cannabinoids may have potential use for patients with spastic neurological disorders such as spinal cord injury and MS, which are not well controlled with available drugs.[35]

Neurologist Dr. Ethan Russo received FDA support in conducting a study looking at the effects of smoked marijuana in the treatment of migraines in the late 1990s. However, his study was halted by the NIDA. He stated the following:

> *"My FDA-approved study on cannabis' ability to reduce migraine was stone-walled because NIDA holds a monopoly on the legal supply of cannabis for research, and they refused to provide it for my study. As a doctor and a citizen, knowing that researchers in other countries are researching and confirming new medical uses for cannabis all the time, such as its ability to protect the brain after head trauma or stroke, I am dismayed by policies that prevent us from fully utilizing the healing potential of this plant and preventing people from using the best medicine for their condition."*[36]

Many physicians are pushing for schedule reclassification of cannabis allowing medicinal cannabis for the treatment of a multitude of ailments, and allowing research. In a 2013 apology article retracting his previous anti-marijuana stance, Dr. Sanjay Gupta MD, CNN Chief Medical Correspondent, stated:

> *"Well, I am here to apologize. I apologize because I didn't look hard enough, until now. I didn't look far enough. I didn't review papers from smaller labs in other countries doing some remarkable research, and I was too dismissive of the loud chorus of legitimate patients whose symptoms improved on cannabis. Instead, I lumped them with the high-visibility malingerers, just*

looking to get high. I mistakenly believed the Drug Enforcement Agency listed marijuana as a Schedule 1 substance because of sound scientific proof. Surely, they must have quality reasoning as to why marijuana is in the category of the most dangerous drugs that have "no accepted medicinal use and a high potential for abuse." They didn't have the science to support that claim, and I now know that when it comes to marijuana neither of those things are true. It doesn't have a high potential for abuse, and there are very legitimate medical applications. In fact, sometimes marijuana is the only thing that works. We have been terribly and systematically misled for nearly 70 years in the United States, and I apologize for my own role in that."[25]

Dr. Gupta also noted that of more than 20,000 papers published in recent times, only 6% of the studies look at the potential benefits of cannabis, while all the rest investigate potential harm, leading to an inherent bias and a profoundly distorted view.[25]

A poll by WebMD/Medscape revealed that the majority of 1544 physicians from more than 12 specialties and 48 states said that medicinal marijuana should be legalized nationally, and agreed that it should be an option for patients.[37] The rapidly increasing anecdotal reports about its benefits and subsequent exodus of families being forced to move to Colorado for legal use of a special strain of marijuana called *Charlotte's Web*[38] to treat their children's refractory seizure disorders seems cruel and senseless, and has led to stronger calls for legal research and availability.

The Epilepsy Foundation has asked the DEA to relax its marijuana restrictions to allow for medical research to proceed, and in April 2014, the American Academy of Neurology published a consensus statement on the use of medical marijuana in neurologic disorders.[39] It was based on a systematic review of studies involving marijuana or synthetic cannabinoid treatment for symptoms of only MS, epilepsy, and movement disorders between 1948 and November 2013. In that consensus, they concluded that certain forms of medical marijuana, cannabinoids, and synthetic formulations can effectively treat some symptoms of MS, including spasticity, painful spasms, central pain, and overactive bladder, although efficacy was uncertain for the other neurologic conditions evaluated. They recommended that cannabinoids should be studied as other drugs are in order to continue seeking answers as to the potential benefits of marijuana use in patients who have neurologic illness, and if found to be effective, it should be prescribed. Most recently in January 2015, the American Academy of Pediatrics recommended that the government and DEA re-classify marijuana as a Schedule 2 drug to allow further research to be done on its therapeutic benefits.

In 1996, California was the first state to pass the Compassionate Use Act, which allowed the legal use of marijuana for medicinal purposes. Since then, at the time of this writing (March 2015), the number of states which have legalized medical marijuana is rapidly growing, currently at 23 (AK, AZ, CA, CO, CT, DE, HI, IL, ME, MD, MA, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA), in addition to Washington, DC. Furthermore, 10 states (AL, FL, IA, KY, MO, MS, SC, TN, UT, WI) have legalized CBD-only (CBD; extracted from cannabis) medical marijuana bills, and 4 states (AK, CO, OR, WA) and Washington, DC have successfully voted to legalize marijuana for both medical and recreational purposes. More states will be voting on upcoming election ballots for similar variable measures, increasing its availability for self-medication and/or physician-prescribed medication. Several Congress members introduced the "Charlotte's Web Medical Hemp Act of 2014 (H.R.)" to Congress on July 28, 2014. The bill proposes to exclude industrial hemp and CBD from the definition of marijuana in the Controlled Substances Act, so that patients can have legal access to CBD oil and therapeutic hemp.

THE ENDOCANNABINOID SYSTEM

A breakthrough in the understanding of how cannabis works in the brain occurred with the discovery of the endogenous cannabinoids and receptors,[40-44] which comprise the endocannabinoid system. The endocannabinoid system is widely distributed throughout the brain and spinal cord, and plays a role in many regulatory physiological processes including inflammation, appetite regulation, metabolism, energy balance, thermogenesis, neural development, immune function, cardiovascular function, digestion, synaptic plasticity and learning, pain, memory, psychiatric disease, movement, nociception/pain, psychomotor behavior, sleep/wake cycles, regulation of stress and emotion, and digestion.[45-50]

The endocannabinoid system consists of the cannabinoid 1 (CB1) and 2 (CB2) receptors, the endogenous cannabinoid receptor ligands (endogenous cannabinoids) N-arachidonoylethanolamine (anandamide, or AEA) and 2-arachidonoylglycerol (2-AG), as well as their degrading enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, respectively.[40,46,51,52] The CB1 and CB2 receptors were cloned in 1990 and 1993, respectively.[53-55] The CB1 receptor is primarily expressed on presynaptic peripheral and central nerve terminals, and to a lesser degree on many other peripheral organs. This is in contrast to CB2 receptors, which are concentrated primarily in the peripheral tissues and immune cells where they influence the release of cytokines and cell migration, although are also present to a lesser degree in the nervous system.[56-58] Discovery of AEA, which notably is the ethanolamide of arachidonic acid, occurred in 1992,[40] and this is a primary mediator of endocannabinoid signaling, although a multitude of other endogenous mediators with "cannabinoid-like" effects continue to be discovered.[46,51,59-61]

The CB1 and CB2 receptors are both located pre-synaptically and modulate neurotransmitter release.[56] The endocannabinoids AEA and 2-AG, as well as the phytocannabinoids found in cannabis, bind to and activate (with variable affinities) the

pre-synaptic G-protein coupled CB1 and CB2 receptors.[62-64] Activation of these receptors leads to opening of potassium channels causing a hyperpolarization of the pre-synaptic terminal, and closing of calcium channels which inhibits release of stored inhibitory and excitatory neurotransmitters, including glutamate, acetylcholine, and dopamine when neuronal excitation is present.[48,52,65] Indirect effects on 5-hydroxytryptamine (5HT) (serotonin), N-methyl-D-aspartate (NMDA), opiate, and γ-aminobutyric acid (GABA) receptors allow endocannabinoids to modulate other networks.[66] AEA is a partial agonist at CB receptors, and binds with slightly higher affinity at CB1 compared with CB2 receptors, as does 2-AG.[46,53,67]

In the central nervous system, CB1 activation inhibits neurotransmitter release of GABA, glutamate, serotonin, dopamine, acetylcholine, noradrenaline, cholecystokinin, and D-aspartate at both inhibitory and excitatory synapses.[46,58,68] The CB1 receptor is one of the most abundant G-protein coupled receptors in both the peripheral and central nervous system.[62] Notably, CB1 receptors are prominent not only in the anatomical pain pathways including the periaqueductal gray (PAG) matter, rostral ventrolateral medulla (RVM), dorsal primary afferent and substantia gelatinosa spinal cord regions, spinal interneurons, and peripheral nerves/nociceptors, but also in other brain regions such as the amygdala, cerebral cortex, hippocampus, substantia nigra pars reticulata, basal ganglia, globus pallidus (internal and external segments), and molecular layer of the cerebellum.[45,58,69,70] The cardiopulmonary centers in the brainstem are sparsely populated with CB1 receptors, which is why there is a lack of respiratory depression with the cannabinoids, as opposed to opiate receptors.[11]

The presence of CB1 receptors in this wide array throughout the central and peripheral nervous system provides the substrate for a multitude of potential therapeutic neurologic targets. The CB1 receptors are widely expressed throughout the rest of the body and organ systems, but this is beyond the scope of this review. The CB2 receptors are primarily concentrated in the peripheral tissues, especially cells of the immune system, but can be found in lower concentrations in some brain regions including the PAG and some neuronal subpopulations astrocytes, microglia, and oligodendrocytes.[39,71,72] AEA and other cannabinoid agonists have also been shown to have inhibitory effects on serotonin type 3 ($5HT_3$) receptors, which further suggests its role as an anti-emetic and in analgesia.[73]

The endocannabinoids are arachidonic acid derivatives synthesized "on demand" in the post-synaptic terminals from membrane phospholipid precursors in response to cellular metabolic needs, and there appears to be cross-talk between the eicosanoid and endocannabinoid pathways.[46,52,74-76] The CB1 receptor mediated anti-inflammatory effects of cannabinoids are suspected to be secondary to inhibition of arachidonic acid conversion by cyclooxygenase,[11,77] although CB2 receptor activation induces immunosuppression, which also reduces inflammation.[78]

THE PHYTOCANNABINOIDS

The plant genus *Cannabis* is within the plant family Cannabaceae. Three cannabis species are described: *C. sativa*, *C. indica*, and *C. ruderalis*, although there has been a long-standing debate among taxonomists regarding classification of these variants into species, so a biochemical method to classify cannabis variants is typically used.[1] As noted previously, cannabis that has high levels of the psychoactive cannabinoid, Δ^9-THC, and low levels of the non/anti-psychoactive cannabinoid, CBD, is generally referred to as "marijuana," while cannabis that has high levels of CBD and very low insignificant levels of Δ^9-THC is referred to as "industrial hemp," or "hemp."

The leaves and flowering tops of cannabis plants contain at least 489 distinct compounds among 18 different chemical classes, and contain at least 100 different phytocannabinoid compounds identified thus far, potentially holding therapeutic benefit individually, or in variable combinations.[79,80] The primary cannabinoids studied to date include Δ^9-THC, CBD, cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV), although there are many others.[79,81-84] The percentage present of these and other cannabinoids vary depending on the cannabis strain, climate, soil, and techniques of cultivation, and these factors also account for the wide variability in medicinal benefits as well as side effects.[85,86] Delta^9-THC is the most studied and responsible for most of the physical, and particularly the psychotropic effects of cannabis.[87] All species contain the psychoactive component, Δ^9-THC, in variable amounts, although *C. sativa* contains the highest Δ^9-THC, while *C. ruderalis* contains the least.[1,78] The other cannabinoids including CBD, CBN, and CBG have little to no psychotropic properties,[87] which makes them very attractive for potential therapeutics.

Delta^9-THC was first isolated in 1964,[88] and is a partial agonist at both CB1 and CB2 receptors, but also acts at other non-CB receptors. Its actions at the CB1 receptor account for the psychoactive effects of cannabis, thought to be mediated to some extent by suppression of both glutamate and GABA release.[39,64,89-91]

CBD was isolated in 1963, lacks psychoactivity, and does not appear to bind to CB1 or CB2 receptors, but rather interacts with a multitude of various ion channels, enzymes, and other receptors that are felt to explain its potential analgesic, anti-epileptic, anti-nausea, anti-emetic, anti-inflammatory, anxiolytic, anti-psychotic, and anti-ischemic properties.[39,64,92-95] Its potential analgesic and anti-inflammatory effects are mediated by both cyclooxygenase and lipoxygenase inhibition, and its anti-inflammatory effect is several hundred times more potent than aspirin in animal studies.[84,96] Both CBD and Δ^9-THC also have strong anti-oxidant actions, more potent than α-tocopherol and ascorbate, and have been shown to reduce NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate, and kainate receptor-mediated neurotoxicities.[97,98]

CBN may have some immunosuppressive properties, and CBG may have some analgesic and anti-inflammatory properties as a partial agonist at CB1 and CB2, as well as actions as a $5HT^{1A}$ receptor antagonist and α2-adrenoceptor agonist.[94,99-103] It has also been suggested that THCV may have some anti-convulsant properties[104,105] by acting as a CB1 receptor antagonist and CB2 receptor partial agonist.[106,107]

Cannabinoids including Δ^9-THC have been shown to have anti-nociceptive effects in the PAG gray matter,[108] an area in the brainstem that has been suspected to play an integral role in migraine generation,[109] as well as involvement in both descending and ascending pain transmission.[108,110] CB1 receptors have also been shown to have a dense concentration in the hypothalamus.[56] Cannabinoid analgesic properties are mediated through CB1 receptors[111] in the brain, spinal cord, and peripheral nerves.[108,110,112-117] Studies suggest that the endogenous cannabinoid system may modulate anti-nociceptive effects in isolation, or through simultaneous potentiation of specific opioid receptors.[118-129] CB1 receptors are 10 times more concentrated then μ-opioid receptors in the brain, and cannabinoid receptors co-localize with opioid receptors in many regions such as the dorsal horn of the spinal cord, leading to synergistic augmentation of the analgesic opioid effects, with subsequent lower dose requirements of opioid therapy.[11,119,120,123,127,130-135] Administration of cannabinoid receptor agonists leads to endogenous opioid peptide release and chronic Δ^9-THC use increases endogenous opioid precursor gene expression in supraspinal and spinal structures involved in pain perception.[130] This interaction is suspected to be from pharmacodynamic mechanisms, since studies show marijuana use does not affect blood levels of oxycodone or morphine.[11,136]

Little is known about the potential therapeutic role of the extensive number of other compounds that cannabis contains, including flavonoids, terpenes, phenols, amino acids, vitamins, proteins, steroids, nitrogenous compounds, enzymes, glycoproteins, simple alcohols, hydrocarbons, ketones, aldehydes, fatty acids, simple esters and lactones, and pigments.[79,137] This makes it difficult to appropriately assess the potential beneficial contribution by each of these compounds in studies evaluating possible therapeutic uses of cannabis, since different strains have different ratios of Δ^9-THC, CBD, additional cannabinoids, and other compounds. Variable routes of administration add to this complexity. Ultimately, studying each isolated constituent is mandatory to determine each compound's individual therapeutic benefits. For example, the terpenes are thought to contribute to the distinctive differences in fragrance among cannabis strains, as well as the smoking qualities and character of the subsequent "high."[86] However, terpenes have a broad range of other actions including anti-inflammatory, anti-anxiety, anti-oxidant, anti-neoplastic, anti-bacterial, and anti-malarial properties.[86]

POTENTIAL MEDICINAL USES OF CANNABIS FOR HEADACHE

Literature review shows that medicinal marijuana and its derived cannabinoids have reported therapeutic benefit in an extensively wide area of medicine encompassing many specialties,[118,137,138] as compiled and referenced in Table 1. This is not an all-inclusive list, and it is important to remember that much of the included data are anecdotal, case based, or laboratory-based scientific research, although there are some randomized trials as well. One of the most documented uses of medicinal marijuana is in the treatment of pain, particularly chronic pain, and suppression of hyperalgesia and allodynia, with most studies involving endocannabinoids, Δ^9-THC, or synthetic cannabinoids.[58,139,140] The cannabinoid–opioid interactions and "opioid-sparing effect" of cannabinoids has attracted interest in medicinal marijuana for a possible alternative to narcotics with less potential for dependence, addiction, and abuse. These interactions also raise the question of a theoretical role in helping patients to wean down or off of opiates.

Components of the endocannabinoid system are found throughout the nervous system in supraspinal, spinal, and peripheral pain pathways. Both Δ^9-THC and CBD have analgesic properties, although they act through different mechanisms, and the psychotropic side effects of Δ^9-THC may be a limiting factor in its use.[141-144] Medicinal cannabis and its cannabinoid extracts increase pain thresholds[145] and possess analgesic properties.[66,146-149] Delta-9-THC doses of 15-20 mg have been shown to be comparable to the analgesic effects of codeine 60-120 mg.[150] Therapeutic uses of cannabis are reported in a wide range of chronic pain disorders as detailed and referenced in Table 1. A review of 38 published randomized controlled trials evaluating cannabinoids in pain management revealed that 71% (27) concluded that cannabinoids had empirically demonstrable and statistically significant pain-relieving effects, whereas 29% (11) did not.[45]

Given the pharmacology and reported therapeutic benefits of cannabis in pain medicine, it is only logical that this benefit may extend to the arena of headache medicine, including migraine. There is supporting literature for this, although it is primarily anecdotal and case based. Cannabinoids are active through CB1 receptors in areas of the brain and brainstem involved with migraine pathophysiology including the PAG (which may be a migraine generator area), rostral medulla, area postrema of the medulla, nucleus trigeminal caudalis,[49,151-156] and trigeminal ganglia.[11]

The endogenous endocannabinoid AEA modulates pain signaling in the central nervous system in various ways. AEA inhibits dural blood vessel dilation induced from neurogenic, calcitonin gene-related peptide (CGRP), electrical stimulation, capsaicin, and nitric oxide (NO) sources, and this effect is reversed by a cannabinoid antagonist.[40,153,154,157,158] AEA also activates the transient receptor potential vanilloid receptor on

Table 1.—Medicinal Uses Reported With Cannabis and Cannabinoids

Central Nervous System (CNS)
Chronic non-cancer pain:[45,58,136,140,150,267-289] chronic neuropathic pain,[136,139,277,287-301] phantom limb pain,[302] fibromyalgia,[300,303-307] rheumatoid arthritis,[308-311] chronic abdominal pain from inflammatory bowel diseases,[312-318] cancer-related pain (especially with potent opiate failure)[150,244,268,319,320]
Headache and facial pain: chronic headaches,[146,196] migraine,[49,192-196,321] cluster headache,[217,221,222] pseudotumor cerebri,[198] multiple sclerosis-associated trigeminal neuralgia[226]
Epilepsy[80,104,105,322-339]
Spasticity and related central pain and bladder dysfunction in multiple sclerosis[35,121,140,226,250,328,340-376] and spinal cord injury[121,140,328,340,341,362,377-382]
Additional multiple sclerosis associated symptoms: tremor,[343] pendular nystagmus suppression,[383] dystonia[345]
Reduce muscle cramps and fasciculations in amyotrophic lateral sclerosis (ALS),[384] and delay disease progression (ALS and MS)[385-387]
Reduce intracranial pressure in traumatic brain injury, aid in cerebral ischemia and neuro/excitotoxicity,[199-203,388] and regulation of neuroinflammatory response[372,373,389-391]
Tourette's syndrome[392-403]
Dystonic movement disorders,[399,404-408] oral dyskinesia[409]
Parkinson's disease; reduction of levodopa-induced dyskinesia,[399,410] and disease progression[411-414]
Huntington's disease[415-417]
Meige's syndrome[418]
Intractable hiccups[419]
Depression, anxiety, and mood disorders[143,144,203,266,290,376,420-437]
Post-traumatic stress disorder (PTSD)[242,438-448]
Neuroprotective antioxidants[97,98,201,202,391]
Alzheimer's; behavioral/agitation,[449-451] disease progression and cognitive symptoms[452,453]
Insomnia (majority in setting of pain relief)[242,277,290,297,303,306-308,314,346,347,349,362,377,379,435-437,454,455]
Fulminant hepatic encephalopathy[456]
Autism and autistic spectrum disorders[457-461]
General Medical Systems
Nausea and vomiting from chemotherapy in adults[93,276,462-497] and children[497-500]
Appetite stimulation in healthy subjects as well as cancer and AIDS-associated anorexia/cachexia syndrome ± altered chemosensory perception[143,162,203,435-437,455,463,482,497,501-519] and associated nausea[519-521]
Reducing intraocular pressure in glaucoma[204-216]
Gastrointestinal disorders (irritable bowel syndrome, inflammatory bowel disease, pain)[312-318,522-536]
Anti-cancer/neoplastic including breast, brain (glioma), lung, colon, skin cancer (melanoma), leukemia[489,537-568]
Asthma (oral or aerosol rather than smoked)[569-571]
Regulation and decrease of inflammation associated with autoimmune diseases[572-574]

trigeminal ganglion neurons, modulating the release of CGRP, and influencing vasomotor tone.[157,159]

Modulation of serotonergic pain transmission is well established in migraine treatment, particularly with the mechanism of action of the triptans. Endocannabinoids interact with serotonergic neurons in the brainstem dorsal raphe to modulate pain mechanisms,[160,161] and AEA potentiates $5HT_{1A}$ and inhibits $5HT_{2A}$ receptors.[153,154] Cannabinoids have been shown to inhibit 5HT release from platelets during a migraine.[162] Endocannabinoids, via CB1 receptor activation, have anti-nociceptive effects by descending modulation of pain at the spinal level through PAG and RVM connections,[163-168] and modulation of descending cutaneous-evoked C-fiber spinal nociceptive responses from the brainstem regions including the ventrolateral PAG and RVM.[168,169] CB1 receptor activation inhibits dural trigeminovascular nociceptive responses.[158,170] When CB1 receptors are activated in the ventrolateral PAG, there is subsequent descending attenuation and modulation of dural-evoked nociceptive trigeminovascular processing and transmission, including Aδ-fiber and C-fiber responses, and basal trigeminal neuronal tone in the trigeminocervical complex.[171-174] Furthermore, variations in the *cnr1* gene on chromosome 6, which encodes for the CB1 receptor, in a region that has shown linkage with migraine, are associated with a greater risk of developing migraine.[175,176]

The CB1 activation pathways are notable, given that triptan activation of $5HT_{1B/1D}$ receptors in the ventrolateral PAG also leads to descending modulatory inhibition of dural nociceptive Aδ-fiber and C-fiber neuronal responses and basal trigeminal neuronal tone in the trigeminal nucleus caudalis, but not cutaneous responses.[177] Experimental studies show that in the ventrolateral PAG, the CB1 receptor-mediated trigeminovascular responses are modulated by the serotonergic system, particularly via the $5HT_{1B/1D}$ triptan receptor,[171] and other studies of neuropathic pain models have shown that serotonergic neuron firing in

the brainstem dorsal raphe are modulated by CB1 receptor activation.[160,161] Furthermore, $5HT_{1B/1D}$ antagonists inhibit CB1 responses in the ventrolateral PAG.[171] These findings show how serotonergic and endocannabinoid neurons in the brainstem can modulate the effects of either system as trigeminal or spinal nociceptive inputs are processed.[171] This suggests that the endocannabinoid neurotransmitter system is a potential target for treating migraine, and that triptans may help to break migraines by activating the brain's endocannabinoid system.[171]

Triptans are suspected to inhibit GABAergic and glutamatergic signaling in the PAG by preventing neurotransmitter release from nerve terminals as part of their mechanism of action.[178] Similarly, activation of CB1 receptors in the PAG and RVM also inhibit GABAergic and glutamatergic transmission by preventing release of neurotransmitters.[179,180] Triptan action may in part be secondary to modulation of endocannabinoidergic neurons in the brainstem, and descending control of trigeminovascular nociceptive transmission may occur through interactions between serotonergic and endocannabinoid receptor systems.[171] Pharmacological manipulation of the CB2 receptor suggests a potential therapeutic target for the treatment of migraine as well.[181]

The endogenous endocannabinoid AEA, the phytocannabinoid Δ^9-THC, and synthetic cannabinoids suppress glutamatergic neurotransmission via inhibitory modulation of the NMDA receptors, mediated by CB1 receptors.[153,154,182-186] Activation of CB1 receptors suppresses cortical spreading depression (CSD). This is suspected to be due to decreased glutamatergic transmission via inhibitory NMDA modulation, although modulation of NO, CGRP, or lipoxygenase and cyclooxygenase pathways are also possible contributors to the suppressive effect of cannabinoids on CSD.[183] Activation of CB1 receptors may stop migraine pain by inhibition of CSD and subsequent trigeminal neuronal activation.[183]

Endocannabinoid deficiency has been theorized as a possible cause for migraine and other chronic pain disorders, including chronic migraine and medication overuse headache.[187,188] Levels of AEA are decreased in the cerebrospinal fluid of individuals with chronic migraine compared with normal controls, while levels of CGRP and NO (normally inhibited by AEA) are increased.[153,189,190] Platelets of female migraineurs as opposed to male have also shown increased activity of the AEA-degrading enzyme FAAH, suggesting increased endocannabinoid degradation.[191] A widely recognized migraine trigger, nitroglycerin, increases activity of endocannabinoid degrading enzymes, leading to increased breakdown of endogenous endocannabinoids in the midbrain, where the PAG is located.[156]

Unfortunately, there have been no controlled clinical trials evaluating smoked or oral formulations of medicinal cannabis or prescription cannabinoids for either acute or prophylactic therapy in migraine or other headache disorders. A small case series of cannabis use for patients with pain included 3 subjects with chronic headaches that were relieved by smoking cannabis, with results similar or superior to ergotamine and aspirin.[146] Another small case series of 3 patients reported that abrupt cessation of chronic daily marijuana smoking was followed by migraine attacks, while subsequent remission of headaches was seen with resumption of episodic marijuana use in 1 of the patients.[192] It is not certain whether this suggests effective prevention by the marijuana or medication overuse headache with withdrawal headache upon cessation.

A case of a migraineur who had failed standard medical therapy, and ultimately received relief with small doses of smoked marijuana was reported.[193] Similarly, this author has encountered multiple patients with chronic migraine, and a similar history of failing all standard medical therapy, but receiving a significant positive response to smoked cannabis (usually admitted reluctantly) or synthetic cannabinoids.

One study suggested that cannabinoid compounds may provide benefit in migraine treatment due to platelet stabilization and inhibition of serotonin release.[194] A small survey of 54 patients in a drug treatment center reported that marijuana use was commonly used as a self-medication treatment for migraine.[195]

An anonymous standardized survey investigating reasons for self-medication with cannabis in Germany, Austria, and Switzerland was conducted by the Association for Cannabis as Medicine (Cologne, Germany).[196] There were 128 patient questionnaires evaluated, and of the many reported medical uses, 6.6% used cannabis for migraine, and 3.6% used it for headache. Another survey of 2480 patients of the Oakland Cannabis Buyer's Club revealed that 5% used it for migraine relief.[197]

Medicinal cannabis may have a role in headache disorders other than migraine as well. A case study reported a woman with pseudotumor cerebri would smoke a marijuana cigarette about once per week when her headache was more severe. She would have complete resolution of her headache within 5 minutes, and it would not recur that day.[198] This is interesting given other studies that suggest that cannabinoids may reduce intracranial pressure in traumatic brain injury,[199-203] as well as intraocular pressure in glaucoma.[204-216] The synthetic cannabinoid, Dexabinol, has no psychotropic activity, but blocks NMDA receptors, and suppresses production of tumor necrosis factor. In phase II trials in Israeli hospitals, it lowered intracranial pressure with a trend toward faster and better neurologic outcome.[199,203]

Cannabis has been reported to treat cluster headache. In a case report,[217] a 19-year-old male who was refractory to a multitude of preventive and abortive medications reported that smoking marijuana at the onset of a cluster headache attack would consistently give complete headache relief within 5 minutes of inhalation, and was the only thing that helped. Given the dramatic improvement with smoked cannabis, his physician decided to substitute the smoked cannabis with Dronabinol (Marinol®) 5 mg, a synthetic cannabinoid. Dronabinol taken at the onset of cluster headache consistently provided complete and rapid relief within 5-15

minutes. Notably, CB1 receptors have a dense concentration in the hypothalamus,[56] of which the posterior inferior ipsilateral hypothalamus has been suspected to be a site of activation in cluster headache.[218-220]

A survey of 113 patients with chronic cluster headaches in France found that 26% regularly consumed cannabis, although whether cannabis was used for treatment of cluster headache or only recreationally was not further evaluated.[221] In another study conducted in 2 French headache centers with a patient questionnaire evaluating marijuana use in cluster headache patients, 63/139 (45.3%) had a history of cannabis use, of which 27 patients (19.4% of total cohort) had used it to treat cluster headache attacks.[222] Efficacy was reported in 25.9%, variable or uncertain effects in 51.8%, and negative effects in 22.3%. Thus, in almost three quarters, the cluster headache subjects did not report efficacy. The authors noted the need for controlled trials with synthetic selective cannabinoids to show a more convincing therapeutic benefit.

Similar to cluster headache, this hypothalamic region is also activated during short-lasting unilateral neuralgiform headache attacks, including those with specific conjunctival injection and tearing,[223] paroxysmal hemicranias,[224] and hemicrania continua,[225] raising a theoretical question of whether refractory cases of these headache disorders may also be responsive to medical cannabis and the cannabinoids.

A trial of 112 patients with MS who smoked cannabis reported that 90% had significant chronic pain relief, and particularly 70% had relief of MS-associated trigeminal neuralgia.[226]

PHARMACOKINETICS

Cannabis can be used by smoked, vaporized, oral, oral mucosal, topical, or rectal routes of administration. The majority of cannabinoid metabolism occurs in the liver, with variable levels of different metabolites, dependent on the route of administration.[227-229] Health Canada (US FDA equivalent) published an excellent in-depth review of the pharmacokinetics and pharmacodynamics of cannabis, and it is recommended for more detailed discussion of these topics.[137]

Smoked cannabis results in the fastest onset of action, within minutes, due to the lipophilicity of Δ^9-THC, and results in higher cannabinoid blood levels and shorter duration of effects compared with oral routes.[227,228] When smoked, the psychotropic effects start within seconds to a few minutes, peak in 15-30 minutes, and wear off within 2-3 hours. Depending on efficiency and method of smoking, bioavailability of Δ^9-THC ranges from 2% to 56% based on puff duration, breath hold duration, and depth of inhalation, but typical use is predicted to be about 25-27%.[228,230-232]

Smoking cannabis by vaporization is a more recent technique of smoking cannabis, developed due to the fact that inhalation of a combustion product is an undesirable delivery system.[233] The goal of this technique is to suppress irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where smoke and associated toxins are produced.[234] Vaporization may be advantageous to smoking due to less toxic byproducts such as tar, polycyclic aromatic hydrocarbons, carbon monoxide, and more efficient extraction of Δ^9-THC.[234-238] Plasma concentrations and effects are similar to those of smoking cannabis by standard methods, although absorption has been suggested to occur faster.[233]

Oral administration is associated with a slower onset of action with delayed psychotropic effects beginning in 30-90 minutes, slower peak at 2-3 hours, lower peak blood Δ^9-THC levels (5-6 times lower as compared with smoking[239]), and longer duration of action and effects lasting 4-12 hours, depending on dose and specific psychotropic effect.[227,230] Delta-9-THC is often ingested by adding it to foods such as brownies, oils, butters, cookies, and teas.

There are 2 synthetic pharmaceutical versions of oral Δ^9-THC available. The first is Dronabinol (Marinol®), which comes in 2.5 mg, 5 mg, or 10 mg Δ^9-THC tablets. It is typically used once to twice daily, and dose ranges vary from 2.5 to 40 mg/day.[240] It is Schedule III and approved by the FDA for nausea/vomiting associated with chemotherapy, and acquired immune deficiency syndrome (AIDS)-associated anorexia and weight loss.

The second is Nabilone (Cesamet®), which comes in 0.25, 0.5, and 1 mg Δ^9-THC tablets, and is used once to 3 times daily, with dose ranges varying from 0.2 to 6 mg/day.[241,242] It is Schedule II and FDA approved for nausea/vomiting associated with chemotherapy. These 2 medications contain only Δ^9-THC, without other cannabinoids such as CBD, which typically provides much of the analgesic effects of cannabis. Another oral formulation from the United Kingdom is called Epidiolex©. It has received Orphan Drug Designation from the FDA for the treatment of severe, drug-resistant epilepsy syndromes such as Dravet and Lennox-Gastaut syndromes, and is currently in clinical trials.

An oral mucosal formulation called Nabiximols (Sativex®) is available in the United Kingdom for spasticity in MS. It is also approved by Health Canada as an adjunct treatment for neuropathic pain in MS, and for moderate to severe cancer-related pain for patients who have failed the highest tolerated opiate dosing. In April 2014, the FDA granted Fast Track designation to Sativex® for the treatment of pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy, and it is currently undergoing phase III clinical trials in the US for this indication. It is also undergoing phase III trials in the US for MS spasticity. Each spray delivers a total dose of 2.7 mg Δ^9-THC and 2.5 mg CBD, along with additional cannabinoids, flavonoids, and terpenoids since it is a tincture of cannabis, made from cannabis plants rather than a synthetic form, and doses range from 1 to 16 sprays per day.[243,244] Peak plasma concentrations of the CBD and Δ^9-THC occur in 2-4 hours, although there is wide variation between patients in

peak blood levels, time to onset, and peak of effects.[243] Similar to the oral formulations, Δ^9-THC and cannabinoid blood levels are lower as compared with smoking, although Δ^9-THC blood levels are similar to Dronabinol.[243,245]

Topical transdermal formulations of cannabinoids exist in ointments, creams, and lotions, although there are no clinical studies evaluating these. However, some research has been done evaluating a dermal patch for delivery of synthetic cannabinoids with good permeation results, suggesting the utility for development of a transdermal therapeutic system.[246-248]

Rectal formulations have been studied, and blood concentrations of Δ^9-THC are dose and vehicle dependent.[249] The prodrug Δ^9-THC hemisuccinate is absorbed rectally rather than Δ^9-THC, and this in combination with decreased first-pass metabolism leads to higher bioavailability of Δ^9-THC (52-61%) as compared with the oral route.[249-253]

Intramuscular and intravenous Δ^9-THC has been evaluated in limited studies,[251,254] and the authors of 1 study involving monkeys suggested that intramuscular Δ^9-THC may be a useful alternative route of administration, since it is more completely bioavailable as compared with the oral route.[251]

ADVERSE EFFECTS OF CANNABIS

There are a multitude of variables that may influence the presence or severity of adverse effects with cannabis use, as well as benefits. The majority of information regarding adverse effects reported with cannabis use come from studies and case reports primarily evaluating recreational users, rather than from controlled therapeutic clinical studies. It is important to remember that none of the studies or reported adverse effects of cannabis specifically compare and take into account many potential variables. These include route of administration, patient age, concurrent medications being taken, patient comorbidities, standardized dosing, type of cannabis strain, ratio of the phytocannabinoids in the cannabis strain (particularly the CBD:THC ratio), sterility of cannabis growing conditions, cannabis analyzation for commonly encountered issues of toxins, pesticides, and fungal and bacterial microbial contaminants, among others.

The importance of sterility and potential side effects from non-sterile growing environments is illustrated by a case of allergic bronchopulmonary aspergillosis due to microbial contamination from smoking moldy cannabis.[255] These variables will be extremely important in future studies, as there are suspected to be at least 100 different types of phytocannabinoids, and only a few of them have been studied and evaluated. Some (such as Δ^9-THC) cause psychoactive side effects, while others (such as CBD) have no psychoactive side effects, as previously discussed. Therefore, these reported adverse side effects are based on entirely non-standardized evaluations, similar to many of the anecdotal and case-based reports suggesting benefit. This is synonymous to evaluating adverse reactions in a random combination of the widely variable antidepressant medications, and then lumping all reported adverse effects into the same adverse effect profile for antidepressants as a general class. However, in reality, it is understood that different antidepressants have different pharmacologic properties and adverse reactions. Cannabis use as a medication should be thought of no differently. Therefore, these reported adverse side effects should not be assumed to be universal cannabis side effects, but need to be more appropriately correlated with specific phytocannabinoids, phytocannabinoid ratios, and the aforementioned variables as medical research moves forward. This is critical for evaluating adverse side effects, as well as therapeutic benefits.

Unfortunately, cannabinoid science and associated medical research is in its infancy, and these many variables and factors have yet to be evaluated and incorporated into research for more specific data regarding both benefits and adverse side effects. With that said, adverse reactions reported in the central nervous system and cardiovascular system are seen in Table 2, while adverse reactions in the respiratory system, gastrointestinal, reproductive, and immune systems are reported in Table 3.

Regarding cannabis dependency, the problem may be less significant compared with other substances. A study reported by the health arm of the National Academy of Sciences, The Institute of Medicine, showed that dependency occurs in 32% of tobacco users, 23% of heroin users, 17% of cocaine users, 15% of alcohol drinkers, and 9% of marijuana users.[256] Withdrawal symptoms following prolonged cannabis use have been reported to include anger, depressed mood, irritability, anxiety, restlessness, insomnia, strange dreams, weight loss, and decreased appetite. The question of cannabis overuse headache and withdrawal headache remains unstudied.[257-259]

To date, there has been no documented evidence of death exclusively attributed to cannabis overdose or use.[137] A recent comparative risk assessment to quantify the risk of death associated with commonly used recreational substances using the margin of exposure approach was conducted.[260] The *margin of exposure* is defined as a ratio between toxicological threshold (benchmark dose) and estimated human intake. This method uses the most recent guidelines for risk assessment of chemical substances, which also takes the population-based exposure into account. The toxicological margin of exposure approach validates epidemiological and social science-based drug ranking approaches. Results showed that alcohol was the deadliest substance, followed by heroin, cocaine, tobacco, ecstasy, methamphetamine, and lastly, cannabis. These results suggested that cannabis was approximately 114 times less lethal than alcohol, and reinforced similar results in comparative toxicology studies and drug safety rankings developed decades prior under different methodologies.[261,262]

The ratio between Δ^9-THC and CBD appears to be an important factor in relation to side effects based on currently available literature, and some cannabinoids such as CBD may modulate

Table 2.—Adverse Effects Reported With Use of Cannabis and Cannabinoids on Central Nervous and Cardiovascular Systems

Central Nervous System (CNS)	Adverse Effects Reported
Sedative	Somnolence, generalized CNS depression, additive with other CNS depressants, amotivational syndrome in chronic use[137,232,272,290-292,303,314,346,347,435,436,575-578]
Psychological	Euphoria ("high"), dysphoria, depersonalization, anxiety/panic attacks (primarily from Δ^9-THC and lessened by presence of CBD), aggravation of psychosis in those predisposed for or having psychotic disorders (however, a study of 10,000 psychiatric hospital admissions found no evidence that use of cannabis induced psychosis in previously asymptomatic patients,[578] and a recent study reported no correlation with high risk individuals and development of psychosis from cannabis use[579])[87,137,232,259,292,303,314,427,580-603]
Perception	Synesthesia (stimulation of 1 sense stimulates a totally different sense; hearing colors, seeing sounds, feeling/tasting sounds, etc.), distortion of sense of time and space, heightened sensory perception, misperceptions, hallucinations[137,259,488,594,597,604-607]
Motor function	Ataxia, weakness, disequilibrium, incoordination, dysarthria[84,137,232,291,605,608]
Psychomotor/cognitive function	Mental clouding, thought fragmentation, impaired memory, impairment in general cognitive performance (especially complex/demanding tasks), and driving may be impaired in occasional > chronic smokers (less as compared with alcohol, but increased in combination with alcohol),[137,314,605,609-627] possible impairment in neurocognitive brain development in users who begin at a younger age including adolescence[628,629]
Dependence	Physical and psychological dependence associated with chronic, heavy cannabis use[258,259,630-632]
Stroke	Limited and somewhat loosely associated case reports of stroke following recent use of smoked cannabis (one of which was cardioembolic from myocardial infarction)[137,633-636]
Cerebral blood flow	Increased with acute cannabis use, chronic use may decrease, variations exist between regions,[137,637,638] possible association with reversible cerebral vasoconstriction syndrome (RCVS),[639] and multifocal intracranial stenosis[636]
Other	Headache,[240,241,243,290,359,362] especially with withdrawal[640]
Cardiovascular	**Adverse Effects Reported**
Peripheral circulation	Conjunctival injection, vasodilatation, postural hypotension, supine hypertension,[137,144,490,577,635,637,641-643] and arteritis[644-647]
Heart rate	Tachycardia with acute use, but tolerance develops with chronic use[137,144,232,303,314,490,637,648-654]
Heart rhythm	Ventricular arrhythmia, atrial fibrillation, premature ventricular contractions[635,652,653,655-658]
Myocardial infarction (MI)	Possible increased risk of MI after acutely smoking cannabis, particularly with pre-existing cardiovascular disease, increased myocardial oxygen demand[137,642,653,659,660]

the activity of Δ^9-THC.[263] Delta^9-THC accounts for the vast majority of the psychotropic and physical side effects of cannabis.[87]

In contrast, as noted, CBD lacks psychoactivity, which is why the specialized bred high-CBD, low-THC strain of *Charlotte's Web*™ has become such a popular treatment for refractory childhood epilepsy.[38] CBD-mediated attenuation of Δ^9-THC side effects may be observed when the CBD:THC ratio is at least 8:1 (± 11.1),[264,265] while CBD may potentiate some of the THC side effects when the CBD:THC ratio is around 2:1 (± 1.4).[264] CBD has been shown to have anxiolytic effects in animals and humans by reducing the anxiety reaction induced by Δ^9-THC.[266]

There are no studies evaluating the therapeutic benefits correlating to varying cannabis strains or CBD:THC ratios, despite the wide spectrum of diseases and symptoms that the medical literature suggests cannabis is beneficial for. This is clearly a wide open area containing many potential therapeutic medical treatments for which research is desperately needed. Determining which cannabis strains and CBD:THC ratios are the most effective for specific diseases and symptoms, including acute and chronic pain should be a primary research focus.

There are an extensive number of variables that make it difficult for establishing standardized dosing schedules. Some of these variables include the complex cannabinoid pharmacology, potency of cannabis being used such as CBD:THC ratios, the large number of other compounds found in cannabis, different dosing regimens, different routes of administration, tolerance to cannabinoids, inter-individual differences in cannabinoid receptor structure, function, and density, as well as differences in cannabinoid metabolism.[137] Current dosing recommendations are highly individualized, relying significantly on titration.[231]

For new patients, it is recommended that waiting a few minutes between puffs of smoked/inhaled cannabis, and waiting 30-60 minutes between bites of cannabis-based oral products to monitor for effects or adverse symptoms is most prudent.[137] Based on peer-reviewed literature, the majority of patients using smoked or orally ingested cannabis for medical purposes have been observed to use between 10 and 20 g of cannabis per week, or approximately 1-3 g per day.[137] Detailed estimated dose amounts and percentages of Δ^9-THC between various routes of administration, including conversion factors between smoked and oral forms can be seen in Health Canada's publication of

Table 3.—Adverse effects Reported With Use of Cannabis and Cannabinoids on Respiratory, Gastrointestinal, Reproductive, and Immune Systems

Respiratory System	Adverse Effects Reported
Carcinogenesis	Cannabis smoke contains many similar chemicals as tobacco smoke, and cannabis smoke condensates may be more cytotoxic and mutagenic then tobacco smoke condensates,[137,661,662] although evidence linking cancer and cannabis smoke are conflicting and inconclusive[137,663-666]
Inflammation	Chronic cannabis smoking associated with histopathologic changes, cough, wheezing, bronchitis, and phlegm production[137,667-671]
Bronchial tone	Acute use of smoked cannabis causes bronchodilatation,[667,672-674] but long term heavy smoking may lead to increased obstruction and decreased lung function[137,667,670,671,675,676]
Gastrointestinal System	**Adverse Effects Reported**
General	Decreased secretion, decreased motility and gastric/colonic emptying, anti-inflammatory[137,312-315,535]
Pancreas	Pancreatitis has been reported with heavy acute and chronic daily use[137,677-680]
Liver	Possible increased risk of hepatic fibrosis/steatosis, particularly in patients with hepatitis C[137,681-686]
Reproductive System	**Adverse Effects Reported**
Females	Inconclusive and unclear as most data are from animal studies; dose-dependent stimulatory or inhibitory effects on sexual behavior,[137,687] possible ovulation suppression and menstrual cycle changes[137,688-690]
Males	Inconclusive as most data are from animal studies with limited human studies. With chronic and daily use, possibly decreased sperm count, morphology, and motility, anti-androgenic,[137,490,689,691-693] possible inhibitory sexual effects[220,304]
Immune System	**Adverse Effects Reported**
General	Complex and unclear with both suppressive and stimulatory actions reported[137,574,694,695]

Information for Health Care Professionals: *Cannabis (marihuana, marijuana) and the cannabinoids*.[137] There are no standard clinical guidelines in terms of contraindications for use of cannabis and cannabinoids, although Health Canada has outlined some suggestions, as modified and seen in Table 4.[137] The risk/benefit ratio needs to be evaluated in patients with certain medical conditions until further research becomes available to form more standardized guidelines.

CONCLUSIONS AND SUMMARY

The historical use of cannabis for medicinal purposes is described for numerous diseases. There is an abundance of support for its many medicinal uses as well as potential benefit in some forms of headache disorders, including migraine and cluster. With the majority of the US now legalizing medicinal cannabis and/or limited CBD-only use, it is important for physicians to be educated on the history and proper clinical use of cannabis, because patients will become increasingly aware of it as a potential treatment, including for chronic pain and headache disorders. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a small fraction are understood, so many therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action,

Table 4.—Suggested Contraindications and/or Precautions Requiring Evaluation of Risk/Benefit Ratio of Cannabis and Cannabinoids

- Use with caution in patients with a history of substance abuse including alcohol, given abuse potential.
- Use with caution in patients using sedative-hypnotics, alcohol, or other psychoactive drugs due to potential synergistic sedative effects.
- Use with caution in severe renal or liver disease, including chronic hepatitis C (daily use not recommended due to potential for worsening steatosis severity).
- Avoid use under the age of 18 due to potential for increased adverse effects on mental health during development and adolescence.
- Avoid use while driving, operating heavy machinery, or performing other hazardous tasks or activities.
- Avoid use with history of cannabinoid or smoke hypersensitivity.
- Avoid use in patients with severe cardio-pulmonary disease due to risk for potential hypotension, hypertension, tachycardia, or syncope.
- Avoid use of smoked cannabis in patients with pulmonary diseases including asthma and chronic obstructive pulmonary disease.
- Avoid use in women who are pregnant or breastfeeding. Use with caution in women of childbearing age who are planning pregnancy or not using a reliable contraceptive.
- Avoid use in patients with psychiatric disease, particularly schizophrenia, or a family history of schizophrenia.
- Careful psychiatric monitoring is recommended for patients with mania or depression.

and opiate pathways, suggesting a potential synergistic or related benefit. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways such as inhibition of endocannabinoid-degrading enzymes, or combining cannabinoids with other analgesics for synergistic effects, may provide the basis for many new classes of medications. Despite the limited evidence and research suggesting a therapeutic role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are necessary for confirmation and further evaluation.

References

1. Schultes RE, Klein WM, Plowman T, Lockwood TE. Cannabis: An example of taxonomic neglect. *Bot Mus Lealf Harv Univ*. 1974;23:337-367.
2. Kuddus M, Ginawi IAM, Al-Hazimi A. Cannabis sativa: An ancient wild edible plant of India. *Emir J Food Agric*. 2013;25:736-745.
3. Li H. An archaeological and historical account of cannabis in China. *Econ Bot*. 1974;28:437-448.
4. Russo E. Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. *Pain*. 1998;76:3-8.
5. Indian Hemp Drugs Commission Report. Note by Mr. G.A. Grierson, C.I.E., Magistrate and Collector, Howrah, on references to the Hemp Plant Occurring in Sanskrit and Hindi Literature. Last updated January, 2011. Available at http://www.druglibrary.org/schaffer/library/studies/inhemp/6app1.htm (Accessed March 20, 2015).
6. Chopra IC, Chopra RW. The use of cannabis drugs in India. *Bull. Narcotics*. 1957;9:4-29.
7. Brunner TF. Marijuana in ancient Greece and Rome? The literary evidence. *Bull Hist Med*. 1973;47:344-355.
8. Mikuriya TH. *Marijuana: Medical Papers 1839-1972*. Oakland, CA: Medi-Comp Press; 1973.
9. Walton RP. *Marihuana: America's New Drug Problem: A Sociologic Question With its Basic Explanation Dependent on Biologic and Medical Principles*. Philadelphia, PA: Lippincott; 1938.
10. O'Shaughnessy WB. On the preparations of the Indian hemp, or gunjah (Cannabis Indica): Their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Prov Med J Retrosp Med Sci*. 1843;5:363-369.
11. McGeeney BE. Cannabinoids and hallucinogens for headache. *Headache*. 2013;53:447-458.
12. McGeeney BE. Hallucinogens and cannabinoids for headache. *Headache*. 2012;52(Suppl. 2):94-97.
13. Clendinning J. Observations on the medical properties of the cannabis sativa of India. *Med Chir Trans*. 1843;26:188-210.
14. Greene R. Cannabis indica in the treatment of migraine. *Practitioner*. 1872;41:267-270.
15. Osler W, McCrae T. *The Principles and Practice of Medicine*. New York: Appleton; 1915.
16. Mackenzie S. Remarks on the value of Indian hemp in the treatment of a certain type of headache. *Br Med J*. 1887;1:97-98.
17. Farlow JW. On the use of Belladonna and cannabis indica by the rectum in gynecological practice. *Boston Med Surg J*. 1889;120:507-509.
18. Reynolds JR. On the therapeutic uses and toxic effects of cannabis indica. *Lancet*. 1890;135:637-638.
19. Earleywine M. *Understanding Marijuana: A New Look at the Scientific Evidence*. New York, NY: Oxford University Press; 2002.
20. French L, Manzanarez M. *NAFTA & Neocolonialism: Comparative Criminal, Human & Social Justice*. Lanham, MD: University Press of America; 2004.
21. Peet P. *Under the Influence: The Disinformation Guide to Drugs*. Minneapolis, MN: Consortium Book Sales & Distribution; 2004.
22. Bonnie RJ, Whitebread IICH. *The Marihuana Conviction: A History of Marihuana Prohibition in the United States*. Charlottesville, VA: University Press of Virginia; 1974.
23. National Commission on Marihuana and Drug Abuse. *Marihuana: A Signal of Misunderstanding*. New York: New American Library; 1972.
24. Fishbein M. Migraine associated with menstruation. *J Am Med Assoc*. 1942;237:326.
25. Gupta S. Why I changed my mind on weed. 2013. Available at http://www.cnn.com/2013/08/08/health/gupta-changed-mind-marijuana/ (Accessed March 20, 2015).
26. Hampson AJ, Axelrod J, Grimaldi M. Cannabinoids as antioxidants and neuroprotectants. 2003. U.S. Patent #6,630,507. Available at http://www.google.com/patents/US6630507 (Accessed March 20, 2015).
27. AJPH. Access to therapeutic marijuana/cannabis. *Am J Public Health*. 1996;86:441-442.
28. Young FL. In the Matter of Marijuana Rescheduling Petition, Docket 86-22, Opinion, Recommended Ruling, Findings of Fact, Conclusions of Law, and Decision of Administrative Law Judge, 1988. Department of Justice, Drug Enforcement Administration.
29. Randall RC. *Marijuana, Medicine, and the Law*. Washington, DC: Galen Press; 1988.
30. Randall RC. *Marijuana, Medicine, and the Law*, Vol. 2. Washington, DC: Galen Press; 1989.
31. Cotton P. Government extinguishes marijuana access, advocates smell politics. *JAMA*. 1992;267:2573-2574.
32. Hefler J. Unusual witness presses medical marijuana cause in PA. 2014. Available at http://articles.philly.com/2014-06-12/news/50511479_1_compassionate-investigative-new-drug-irvin-rosenfeld-marijuana-bill (Accessed March 20, 2015).
33. Smith R. The war on drugs. *BMJ*. 1995;311:1655-1656.
34. Grinspoon L, Bakalar JB. Marihuana as medicine. A plea for reconsideration. *JAMA*. 1995;273:1875-1876.
35. British Medical Association. *Therapeutic Uses of Cannabis*. Amsterdam: Harwood Academic Publishers; 1997.
36. Brady P. Pot Pioneer. 2002. Available at http://www.cannabisculture.com/articles/2302.html (Accessed March 20, 2015).
37. Rappold RS. Legalize Medical Marijuana, Doctors Say in Survey. 2014. http://www.webmd.com/news/breaking-news/marijuana-on-main-street/20140225/webmd-marijuana-survey-web (Accessed March 20, 2015).

38. Realm of Caring. Charlotte's Web and Zaki's Journey. 2013. Available at https://www.youtube.com/watch?v=BH5yzEu3JGQ (Accessed March 20, 2015).
39. Koppel BS, Brust JC, Fife T, et al. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:1556-1563.
40. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258:1946-1949.
41. Galiègue S, Mary S, Marchand J, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur J Biochem*. 1995;232:54-61.
42. Gerard CM, Mollereau C, Vassart G, Parmentier M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem J*. 1991;279(Pt 1):129-134.
43. Mechoulam R, Ben-Shabat S, Hanus L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol*. 1995;50:83-90.
44. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365:61-65.
45. Aggarwal SK. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain*. 2013;29:162-171.
46. Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. *Pharmacol Ther*. 2011;132:215-241.
47. Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: Physiology and pharmacology. *Alcohol Alcohol*. 2005;40:2-14.
48. Maccarrone M, Gasperi V, Catani MV, et al. The endocannabinoid system and its relevance for nutrition. *Annu Rev Nutr*. 2010;30:423-440.
49. Greco R, Gasperi V, Maccarrone M, Tassorelli C. The endocannabinoid system and migraine. *Exp Neurol*. 2010;224:85-91.
50. Howlett AC. Efficacy in CB1 receptor-mediated signal transduction. *Br J Pharmacol*. 2004;142:1209-1218.
51. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: From the early to the latest concepts. *Best Pract Res Clin Endocrinol Metab*. 2009;23:1-15.
52. Battista N, Di Tommaso M, Bari M, Maccarrone M. The endocannabinoid system: An overview. *Front Behav Neurosci*. 2012;6:1-7.
53. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev*. 2002;54:161-202.
54. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990;346:561-564.
55. Matsuda LA. Molecular aspects of cannabinoid receptors. *Crit Rev Neurobiol*. 1997;11:143-166.
56. Iversen L. Cannabis and the brain. *Brain*. 2003;126:1252-1270.
57. Napchan U, Buse DC, Loder EW. The use of marijuana or synthetic cannabinoids for the treatment of headache. *Headache*. 2011;51:502-505.
58. Kraft B. Is there any clinically relevant cannabinoid-induced analgesia? *Pharmacology*. 2012;89:237-246.
59. De Petrocellis L, Di Marzo V. Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: Focus on G-protein-coupled receptors and transient receptor potential channels. *J Neuroimmune Pharmacol*. 2010;5:103-121.
60. O'Sullivan SE, Kendall DA. Cannabinoid activation of peroxisome proliferator-activated receptors: Potential for modulation of inflammatory disease. *Immunobiology*. 2010;215:611-616.
61. Bradshaw HB, Walker JM. The expanding field of cannabimimetic and related lipid mediators. *Br J Pharmacol*. 2005;144:459-465.
62. Di Marzo V, Piscitelli F, Mechoulam R. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. *Handb Exp Pharmacol*. 2011;203:75-104.
63. Di Marzo V, Petrocellis LD. Plant, synthetic, and endogenous cannabinoids in medicine. *Annu Rev Med*. 2006;57:553-574.
64. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Delta^9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153:199-215.
65. Grant I, Atkinson JH, Gouaux B, Wilsey B. Medical marijuana: Clearing away the smoke. *Open Neurol J*. 2012;6:18-25.
66. Raichlen DA, Foster AD, Gerdeman GL, Seillier A, Giuffrida A. Wired to run: Exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high. *J Exp Biol*. 2012;215:1331-1336.
67. Pertwee RG, Howlett AC, Abood ME, et al. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: Beyond CB_1 and CB_2. *Pharmacol Rev*. 2010;62:588-631.
68. Katona I, Freund TF. Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. *Nat Med*. 2008;14:923-930.
69. Guindon J, Hohmann AG. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets*. 2009;8:403-421.
70. Guindon J, Beaulieu P. The role of the endogenous cannabinoid system in peripheral analgesia. *Curr Mol Pharmacol*. 2009;2:134-139.
71. Mackie K. Signaling via CNS cannabinoid receptors. *Mol Cell Endocrinol*. 2008;286:S60-S65.
72. Klein TW, Cabral GA. Cannabinoid-induced immune suppression and modulation of antigen-presenting cells. *J Neuroimmune Pharmacol*. 2006;1:50-64.
73. Fan P. Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion neurons. *J Neurophysiol*. 1995;73:907-910.
74. Quarta C, Mazza R, Obici S, Pasquali R, Pagotto U. Energy balance regulation by endocannabinoids at central and peripheral levels. *Trends Mol Med*. 2011;17:518-526.
75. Horvath B, Mukhopadhyay P, Hasko G, Pacher P. The endocannabinoid system and plant-derived cannabinoids in diabetes and diabetic complications. *Am J Pathol*. 2012;180:432-442.
76. Rouzer CA, Marnett LJ. Endocannabinoid oxygenation by cyclooxygenases, lipoxygenases, and cytochromes P450: Cross-talk

between the eicosanoid and endocannabinoid signaling pathways. *Chem Rev*. 2011;111:5899-5921.
77. Fimiani C, Liberty T, Aquirre AJ, Amin I, Ali N, Stefano GB. Opiate, cannabinoid, and eicosanoid signaling converges on common intracellular pathways nitric oxide coupling. *Prostaglandins Other Lipid Mediat*. 1999;57:23-34.
78. Mechoulam R, Parker LA. The endocannabinoid system and the brain. *Annu Rev Psychol*. 2013;64:21-47.
79. Elsohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. *Life Sci*. 2005;78:539-548.
80. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacol Ther*. 2012;133:79-97.
81. Yamaori S, Kushihara M, Yamamoto I, Watanabe K. Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. *Biochem Pharmacol*. 2010;79:1691-1698.
82. Zhu HJ, Wang JS, Markowitz JS, et al. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. *J Pharmacol Exp Ther*. 2006;317:850-857.
83. Balducci C, Nervegna G, Cecinato A. Evaluation of principal cannabinoids in airborne particulates. *Anal Chim Acta*. 2009;641:89-94.
84. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs*. 2000;60:1303-1314.
85. Mehmedic Z, Chandra S, Slade D, et al. Potency trends of Delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci*. 2010;55:1209-1217.
86. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). *Am J Bot*. 2004;91:966-975.
87. Ashton CH. Pharmacology and effects of cannabis: A brief review. *Br J Psychiatry*. 2001;178:101-106.
88. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc*. 1964;86:1646-1647.
89. Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Curr Med Chem*. 2010;17:1360-1381.
90. Hajos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. *Neuroscience*. 2001;106:1-4.
91. Govaerts SJ, Hermans E, Lambert DM. Comparison of cannabinoid ligands affinities and efficacies in murine tissues and in transfected cells expressing human recombinant cannabinoid receptors. *Eur J Pharm Sci*. 2004;23:233-243.
92. Brown AJ. Novel cannabinoid receptors. *Br J Pharmacol*. 2007;152:567-575.
93. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. *Br J Pharmacol*. 2011;163:1411-1422.
94. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: New therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci*. 2009;30:515-527.
95. Zuardi AW. Cannabidiol: From an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr*. 2008;30:271-280.
96. Evans FJ. Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Med*. 1991;57:S60-S67.
97. Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. *Ann N Y Acad Sci*. 2000;899:274-282.
98. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A*. 1998;95:8268-8273.
99. Musty RE. Natural Cannabinoids: Interactions and Effects. In: Guy GW, Whittle BA, Robson P, eds. *The Medicinal Uses of Cannabis and Cannabinoids*. London: Pharmaceutical Press; 2004:165-204.
100. De Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol*. 2011;163:1479-1494.
101. Ruhaak LR, Felth J, Karlsson PC, Rafter JJ, Verpoorte R, Bohlin L. Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from Cannabis sativa. *Biol Pharm Bull*. 2011;34:774-778.
102. Institute of Medicine. Cannabinoids and Animal Physiology. In: Joy JE, Watson SJ, Benson JA, eds. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:33-82.
103. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. *Br J Pharmacol*. 2010;159:129-141.
104. Hill TD, Cascio MG, Romano B, et al. Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. *Br J Pharmacol*. 2013;170:679-692.
105. Hill AJ, Weston SE, Jones NA, et al. Delta(9)-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia*. 2010;51:1522-1532.
106. Bolognini D, Costa B, Maione S, et al. The plant cannabinoid Delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *Br J Pharmacol*. 2010;160:677-687.
107. Thomas A, Stevenson LA, Wease KN, et al. Evidence that the plant cannabinoid Delta9-tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist. *Br J Pharmacol*. 2005;146:917-926.
108. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. *J Pharmacol Exp Ther*. 1996;276:585-593.
109. Goadsby PJ, Gundlach AL. Localization of 3H-dihydroergotamine-binding sites in the cat central nervous system: Relevance to migraine. *Ann Neurol*. 1991;29:91-94.

110. Martin WJ, Coffin PO, Attias E, Balinsky M, Tsou K, Walker JM. Anatomical basis for cannabinoid-induced antinociception as revealed by intracerebral microinjections. *Brain Res*. 1999;822: 237-242.
111. Compton DR, Aceto MD, Lowe J, Martin BR. In vivo characterization of a specific cannabinoid receptor antagonist (SR141716A): Inhibition of delta 9-tetrahydrocannabinol-induced responses and apparent agonist activity. *J Pharmacol Exp Ther*. 1996;277:586-594.
112. Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. *J Pharmacol Exp Ther*. 1991;258:517-523.
113. Lichtman AH, Martin BR. Cannabinoid-induced antinociception is mediated by a spinal alpha 2-noradrenergic mechanism. *Brain Res.* 1991;559:309-314.
114. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain*. 1998;75:111-119.
115. Smith PB, Martin BR. Spinal mechanisms of delta 9-tetrahydrocannabinol-induced analgesia. *Brain Res*. 1992;578:8-12.
116. Calignano A, La Rana G, Loubet-Lescoulie P, Piomelli D. A role for the endogenous cannabinoid system in the peripheral control of pain initiation. *Prog Brain Res*. 2000;129:471-482.
117. Clapper JR, Moreno-Sanz G, Russo R, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. *Nat Neurosci*. 2010;13:1265-1270.
118. Bagshaw SM, Hagen NA. Medical efficacy of cannabinoids and marijuana: A comprehensive review of the literature. *J Palliat Care*. 2002;18:111-122.
119. Cichewicz DL, Welch SP, Smith FL. Enhancement of transdermal fentanyl and buprenorphine antinociception by transdermal delta9-tetrahydrocannabinol. *Eur J Pharmacol*. 2005;525:74-82.
120. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement mu opioid antinociception by oral delta9-tetrahydrocannabinol: Dose-response analysis and receptor identification. *J Pharmacol Exp Ther*. 1999;289:859-867.
121. Piomelli D, Giuffrida A, Calignano A, Rodriguez de Fonseca F. The endocannabinoid system as a target for therapeutic drugs. *Trends Pharmacol Sci*. 2000;21:218-224.
122. Ameri A. The effects of cannabinoids on the brain. *Prog Neurobiol*. 1999;58:315-348.
123. Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice. *J Pharmacol Exp Ther*. 1992;262:10-18.
124. Reche I, Fuentes JA, Ruiz-Gayo M. Potentiation of delta 9-tetrahydrocannabinol-induced analgesia by morphine in mice: Involvement of mu- and kappa-opioid receptors. *Eur J Pharmacol*. 1996;318:11-16.
125. Vela G, Ruiz-Gayo M, Fuentes JA. Anandamide decreases naloxone-precipitated withdrawal signs in mice chronically treated with morphine. *Neuropharmacology*. 1995;34:665-668.
126. Ledent C, Valverde O, Cossu G, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science*. 1999;283:401-404.
127. Smith FL, Cichewicz D, Martin ZL, Welch SP. The enhancement of morphine antinociception in mice by delta9-tetrahydrocannabinol. *Pharmacol Biochem Behav*. 1998;60: 559-566.
128. Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. *Nature*. 1998;394:277-281.
129. Martin BR, Lichtman AH. Cannabinoid transmission and pain perception. *Neurobiol Dis*. 1998;5:447-461.
130. Bushlin I, Rozenfeld R, Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Curr Opin Pharmacol*. 2010;10:80-86.
131. Parolaro D, Rubino T, Vigano D, Massi P, Guidali C, Realini N. Cellular mechanisms underlying the interaction between cannabinoid and opioid system. *Curr Drug Targets*. 2010;11:393-405.
132. Pugh G Jr, Smith PB, Dombrowski DS, Welch SP. The role of endogenous opioids in enhancing the antinociception produced by the combination of delta 9-tetrahydrocannabinol and morphine in the spinal cord. *J Pharmacol Exp Ther*. 1996;279:608-616.
133. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci*. 2004;74:1317-1324.
134. Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther*. 2003;304:1010-1015.
135. Smith PA, Selley DE, Sim-Selley LJ, Welch SP. Low dose combination of morphine and delta9-tetrahydrocannabinol circumvents antinociceptive tolerance and apparent desensitization of receptors. *Eur J Pharmacol*. 2007;571:129-137.
136. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther*. 2011;90:844-851.
137. Health Canada, Abramovici H. *Information for Health Care Professionals: Cannabis (Marihuana, Marijuana) and the Cannabinoids*. Ottawa, ON: Health Canada; 2013. Available at http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf (Accessed March 20, 2015).
138. Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: Pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci*. 2012;367:3353-3363.
139. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: From the bench to the bedside. *Neurother*. 2009;6:713-737.
140. Karst M, Wippermann S, Ahrens J. Role of cannabinoids in the treatment of pain and (painful) spasticity. *Drugs*. 2010;70:2409-2438.
141. Pertwee RG. Cannabis and cannabinoids: Pharmacology and rationale for clinical use. *Forsch Komplementarmed*. 1999; 6(Suppl. 3):12-15.
142. Evans FJ. The medicinal chemistry of cannabis: O'Shaughnessy's legacy. *Pharmaceutical Sci*. 1997;3:533-537.
143. Hirst RA, Lambert DG, Notcutt WG. Pharmacology and potential therapeutic uses of cannabis. *Br J Anaesth*. 1998;81:77-84.
144. Formukong EA, Evans AT, Evans FJ. The medicinal uses of cannabis and its constituents. *Phytother Res*. 1989;3:219-231.

145. Milstein SL, MacCannell K, Karr G, Clark S. Marijuana-produced changes in pain tolerance. Experienced and non-experienced subjects. *Int Pharmacopsychiatry*. 1975;10:177-182.
146. Noyes R Jr, Baram DA. Cannabis analgesia. *Compr Psychiatry*. 1974;15:531-535.
147. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology*. 2006;104:1040-1046.
148. Chiou LC, Hu SS, Ho YC. Targeting the cannabinoid system for pain relief? *Acta Anaesthesiol Taiwan*. 2013;51:161-170.
149. Maione S, Costa B, Di Marzo V. Endocannabinoids: A unique opportunity to develop multitarget analgesics. *Pain*. 2013;154(Suppl. 1):S87-S93.
150. Noyes R Jr, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther*. 1975;18:84-89.
151. Mailleux P, Vanderhaeghen JJ. Localization of cannabinoid receptor in the human developing and adult basal ganglia. Higher levels in the striatonigral neurons. *Neurosci Lett*. 1992;148:173-176.
152. Moldrich G, Wenger T. Localization of the CB1 cannabinoid receptor in the rat brain. An immunohistochemical study. *Peptides*. 2000;21:1735-1742.
153. Russo EB. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett*. 2008;29:192-200.
154. Russo EB. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett*. 2004;25:31-39.
155. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci*. 2011;12:570-584.
156. Greco R, Gasperi V, Sandrini G, et al. Alterations of the endocannabinoid system in an animal model of migraine: Evaluation in cerebral areas of rat. *Cephalalgia*. 2010;30:296-302.
157. Akerman S, Kaube H, Goadsby PJ. Anandamide acts as a vasodilator of dural blood vessels in vivo by activating TRPV1 receptors. *Br J Pharmacol*. 2004;142:1354-1360.
158. Akerman S, Kaube H, Goadsby PJ. Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. *J Pharmacol Exp Ther*. 2004;309:56-63.
159. Tognetto M, Amadesi S, Harrison S, et al. Anandamide excites central terminals of dorsal root ganglion neurons via vanilloid receptor-1 activation. *J Neurosci*. 2001;21:1104-1109.
160. Haj-Dahmane S, Shen RY. Endocannabinoids suppress excitatory synaptic transmission to dorsal raphe serotonin neurons through the activation of presynaptic CB1 receptors. *J Pharmacol Exp Ther*. 2009;331:186-196.
161. Palazzo E, de Novellis V, Petrosino S, et al. Neuropathic pain and the endocannabinoid system in the dorsal raphe: Pharmacological treatment and interactions with the serotonergic system. *Eur J Neurosci*. 2006;24:2011-2020.
162. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Ann Intern Med*. 1997; 126:791-798.
163. Kelly S, Chapman V. Selective cannabinoid CB1 receptor activation inhibits spinal nociceptive transmission in vivo. *J Neurophysiol*. 2001;86:3061-3064.
164. Meng ID, Johansen JP. Antinociception and modulation of rostral ventromedial medulla neuronal activity by local microinfusion of a cannabinoid receptor agonist. *Neuroscience*. 2004;124:685-693.
165. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. *Nature*. 1998;395:381-383.
166. Palazzo E, Marabese I, de Novellis V, et al. Metabotropic and NMDA glutamate receptors participate in the cannabinoid-induced antinociception. *Neuropharmacology*. 2001;40:319-326.
167. Finn DP, Jhaveri MD, Beckett SR, et al. Effects of direct periaqueductal grey administration of a cannabinoid receptor agonist on nociceptive and aversive responses in rats. *Neuropharmacology*. 2003;45:594-604.
168. Maione S, Bisogno T, de Novellis V, et al. Elevation of endocannabinoid levels in the ventrolateral periaqueductal grey through inhibition of fatty acid amide hydrolase affects descending nociceptive pathways via both cannabinoid receptor type 1 and transient receptor potential vanilloid type-1 receptors. *J Pharmacol Exp Ther*. 2006;316:969-982.
169. de Novellis V, Mariani L, Palazzo E, et al. Periaqueductal grey CB1 cannabinoid and metabotropic glutamate subtype 5 receptors modulate changes in rostral ventromedial medulla neuronal activities induced by subcutaneous formalin in the rat. *Neuroscience*. 2005;134:269-281.
170. Akerman S, Holland PR, Goadsby PJ. Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. *J Pharmacol Exp Ther*. 2007;320:64-71.
171. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. Endocannabinoids in the brainstem modulate dural trigeminovascular nociceptive traffic via CB1 and "triptan" receptors: Implications in migraine. *J Neurosci*. 2013;33:14869-14877.
172. Knight YE, Goadsby PJ. The periaqueductal grey matter modulates trigeminovascular input: A role in migraine? *Neuroscience*. 2001;106:793-800.
173. Knight YE, Bartsch T, Kaube H, Goadsby PJ. P/Q-type calcium-channel blockade in the periaqueductal gray facilitates trigeminal nociception: A functional genetic link for migraine? *J Neurosci*. 2002;22:1-6.
174. Knight YE, Bartsch T, Goadsby PJ. Trigeminal antinociception induced by bicuculline in the periaqueductal gray (PAG) is not affected by PAG P/Q-type calcium channel blockade in rat. *Neurosci Lett*. 2003;336:113-116.
175. Juhasz G, Lazary J, Chase D, et al. Variations in the cannabinoid receptor 1 gene predispose to migraine. *Neurosci Lett*. 2009;461: 116-120.
176. Nyholt DR, Morley KI, Ferreira MA, et al. Genomewide significant linkage to migrainous headache on chromosome 5q21. *Am J Hum Genet*. 2005;77:500-512.
177. Bartsch T, Knight YE, Goadsby PJ. Activation of 5-HT(1B/1D) receptor in the periaqueductal gray inhibits nociception. *Ann Neurol*. 2004;56:371-381.

178. Jeong HJ, Chenu D, Johnson EE, Connor M, Vaughan CW. Sumatriptan inhibits synaptic transmission in the rat midbrain periaqueductal grey. *Mol Pain*. 2008;4:1-11.
179. Vaughan CW, Connor M, Bagley EE, Christie MJ. Actions of cannabinoids on membrane properties and synaptic transmission in rat periaqueductal gray neurons in vitro. *Mol Pharmacol*. 2000;57:288-295.
180. Vaughan CW, McGregor IS, Christie MJ. Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons in vitro. *Br J Pharmacol*. 1999;127: 935-940.
181. Greco R, Mangione AS, Sandrini G, Nappi G, Tassorelli C. Activation of CB2 receptors as a potential therapeutic target for migraine: Evaluation in an animal model. *J Headache Pain*. 2014;15:2377-15-14.
182. Hampson AJ, Bornheim LM, Scanziani M, et al. Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission. *J Neurochem*. 1998;70:671-676.
183. Kazemi H, Rahgozar M, Speckmann EJ, Gorji A. Effect of cannabinoid receptor activation on spreading depression. *Iran J Basic Med Sci*. 2012;15:926-936.
184. Shen M, Thayer SA. Delta9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. *Mol Pharmacol*. 1999;55:8-13.
185. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *J Neurosci*. 1996;16:4322-4334.
186. Sullivan JM. Mechanisms of cannabinoid-receptor-mediated inhibition of synaptic transmission in cultured hippocampal pyramidal neurons. *J Neurophysiol*. 1999;82:1286-1294.
187. Cupini LM, Costa C, Sarchielli P, et al. Degradation of endocannabinoids in chronic migraine and medication overuse headache. *Neurobiol Dis*. 2008;30:186-189.
188. Rossi C, Pini LA, Cupini ML, Calabresi P, Sarchielli P. Endocannabinoids in platelets of chronic migraine patients and medication-overuse headache patients: Relation with serotonin levels. *Eur J Clin Pharmacol*. 2008;64:1-8.
189. Sarchielli P, Pini LA, Coppola F, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. *Neuropsychopharmacology*. 2007;32:1384-1390.
190. Villalon CM, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. *Pharmacol Ther*. 2009;124:309-323.
191. Cupini LM, Bari M, Battista N, et al. Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. *Cephalalgia*. 2006;26:277-281.
192. el Mallakh RS. Marijuana and migraine. *Headache*. 1987;27:442-443.
193. Grinspoon L, Bakalar JB. *Marihuana: The Forbidden Medicine*. New Haven, CT: Yale University; 1993.
194. Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *Int J Clin Pharmacol Res*. 1985;5:243-246.
195. el Mallakh RS. Migraine headaches and drug abuse. *South Med J*. 1989;82:805.
196. Schnelle M, Grotenhermen F, Reif M, Gorter RW. Results of a standardized survey on the medical use of cannabis products in the German-speaking area. *Forsch Komplementarmed*. 1999; 6(Suppl. 3):28-36.
197. Gieringer D. Medical use of cannabis: Experience in California. In: Grotenhermen F, Russo EB, eds. *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential*. Binghamton, NY: The Hawthorn Press, Inc; 2002:143-152.
198. Evans RW, Ramadan NM. Are cannabis-based chemicals helpful in headache? *Headache*. 2004;44:726-727.
199. Knoller N, Levi L, Shoshan I, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: A randomized, placebo-controlled, phase II clinical trial. *Crit Care Med*. 2002;30:548-554.
200. Biegon A. Cannabinoids as neuroprotective agents in traumatic brain injury. *Curr Pharm Des*. 2004;10:2177-2183.
201. van der Stelt M, Di Marzo V. Cannabinoid receptors and their role in neuroprotection. *Neuromolecular Med*. 2005;7:37-50.
202. van der Stelt M, Veldhuis WB, Bar PR, Veldink GA, Vliegenthart JF, Nicolay K. Neuroprotection by Delta^9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. *J Neurosci*. 2001;21:6475-6479.
203. Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: The ongoing story of cannabis. *Nat Prod Rep*. 1999;16:131-143.
204. Hepler RS, Frank IR. Marihuana smoking and intraocular pressure. *JAMA*. 1971;217:1392.
205. Colasanti BK. Ocular hypotensive effect of marihuana cannabinoids: Correlate of central action or separate phenomenon? *J Ocul Pharmacol*. 1986;2:295-304.
206. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: A pilot study. *J Glaucoma*. 2006;15:349-353.
207. Tomida I, Pertwee RG, Azuara-Blanco A. Cannabinoids and glaucoma. *Br J Ophthalmol*. 2004;88:708-713.
208. Green K. Marijuana smoking vs cannabinoids for glaucoma therapy. *Arch Ophthalmol*. 1998;116:1433-1437.
209. Green K, Wynn H, Bowman KA. A comparison of topical cannabinoids on intraocular pressure. *Exp Eye Res*. 1978;27:239-246.
210. Merritt JC, Olsen JL, Armstrong JR, McKinnon SM. Topical delta 9-tetrahydrocannabinol in hypertensive glaucomas. *J Pharm Pharmacol*. 1981;33:40-41.
211. Merritt JC, Perry DD, Russell DN, Jones BF. Topical delta 9-tetrahydrocannabinol and aqueous dynamics in glaucoma. *J Clin Pharmacol*. 1981;21:467S-71S.
212. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology*. 1980;87:222-228.
213. Flach AJ. Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. *Trans Am Ophthalmol Soc*. 2002;100:215-224.
214. Wan MJ, Daniel S, Kassam F, et al. Survey of complementary and alternative medicine use in glaucoma patients. *J Glaucoma*. 2012;21:79-82.
215. Zhan GL, Camras CB, Palmberg PF, Toris CB. Effects of marijuana on aqueous humor dynamics in a glaucoma patient. *J Glaucoma*. 2005;14:175-177.

216. Maor D, Treves T, Korczyn AD. Lack of effect of cannabinoids on carbonic anhydrase. *J Neural Transm*. 1980;49:205-206.
217. Robbins MS, Tarshish S, Solomon S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. *Headache*. 2009;49:914-916.
218. May A, Goadsby PJ. Hypothalamic involvement and activation in cluster headache. *Curr Pain Headache Rep*. 2001;5:60-66.
219. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. *Lancet*. 1998;352:275-278.
220. Goadsby PJ, May A. PET demonstration of hypothalamic activation in cluster headache. *Neurology*. 1999;52:1522.
221. Donnet A, Lanteri-Minet M, Guegan-Massardier E, et al. Sociêtê Française d'Etude des Migraines et Cêphalêes (SFEMC). Chronic cluster headache: A French clinical descriptive study. *J Neurol Neurosurg Psychiatry*. 2007;78:1354-1358.
222. Leroux E, Taifas I, Valade D, Donnet A, Chagnon M, Ducros A. Use of cannabis among 139 cluster headache sufferers. *Cephalalgia*. 2013;33:208-213.
223. May A, Bahra A, Buchel C, Turner R, Goadsby PJ. Functional magnetic resonance imaging in spontaneous attacks of SUNCT: Short-lasting neuralgiform headache with conjunctival injection and tearing. *Ann Neurol*. 1999;46:791-794.
224. Matharu MS, Cohen AS, Frackowiak RS, Goadsby PJ. Posterior hypothalamic activation in paroxysmal hemicrania. *Ann Neurol*. 2006;59:535-545.
225. Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RS, Goadsby PJ. Posterior hypothalamic and brainstem activation in hemicrania continua. *Headache*. 2004;44:747-761.
226. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol*. 1997;38:44-48.
227. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4:1770-1804.
228. Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta9-tetrahydrocannabinol, cannabidiol and cannabinol. *Handb Exp Pharmacol*. 2005;168:657-690.
229. Agurell S, Halldin M, Lindgren JE, et al. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev*. 1986;38:21-43.
230. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42:327-360.
231. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medicinal cannabis: Rational guidelines for dosing. *IDrugs*. 2004;7:464-470.
232. Zuurman L, Ippel AE, Moin E, van Gerven JM. Biomarkers for the effects of cannabis and THC in healthy volunteers. *Br J Clin Pharmacol*. 2009;67:5-21.
233. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: A pilot study. *Clin Pharmacol Ther*. 2007;82:572-578.
234. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci*. 2006;95:1308-1317.
235. Pomahacova B, Van der Kooy F, Verpoorte R. Cannabis smoke condensate III: The cannabinoid content of vaporised Cannabis sativa. *Inhal Toxicol*. 2009;21:1108-1112.
236. Gieringer DH, St Laurent J, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. *J Cannabis Ther*. 2004;4:7-27.
237. Gieringer DH. Cannabis "vaporization." *J Cannabis Ther*. 2001;1:153-170.
238. Zuurman L, Roy C, Schoemaker RC, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol*. 2008;22:707-716.
239. Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H. Comparison of the subjective effects of Delta(9)-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology (Berl)*. 2002;161:331-339.
240. Abbott Products Inc. Marinol Product Monograph, North Chicago, IL; 2010.
241. Valeant Canada. Cesamet Product Monograph, Somerset, NJ; 2009.
242. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neurosci Ther*. 2009;15:84-88.
243. GW Pharmaceuticals. Sativex Product Monograph, Salisbury, Wiltshire, UK; 2010.
244. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: A randomized, placebo-controlled, graded-dose trial. *J Pain*. 2012;13:438-449.
245. Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. *Clin Chem*. 2011;57:66-75.
246. Stinchcomb AL, Valiveti S, Hammell DC, Ramsey DR. Human skin permeation of Delta8-tetrahydrocannabinol, cannabidiol and cannabinol. *J Pharm Pharmacol*. 2004;56:291-297.
247. Valiveti S, Kiptoo PK, Hammell DC, Stinchcomb AL. Transdermal permeation of WIN 55,212-2 and CP 55,940 in human skin in vitro. *Int J Pharm*. 2004;278:173-180.
248. Valiveti S, Hammell DC, Earles DC, Stinchcomb AL. Transdermal delivery of the synthetic cannabinoid WIN 55,212-2: in vitro/in vivo correlation. *Pharm Res*. 2004;21:1137-1145.
249. Elsohly MA, Little TL Jr, Hikal A, Harland E, Stanford DF, Walker L. Rectal bioavailability of delta-9-tetrahydrocannabinol from various esters. *Pharmacol Biochem Behav*. 1991;40:497-502.
250. Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: A pilot study with 2 patients. *Int J Clin Pharmacol Ther*. 1996;34:446-452.
251. Perlin E, Smith CG, Nichols AI, et al. Disposition and bioavailability of various formulations of tetrahydrocannabinol in the rhesus monkey. *J Pharm Sci*. 1985;74:171-174.
252. Mattes RD, Shaw LM, Edling-Owens J, Engelman K, Elsohly MA. Bypassing the first-pass effect for the therapeutic use of cannabinoids. *Pharmacol Biochem Behav*. 1993;44:745-747.

253. ElSohly MA, Stanford DF, Harland EC, et al. Rectal bioavailability of delta-9-tetrahydrocannabinol from the hemisuccinate ester in monkeys. *J Pharm Sci*. 1991;80:942-945.
254. Agurell S, Leander K. Stability, transfer and absorption of cannabinoid constituents of cannabis (hashish) during smoking. *Acta Pharm Suec*. 1971;8:391-402.
255. Llamas R, Hart DR, Schneider NS. Allergic bronchopulmonary aspergillosis associated with smoking moldy marihuana. *Chest*. 1978;73:871-872.
256. Institute of Medicine. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999.
257. Allsop DJ, Norberg MM, Copeland J, Fu S, Budney AJ. The Cannabis Withdrawal Scale development: Patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend*. 2011;119:123-129.
258. Lichtman AH, Martin BR. Cannabinoid tolerance and dependence. *Handb Exp Pharmacol*. 2005;168:691-717.
259. Vandrey R, Haney M. Pharmacotherapy for cannabis dependence: How close are we? *CNS Drugs*. 2009;23:543-553.
260. Lachenmeier DW, Rehm J. Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Sci Rep*. 2015;5:1-7.
261. Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*. 2004;99:686-696.
262. Gable RS. Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *Am J Drug Alcohol Abuse*. 1993;19:263-281.
263. Petitet F, Jeantaud B, Reibaud M, Imperato A, Dubroeucq MC. Complex pharmacology of natural cannabinoids: Evidence for partial agonist activity of delta9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sci*. 1998;63:PL1-PL6.
264. Zuardi AW, Hallak JE, Crippa JA. Interaction between cannabidiol (CBD) and (9)-tetrahydrocannabinol (THC): Influence of administration interval and dose ratio between the cannabinoids. *Psychopharmacology (Berl)*. 2012;219:247-249.
265. Zuardi AW, Finkelfarb E, Bueno OF, Musty RE, Karniol IG. Characteristics of the stimulus produced by the mixture of cannabidiol with delta 9-tetrahydrocannabinol. *Arch Int Pharmacodyn Ther*. 1981;249:137-146.
266. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)*. 1982;76:245-250.
267. Johnson MR, Melvin LS, Althuis TH, et al. Selective and potent analgetics derived from cannabinoids. *J Clin Pharmacol*. 1981;21:271S-82S.
268. Noyes R Jr, Brunk SF, Baram DA, Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol*. 1975;15:139-143.
269. Staquet M, Gantt C, Machin D. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clin Pharmacol Ther*. 1978;23:397-401.
270. Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. *Lancet*. 1999;353:560.
271. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia*. 1997;52:483-486.
272. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol*. 2011;72:735-744.
273. Greenwald MK, Stitzer ML. Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug Alcohol Depend*. 2000;59:261-275.
274. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology*. 2007;107:785-796.
275. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. *J Pain Symptom Manage*. 2006;32:497-501.
276. Sutton IR, Daeninck P. Cannabinoids in the management of intractable chemotherapy-induced nausea and vomiting and cancer-related pain. *J Support Oncol*. 2006;4:531-535.
277. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med*. 2006;7:25-29.
278. Notcutt WG, Price M, Chapman G. Clinical experience with nabilone for chronic pain. *Pharm Sci*. 1997;3:551-555.
279. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: Results of a prospective survey. *Pain*. 2003;102:211-216.
280. Ware MA, Gamsa A, Persson J, Fitzcharles MA. Cannabis for chronic pain: Case series and implications for clinicians. *Pain Res Manag*. 2002;7:95-99.
281. Manzanares J, Julian M, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. *Curr Neuropharmacol*. 2006;4:239-257.
282. Christie MJ, Mallet C. Endocannabinoids can open the pain gate. *Sci Signal*. 2009;2:pe57.
283. Walker JM, Huang SM. Cannabinoid analgesia. *Pharmacol Ther*. 2002;95:127-135.
284. Walker JM, Strangman NM, Huang SM. Cannabinoids and pain. *Pain Res Manag*. 2001;6:74-79.
285. Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. *Life Sci*. 1999;65:665-673.
286. Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci U S A*. 1999;96:12198-12203.
287. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556:75-83.
288. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain*. 2013;14:136-148.
289. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain*. 2008;9:254-264.

290. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ*. 2010;182:E694-E701.
291. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9:506-521.
292. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology*. 2007;68:515-521.
293. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34:672-680.
294. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: A randomized controlled trial. *JAMA*. 2003;290:1757-1762.
295. Grant I. Medicinal cannabis and painful sensory neuropathy. *Virtual Mentor*. 2013;15:466-469.
296. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133:210-220.
297. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain*. 2012;153:2073-2082.
298. Ashton JC, Milligan ED. Cannabinoids for the treatment of neuropathic pain: Clinical evidence. *Curr Opin Investig Drugs*. 2008;9:65-75.
299. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomised controlled trial. *Pain*. 2004;112:299-306.
300. Weber J, Schley M, Casutt M, et al. Tetrahydrocannabinol (Delta 9-THC) treatment in chronic central neuropathic pain and fibromyalgia patients: Results of a multicenter survey. *Anesthesiol Res Pract*. 2009(Article ID 827290):1-9.
301. Martin Fontelles MI, Goicoechea Garcia C. Role of cannabinoids in the management of neuropathic pain. *CNS Drugs*. 2008;22: 645-653.
302. Select Committee on Science and Technology. *Cannabis: The Scientific and Medical Evidence. The House of Lords Session 1997-8*. London: The Stationary Office; 1998. 9th report [HL paper 151].
303. Fiz J, Duran M, Capella D, Carbonell J, Farre M. Cannabis use in patients with fibromyalgia: Effect on symptoms relief and health-related quality of life. *PLoS One*. 2011;6:e18440.
304. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. *Curr Med Res Opin*. 2006;22:1269-1276.
305. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain*. 2008;9:164-173.
306. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: Results of a randomized controlled trial. *Anesth Analg*. 2010;110:604-610.
307. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: Executive summary. *Pain Res Manag*. 2013;18:119-126.
308. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45:50-52.
309. Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of delta9-tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav*. 1998;60:183-191.
310. Cox ML, Haller VL, Welch SP. Synergy between delta9-tetrahydrocannabinol and morphine in the arthritic rat. *Eur J Pharmacol*. 2007;567:125-130.
311. Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. *Inflammation*. 1988;12:361-371.
312. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: A prospective placebo-controlled study. *Clin Gastroenterol Hepatol*. 2013;11:1280-e1.
313. Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: An observational study. *Isr Med Assoc J*. 2011;13:455-458.
314. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2011;23:891-896.
315. Lahat A, Lang A, Ben-Horin S. 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;85:1-8.
316. Sanson M, Bueno L, Fioramonti J. Involvement of cannabinoid receptors in inflammatory hypersensitivity to colonic distension in rats. *Neurogastroenterol Motil*. 2006;18:949-956.
317. Brusberg M, Arvidsson S, Kang D, Larsson H, Lindstrom E, Martinez V. CB1 receptors mediate the analgesic effects of cannabinoids on colorectal distension-induced visceral pain in rodents. *J Neurosci*. 2009;29:1554-1564.
318. Kimball ES, Wallace NH, Schneider CR, D'Andrea MR, Hornby PJ. Small intestinal cannabinoid receptor changes following a single colonic insult with oil of mustard in mice. *Front Pharmacol*. 2010;1:1-8.
319. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J Pain Symptom Manage*. 2013;46:207-218.
320. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 2010;39:167-179.
321. Gorji A. Pharmacological treatment of headache using traditional Persian medicine. *Trends Pharmacol Sci*. 2003;24:331-334.

322. Feeney DM. Letter: Marihuana use among epileptics. *JAMA*. 1976;235:1105.
323. Karler R, Turkanis SA. The cannabinoids as potential antiepileptics. *J Clin Pharmacol*. 1981;21:437S-48S.
324. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology*. 1980;21:175-185.
325. Consroe PF, Wood GC, Buchsbaum H. Anticonvulsant nature of marihuana smoking. *JAMA*. 1975;234:306-307.
326. Karler R, Turkanis SA. Subacute cannabinoid treatment: Anticonvulsant activity and withdrawal excitability in mice. *Br J Pharmacol*. 1980;68:479-484.
327. Consroe P, Martin A, Singh V. Antiepileptic potential of cannabidiol analogs. *J Clin Pharmacol*. 1981;21:428S-36S.
328. Consroe P. Brain cannabinoid systems as targets for the therapy of neurological disorders. *Neurobiol Dis*. 1998;5:534-551.
329. Chiu P, Olsen DM, Borys HK, Karler R, Turkanis SA. The influence of cannabidiol and delta 9-tetrahydrocannabinol on cobalt epilepsy in rats. *Epilepsia*. 1979;20:365-375.
330. Ellison JM, Gelwan E, Ogletree J. Complex partial seizure symptoms affected by marijuana abuse. *J Clin Psychiatry*. 1990;51:439-440.
331. Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther*. 2003;307:129-137.
332. Romigi A, Bari M, Placidi F, et al. Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy. *Epilepsia*. 2010;51:768-772.
333. Ludanyi A, Eross L, Czirjak S, et al. Downregulation of the CB1 cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus. *J Neurosci*. 2008;28:2976-2990.
334. Falenski KW, Carter DS, Harrison AJ, Martin BR, Blair RE, DeLorenzo RJ. Temporal characterization of changes in hippocampal cannabinoid CB(1) receptor expression following pilocarpine-induced status epilepticus. *Brain Res*. 2009;1262:64-72.
335. Falenski KW, Blair RE, Sim-Selley LJ, Martin BR, DeLorenzo RJ. Status epilepticus causes a long-lasting redistribution of hippocampal cannabinoid type 1 receptor expression and function in the rat pilocarpine model of acquired epilepsy. *Neuroscience*. 2007;146:1232-1244.
336. Wallace MJ, Martin BR, DeLorenzo RJ. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. *Eur J Pharmacol*. 2002;452:295-301.
337. Mechoulam R, Lichtman AH. Neuroscience. Stout guards of the central nervous system. *Science*. 2003;302:65-67.
338. Shafaroodi H, Samini M, Moezi L, et al. The interaction of cannabinoids and opioids on pentylenetetrazole-induced seizure threshold in mice. *Neuropharmacology*. 2004;47:390-400.
339. Smith PF. Cannabinoids as potential anti-epileptic drugs. *Curr Opin Investig Drugs*. 2005;6:680-685.
340. Petro DJ. Marihuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics*. 1980;21:81-85.
341. Petro DJ, Ellenberger C Jr. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *J Clin Pharmacol*. 1981;21:413S-6S.
342. Meinck HM, Schonle PW, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *J Neurol*. 1989;236:120-122.
343. Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Ann Neurol*. 1983;13:669-671.
344. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse*. 1987;7:39-50.
345. Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis. *Lancet*. 1995;345:579.
346. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. *Neurology*. 2004;62:2098-2100.
347. Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci*. 2003;30:201-205.
348. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ*. 2012;184:1143-1150.
349. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG, MUSEC Research Group. Multiple sclerosis and extract of cannabis: Results of the MUSEC trial. *J Neurol Neurosurg Psychiatry*. 2012;83:1125-1132.
350. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: Safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry*. 2005;76:1664-1669.
351. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicentre randomised placebo-controlled trial. *Lancet*. 2003;362:1517-1526.
352. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: A multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J Pelvic Floor Dysfunct*. 2006;17:636-641.
353. Zajicek JP, Apostu VI. Role of cannabinoids in multiple sclerosis. *CNS Drugs*. 2011;25:187-201.
354. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol*. 2013;260:984-997.
355. Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled, crossover study. *Mult Scler*. 2004;10:417-424.
356. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol*. 2011;18:1122-1131.

357. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*. 2004;10:434-441.
358. Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res*. 2010;32:451-459.
359. Collin C, Davies P, Mutiboko IK, Ratcliffe S, Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol*. 2007;14:290-296.
360. Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex(R) (nabiximols). *Mult Scler*. 2012;18:219-228.
361. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler*. 2006;12:639-645.
362. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 2003;17:21-29.
363. Serpell MG, Notcutt W, Collin C. Sativex long-term use: An open-label trial in patients with spasticity due to multiple sclerosis. *J Neurol*. 2013;260:285-295.
364. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65:812-819.
365. Svendsen KB, Jensen TS, Bach FW. Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis – secondary publication. *Ugeskr Laeger*. 2005;167:2772-2774.
366. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*. 2004;329:253.
367. Kavia RB, De Ridder D, Constantinescu CS, Stott CG, Fowler CJ. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler*. 2010;16:1349-1359.
368. Baker D, Pryce G, Croxford JL, et al. Endocannabinoids control spasticity in a multiple sclerosis model. *FASEB J*. 2001;15:300-302.
369. Pertwee RG. Cannabinoids and multiple sclerosis. *Mol Neurobiol*. 2007;36:45-59.
370. Pertwee RG. Cannabinoids and multiple sclerosis. *Pharmacol Ther*. 2002;95:165-174.
371. Baker D, Pryce G, Croxford JL, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature*. 2000;404:84-87.
372. Pryce G, Baker D. Potential control of multiple sclerosis by cannabis and the endocannabinoid system. *CNS Neurol Disord Drug Targets*. 2012;11:624-641.
373. Pryce G, Baker D. Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors. *Br J Pharmacol*. 2007;150:519-525.
374. Chong MS, Wolff K, Wise K, Tanton C, Winstock A, Silber E. Cannabis use in patients with multiple sclerosis. *Mult Scler*. 2006;12:646-651.
375. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler*. 2004;10:425-433.
376. Page SA, Verhoef MJ. Medicinal marijuana use: Experiences of people with multiple sclerosis. *Can Fam Physician*. 2006;52:64-65.
377. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Clin Neurosci*. 1990;240:1-4.
378. Malec J, Harvey RF, Cayner JJ. Cannabis effect on spasticity in spinal cord injury. *Arch Phys Med Rehabil*. 1982;63:116-118.
379. Institute of Medicine. The medical value of marijuana and related substances. In: Joy JE, Watson SJ, Benson JA, eds. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:137-192.
380. Pooyania S, Ethans K, Szturm T, Casey A, Perry D. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. *Arch Phys Med Rehabil*. 2010;91:703-707.
381. Hagenbach U, Luz S, Ghafoor N, et al. The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. *Spinal Cord*. 2007;45:551-562.
382. Hama AT, Sagen J. Cannabinoid receptor-mediated antinociception with acetaminophen drug combinations in rats with neuropathic spinal cord injury pain. *Neuropharmacology*. 2010;58:758-766.
383. Schon F, Hart PE, Hodgson TL, et al. Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology*. 1999;53:2209-2210.
384. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2004;21:95-104.
385. Rossi S, Bernardi G, Centonze D. The endocannabinoid system in the inflammatory and neurodegenerative processes of multiple sclerosis and of amyotrophic lateral sclerosis. *Exp Neurol*. 2010;224:92-102.
386. Scotter EL, Abood ME, Glass M. The endocannabinoid system as a target for the treatment of neurodegenerative disease. *Br J Pharmacol*. 2010;160:480-498.
387. Centonze D, Rossi S, Finazzi-Agro A, Bernardi G, Maccarrone M. The (endo)cannabinoid system in multiple sclerosis and amyotrophic lateral sclerosis. *Int Rev Neurobiol*. 2007;82:171-186.
388. Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. *Mol Pharmacol*. 1998;54:459-462.
389. Maresz K, Pryce G, Ponomarev ED, et al. Direct suppression of CNS autoimmune inflammation via the cannabinoid receptor CB1 on neurons and CB2 on autoreactive T cells. *Nat Med*. 2007;13:492-497.

390. Croxford JL, Pryce G, Jackson SJ, et al. Cannabinoid-mediated neuroprotection, not immunosuppression, may be more relevant to multiple sclerosis. *J Neuroimmunol*. 2008;193:120-129.
391. Sanchez AJ, Garcia-Merino A. Neuroprotective agents: Cannabinoids. *Clin Immunol*. 2012;142:57-67.
392. Muller-Vahl KR. Treatment of Tourette syndrome with cannabinoids. *Behav Neurol*. 2013;27:119-124.
393. Muller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): No influence on neuropsychological performance. *Neuropsychopharmacology*. 2003;28: 384-388.
394. Muller-Vahl KR, Schneider U, Prevedel H, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *J Clin Psychiatry*. 2003;64:459-465.
395. Muller-Vahl KR. Cannabinoids reduce symptoms of Tourette's syndrome. *Expert Opin Pharmacother*. 2003;4:1717-1725.
396. Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): A randomized crossover trial. *Pharmacopsychiatry*. 2002;35:57-61.
397. Muller-Vahl KR, Koblenz A, Jobges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry*. 2001;34:19-24.
398. Muller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *Am J Psychiatry*. 1999;156:495.
399. Muller-Vahl KR, Kolbe H, Schneider U, Emrich HM. Cannabis in movement disorders. *Forsch Komplementarmed*. 1999; 6(Suppl. 3):23-27.
400. Muller-Vahl KR, Kolbe H, Schneider U, Emrich HM. Cannabinoids: Possible role in patho-physiology and therapy of Gilles de la Tourette syndrome. *Acta Psychiatr Scand*. 1998;98:502-506.
401. Muller-Vahl KR, Kolbe H, Dengler R. Gilles de la Tourette syndrome. Effect of nicotine, alcohol and marihuana on clinical symptoms. *Nervenarzt*. 1997;68:985-989.
402. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome. *J Clin Psychopharmacol*. 1988;8:444-445.
403. Hemming M, Yellowlees PM. Effective treatment of Tourette's syndrome with marijuana. *J Psychopharmacol*. 1993;7:389-391.
404. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci*. 1986;30:277-282.
405. Sandyk R, Snider SR, Consroe P, Elias SM. Cannabidiol in dystonic movement disorders. *Psychiatry Res*. 1986;18:291.
406. Richter A, Loscher W. Effects of pharmacological manipulations of cannabinoid receptors on severity of dystonia in a genetic model of paroxysmal dyskinesia. *Eur J Pharmacol*. 2002;454:145-151.
407. Richter A, Loscher W. WIN 55,212-2, a novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *Eur J Pharmacol*. 1994;264:371-377.
408. Jabusch HC, Schneider U, Altenmuller E. Delta9-tetrahydrocannabinol improves motor control in a patient with musician's dystonia. *Mov Disord*. 2004;19:990-991.
409. Madsen MV, Peacock LP, Werge T, Andersen MB, Andreasen JT. Effects of cannabinoid CB1 receptor agonism and antagonism on SKF81297-induced dyskinesia and haloperidol-induced dystonia in Cebus apella monkeys. *Neuropharmacology*. 2011;60:418-422.
410. Sieradzan KA, Fox SH, Hill M, Dick JP, Crossman AR, Brotchie JM. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study. *Neurology*. 2001;57:2108-2111.
411. Garcia-Arencibia M, Gonzalez S, de Lago E, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: Importance of antioxidant and cannabinoid receptor-independent properties. *Brain Res*. 2007;1134:162-170.
412. Fernandez-Ruiz J, Moreno-Martet M, Rodriguez-Cueto C, Palomo-Garo C, Gómez-Cañas M. Prospects for cannabinoid therapies in basal ganglia disorders. *Br J Pharmacol*. 2011;163: 1365-1378.
413. Garcia-Arencibia M, Garcia C, Fernandez-Ruiz J. Cannabinoids and Parkinson's disease. *CNS Neurol Disord Drug Targets*. 2009;8:432-439.
414. Sevcik J, Masek K. Potential role of cannabinoids in Parkinson's disease. *Drugs Aging*. 2000;16:391-395.
415. Curtis A, Mitchell I, Patel S, Ives N, Rickards H. A pilot study using nabilone for symptomatic treatment in Huntington's disease. *Mov Disord*. 2009;24:2254-2259.
416. Curtis A, Rickards H. Nabilone could treat chorea and irritability in Huntington's disease. *J Neuropsychiatry Clin Neurosci*. 2006;18:553-554.
417. Blazquez C, Chiarlone A, Sagredo O, et al. Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. *Brain*. 2011;134:119-136.
418. Snider SR, Consroe P. Treatment of Meige's syndrome with cannabidiol. *Neurology*. 1984;34(Suppl.):147.
419. Gilson I, Busalacchi M. Marijuana for intractable hiccups. *Lancet*. 1998;351:267.
420. Gruber AJ, Pope HG Jr, Brown ME. Do patients use marijuana as an antidepressant? *Depression*. 1996;4:77-80.
421. Bambico FR, Duranti A, Tontini A, Tarzia G, Gobbi G. Endocannabinoids in the treatment of mood disorders: Evidence from animal models. *Curr Pharm Des*. 2009;15:1623-1646.
422. Bambico FR, Katz N, Debonnel G, Gobbi G. Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. *J Neurosci*. 2007;27:11700-11711.
423. Gobbi G, Bambico FR, Mangieri R, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad Sci U S A*. 2005;102:18620-18625.
424. Ashton CH, Moore PB. Endocannabinoid system dysfunction in mood and related disorders. *Acta Psychiatr Scand*. 2011;124:250-261.
425. Ashton CH, Moore PB, Gallagher P, Young AH. Cannabinoids in bipolar affective disorder: A review and discussion of their therapeutic potential. *J Psychopharmacol*. 2005;19:293-300.
426. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: Results of a nationwide survey. *Int J Clin Pract*. 2005;59:291-295.

427. Crippa JA, Zuardi AW, Martin-Santos R, et al. Cannabis and anxiety: A critical review of the evidence. *Hum Psychopharmacol*. 2009;24:515-523.
428. Denson TF, Earleywine M. Decreased depression in marijuana users. *Addict Behav*. 2006;31:738-742.
429. Witkin JM, Tzavara ET, Davis RJ, Li X, Nomikos GG. A therapeutic role for cannabinoid CB1 receptor antagonists in major depressive disorders. *Trends Pharmacol Sci*. 2005;26:609-617.
430. Witkin JM, Tzavara ET, Nomikos GG. A role for cannabinoid CB1 receptors in mood and anxiety disorders. *Behav Pharmacol*. 2005;16:315-331.
431. Moreira FA, Wotjak CT. Cannabinoids and anxiety. *Curr Top Behav Neurosci*. 2010;2:429-450.
432. Bambico FR, Gobbi G. The cannabinoid CB1 receptor and the endocannabinoid anandamide: Possible antidepressant targets. *Expert Opin Ther Targets*. 2008;12:1347-1366.
433. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. *J Pain Symptom Manage*. 2005;29:358-367.
434. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology*. 2011;36:1219-1226.
435. Haney M, Gunderson EW, Rabkin J, et al. Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. *J Acquir Immune Defic Syndr*. 2007;45:545-554.
436. Haney M, Rabkin J, Gunderson E, Foltin RW. Dronabinol and marijuana in HIV(+) marijuana smokers: Acute effects on caloric intake and mood. *Psychopharmacology (Berl)*. 2005;181:170-178.
437. Bedi G, Foltin RW, Gunderson EW, et al. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: A controlled laboratory study. *Psychopharmacology (Berl)*. 2010;212:675-686.
438. Marsicano G, Wotjak CT, Azad SC, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature*. 2002;418:530-534.
439. Passie T, Emrich HM, Karst M, Brandt SD, Halpern JH. Mitigation of post-traumatic stress symptoms by Cannabis resin: A review of the clinical and neurobiological evidence. *Drug Test Anal*. 2012;4:649-659.
440. Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. *Neuropsychopharmacology*. 2005;30:516-524.
441. Pamplona FA, Prediger RD, Pandolfo P, Takahashi RN. The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. *Psychopharmacology (Berl)*. 2006;188:641-649.
442. Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral delta(9)-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clin Drug Investig*. 2014;34:587-591.
443. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *J Psychoactive Drugs*. 2014;46:73-77.
444. Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). *Front Behav Neurosci*. 2013;7:1-5.
445. Ganon-Elazar E, Akirav I. Cannabinoids prevent the development of behavioral and endocrine alterations in a rat model of intense stress. *Neuropsychopharmacology*. 2012;37:456-466.
446. Akirav I. Cannabinoids and glucocorticoids modulate emotional memory after stress. *Neurosci Biobehav Rev*. 2013;37:2554-2563.
447. Ganon-Elazar E, Akirav I. Cannabinoids and traumatic stress modulation of contextual fear extinction and GR expression in the amygdala-hippocampal-prefrontal circuit. *Psychoneuroendocrinology*. 2013;38:1675-1687.
448. Korem N, Akirav I. Cannabinoids prevent the effects of a footshock followed by situational reminders on emotional processing. *Neuropsychopharmacology*. 2014;39:2709-2722.
449. Passmore MJ. The cannabinoid receptor agonist nabilone for the treatment of dementia-related agitation. *Int J Geriatr Psychiatry*. 2008;23:116-117.
450. Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl)*. 2006;185:524-528.
451. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 1997;12:913-919.
452. Aso E, Juves S, Maldonado R, Ferrer I. CB2 cannabinoid receptor agonist ameliorates Alzheimer-like phenotype in AbetaPP/PS1 mice. *J Alzheimers Dis*. 2013;35:847-858.
453. Bachmeier C, Beaulieu-Abdelahad D, Mullan M, Paris D. Role of the cannabinoid system in the transit of beta-amyloid across the blood-brain barrier. *Mol Cell Neurosci*. 2013;56:255-262.
454. Gelinas DF, Miller RG, Abood M. Pilot study of safety and tolerability of delta 9-THC (Marinol) treatment for ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2002;3:23-24.
455. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: Results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*. 2011;22:2086-2093.
456. Avraham Y, Grigoriadis N, Poutahidis T, et al. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. *Br J Pharmacol*. 2011;162:1650-1658.
457. Hadland SE, Knight JR, Harris SK. Medical marijuana: Review of the science and implications for developmental-behavioral pediatric practice. *J Dev Behav Pediatr*. 2015;36:115-123.
458. Siniscalco D, Sapone A, Giordano C, et al. Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders. *J Autism Dev Disord*. 2013;43:2686-2695.
459. Bou Khalil R. Would some cannabinoids ameliorate symptoms of autism? *Eur Child Adolesc Psychiatry*. 2012;21:237-238.
460. Busquets-Garcia A, Gomis-Gonzalez M, Guegan T, et al. Targeting the endocannabinoid system in the treatment of fragile X syndrome. *Nat Med*. 2013;19:603-607.

461. Onaivi ES, Benno R, Halpern T, et al. Consequences of cannabinoid and monoaminergic system disruption in a mouse model of autism spectrum disorders. *Curr Neuropharmacol*. 2011;9:209-214.
462. Sallan SE, Zinberg NE, Frei E III. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med*. 1975;293:795-797.
463. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med*. 1980;302:135-138.
464. Vinciguerra V, Moore T, Brennan E. Inhalation marijuana as an antiemetic for cancer chemotherapy. *N Y State J Med*. 1988;88:525-527.
465. Carey MP, Burish TG, Brenner DE. Delta-9-tetrahydrocannabinol in cancer chemotherapy: Research problems and issues. *Ann Intern Med*. 1983;99:106-114.
466. Lucas VS Jr, Laszlo J. delta 9-Tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. *JAMA*. 1980;243:1241-1243.
467. Frytak S, Moertel CG, O'Fallon JR, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Ann Intern Med*. 1979;91:825-830.
468. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: A comparison of oral delta-9-THC and prochlorperazine. *Cancer*. 1982;50:636-645.
469. Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Arch Intern Med*. 1980;140:1431-1433.
470. Orr LE, McKernan JF. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. *J Clin Pharmacol*. 1981;21:76S-80S.
471. Levitt M, Wilson A, Bowman D, et al. Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. *J Clin Pharmacol*. 1981;21:103S-9S.
472. McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. *Invest New Drugs*. 1988;6:243-246.
473. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *Am J Clin Oncol*. 1985;8:336-340.
474. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med*. 1979;300:1295-1297.
475. Vincent BJ, McQuiston DJ, Einhorn LH, Nagy CM, Brames MJ. Review of cannabinoids and their antiemetic effectiveness. *Drugs*. 1983;25(Suppl. 1):52-62.
476. Einhorn L. Nabilone: An effective antiemetic agent in patients receiving cancer chemotherapy. *Cancer Treat Rev*. 1982;9(Suppl. B):55-61.
477. Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: An effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol*. 1981;21:64S-9S.
478. Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *Br J Cancer*. 1983;48:657-663.
479. Garb S, Beers AL, Bograd M, et al. Two-pronged study of tetrahydrocannabinol (THC) prevention of vomiting for cancer chemotherapy. *IRCS Med Sci*. 1980;8:203-204.
480. Lane M, Smith FE, Sullivan RA, Plasse TF. Dronabinol and prochlorperazine alone and in combination as antiemetic agents for cancer chemotherapy. *Am J Clin Oncol*. 1990;13:480-484.
481. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Symptom Manage*. 1991;6:352-359.
482. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacol Biochem Behav*. 1991;40:695-700.
483. Cunningham D, Forrest GJ, Soukop M, Gilchrist NL, Calder IT, McArdle CS. Nabilone and prochlorperazine: A useful combination for emesis induced by cytotoxic drugs. *Br Med J (Clin Res Ed)*. 1985;291:864-865.
484. Gonzalez-Rosales F, Walsh D. Intractable nausea and vomiting due to gastrointestinal mucosal metastases relieved by tetrahydrocannabinol (dronabinol). *J Pain Symptom Manage*. 1997;14:311-314.
485. Chang AE, Shiling DJ, Stillman RC, et al. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med*. 1979;91:819-824.
486. Staquet M, Bron D, Rozencweig M, Kenis Y. Clinical studies with a THC analog (BRL-4664) in the prevention of cisplatin-induced vomiting. *J Clin Pharmacol*. 1981;21:60S-3S.
487. Sharkey KA, Darmani NA, Parker LA. Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. *Eur J Pharmacol*. 2014;722:134-146.
488. Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: Quantitative systematic review. *BMJ*. 2001;323:16-21.
489. Pisanti S, Malfitano AM, Grimaldi C, et al. Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. *Best Pract Res Clin Endocrinol Metab*. 2009;23:117-131.
490. Gurley RJ, Aranow R, Katz M. Medicinal marijuana: A comprehensive review. *J Psychoactive Drugs*. 1998;30:137-147.
491. Tortorice PV, O'Connell MB. Management of chemotherapy-induced nausea and vomiting. *Pharmacotherapy*. 1990;10:129-145.
492. Cunningham D, Bradley CJ, Forrest GJ, et al. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. *Eur J Cancer Clin Oncol*. 1988;24:685-689.

493. Soderpalm AH, Schuster A, de Wit H. Antiemetic efficacy of smoked marijuana: Subjective and behavioral effects on nausea induced by syrup of ipecac. *Pharmacol Biochem Behav*. 2001; 69:343-350.
494. Machado Rocha FC, Stefano SC, De Cassia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: Systematic review and meta-analysis. *Eur J Cancer Care (Engl)*. 2008;17:431-443.
495. Musty R, Rossi R. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. *J Cannabis Ther*. 2001;1:29-42.
496. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin*. 2007;23:533-543.
497. Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. *Med J Aust*. 1979;2: 657-659.
498. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: A double-blind, crossover trial. *Pediatrics*. 1987;79:946-952.
499. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: An alternative antiemetic for cancer chemotherapy. *Arch Dis Child*. 1986;61: 502-505.
500. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sci*. 1995;56: 2097-2102.
501. Regelson W, Butler JR, Schultz J, et al. Delta-9-THC as an effective antidepressant and appetite stimulating agent in advanced cancer patients. In: Szara S, Braude MC, eds. *Proceedings of the International Conference on the Pharmacology of Cannabis*. Savannah, GA: Raven Press; 1974.
502. Nelson K, Walsh D, Deeter P, Sheehan F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. *J Palliat Care*. 1994;10:14-18.
503. Foltin RW, Fischman MW, Byrne MF. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite*. 1988;11:1-14.
504. Dansak DA. Medical use of recreational drugs by AIDS patients. *J Addict Dis*. 1997;16:25-30.
505. Mattes RD, Engelman K, Shaw LM, Elsohly MA. Cannabinoids and appetite stimulation. *Pharmacol Biochem Behav*. 1994;49:187-195.
506. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage*. 1997;14:7-14.
507. Hollister LE. Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine. *Clin Pharmacol Ther*. 1971;12: 44-49.
508. Abel EL. Effects of marihuana on the solution of anagrams, memory and appetite. *Nature*. 1971;231:260-261.
509. Gagnon MA, Elie R. Effects of marijuana and D-amphetamine on the appetite, food consumption and various cardio-respiratory variables in man. *Union Med Can*. 1975;104:914-921.
510. Regelson W, Butler JR, Schulz J, et al. Delta-9-tetracannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: Braude MC, Szara S, eds. *The Pharmacology of Marijuana*. New York: Raven Press; 1976:763-775.
511. Gorter RW. Experiences with dronabinol (delta-tetrahydrocannabinol) in oncological patients with anorexia-cachexia syndrome. Illustration of clinical problems and therapy based on 2 case reports. *Schmerz*. 2004;18(Suppl. 2):S31-S33.
512. Gorter RW. Cancer cachexia and cannabinoids. *Forsch Komplementarmed*. 1999;6(Suppl. 3):21-22.
513. Gorter R, Seefried M, Volberding P. Dronabinol effects on weight in patients with HIV infection. *AIDS*. 1992;6:127.
514. Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. *AIDS Res Hum Retroviruses*. 1997;13: 305-315.
515. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage*. 1995;10:89-97.
516. Abrams DI, Leiser RJ, Shade SB, et al. (THC Study Group). Short-term effects of cannabinoids on HIV-1 viral load [abstract]. *Int Conf AIDS*. 2000;13:45.
517. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology (Berl)*. 1999;141:395-404.
518. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology (Berl)*. 1999;141:385-394.
519. Cat LK, Coleman RL. Treatment for HIV wasting syndrome. *Ann Pharmacother*. 1994;28:595-597.
520. Green ST, Nathwani D, Goldberg DJ, Kennedy DH. Nabilone as effective therapy for intractable nausea and vomiting in AIDS. *Br J Clin Pharmacol*. 1989;28:494-495.
521. Flynn J, Hanif N. Nabilone for the management of intractable nausea and vomiting in terminally staged AIDS. *J Palliat Care*. 1992;8:46-47.
522. Kalant H. Medicinal use of cannabis: History and current status. *Pain Res Manag*. 2001;6:80-91.
523. Mikuriya TH. Marijuana in medicine: Past, present and future. *Calif Med*. 1969;110:34-40.
524. Zuardi AW. History of cannabis as a medicine: A review. *Rev Bras Psiquiatr*. 2006;28:153-157.
525. Wong BS, Camilleri M, Busciglio I, et al. Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. *Gastroenterology*. 2011;141:1638-1647.
526. D'Argenio G, Valenti M, Scaglione G, Cosenza V, Sorrentini I, Di Marzo V. Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. *FASEB J*. 2006;20:568-570.

527. Massa F, Marsicano G, Hermann H, et al. The endogenous cannabinoid system protects against colonic inflammation. *J Clin Invest*. 2004;113:1202-1209.
528. Storr M, Emmerdinger D, Diegelmann J, et al. The role of fatty acid hydrolase gene variants in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2009;29:542-551.
529. Jamontt JM, Molleman A, Pertwee RG, Parsons ME. The effects of Delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. *Br J Pharmacol*. 2010;160:712-723.
530. Engel MA, Kellermann CA, Burnat G, Hahn EG, Rau T, Konturek PC. Mice lacking cannabinoid CB1-, CB2-receptors or both receptors show increased susceptibility to trinitrobenzene sulfonic acid (TNBS)-induced colitis. *J Physiol Pharmacol*. 2010;61:89-97.
531. Borrelli F, Aviello G, Romano B, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. *J Mol Med (Berl)*. 2009;87:1111-1121.
532. Schicho R, Storr M. Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice. *Pharmacology*. 2012;89:149-155.
533. Alhouayek M, Lambert DM, Delzenne NM, Cani PD, Muccioli GG. Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. *FASEB J*. 2011; 25:2711-2721.
534. Izzo AA, Capasso R, Aviello G, et al. Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice. *Br J Pharmacol*. 2012;166:1444-1460.
535. Izzo AA, Sharkey KA. Cannabinoids and the gut: New developments and emerging concepts. *Pharmacol Ther*. 2010;126:21-38.
536. Singh UP, Singh NP, Singh B, Price RL, Nagarkatti M, Nagarkatti PS. Cannabinoid receptor-2 (CB2) agonist ameliorates colitis in IL-10(-/-) mice by attenuating the activation of T cells and promoting their apoptosis. *Toxicol Appl Pharmacol*. 2012;258:256-267.
537. Malfitano AM, Ciaglia E, Gangemi G, Gazzerro P, Laezza C, Bifulco M. Update on the endocannabinoid system as an anticancer target. *Expert Opin Ther Targets*. 2011;15:297-308.
538. Grimaldi C, Capasso A. The endocannabinoid system in the cancer therapy: An overview. *Curr Med Chem*. 2011;18:1575-1583.
539. Pisanti S, Bifulco M. Endocannabinoid system modulation in cancer biology and therapy. *Pharmacol Res*. 2009;60:107-116.
540. Proto MC, Gazzerro P, Di Croce L, et al. Interaction of endocannabinoid system and steroid hormones in the control of colon cancer cell growth. *J Cell Physiol*. 2012;227:250-258.
541. Cudaback E, Marrs W, Moeller T, Stella N. The expression level of CB1 and CB2 receptors determines their efficacy at inducing apoptosis in astrocytomas. *PLoS One*. 2010;5:e8702.
542. McAllister SD, Chan C, Taft RJ, et al. Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells. *J Neurooncol*. 2005;74:31-40.
543. Caffarel MM, Andradas C, Mira E, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Mol Cancer*. 2010;9:196. 4598-9-196.
544. Caffarel MM, Moreno-Bueno G, Cerutti C, et al. JunD is involved in the antiproliferative effect of Delta9-tetrahydrocannabinol on human breast cancer cells. *Oncogene*. 2008;27:5033-5044.
545. Caffarel MM, Sarrio D, Palacios J, Guzman M, Sanchez C. Delta9-tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. *Cancer Res*. 2006;66:6615-6621.
546. Patsos HA, Hicks DJ, Greenhough A, Williams AC, Paraskeva C. Cannabinoids and cancer: Potential for colorectal cancer therapy. *Biochem Soc Trans*. 2005;33:712-714.
547. Patsos HA, Greenhough A, Hicks DJ, et al. The endogenous cannabinoid, anandamide, induces COX-2-dependent cell death in apoptosis-resistant colon cancer cells. *Int J Oncol*. 2010;37:187-193.
548. Greenhough A, Patsos HA, Williams AC, Paraskeva C. The cannabinoid delta(9)-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. *Int J Cancer*. 2007;121:2172-2180.
549. Galve-Roperh I, Sanchez C, Cortes ML, Gomez del Pulgar T, Izquierdo M, Guzman M. Anti-tumoral action of cannabinoids: Involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nat Med*. 2000;6:313-319.
550. Preet A, Ganju RK, Groopman JE. Delta9-tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. *Oncogene*. 2008;27:339-346.
551. Ligresti A, Moriello AS, Starowicz K, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther*. 2006;318:1375-1387.
552. McAllister SD, Murase R, Christian RT, et al. Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Res Treat*. 2011;129:37-47.
553. Carracedo A, Lorente M, Egia A, et al. The stress-regulated protein p8 mediates cannabinoid-induced apoptosis of tumor cells. *Cancer Cell*. 2006;9:301-312.
554. Torres S, Lorente M, Rodriguez-Fornes F, et al. A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Mol Cancer Ther*. 2011;10:90-103.
555. Guzman M, Duarte MJ, Blazquez C, et al. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer*. 2006;95:197-203.
556. Velasco G, Carracedo A, Blazquez C, et al. Cannabinoids and gliomas. *Mol Neurobiol*. 2007;36:60-67.
557. Marcu JP, Christian RT, Lau D, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Mol Cancer Ther*. 2010;9:180-189.
558. Massi P, Vaccani A, Ceruti S, Colombo A, Abbracchio MP, Parolaro D. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther*. 2004;308:838-845.
559. Solinas M, Massi P, Cinquina V, et al. Cannabidiol, a non-psychoactive cannabinoid compound, inhibits proliferation and

invasion in U87-MG and T98G glioma cells through a multitarget effect. *PLoS One*. 2013;8:e76918.
560. Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther*. 2011;10:1161-1172.
561. McKallip RJ, Jia W, Schlomer J, Warren JW, Nagarkatti PS, Nagarkatti M. Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in the regulation of p22phox and Nox4 expression. *Mol Pharmacol*. 2006;70:897-908.
562. Nabissi M, Morelli MB, Santoni M, Santoni G. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. *Carcinogenesis*. 2013;34:48-57.
563. Singh Y, Bali C. Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation. *Case Rep Oncol*. 2013;6:585-592.
564. Powles T, te Poele R, Shamash J, et al. Cannabis-induced cytotoxicity in leukemic cell lines: The role of the cannabinoid receptors and the MAPK pathway. *Blood*. 2005;105:1214-1221.
565. Salazar M, Carracedo A, Salanueva IJ, et al. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. *J Clin Invest*. 2009;119:1359-1372.
566. Adinolfi B, Romanini A, Vanni A, et al. Anticancer activity of anandamide in human cutaneous melanoma cells. *Eur J Pharmacol*. 2013;718:154-159.
567. Armstrong JL, Hill DS, McKee CS, et al. Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death. *J Invest Dermatol*. 2015;Feb 10 [Epub ahead of print].
568. Takeda S, Okajima S, Miyoshi H, et al. Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration. *Toxicol Lett*. 2012;214:314-319.
569. Abboud RT, Sanders HD. Effect of oral administration of delta-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects. *Chest*. 1976;70:480-485.
570. Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax*. 1976;31:720-723.
571. Hartley JP, Nogrady SG, Seaton A. Bronchodilator effect of delta1-tetrahydrocannabinol. *Br J Clin Pharmacol*. 1978;5:523-525.
572. Sido JM, Nagarkatti PS, Nagarkatti M. Role of endocannabinoid activation of peripheral CB1 receptors in the regulation of autoimmune disease. *Int Rev Immunol*. 2014;Jun 9 [Epub ahead of print].
573. Yang X, Hegde VL, Rao R, Zhang J, Nagarkatti PS, Nagarkatti M. Histone Modifications are associated with Delta9-tetrahydrocannabinol-mediated alterations in antigen-specific T cell responses. *J Biol Chem*. 2014;289:18707-18718.
574. Tanasescu R, Constantinescu CS. Cannabinoids and the immune system: An overview. *Immunobiology*. 2010;215:588-597.
575. Ronen A, Chassidim HS, Gershon P, et al. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. *Accid Anal Prev*. 2010;42:1855-1865.
576. Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. *Am J Addict*. 2009;18:185-193.
577. Bramness JG, Khiabani HZ, Morland J. Impairment due to cannabis and ethanol: Clinical signs and additive effects. *Addiction*. 2010;105:1080-1087.
578. Pope HG Jr, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: The current status of research. *Drug Alcohol Depend*. 1995;38:25-34.
579. Buchy L, Perkins D, Woods SW, Liu L, Addington J. Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis. *Schizophr Res*. 2014;156:277-280.
580. Zammit S, Moore TH, Lingford-Hughes A, et al. Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *Br J Psychiatry*. 2008;193:357-363.
581. Johns A. Psychiatric effects of cannabis. *Br J Psychiatry*. 2001;178:116-122.
582. De Hert M, Wampers M, Jendricko T, et al. Effects of cannabis use on age at onset in schizophrenia and bipolar disorder. *Schizophr Res*. 2011;126:270-276.
583. van Rossum I, Boomsma M, Tenback D, Reed C, van Os J, Advisory EMBLEM Board. Does cannabis use affect treatment outcome in bipolar disorder? A longitudinal analysis. *J Nerv Ment Dis*. 2009;197:35-40.
584. Henquet C, Krabbendam L, Spauwen J, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ*. 2005;330:11.
585. Henquet C, van Os J, Kuepper R, et al. Psychosis reactivity to cannabis use in daily life: An experience sampling study. *Br J Psychiatry*. 2010;196:447-453.
586. Korver N, Nieman DH, Becker HE, et al. Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls. *Aust N Z J Psychiatry*. 2010;44:230-236.
587. D'Souza DC, Abi-Saab WM, Madonick S, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. *Biol Psychiatry*. 2005;57:594-608.
588. D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology*. 2004;29:1558-1572.
589. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: A longitudinal population-based study. *Am J Epidemiol*. 2002;156:319-327.
590. Institute of Medicine. First, do no harm: Consequences of marijuana use and abuse. In: Joy JE, Watson SJ, Benson JA, eds. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:83-136.
591. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet*. 2007;370:319-328.
592. Favrat B, Menetrey A, Augsburger M, et al. Two cases of "cannabis acute psychosis" following the administration of oral cannabis. *BMC Psychiatry*. 2005;5:17.

593. Ongur D, Lin L, Cohen BM. Clinical characteristics influencing age at onset in psychotic disorders. *Compr Psychiatry*. 2009;50:13-19.
594. Harder S, Rietbrock S. Concentration-effect relationship of delta-9-tetrahydrocannabiol and prediction of psychotropic effects after smoking marijuana. *Int J Clin Pharmacol Ther*. 1997;35:155-159.
595. Boyce A, McArdle P. Long-term effects of cannabis. *Paediatr Child Health*. 2008;18:37-41.
596. Moreira FA, Grieb M, Lutz B. Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: Focus on anxiety and depression. *Best Pract Res Clin Endocrinol Metab*. 2009;23:133-144.
597. Corcoran CM, Kimhy D, Stanford A, et al. Temporal association of cannabis use with symptoms in individuals at clinical high risk for psychosis. *Schizophr Res*. 2008;106:286-293.
598. Kimhy D, Durbin K, Corcoran CM. Cannabis and psychosis: What can daily diaries tell us about who is vulnerable? *Prim Psychiatry*. 2009;16:44-48.
599. Cohen M, Solowij N, Carr V. Cannabis, cannabinoids and schizophrenia: Integration of the evidence. *Aust N Z J Psychiatry*. 2008;42:357-368.
600. Hollister LE. Health aspects of cannabis: Revisited. *Int J Neuropsychopharmacol*. 1998;1:71-80.
601. Ries RK. The dually diagnosed patient with psychotic symptoms. *J Addict Dis*. 1993;12:103-122.
602. Fishman SM, Rosenbaum JF, Yabusaki DI, Carr DB. Marijuana-related anxiety: A questionnaire-based pilot study of normal and psychiatric populations. *Res Commun Subst Abuse*. 1988;9:219-226.
603. Fride E, Barg J, Levy R, et al. Low doses of anandamides inhibit pharmacological effects of delta 9-tetrahydrocannabinol. *J Pharmacol Exp Ther*. 1995;272:699-707.
604. McArdle PA. Cannabis use by children and young people. *Arch Dis Child*. 2006;91:692-695.
605. Hunault CC, Mensinga TT, Bocker KB, et al. Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC). *Psychopharmacology (Berl)*. 2009;204:85-94.
606. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana. *Sleep Med Rev*. 2008;12:381-389.
607. Scott J, Martin G, Bor W, Sawyer M, Clark J, McGrath J. The prevalence and correlates of hallucinations in Australian adolescents: Results from a national survey. *Schizophr Res*. 2009;107:179-185.
608. Weinstein A, Brickner O, Lerman H, et al. Brain imaging study of the acute effects of Delta9-tetrahydrocannabinol (THC) on attention and motor coordination in regular users of marijuana. *Psychopharmacology (Berl)*. 2008;196:119-131.
609. Yesavage JA, Leirer VO, Denari M, Hollister LE. Carry-over effects of marijuana intoxication on aircraft pilot performance: A preliminary report. *Am J Psychiatry*. 1985;142:1325-1329.
610. Leirer VO, Yesavage JA, Morrow DG. Marijuana carry-over effects on aircraft pilot performance. *Aviat Space Environ Med*. 1991;62:221-227.
611. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Cognitive measures in long-term cannabis users. *J Clin Pharmacol*. 2002;42:41S-7S.
612. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry*. 2001;58:909-915.
613. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*. 2002;287:1123-1131.
614. Honarmand K, Tierney MC, O'Connor P, Feinstein A. Effects of cannabis on cognitive function in patients with multiple sclerosis. *Neurology*. 2011;76:1153-1160.
615. Downey LA, King R, Papafotiou K, et al. The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. *Accid Anal Prev*. 2013;50:879-886.
616. Smiley A. Marijuana: On-road and driving-simulator studies. In: Kalant H, Corrigall W, Hall W, Smart R, eds. *The Health Effects of Cannabis*. Toronto: Center of Addiction and Mental Health; 1999:173-191.
617. Hansteen RW, Miller RD, Lonero L, Reid LD, Jones B. Effects of cannabis and alcohol on automobile driving and psychomotor tracking. *Ann N Y Acad Sci*. 1976;282:240-256.
618. Hart CL, Ilan AB, Gevins A, et al. Neurophysiological and cognitive effects of smoked marijuana in frequent users. *Pharmacol Biochem Behav*. 2010;96:333-341.
619. Ilan AB, Gevins A, Coleman M, ElSohly MA, de Wit H. Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. *Behav Pharmacol*. 2005;16:487-496.
620. Ilan AB, Smith ME, Gevins A. Effects of marijuana on neurophysiological signals of working and episodic memory. *Psychopharmacology (Berl)*. 2004;176:214-222.
621. O'Kane CJ, Tutt DC, Bauer LA. Cannabis and driving: A new perspective. *Emerg Med (Fremantle)*. 2002;14:296-303.
622. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ*. 2012;344:e536.
623. Elvik R. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accid Anal Prev*. 2013;60:254-267.
624. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem*. 2013;59:478-492.
625. Robbe H. Marijuana's impairing effects on driving are moderate when taken alone but severe when combined with alcohol. *Hum Psychopharmacol Clin Ther*. 1998;13:S70-S78.
626. Hall W. Driving while under the influence of cannabis. *BMJ*. 2012;344:e595.
627. Brady JE, Li G. Trends in alcohol and other drugs detected in fatally injured drivers in the United States, 1999-2010. *Am J Epidemiol*. 2014;179:692-699.
628. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012;109:E2657-E2664.

629. Zalesky A, Solowij N, Yucel M, et al. Effect of long-term cannabis use on axonal fibre connectivity. *Brain*. 2012;135:2245-2255.
630. Hall W, Degenhardt L. The adverse health effects of chronic cannabis use. *Drug Test Anal*. 2014;6:39-45.
631. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374:1383-1391.
632. Hall W, Solowij N. Adverse effects of cannabis. *Lancet*. 1998;352:1611-1616.
633. Singh NN, Pan Y, Muengtaweeponsa S, Geller TJ, Cruz-Flores S. Cannabis-related stroke: Case series and review of literature. *J Stroke Cerebrovasc Dis*. 2012;21:555-560.
634. Renard D, Taieb G, Gras-Combe G, Labauge P. Cannabis-related myocardial infarction and cardioembolic stroke. *J Stroke Cerebrovasc Dis*. 2012;21:82-83.
635. Jones RT. Cardiovascular system effects of marijuana. *J Clin Pharmacol*. 2002;42:58S-63S.
636. Wolff V, Lauer V, Rouyer O, et al. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: A prospective study in 48 consecutive young patients. *Stroke*. 2011;42:1778-1780.
637. O'Leary DS, Block RI, Koeppel JA, et al. Effects of smoking marijuana on brain perfusion and cognition. *Neuropsychopharmacology*. 2002;26:802-816.
638. Lundqvist T. Cognitive consequences of cannabis use: Comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav*. 2005;81:319-330.
639. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain*. 2007;130:3091-3101.
640. Levin KH, Copersino ML, Heishman SJ, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend*. 2010;111:120-127.
641. Mathew RJ, Wilson WH, Davis R. Postural syncope after marijuana: A transcranial Doppler study of the hemodynamics. *Pharmacol Biochem Behav*. 2003;75:309-318.
642. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation*. 2001;103:2805-2809.
643. Gorelick DA, Heishman SJ. Methods for clinical research involving cannabis administration. *Methods Mol Med*. 2006;123:235-253.
644. Disdier P, Granel B, Serratrice J, et al. Cannabis arteritis revisited – ten new case reports. *Angiology*. 2001;52:1-5.
645. Noel B, Ruf I, Panizzon RG. Cannabis arteritis. *J Am Acad Dermatol*. 2008;58:S65-S67.
646. Cottencin O, Karila L, Lambert M, et al. Cannabis arteritis: Review of the literature. *J Addict Med*. 2010;4:191-196.
647. Combemale P, Consort T, Denis-Thelis L, Estival JL, Dupin M, Kanitakis J. Cannabis arteritis. *Br J Dermatol*. 2005;152:166-169.
648. Trouve R, Nahas G. Cardiovascular effects of marihuana and cannabinoids. In: Nahas GG, Sutin KM, Harvey D, Agurell S, Pace N, Cancro R, eds. *Marihuana and Medicine*. New Jersey: Humana Press; 1999:291-304.
649. Clark SC. Marihuana and the cardiovascular system. *Pharmacol Biochem Behav*. 1975;3:299-306.
650. Clark SC, Greene C, Karr GW, MacCannell KL, Milstein SL. Cardiovascular effects of marihuana in man. *Can J Physiol Pharmacol*. 1974;52:706-719.
651. Renault PF, Schuster CR, Heinrich R, Freeman DX. Marihuana: Standardized smoke administration and dose effect curves on heart rate in humans. *Science*. 1971;174:589-591.
652. Beaconsfield P, Ginsburg J, Rainsbury R. Marihuana smoking. Cardiovascular effects in man and possible mechanisms. *N Engl J Med*. 1972;287:209-212.
653. Aryana A, Williams MA. Marijuana as a trigger of cardiovascular events: Speculation or scientific certainty? *Int J Cardiol*. 2007;118:141-144.
654. Perez-Reyes M. Marijuana smoking: Factors that influence the bioavailability of tetrahydrocannabinol. *NIDA Res Monogr*. 1990;99:42-62.
655. Hollister LE. Health aspects of cannabis. *Pharmacol Rev*. 1986;38:1-20.
656. Beaconsfield P. Some cardiovascular effects of cannabis. *Am Heart J*. 1974;87:143-146.
657. Lindsay AC, Foale RA, Warren O, Henry JA. Cannabis as a precipitant of cardiovascular emergencies. *Int J Cardiol*. 2005;104:230-232.
658. Miller RH, Dhingra RC, Kanakis C Jr, Amat-y-Leon F, Rosen KM. The electrophysiological effects of delta-9-tetrahydrocannabinol (cannabis) on cardiac conduction in man. *Am Heart J*. 1977;94:740-747.
659. Jouanjus E, Lapeyre-Mestre M, Micallef J, French Association of the Regional Abuse and Dependence Monitoring Centres (CEIP-A) Working Group on Cannabis Complications*. Cannabis use: Signal of increasing risk of serious cardiovascular disorders. *J Am Heart Assoc*. 2014;3:e000638.
660. Rezkalla S, Kloner RA. Recreational marijuana use: Is it safe for your patient? *J Am Heart Assoc*. 2014;3:e000904.
661. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol*. 2008;21:494-502.
662. Maertens RM, White PA, Rickert W, et al. The genotoxicity of mainstream and sidestream marijuana and tobacco smoke condensates. *Chem Res Toxicol*. 2009;22:1406-1414.
663. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2006;15:1829-1834.
664. Sidney S, Quesenberry CP Jr, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). *Cancer Causes Control*. 1997;8:722-728.
665. Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: A case-control study. *Eur Respir J*. 2008;31:280-286.
666. Zhang ZF, Morgenstern H, Spitz MR, et al. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol Biomarkers Prev*. 1999;8:1071-1078.
667. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Arch Intern Med*. 2007;167:221-228.

668. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest*. 1997;112:319-326.
669. Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD. Respiratory effects of non-tobacco cigarettes: A longitudinal study in general population. *Int J Epidemiol*. 1991;20:132-137.
670. Tashkin DP, Coulson AH, Clark VA, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *Am Rev Respir Dis*. 1987;135:209-216.
671. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med*. 1998;157:928-937.
672. Tashkin DP. Airway effects of marijuana, cocaine, and other inhaled illicit agents. *Curr Opin Pulm Med*. 2001;7:43-61.
673. Tashkin DP, Shapiro BJ, Frank IM. Acute effects of smoked marijuana and oral delta9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. *Am Rev Respir Dis*. 1974;109:420-428.
674. Tashkin DP, Shapiro BJ, Frank IM. Acute pulmonary physiologic effects of smoked marijuana and oral 9-tetrahydrocannabinol in healthy young men. *N Engl J Med*. 1973;289:336-341.
675. Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MD. Respiratory effects of non-tobacco cigarettes. *Br Med J (Clin Res Ed)*. 1987;295:1516-1518.
676. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307:173-181.
677. Bournet B, Buscail L. Cannabis: A rare cause of acute pancreatitis. *Gastroenterol Clin Biol*. 2008;32:922-923.
678. Grant P, Gandhi P. A case of cannabis-induced pancreatitis. *JOP*. 2004;5:41-43.
679. Belze O Jr, Legras A, Ehrmann S, Garot D, Perrotin D. Cannabis-induced acute pancreatitis. *Am J Emerg Med*. 2011;29:131-e3,131.e4.
680. Wargo KA, Geveden BN, McConnell VJ. Cannabinoid-induced pancreatitis: A case series. *JOP*. 2007;8:579-583.
681. Mallat A, Teixeira-Clerc F, Deveaux V, Manin S, Lotersztajn S. The endocannabinoid system as a key mediator during liver diseases: New insights and therapeutic openings. *Br J Pharmacol*. 2011;163:1432-1440.
682. Reichenbach V, Ros J, Fernandez-Varo G, et al. Prevention of fibrosis progression in CCl4-treated rats: Role of the hepatic endocannabinoid and apelin systems. *J Pharmacol Exp Ther*. 2012;340:629-637.
683. Patsenker E, Stoll M, Millonig G, et al. Cannabinoid receptor type I modulates alcohol-induced liver fibrosis. *Mol Med*. 2011;17:1285-1294.
684. Trebicka J, Racz I, Siegmund SV, et al. Role of cannabinoid receptors in alcoholic hepatic injury: Steatosis and fibrogenesis are increased in CB2 receptor-deficient mice and decreased in CB1 receptor knockouts. *Liver Int*. 2011;31:860-870.
685. Hezode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: A novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology*. 2008;134:432-439.
686. Purohit V, Rapaka R, Shurtleff D. Role of cannabinoids in the development of fatty liver (steatosis). *AAPS J*. 2010;12:233-237.
687. Gorzalka BB, Hill MN, Chang SC. Male-female differences in the effects of cannabinoids on sexual behavior and gonadal hormone function. *Horm Behav*. 2010;58:91-99.
688. Brown TT, Dobs AS. Endocrine effects of marijuana. *J Clin Pharmacol*. 2002;42:90S-6S.
689. Sadeu JC, Hughes CL, Agarwal S, Foster WG. Alcohol, drugs, caffeine, tobacco, and environmental contaminant exposure: Reproductive health consequences and clinical implications. *Crit Rev Toxicol*. 2010;40:633-652.
690. Shamloul R, Bella AJ. Impact of cannabis use on male sexual health. *J Sex Med*. 2011;8:971-975.
691. Nahas GG, Frick HC, Lattimer JK, Latour C, Harvey D. Pharmacokinetics of THC in brain and testis, male gametotoxicity and premature apoptosis of spermatozoa. *Hum Psychopharmacol*. 2002;17:103-113.
692. Hembree WC, Nahas GG, Zeidenberg P, Huang HFS. Changes in human spermatozoa associated with high-dose marihuana smoking. In: Nahas GG, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and Medicine*. Totowa: Humana Press; 1999:367-378.
693. Hong CY, Chaput de Saintonge DM, Turner P, Fairbairn JW. Comparison of the inhibitory action of delta-9-tetrahydrocannabinol and petroleum spirit extract of herbal cannabis on human sperm motility. *Hum Toxicol*. 1982;1:151-154.
694. Tanasescu R, Gran B, Constantinescu CS. The endocannabinoid system: A revolving plate in neuro-immune interaction in health and disease. *Amino Acids*. 2013;45:95-112.
695. Greineisen WE, Turner H. Immunoactive effects of cannabinoids: Considerations for the therapeutic use of cannabinoid receptor agonists and antagonists. *Int Immunopharmacol*. 2010;10:547-555.