Article

Cannabis-Derived Pharmaceuticals

Clifford S. Mintz
is President and Founder of BioInsights Inc.

Evan Nison
is Director of the East Coast Cannabis Division of Terra Tech Corp.

AJ Fabrizio
is Director of Research at Terra Tech Corp.

ABSTRACT

Cannabis, commonly known as marijuana, weed or pot, is a natural product derived from the Cannabis sativa plant. It has been used medicinally for thousands of years. Recent legislation allowing the use of medical marijuana in over 23 US states has spurred interest in developing pharmaceutical-derived Cannabis products to treat a variety of clinical indications ranging from pain relief to epilepsy. Many products are in late stage clinical development in the US and elsewhere. This article reviews the medicinal properties of Cannabis and describes pharmaceutical-derived Cannabis products that are currently being developed for theUS market.

Journal of Commercial Biotechnology (2015) 21(3), 16–31. doi: 10.5912/jcb709
Keywords: *Cannabis*, pharmaceuticals, medical marijuana, commercialization, companies

INTRODUCTION

Cannabis, commonly known as marijuana, weed or pot, is a natural product derived from the *Cannabis sativa* plant. It has been used medicinally for thousands of years in China, India, The Middle East and in the West through much of the 19th century.[1,2] Anecdotally, and in the medical literature, *Cannabis* has been recommended as a treatment for numerous diseases including pain, arthritis, glaucoma, neurological disorders including epilepsy, multiple sclerosis (MS) and Parkinson's disease and diabetes and a variety of ailments including loss of appetite, anxiety, nausea and vomiting and menstrual cramps.[3,4]

The plethora of therapeutic benefits offered by *Cannabis* has largely been attributed to a class of naturally-occurring, plant-derived terpenophenolic compounds known as phytocannabinoids.[5,6] Inhalation (smoking and vaporization) and ingestion are the most common routes of administration of *Cannabis* products but other routes including rectal, sublingual, transdermal, ophthalmic, intrathecal and intravenous routes have been used.[7]

Correspondence:
Clifford S. Mintz, BioInsights, Inc, US. Email1: cliffmz@yahoo.com

In addition to the phytocannabinoids, endogenous or endocannabinoids that are produced by the body have been identified and characterized. Endocannabinoids are thought to modulate or play a regulatory role in a variety of physiological processing including appetite, pain-sensation, mood, memory, inflammation, insulin sensitivity and fat and energy metabolism.[8,9] Finally, a number of synthetic cannabinoids (mimetics of naturally-occurring endocannabinoids) have been developed to better understand cannabinoid receptor biology/function/selectivity and, also, as possible treatments for a variety of therapeutic indications including pain management, inflammation, cancer and neurodegenerative diseases.[9]

MECHANISM OF ACTION

Cannabinoids (endogenous, synthetic and phytocannabinoids) are thought to exert their physiological effects by interacting with CB1 and CB2, G-coupled protein cannabinoid receptors that are widely distributed and found throughout the body.[10-13]

CB1 receptors which constitute the most prevalent neurotransmitter system in the brain and central nervous systems (CNS) are primarily found in basal ganglia, hippocampus and cerebellum.[10,11] In contrast, CB2 receptors are found almost exclusively on cells of the immune system including T and B cells and mainly appear in

tissues when there is cellular pathology. CB1 receptors are thought to be involved in the effects of *Cannabis* on appetite, mood motor function and neurocognition[12,14] whereas CB2 receptors appear to be responsible for mediating the anti-inflammatory and analgesic effects of *Cannabis*.[15-18]

Recent studies showed that certain cannabinoids such as CBD interact with the transient receptor potential vanilloid channels of the endovanilloid system, e.g, capsaicin receptors that are thought to modulate neuropathic pain and were recently shown to be involved in bone growth.[19-21] Also, other studies suggest that cannabinoids may exert therapeutic their effects by targeting α3 glycine receptors, stimulating PPARγ receptor activity, increasing intracellular Ca^2 and antagonizing GPR55 receptors.[22,23] The mechanisms of action of cannabinoids for a variety of clinical indications including chronic pain, cancer, and multiple sclerosis (MS) has been extensively reviewed elsewhere.[5,17,24,25,26-29]

PHARMACOLOGICALLY-ACTIVE PHYTOCANNABINOIDS

To date, over 60 cannabinoids unique to *Cannabis* have been identified, including the most psychoactive cannabinoid, Δ-9-tetrahydrocannabinol commonly referred to as THC. Other medically- relevant and well characterized cannabinoids include; Δ-9–tetrahydrocannabivarin (THCV), cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC) cannabinol (CBN) and cannabidivarin (CBDV); with THC, CBD and CBN being the most abundant phytocannabinoids (Table 1).[30]

THC is the main active cannabinoid in *Cannabis* and is primarily responsible for its psychoactive properties. It was the first cannabinoid to be isolated and identified (1964) in *Cannabis* resin and flowers.[31] The concentration of THC found in *Cannabis* and its extracts can vary based on plant variety, cultivation techniques and type of preparation. Pure THC can be derived from natural sources (extraction from cannabis plants) or produced synthetically.[32] The molecule acts as a partial agonist of CB1 receptors found in the CNS and CB2 receptors found on immune cells.[32]

While THC exhibits potent anti-inflammatory and anti-emetic properties, its development as a therapeutic drug treatment has been hindered by its accompanying psychotropic effects. Nevertheless, in the past, dronabinol (Marinol™) a synthetic THC and nabilone (Cesamet™) a synthetic THC-mimetic received FDA approval as appetite stimulants and treatments for chemotherapy induced nausea and vomiting (CINV).[7] However, neither drug is widely prescribed. Finally, possible development of tolerance to THC could limit the long term clinical and therapeutic uses of the molecule.

Δ-9-tetrahydrocannabivarin (THCV) is a relatively abundant non-psychoactive phytocannabinoid present in *Cannabis*.[33] THCV is a CB1 receptor antagonist and a partial agonist for CB2 receptors. Several studies showed that THCV has anti-convulsive effects in animal models and that it may be useful as a treatment for epilepsy and other CNS diseases.[33-35]

Cannabidiol (CBD) is the major non-psychotropic cannabinoid found in *Cannabis*. It has been found to possess anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and antipsychotic activity and reduces the psychoactive effects of THC.[36,22,23] Unlike THC, the mode of action of CBD is not fully understood and it is thought to act via non-CB1 receptor mechanisms because it has low affinity for CB1 and CB2 receptors.[35] Recent studies suggest that CBD may exert its action by targeting α3 glycine receptors, stimulating PPARγ receptor activity, increasing intracellular Ca^2 and antagonizing GPR55 receptors.[22,23] Other studies suggest that CBD may be a CB1 receptor antagonist[37] and may also exerts its effects by stimulating the vanilloid receptor type 1 (VR_1) with efficacy similar to that of capsaicin.[20,21,38] Also, CBD is thought to inhibit the degradation of the endocannabinoid anandamide[38] and may interfere with THC metabolism.[39] CBD is being evaluated as a possible treatment for epilepsy[40], schizophrenia[41] and for its anti-tumorigenic effects.[42]

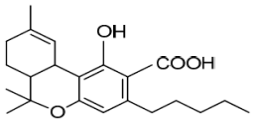
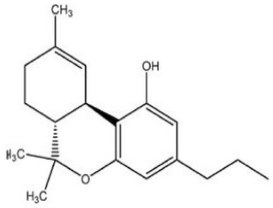
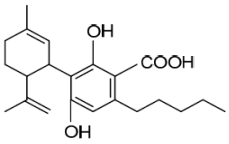
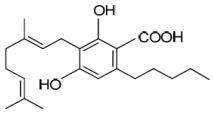
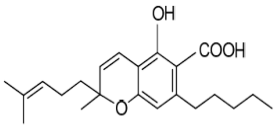
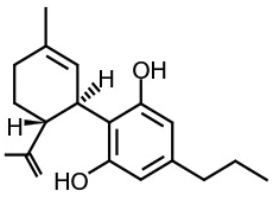
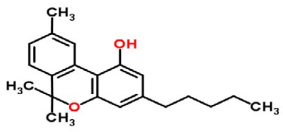
Cannabigerol (CBG) is another non-psychoactive phytocannabinoid found in *Cannabis* and the chemical precursor of THC and CBD. CBG has been reported to relieve intraocular pressure and possesses anti-inflammatory properties.[43-45] The molecule has also been reported to have anti-convulsive effects but these effects have yet to be substantiated.[46] CBG is being evaluated as a possible treatment for multiple sclerosis and inflammatory bowel disease.[45,47]

Another non-psychoactive cannabinoid found in *Cannabis* with possible therapeutic benefits is cannabichromene (CBC). CBC is thought to possess analgesic and anti-inflammatory activity.[48,49] Other studies suggest that CBC may also possess some neuroprotective effects.[34,49]

Cannabidivarin (CBDV) is a non-psychotropic homolog of CBD. CBDV is actively being developed as a therapeutic to treat epilepsy and convulsions because of its previously observed anti-convulsive and anti-epileptic activities in animal models.[34,35,50] CBDV has been reported to act via CB2 cannabinoid receptors-dependent mechanisms but direct CB2 receptor binding has yet to be demonstrated.[50,51]

Cannabinol (CBN) is a weak psychoactive cannabinoid found only in trace amounts in *Cannabis*[52]

Table 1: Pharmacologically active phytocannabinoids

Name	Abbreviation	Structure	Physiologic Effects	Therapeutic Indication(s)
Δ-9 tetrahydrocannabinol	THC		Psychoactive, mild analgesic, anti-emetic, appetite stimulant neuroprotective, reduces neuroinflammation and stimulates neurogenesis	Pain, Nausea, Nutritional wasting, Cancer
Δ-9-tetrahydrocannabivarin	THCV		Non-psychoactive, anti-convulsant, anti-inflammatory,	Epilepsy and other CNS disorders hepatic ischemia
Cannabidiol	CBD		Non-psychoactive, relieves convulsion, inflammation, anxiety and nausea	Schizophrenia, epilepsy, cancer
Cannabigerol	CBG		Non-psychoactive, relieves intraocular pressure, anti-inflammatory, neuroprotective, anti-emetic	Multiple Sclerosis, Glaucoma and inflammatory bowel disease
Cannabichromene	CBC		Non-psychoactive, anti inflammatory and analgesic effects	Pain, Cancer
Cannabidivarin	CBDV		Non-psychoactive,anti-convulsive, anti-inflammatory	Epilepsy
Cannabinol	CBN		Weakly psychoactive (degradation product of THC), immunosuppressant activity, anticonvulsive	Epilepsy

It is mostly a degradation product (metabolite) of THC.[53] Studies suggest that CBN acts as a weak agonist of CB1 receptors and has a higher affinity for CB2 receptors albeit lower than the affinity of THC for CB2 receptors.[54,55] Because CBN is a partially-selective agonist of CB2 receptors it may possess possible anti-inflammatory and immunosuppressant therapeutic effects.

CLINICAL EFFECTS

Over the past decade, despite a challenging legal and regulatory landscape, a surprising number of clinical studies have been conducted with *Cannabis* and cannabinoids for a variety of therapeutic indications.[7,28,56,57] The main areas of clinical research include chronic non-cancer pain, neurological diseases including MS and epilepsy,[28,29,57,58] and oncology including analgesia, anorexia, chemotherapy-induced nausea and vomiting (CINV).[5,7,27,42,59]

A systematic review of 18 randomized controlled clinical trials for chronic non-cancer pain conducted since 2003 revealed that smoked cannabis, cannabis extracts (oromucosal spray) and orally-administered synthetic THC (nabilone and dronabinol) had modest analgesic effects (compared with placebo) on 766 participants with chronic, neuropathic or acute non-cancer pain.[57] The databases that were searched to conduct this retrospective study included PubMed, Em base, CINAHL (EBSCO, PsycInfo, The Cochrane Library (Wiley) ISI Web of Science, ABI Inform (Proquest), Academic Search Premier, Clinical Trials.gov , Trials Central.org and clinical trial sites for Eli Lilly, GlaxoSmithKline, OALster (OCLCC) and Google Scholar.[46] However, the small number of participants, short trial durations and modest efficacy caused the authors to suggest that additional clinical trials will be necessary to conclusively determine the effects of cannabinoids on chronic pain management. To that end, there are currently 11 late-stage US clinical trials in progress to assess the effects of smoked/ vaporized *Cannabis* (6) and cannabis extracts (6) on neuropathic and chronic pain (Table 3). However, it is important to note, that GW Pharma's Sativex® a cannabis extract containing 1:1 ratios of THC: CBD (that is delivered via oromucosal spray) has been approved outside the US as a treatment for chronic neuropathic and cancer-related pain.[60,61]

The immunomodulatory properties of cannabinoids suggested that they might be therapeutically useful in MS which is generally believed to be an autoimmune neurological disease. Based on a search of the PubMed database, 37 controlled clinical trials involving 1300 patients were conducted from 2005 to 2009 to assess the effects of *Cannabis,* cannabis extracts and synthetic THC on MS and MS-related muscle spasticity and pain.[56] The results of these studies showed that cannabis extracts containing different ratios of THC and CBD (Cannador® 2:1 and Sativex® 1;1), as well as THC and nabilone can improve MS-related symptoms of spasticity, pain and urinary incontinence.[56] Additional clinical studies led to the approval of Sativex® in 27 countries (not the US) as a treatment for MS spasticity.[58] At present, in the US, there are 15 late stage clinical trials in progress that are evaluating smoked/vaporized cannabis (2) and Sativex® (13) as treatments for MS and MS-related spasticity, pain and urinary incontinence (Table 3).

More recently, there have been reports that cannabis extracts with high concentrations of CBD may be effective anti-convulsants for children suffering from severe forms of uncontrollable epilepsy known as Dravet Syndrome and Lennox-Gastaut.[40,62] Four, early randomized, placebo-controlled clinical studies conducted between 1978-1990 involving 48 patients with epilepsy found that daily treatment with 200-300 mg of CBD for up to 4 months was safe and well tolerated.[52] The databases that were searched to conduct the study included the Cochrane Epilepsy Group Specialized Register (9 September 2013), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2013, Issue 8), MEDLINE (Ovid) (9 September 2013), ISI Web of Knowledge (9 September 2013), CINAHL (EBSCOhost) (9 September 2013), and ClinicalTrials.gov (9 September 2013). However the small number of patients and short trial duration were not sufficient to draw any conclusions about CBD's efficacy.[63] More recently, GW pharma's Epidiolex, a liquid formulation of highly purified *Cannabis*-derived CBD was granted Orphan Drug Designation by FDA as a treatment for Dravet and Lennox-Gastaut syndromes and other pediatric epilepsy syndrome.[64] Currently, there are 7 mid to late stage clinical trials underway to evaluated Epidiolex's anti-epileptic properties (Table 3).

In the 1970s, purified and synthetic cannabinoids were being evaluated as palliative treatments for cancer related symptoms.[65] This led to the early approval of dronabinol and nabilone as treatments for CINV but their use has not been extended to treat cancer-related pain or wasting (although dronabinol is approved in the US as an appetite stimulant for patients with weight loss from HIV/AIDS). Interestingly, inhaled *Cannabis*, and extracts containing THC and CBD have been clinically found to be more effective in treating cancer-related neuropathic pain than placebo[66] but their effectiveness compared with conventional pain medications is uncertain.[7] Nevertheless, Sativex® is an approved treatment for cancer-related pain in 27 countries outside of the US. Four clinical trials are underway in the

US to determine the effects on Sativex® on advanced cancer pain and chemotherapy induced neuropathic pain (Table 3).

One of the earliest recognized clinical indications for cannabinoids was CINV. A 1988 prospective open label trial found that inhaled cannabis effectively controlled nausea and vomiting in 78% of 56 patients who had inadequate control of nausea and vomiting with conventional anti-emetics.[7] Also, a later report that evaluated 30 trials and over 1300 participants determined that nabilone and dronabinol were more effective than conventional anti-emetics in controlling acute CINV.[67]

There is a growing body of evidence that cannabinoids *exhibit* anti-tumor and cancer – fighting effects.[7,57] Numerous studies have demonstrated inhibition of tumor growth *in vitro* and in a variety of animal models of disease for cancer including glioblastoma, breast, prostate, thyroid, colon, skin, pancreatic, leukemia and lymphoma.[68] The exact mechanism by which cannabinoids exert their anti-tumor effects is thought to occur via suppression of proliferative cell signaling pathways, inhibition of angiogenesis (blood vessel formation) and cell migration, stimulation of apoptosis (programmed cell death) and induction of autophagy (intracellular degradation).[68,69] Interestingly, cannabinoid receptors CB1 and CB2 have been found in higher concentrations on tumor cells than on surrounding normal tissue for a variety of cancers.[70,71] Also, several studies suggest that cannabinoids may selectively inhibit tumor cell growth and proliferation while sparing normal tissue.[59,68] Although cannabinoids exhibit possible anti-tumor effects, only a single Phase 1 clinical trial that assessed the safety and efficacy of THC in 9 patients with treatment refractory glioblastoma mutliforme has been published.[65] However, at present, there are two (2) Phase 2 clinical trials underway (Table 3) to assess the effect of cannabis extracts on solid tumor growth (CBD) and glioblastoma (Sativex®).

Finally, there are a number of mid to late clinical trials underway in the US to assess the effects of cannabis extracts and cannabinoids on other therapeutic indications including Huntington's Disease, ulcerative colitis, Crohn's disease, schizophrenia and graft vs. host disease (Table 3).

COMMERCIALIZING *CANNABIS*-DERIVED PRODUCTS

The current regulatory and legal environments for *Cannabis*-derived products is extremely difficult and fraught with numerous challenges. For example, in the US, *Cannabis* and products derived from it (including hemp) are federally classified as Schedule I drugs according to the US Controlled Substances Act. This means that *Cannabis* and its products have been deemed to have "no currently accepted medical use in treatment in the US" (heroin and LSD are also schedule I drugs), are harmful and consequently, are illegal. Not surprisingly, its Schedule 1 classification has seriously hindered *Cannabis* research in the US and made it extremely challenging for drug companies developing *Cannabis*-derived pharmaceutical products. However, over the past decade or so, 34 states including the District of Columbia have enacted legislation that permits some form of *Cannabis* consumption for medical purposes. Yet, despite this, *Cannabis* and products derived from it remain illegal at the federal level and interstate transport (even between states where medical marijuana has been legalized) is illegal and criminally punishable.

The confusion regarding *Cannabis* use at the state and federal levels has given rise to two distinct types of companies that are attempting to commercialize *Cannabis* and products derived from it. The first of these are commonly referred to as medical marijuana or medical *Cannabis* companies. Typically, products from these companies are botanical extracts or actual plant materials derived from specific *Cannabis* strains with anecdotally-reported medicinal properties that can be topically applied, ingested, smoked or vaporized. Patients require a "prescription" from a state-licensed physician to obtain medical marijuana and it can only be used in states that permit consumption of *Cannabis* for medical purposes. It is important to note, that while a prescription is required for medical *Cannabis* use, these products do not require human clinical testing for safety, tolerability and efficacy (like other prescription drugs) prior to their sale in states where medical marijuana is legal.

In contrast with medical marijuana companies, biopharmaceutical companies including GW Pharma, Kannalife, Aphios and others (Table 1) are committed to developing *Cannabis*-derived pharmaceuticals using conventional US Food and Drug Administration regulatory approval pathways. UK-based GW Pharma is the clear leader in *Cannabis*-derived pharmaceutical space—its flagship product Sativex®, a plant extract, has been approved as a treatment for cancer-related pain and MS spasticity in 27 countries outside the US. In April 2014, FDA granted Sativex® Fast Track designation for the treatment of pain in patients with advanced cancer who experience inadequate analgesia during optimized chronic opioid therapy.[64] Sativex® is currently in US Phase 3 clinical trials for this indication (Table 3). Most of the other companies developing *Cannabis*-derived pharmaceuticals (extracts or individual cannabinoids) are in pre-clinical development or very early stage clinical trials (Table 2).

Table 2: Companies developing *Cannabis*-based therapeutics

Company	Product	Properties	Indication(s)	Stage of Development
AbbVie	Marinol® (dronabinol)	Synthetic Δ-9-THC	Chemotherapy-induced nausea/vomiting (CINV); MS neuropathic pain; HIV/AIDS appetite stimulate	FDA-approved for nausea and vomiting associated CINV (1985) when other anti-emetics fail and appetite stimulant for HIV/AIDS patients(1992) Approved in Denmark for multiple sclerosis neuropathic pain (2003)
Valeant Pharmaceuticals International Inc	Cesamet® (nabilone)	Synthetic Δ-9-THC	Management of nausea/vomiting	Approved in Canada (1982); now available in US and UK
GW Pharma	Sativex® (naviximols)	Mixture of extracts of cannabis plant containing two cannabinoids in 1:1 ratio, Δ-9-THC and CBD (cannabidiol) in 50% alcoholic solution; oro-mucosal delivery (mouth spray)	Neurologic and cancer-related pain; Spasticity in patients with MS	Approved in 27 countries outside US; US Phase III trials for cancer pain/MS muscle spasticity; granted FDA Fast Track designation
	Epidiolex®	CBD (cannabidiol) liquid extract from genetically-defined cannabis strain	Orphan pediatric epilepsy; Dravet Syndrome and Lennox-Gastaut syndrome	Early clinical development; granted FDA orphan drug status
	GWP42003	Not disclosed	Ulcerative colitis	Phase 2a
	GWP42004	Not disclosed	Type 2 diabetes	Phase 2b
	GWP42006	Cannabidivarin (CBDV)	Adult epilepsy	Phase 1
Society for Clinical Research (Germany)	Cannador®	Oral capsule containing whole plant extract with standardized THC:CBD ratio of 2:1	Muscle stiffness; MS spasticity/pain; cachexia in cancer patients, post-operative pain management	Phase 1/2
Kannalife	Not named	Cannabis extract/semi-synthetic CBD (cannabidiol)	Hepatic Encephalopathy	Preclinical; Seeking orphan drug designation for clinical development
Aphios	APH-080	Liposomal formulation of Δ-9-THC	CINV; Appetite stimulant for HIV and cancer patients	Preclinical
	APH-1305	CBG (cannabigerol) liposomal-oral delivery	MS & other neuroinflammatory neurodegenerative disorders	Preclinical

Table 2: Continued

Company	Product	Properties	Indication(s)	Stage of Development
Cannabis Sciences	CS-S/BCC-1	CBN (cannabinol) enriched extracts	Oncology	Preclinical
	CS-TATI-1	Plant extract	Kaposi Sarcoma	Preclinical
	TBN	CBN (cannabinol) plus other cannabinoids	Anxiety, sleep disorders, Alzheimers disease	R&D
Medical Marijuana Sciences	TBN	CBD (cannabidiol) extracts plus microencapsulation technology	Brain and pancreatic cancer	R&D

Regulatory and Commercialization Hurdles

While the business case for developing pharmaceutical *Cannabis*-derived products is a sound one, the time and costs associated with commercializing these products is certain to be greater than those associated with medical marijuana. This is because medical marijuana can be prescribed and sold in states (where it is legal) without scientific review or human clinical testing. And, while FDA has signaled a willingness to review new drug applications for *Cannabis*-derived pharmaceuticals, the agency has yet to issue definitive guidance for regulatory approval of these products. Consequently, the actual costs, regulatory requirements and time required for FDA approval for *Cannabis*-derived products are difficult to gauge at the present time. Nevertheless, garnering FDA approval for *Cannabis*-derived pharmaceuticals may offer several competitive advantages as compared with medical marijuana products that currently dominate the US market.

First, the average cost per patient of Sativex® to treat MS spasticity in countries where it is approved has been estimated to be roughly $16,000.[72] Several studies have suggested,[72,73] that the high price of Sativex® will make it unlikely to be considered cost effective by regulators in countries with government-mandated national formularies like the UK, Ireland and Australia. However, this should not be an impediment for the US market because the US federal government does not set drug prices nor determines formulary placement. Moreover, medical marijuana is currently an out-of-pocket expense for patients whereas newly FDA approved *Cannabis*-derived products are likely to be reimbursed at rates similar to those of synthetic cannabinoids such as dronabinol and nabilone.

Second, unlike medical marijuana (which as previously stated is a Schedule 1 drug), FDA approved *Cannabis*-based pharmaceuticals like dronabinol and nabilone have been classified or reclassified as Schedule 2 (opioids) or Schedule 3 (codeine) drugs. Federal regulators are likely to apply the same scheduling criteria to the next generation of FDA-approved *Cannabis*-derived pharmaceuticals like Sativex® and others. Rescheduling will effectively allow these products to compete with medical marijuana because unlike medical marijuana—which is legal in certain states and cannot be transported across state borders because of Federal law—FDA-approved *Cannabis*-derived pharmaceuticals can be legally prescribed, sold and used in all 50 US states and US territories.

Finally, and perhaps most importantly, physicians may be inclined to prescribe FDA-approved *Cannabis* drugs rather than medical marijuana because the approved products have been medically evaluated in human clinical trials and officially deemed to be safe, effective treatments for specific clincial indications. In contrast, questions or suspicions regarding medical marijuana's safety, effectiveness and quality are likely to linger until industry best practices are clearly established and adopted.

MEDICAL AND TECHNICAL CHALLENGES

In addition to legal and regulatory challenges, there are technical and manufacturing issues that must also be addressed before *Cannabis*-derived pharmaceuticals can be successfully commercialized. First, substantial financial investment in infrastructure, equipment and production facilities will be required to breed and grow different *Cannabis* strains to obtain appropriate chemical compositions and extracts to treat specific therapeutic indications. Industry experts contend that this investment must include research on

Table 3 Current clinical trials for Cannabis-derived pharmaceuticals

Product	Sponsor	Therapeutic Indication	Study Title	Phase	ClinTrial.gov Identifier
Cannabis	University of California, Davis Center for Medicinal *Cannabis* Research, VA Northern California Healthcare System	Neuropathic pain, mlutiple sclerosis, spinal cord injury	Effects of Vaporized Marijuana on Neuropathic Pain	2	NCT01037088
Cannabis	University of California, Davis VA Northern California Healthcare System University of California Davis, National Institute of Drug Abuse	Spinal cord injury pain	Vaporized Cannabis and Spinal Cord Injury Pain	2	NCT01555983
Cannabis	Center for Medicinal *Cannabis* Research	Diabetic neuropathy	Efficacy of Inhaled Cannabis in Diabetic Painful Peripheral Neuropathy	2	NCT00781001
Cannabis	Center for Medicinal *Cannabis* Research	Neuropathic pain	Effects of Smoked Marijuana on Neuropathic Pain	2	NCT00254761
Cannabis	Center for Medicinal *Cannabis* Research	HIV-associated distal, sensory-predominant polyneurophathy (DSPN)	Medicinal Cannabis for Painful HIV Neuropathy	2	NCT00255580
Cannabis	Center for Medicinal *Cannabis* Research	Pain, hyperalgesia	Analgesic Efficacy of Smoked Cannabis	2	NCT00241579
Cannabis vs. dronabinol, Marinol or THC	University of California, Davis, National Multiple Sclerosis Society	Multiple Sclerosis spasticity	Cannabis for Spasticity in Multiple Sclerosis	2	NCT00682929
Cannabis	Center for Medicinal *Cannabis* Research	Multiple Sclerosis spasticity	Short-Term Effects of Medicinal Cannabis Therapy on Spasticity in Multiple Sclerosis	2	NCT00248378
Sativex®	GW Pharma	Cancer pain	A Study of Sativex® for Pain Relief in Patients With Advanced Malignancy (SPRAY)	3	NCT00674609
Sativex®	GW Pharma	Cancer pain	Study to Compare the Safety and Tolerability of Sativex® in Patients With Cancer Related Pain	3	NCT00675948

Sativex®	GW Pharma; Otsuka Pharmaceuticals	Advanced persistent cancer pain	Sativex® for Relieving Persistent Pain in Patients With Advanced Cancer (SPRAY III)	3	NCT01361607
Sativex®	Capital District Health Authority Canada	Neuropathic pain associated with chemotherapy	Sativex for Treatment of Chemotherapy Induced Neuropathic Pain	3	NCT00872144
Sativex®	GW Pharma	Peripheral neuropathy	A Study of Sativex® for Pain Relief of Peripheral Neuropathic Pain, Associated With Allodynia	3	NCT00710554
Sativex®	GW Pharma	Neuropathic pain	A Study to Compare the Safety and Tolerability of Sativex® in Patients With Neuropathic Pain	3	NCT00713323
Sativex®	GW Pharma	Neuropathic pain management	A Study to Determine the Maintenance of Effect After Long-term Treatment of Sativex® in Subjects With Neuropathic Pain	3	NCT00713817
Sativex®	GW Pharma	Diabetic neuropathic pain	A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy	3	NCT00710424
Sativex®	GW Pharma	Spinal cord injury pain	A Study of Cannabis Based Medicine Extracts and Placebo in Patients With Pain Due to Spinal Cord Injury	3	NCT01606202
Sativex® vs. THC	GW Pharma	Brachial plexus injury pain	A Study to Compare Sublingual Cannabis Based Medicine Extracts With Placebo to Treat Brachial Plexus Injury Pain	3	NCT01606189
Sativex®	GW Pharma	Central neuropathic pain due to Multiple Sclerosis	A Study of Sativex in the Treatment of Central Neuropathic Pain Due to Multiple Sclerosis	3	NCT01604265
Sativex®	GW Pharma	Central neuropathic pain due to Multiple Sclerosis	Sativex Versus Placebo When Added to Existing Treatment for Central Neuropathic Pain in MS	3	NCT00391079
Sativex®	GW Pharma	Multiple Sclerosis, pain, spasticity	A Study of the Long-term Safety of Sativex Use	3	NCT01606137

Table 3. Continued

Product	Sponsor	Therapeutic Indication	Study Title	Phase	ClinTrial.gov Identifier
Sativex® vs. THC	GW Pharma	Pain; Multiple Sclerosis	A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin	3	NCT01606176
Sativex®	GW Pharma	Multiple Sclerosis	Neurophysiological Study of Sativex in Multiple Sclerosis (MS) Spasticity (NS-MSS)	3	NCT01538225
Sativex®	GW Pharma	Multiple Sclerosis	An Study to Investigate the Efficacy of Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) in Multiple Sclerosis	3	NCT01610713
Sativex®	GW Pharma	Multiple Sclerosis	An Investigation of Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) in Multiple Sclerosis Patients	3	NCT01610700
Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Study of Sativex® for Relief of Spasticity in Subjects With Multiple Sclerosis	3	NCT00711646
Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Study of the Safety and Effectiveness of Sativex®, for the Relief of Symptoms of Spasticity in Subjects, From Phase B, With Multiple Sclerosis (MS)	3	NCT00681538
Sativex®	GW Pharma	Multiple Sclerosis spasticity	Evaluate the Maintenance of Effect After Long-term Treatment With Sativex® in Subjects With Symptoms of Spasticity Due to Multiple Sclerosis	3	NCT00702468
Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Study to Evaluate the Efficacy of Sativex in Relieving Symptoms of Spasticity Due to Multiple Sclerosis	3	NCT01599234

Sativex®	GW Pharma	Multiple Sclerosis spasticity	A Randomized Study of Sativex on Cognitive Function and Mood: Multiple Sclerosis Patients	4	NCT01964547
Sativex®	GW Pharma	Multiple Sclerosis Detrusor over activity	A Parallel Group Study to Compare Sativex® With Placebo in the Treatment of Detrusor Overactivity in Patients With Multiple Sclerosis	3	NCT00678795
Sativex®	GW Pharma	Huntington's Disease	Neuroprotection by Cannabinoids in Huntington's Disease	2	NCT01502046
Sativex® plus Temozolomide	GW Pharma	Cancer	A Safety Study of Sativex in Combination With Dose-intense Temozolomide in Patients With Recurrent Glioblastoma	2	NCT01812603
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Dravet or Lennox-Gastaut Syndromes	An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet or Lennox-Gastaut Syndromes	3	NCT02224573
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Dravet Syndrome	A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome	3	NCT02224703
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Lennox-Gastaut Seizures	A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults	3	NCT02224560
Epidiolex (GWP42003-P)	GW Pharma	Epilepsy, Lennox-Gastaut Seizures	A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults	3	NCT02224690
Cannabidiol (CBD)	GW Pharma Fancea 66 Foundation	Sturge-Weber Syndrome	Cannabidiol Expanded Access Study in Medically Refractory Sturge-Weber Syndrome	2	NCT02332655
GWP42003	GW Pharma	Schizophrenia or related psychotic disorder	A Study of GWP42003 as Adjunctive Therapy in the First Line Treatment of Schizophrenia or Related Psychotic Disorder	2	NCT02006628
Cannabidiol (CBD)	Meir Medical Center	Ulcerative Colitis	Cannabidiol for Inflammatory Bowel Disease	2	NCT01037322

Table 3. Continued

Product	Sponsor	Therapeutic Indication	Study Title	Phase	ClinTrial.gov Identifier
Cannabinol (CBD) and THC	Meir Medical Center	Crohn's Disease	Combined THC and CBD Drops for Treatment of Crohn's Disease	2	NCT01826188
Cannabidiol (CBD)	Hadassah Medical Organization	Solid Tumors	A Study: Pure CBD as Single-agent for Solid Tumor	2	NCT02255292
Cannabidiol (CBD)	Rabin Medical Center	Graft vs. Host Disease	Safety and Efficacy of Cannabidiol for Grade I/II Acute Graft Versus Host Disease (GVHD) After Allogeneic Stem Cell Transplantation	2	NCT01596075

strain construction, cannabinoid concentrations at different stages of plant growth/harvest times and yield improvements. Also, included in infrastructure costs is applying Current Good Manufacturing Practices (CGMPs) to plant growth, extraction processes, formulation and manufacture of *Cannabis*-derived pharmaceuticals which will guarantee product safety, efficacy and quality. Interestingly, crop failure (not having a redundancy of supply) is a serious issue that all commercial entities in the medical *Cannabis* industry must address and contend with to meet commercial demand.

Second, the route of delivery and dosing regimens for *Cannabis*-based pharmaceuticals for specific indications will be vitally important. While smoking/vaporizing *Cannabis* is currently the most obvious method to deliver desired therapeutic effects,[7] it may not be the most effective to maximize its therapeutic benefits for different indications and individual patients. Over the past few years, there has been a growing interest in exploring oral, oromucosal, topical and sustained release delivery of *Cannabis*-derived pharmaceutical depending upon the therapeutic indication of interest.[74,75]

Finally, safeguards must be put into place to ensure protection against misuse, fraud and abuse of *Cannabis*-derived pharmaceuticals by healthcare providers and patients. The development of novel metered dose devices to deliver these products will help to limit misuse and abuse.

A WAY FORWARD?

Surveys conducted in the 1990s[76] and 2000s[77] found that between 30% and 54% of internists and oncologists were interested in offering cannabis as a therapeutic option for their patients. Yet, despite this, the surveys showed that many physicians were concerned about the legality of making medical cannabis recommendations or writing prescriptions regardless of state laws.[7] Also, the existing confusion about the legality/criminality of *Cannabis*-derived products is certain to have an effect on the behavior of insurers and third party payers. At this point, it is not clear whether or not payers will place *Cannabis*-derived pharmaceuticals on their formularies and reimburse patients who use them. Alternatively, it is possible that insurers may reimburse patients who use FDA-approved *Cannabis* products but continue to treat medical marijuana as an out-of-pocket expense for patients who use it.

The legal patchwork for *Cannabis* that has evolved over time in the US suggests that *Cannabis*-derived products may only be available in the states that have legalized their use. Consequently, companies developing

Cannabis-based pharmaceuticals may have to duplicate commercial operations in states where medical *Cannabis* is legal and underwrite multiple product launches in individual states because interstate transport of these products is illegal. This would be extremely costly (driving up product prices) and also decrease patient access to products that address unmet medical needs. To that point, most companies developing *Cannabis*-derived pharmaceuticals believe that rescheduling of these products from Schedule 1 drugs to Schedule 2 or 3 would obviate these concerns. Others contend that legalization at the federal level will be necessary for the US *Cannabis* market to grow to its full potential.

Finally, because *Cannabis*-derived pharmaceuticals represent a new class of therapeutics, patient and healthcare provider education will be vital to successfully commercialize them. Put simply, if physicians don't understand *Cannabis*-derived pharmaceuticals and are not convinced of product safety and efficacy, then, they will be reluctant to write prescriptions for these products. Nevertheless, the burgeoning popular demand for medical marijuana suggests that commercializing *Cannabis*-derived pharmaceuticals will help to address rising unmet medical needs for a variety of life-altering clinical indications including cancer, neurological disorders and chronic pain.

REFERENCES

1. Russo, E.B. (2007) History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry & biodiversity* 4(8): 1614–1648.
2. Schultes, R.E. HA. (1992) *Plants of the gods: their sacred, healing and hallucinogenic powers.* Rochester, New York: Healing Arts Press.
3. Iversen, L. (2000) *The science of marijuana.* Oxford, England: Oxford University Press.
4. Corey, S. (2005) Recent developments in the therapeutic potential of cannabinoids. *Puerto Rico health sciences journal* 24(1): 19–26.
5. Alexander, A., Smith, P.F., & Rosengren, R.J. (2009) Cannabinoids in the treatment of cancer. *Cancer letters* 285(1): 6–12.
6. Aizpurua-Olaizola, O., Omar, J., Navarro, P., Olivares, M., Etxebarria, N., & Usobiaga, A. (2014) Identification and quantification of cannabinoids in Cannabis sativa L. plants by high performance liquid chromatography-mass spectrometry. *Analytical and bioanalytical chemistry* 406(29): 7549–7560.
7. Bowles, D.W., O'Bryant, C.L., Camidge, D.R., & Jimeno, A. (2012) The intersection between cannabis and cancer in the United States. *Critical reviews in oncology/hematology* 83(1): 1–10.
8. Pacher, P., Batkai, S., & Kunos, G. (2006) The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological reviews* 58(3): 389–462.
9. Pacher, P., & Kunos, G. (2013) Modulating the endocannabinoid system in human health and disease—successes and failures. *The FEBS journal* 280(9): 1918–1943.
10. Elphick, M.R., & Egertova, M. (2001) The neurobiology and evolution of cannabinoid signaling. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* 356(1407): 381–408.
11. Grotenhermen, F. (2005) Cannabinoids. *Current drug targets. CNS and neurological disorders* 4(5): 507–530.
12. Matsuda, L.A., Lolait, S.J., Brownstein, M.J., Young, A.C., & Bonner, T.I. (1990) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346(6284): 561–564.
13. Bosier, B., Muccioli, G.G., Hermans, E., & Lambert, D.M. (2010) Functionally selective cannabinoid receptor signalling: therapeutic implications and opportunities. *Biochemical pharmacology* 80(1): 1–12.
14. Hill, A.J., Mercier, M.S., & Hill, T.D., et al. (2012) Cannabidivarin is anticonvulsant in mouse and rat. *British journal of pharmacology* 167(8): 1629–1642.
15. Guindon, J., & Hohmann, A.G. (Jan 2008) Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. *British journal of pharmacology* 153(2): 319–334.
16. Fernandez-Ruiz, J., Pazos, M.R., Garcia-Arencibia, M., Sagredo, O., Ramos, J.A. (2008) Role of CB2 receptors in neuroprotective effects of cannabinoids. *Molecular and cellular endocrinology* 286(1–2 Suppl 1): S91–S96.
17. Anand, P., Whiteside, G., Fowler, C.J., & Hohmann A.G. (2009) Targeting CB2 receptors and the endocannabinoid system for the treatment of pain. *Brain research reviews* 60(1): 255–266.
18. Pertwee, R.G., & Ross, R.A. (2002) Cannabinoid receptors and their ligands. *Prostaglandins, leukotrienes, and essential fatty acids* 66(2–3): 101–121.
19. Rahn, E.J., & Hohmann, A.G. (2009) Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics* 6(4): 713–737.
20. De Petrocellis, L., Orlando, P., Schiano Moriello, A., Aviello, G., Stott, C., Izzo, A.A., & Di Marzo, V. (2012) Cannabinoid actions at TRPV channels: effects on TRPV3

and TRPV4 and their potential relevance to gastrointestinal inflammation. *ACTA Physiologica* 204: 255–266.

21. Qin, N., Neeper, M.P., Liu, Y., Hutchinson, T.L., Lubin, M.L., Flores, C.M. (2008) TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 28(24): 6231–6238.
22. Campos, A.C., Moreira, F.A., Gomes, F.V., Del Bel, E.A., & Guimaraes, F.S. (2012) Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* 367(1607): 3364–3378.
23. Xiong, W., Cui, T., & Cheng, K., et al. (2012) Cannabinoids suppress inflammatory and neuropathic pain by targeting alpha3 glycine receptors. *The Journal of experimental medicine* 209(6): 1121–1134.
24. Beaulieu, P., & Ware, M. (2007) Reassessment of the role of cannabinoids in the management of pain. *Current opinion in anaesthesiology* 20(5): 473–477.
25. Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., & McGuire, P.K. (2012) Neural mechanisms for the cannabinoid modulation of cognition and affect in man: a critical review of neuroimaging studies. *Current pharmaceutical design* 18(32): 5045–5054.
26. Boychuk, D.G., Goddard, G., Mauro, G., & Orellana, M.F. (Winter 2015) The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *Journal of oral & facial pain and headache* 29(1): 7–14.
27. Chakravarti, B., Ravi, J., & Ganju, R.K. (2014) Cannabinoids as therapeutic agents in cancer: current status and future implications. *Oncotarget* 5(15): 5852–5872.
28. Giacoppo, S., Mandolino, G., Galuppo, M., Bramanti, P., & Mazzon, E. (2014) Cannabinoids: new promising agents in the treatment of neurological diseases. *Molecules* 19(11): 18781–18816.
29. Zajicek, J.P., & Apostu, V.I. (2011) Role of cannabinoids in multiple sclerosis. *CNS drugs* 25(3): 187–201.
30. Gerra, G., Zaimovic, A., & Gerra, M.L., et al. (2010) Pharmacology and toxicology of Cannabis derivatives and endocannabinoid agonists. *Recent patents on CNS drug discovery* 5(1): 46–52.
31. Mechoulam, R., & Gaoni, Y.A. (1965) Total Synthesis of Dl-Delta-1-Tetrahydrocannabinol, the Active Constituent of Hashish. *Journal of the American Chemical Society* 87: 3273–3275.
32. F HAG. (2010) Review on clinical studies with cannabis and cannabinoids 2005–2009. *Cannabinoids* 5(special issue): 1–21.
33. Hill, A.J., Weston, S.E., Jones, N.A., et al. (2010) Delta(9)-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia* 51(8): 1522–1532.
34. Hill, A.J. WC, Whalley, B.J., & Spehens, G.J. (2012) Phytocannabinoids as novel therapeutic agents in CNS disorders *Pharmacology & therapeutics* 133: 79–97.
35. Jones, N.A., Hill, A.J., & Smith, I., et al. (2010) Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *The Journal of pharmacology and experimental therapeutics* 332(2): 569–577.
36. Russo, E., & Guy, G.W. (2006) A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical hypotheses* 66(2): 234–246.
37. Zuardi, A.W., Shirakawa, I., Finkelfarb, E., & Karniol, I.G. (1982) Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* 76(3): 245–250.
38. Bisogno, T., Hanus, L., & De Petrocellis, L., et al. (2001) Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British journal of pharmacology* 134(4): 845–852.
39. Bornheim, L.M., & Grillo, M.P. (1998) Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator. *Chemical research in toxicology* 11(10): 1209–1216.
40. Cilio, M.R., Thiele, E.A., & Devinsky, O. (Jun 2014) The case for assessing cannabidiol in epilepsy. *Epilepsia* 55(6): 787–790.
41. Deiana, S. (Jan 2013) Medical use of cannabis. Cannabidiol: a new light for schizophrenia? *Drug testing and analysis* 5(1): 46–51.
42. Cridge, B.J., & Rosengren, R.J. (2013) Critical appraisal of the potential use of cannabinoids in cancer management. *Cancer management and research* 5: 301–313.
43. Cascio, M.G., Gauson, L.A., Stevenson, L.A., Ross, R.A., & Pertwee, R.G. (2010) Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. *British journal of pharmacology* 159(1): 129–141.
44. Colasanti, B.K. (Winter 1990) A comparison of the ocular and central effects of delta

9-tetrahydrocannabinol and cannabigerol. *Journal of ocular pharmacology* 6(4): 259–269.

45. Borrelli, F., Fasolino, I., & Romano, B., et al. (2013) Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochemical pharmacology* 85(9): 1306–1316.
46. Dos Santos, R.G., Hallak, J.E., Leite, J.P., Zuardi, A.W., & Crippa, J.A. (Dec 4 2014) Phytocannabinoids and epilepsy. *Journal of clinical pharmacy and therapeutics*.
47. Granja, A.G., Carrillo-Salinas, F., & Pagani, A., et al. (2012) A cannabigerol quinone alleviates neuroinflammation in a chronic model of multiple sclerosis. *Journal of Neuroimmune pharmacology: the official journal of the Society on Neuroimmune Pharmacolog* 7(4): 1002–1016.
48. Maione, S., Pisc*y.* Decitelli, F., & Gatta, L., et al. (2011) Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. *British journal of pharmacology* 162(3): 584–596.
49. Shinjyo, N., & Di Marzo, V. (2013) The effect of cannabichromene on adult neural stem/progenitor cells. *Neurochemistry international* 63(5): 432–437.
50. Amada, N., Yamasaki, Y., Williams, C.M., & Whalley, B.J. (2013) Cannabidivarin (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression. *PeerJ* 1: e214.
51. Scutt, A., & Williamson, E.M. (2007) Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors. *Calcified tissue international* 80(1): 50–59.
52. Karniol, I.G., Shirakawa, I., Takahashi, R.N., Knobel, E., & Musty, R.E. (1975) Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology* 13(6): 502–512.
53. McCallum, N.D., Yagen, B., Levy, S., Mechoulam, R. (1975) Cannabinol: a rapidly formed metabolite of delta-1- and delta-6-tetrahydrocannabinol. *Experientia* 31(5): 520–521.
54. Mahadevan, A., Siegel, C., Martin, B.R., Abood, M.E., Beletskaya, I., & Razdan, R.K. (2000) Novel cannabinol probes for CB1 and CB2 cannabinoid receptors. *Journal of medicinal chemistry* 43(20): 3778–3785.
55. Petitet, F., Jeantaud, B., Reibaud, M., Imperato, A., & Dubroeucq, M.C. (1998) Complex pharmacology of natural cannabinoids: evidence for partial agonist activity of delta9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life sciences* 63(1): PL1–6.
56. Hazenkamp, A. G.F. (2010) Review on clinical studies with cannabis and cannabinoids 2005–2009. *Cannabinoids* 5(special issue): 1–21.
57. Lynch, M.E., & Campbell, F. (2011) Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *British journal of clinical pharmacology* 72(5): 735–744.
58. Zajicek, J.P., Hobart, J.C., Slade, A., Barnes, D., Mattison, P.G., & Group, M.R. (2012) Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *Journal of neurology, neurosurgery, and psychiatry* 83(11): 1125–1132.
59. Flygare, J., & Sander, B. (2008) The endocannabinoid system in cancer-potential therapeutic target? *Seminars in cancer biology* 18(3): 176–189.
60. Pharma, G. (2003) Cannabis-based medicines—GW pharmaceuticals: high CBD, high THC, medicinal cannabis—GW pharmaceuticals, THC: CBD. *Drugs in R&D* 4(5): 306–309.
61. Barnes, M.P. (2006) Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert opinion on pharmacotherapy* 7(5): 607–615.
62. Maa, E., & Figi, P. (2014) The case for medical marijuana in epilepsy. *Epilepsia* 55(6): 783–786.
63. Gloss, D., & Vickrey, B. (2014) Cannabinoids for epilepsy. *The Cochrane database of systematic reviews* 3: CD009270.
64. Pharma, G. (2014) GW Pharmaceuticals announces that Sativex receives fast track designation from FDA in cancer pain. http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20that%20Sativex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20in%20Cancer%20Pain.aspx. Accessed April 9, 2015.
65. Guzman, M., Duarte, M.J., & Blazquez, C., et al. (2006) A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *British journal of cancer* 95(2): 197–203.
66. Notcutt, W., Price, M., & Miller, R., et al. (2004) Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia* 59(5): 440–452.
67. Tramer, M.R., Carroll, D., Campbell, F.A., Reynolds, D.J., Moore, R.A., & McQuay, H.J. (2001) Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 323(7303): 16–21.
68. Pisanti, S., Malfitano, A.M., & Grimaldi, C., et al. (2009) Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. *Best practice*

& research. Clinical endocrinology & metabolism 23(1): 117–131.

69. Salazar, M., Carracedo, A., & Salanueva, I.J., et al. (2009) Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. *The Journal of clinical investigation* 119(5): 1359–1372.
70. Caffarel, M.M., Andradas, C., & Mira, E., et al. (2010) Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Molecular cancer* 9: 196.
71. Qamri, Z., Preet, A., & Nasser, M.W., et al. (2009) Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer. *Molecular cancer therapeutics* 8(11): 3117–3129.
72. Pharmacoeconomic NCf. (2014) Cost-effectiveness of Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to MS who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. http://www.ncpe.ie/wp-content/uploads/2013/01/Summary-v1.pdf.
73. Lu, L., Pearce, H., Roome, C., Shearer, J., Lang, I.A., & Stein, K. (2012) Cost effectiveness of oromucosal cannabis-based medicine (Sativex(R)) for spasticity in multiple sclerosis. *PharmacoEconomics* 30(12): 1157–1171.
74. Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B., Sakai, S., & Donaghe, H. (2013) Low-dose vaporized cannabis significantly improves neuropathic pain. *The journal of pain : official journal of the American Pain Society* 14(2): 136–148.
75. Grant, I., Atkinson, J.H., Gouaux, B., & Wilsey, B. (2012) Medical marijuana: clearing away the smoke. *The open neurology journal* 6: 18–25.
76. Doblin, R.E., & Kleiman, M.A. (1991) Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 9(7): 1314–1319.
77. Charuvastra, A., Friedmann, P.D., & Stein, M.D. (2005) Physician attitudes regarding the prescription of medical marijuana. *Journal of addictive diseases* 24(3): 87–93.