Task Force on Researching the Medical and Public Health Properties of Cannabis

Progress Report to the Joint Interim Committee on Marijuana Legalization

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Oregon Health Authority

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I. Introduction

Oregon residents have been able to access cannabis for medical use since 1998 when voters approved the Medical Marijuana Act, which established the Oregon Medical Marijuana Program (OMMP). That program has since registered more than 60,000 medical cannabis patients.[1]

In 2014, the state expanded access to cannabis by becoming the fourth state in the country to allow recreational use of cannabis, joining Colorado, Washington, and Alaska. In addition, in 2014, the state legislature passed Senate Bill 844 requiring the Oregon Health Authority to establish a task force to study the medical and public health properties of cannabis. Specifically, the task force was asked to address the following questions:

(a) Identify and assess the validity of research related to the medical properties of cannabis that have been conducted in other countries and in other states and territories of the United States;

(b) Assess the potential for this state to collaborate with other states that have legalized the medical or recreational use of cannabis for purposes related to researching the medical properties of cannabis;

(c) Identify key research areas related to the medical properties of cannabis;

(d) Identify legal barriers to the establishment of laboratories that research the medical properties of cannabis, including barriers related to the possession, delivery and manufacture of marijuana;

(e) Identify legal barriers to the use of institutional review boards in approving, monitoring and reviewing research involving the medical properties of cannabis;

(f) Propose solutions to structuring and funding research that involves the medical properties of cannabis, including solutions that involve state programs and moneys and solutions that involve investment by private businesses and business sectors; and

(g) Assess the potential of locating a cannabis grow site for research purposes in this state and, if appropriate, setting forth a plan for the establishment of a cannabis grow site for research purposes in this state.

SB 844 designated 15 task force members representing specific areas of expertise. In December, 2015, the Oregon Governor's office appointed the following members to the task force:

Members

Name	**Expertise / Representing**
Mowgli Holmes, PhD, (CHAIR)	Agricultural Research
Christopher Conrady	Oncology
Chris Edwards	Oregon State Senate
Peter Gendron	Marijuana Grow Site
Katrina Hedberg, MD, MPH	Oregon Health Authority
Robert Hitzemann, PhD	Oregon Health and Science University
Jane Ishmael, PhD	Oregon University System
Shannon O'Fallon, JD	Department of Justice
Jeremy Riggle, PhD	THC and CBD Measurement
Colin Roberts, MD	Neurology
David Russo, DO, MPH	Palliative Care
William Schuette	Oregon Liquor Control Commission
Anthony Smith, PhD	Microbiology
Daniel Sudakin, MD, MPH	Substance Abuse Treatment
Carl Wilson	Oregon House of Representatives

The task force has met once, on December 15, 2015 to review current research related to the medical and public health properties of cannabis as well as current state level efforts to contribute to the body of research in that area. A summary of research to date and next steps follows.

II. State of Research on Medicinal Properties of Cannabis

Introduction to Medical Cannabis Research

Cannabis is one of the world's oldest known medicines,[2] with medicinal cannabis use dating back to 2727 B.C. in China.[3] By the 1850s, medicinal cannabis tinctures were patented in the United States and used for numerous ailments including cholera, rabies, dysentery, alcoholism, opiate addiction, insanity, and menstrual bleeding, among others.[4] In 1963, the chemical structures of the main active compounds of the cannabis plant (i.e., cannabinoids) were identified,[5] sparking increasing interest in the pharmacological activity of cannabis. Since then, the number of publications analyzing the health effects of cannabis use increased drastically throughout the 1970s.[6] However, with the passage of the Federal Controlled Substances Act of 1970, research on cannabis shifted to studies of the negative effects of cannabis use, including addiction. Interest in understanding therapeutic effects of cannabis was renewed again in the 1990s in part due to advancements in genetic cloning of specific receptors for cannabinoids in the nervous system.[6] Despite this interest, barriers to research have prevented the development of robust research programs evaluating the medical effects of cannabis.

Clinical research

The cannabis plant is one of the most investigated substances in history, with nearly 22,000 published studies or reviews.[7] However, due to restrictive federal policies described below, only a limited number of randomized controlled trials, considered the "gold standard" of research, have evaluated the medicinal properties of cannabis. As with evaluating any other federally illicit substance, methodological challenges exist including ethical, legal, political, and practical barriers to such clinical trials.[8] True randomization is rare and ethical barriers limit cannabis dosage when controlled human experiments are possible. Other types of research methods such as animal models, pre-clinical trials, and observational studies do provide some information about the potential benefits of cannabis, but generalizability remains problematic. Animal experiments are restrictive, and generalizing health effects to human populations introduces uncertainty. Real world observational data present additional challenges because cannabis users and non-cannabis users differ in many immeasurable ways.[8]

Despite methodological limitations, a significant body of literature on the potential medicinal benefits of cannabis has developed, primarily from researchers outside of the U.S. (See

Table 1). Table 1 summarizes clinical trials, animal models, observational studies, and pre-clinical trials assessing the medicinal properties of cannabis (See Appendix A for a detailed description of the therapeutic benefits of cannabis). Only 13 conditions listed in Table 1 have been studied using clinical trials, many with sample sizes of less than 100 participants. There is strong clinical support that cannabis use relieves many clinical conditions including nausea, chronic pain, and spasms and tics. As illustrated in Table 1, these conditions have the most clinical trials published with 30 or more studies conducted for each condition. There is intermediate evidence that medical cannabis use alleviates side effects of glaucoma, epilepsy, dementia, inflammation, and post-traumatic stress disorder (PTSD). Notwithstanding a plethora of published work on the therapeutic benefits of cannabis there remain significant research gaps for assessing the benefits of medicinal cannabis on diabetes, sleep, alcohol and substance use addiction, amyotrophic lateral sclerosis, leukemia, and Schizophrenia. The two Schizophrenia trials produced mixed results because one study administered CBD, which reduced schizophrenic symptoms, and the other administered THC, exacerbating symptoms. Neuroprotection, inflammation, BMI, and waist circumference research rely on animal models and observational studies with no clinical trials. Emerging studies include PTSD, pediatric epilepsy, and sleep trials (See Table 1).

Current State and Federal Cannabis Research Programs

In the U.S., the literature has been compelling enough for 23 states to enact medical cannabis programs. Each state program specifies a list of conditions for which one may qualify to use medicinal cannabis. Appendix B provides state-specific qualifying conditions nationwide ranging from eight to 16 medical conditions and symptoms. The Oregon Medical Marijuana Program (OMMP) currently recognizes ten qualifying medical conditions including a degenerative or pervasive neurological condition, cachexia, cancer, glaucoma, HIV/AIDS, nausea, PTSD, severe pain, seizures, and persistent muscle spasms. Nearly 90% of Oregon's medical cannabis patients have one of three qualifying conditions: severe pain (74,432 cardholders), muscle spasms including those caused by Multiple sclerosis (22,587 cardholders), and nausea (10,975 cardholders).[9]

Table 1: Strength of Evidence for Clinical Conditions and Symptoms Treated by Cannabinoids

Clinical Condition Or Symptom	Articles[a]	Clinical Trial and Size	Country of Clinical Trial	Animal Trial[a]	Observational/ Pre-Clinical[a]
Nausea; Chemotherapy	Zuardi, 2008[6]; Rock, Limebeer, and Parker, 2014[10]; Amar, 2006[2]*; Grotenhermen, and Müller-Vahl, 2012[11]*	33 (N=8-172)	United States (17), The Netherlands (1), Scotland (1), Canada (3), Finland (2), Ireland (1), France (1), Great Britain (3), Germany (1), New Zealand (1), Switzerland (1), Spain (1)		
Chronic Pain	Martin-Sanchez *et al*., 2009[12]*; Amar, 2006[2]*; Hazekamp and Grotenhermen, 2010[13]*, Grotenhermen, and Müller-Vahl, 2012[11]*	32 (N=1-125)	United States (10), Belgium (2), Sweden (1), Switzerland (1), Great Britain (8), Germany (2), Canada (5), Austria (1), United Kingdom (2)		
Spasms and Tics; Multiple Sclerosis; Spinal Cord Injuries; Tourette's Syndrome	Lakhan and Rowland, 2009[14]*; Amar, 2006[2]*; Hazekamp and Grotenhermen, 2010[13]*; Grotenhermen, and Müller-Vahl, 2012[11]*	30 (N=1-630)	United States (6), The Netherlands (1), Denmark (2), Switzerland (2), Great Britain (12), Italy (3), Austria (1), Germany (2), Canada (1)		
Appetite Stimulation; Wasting Syndrome; Anorexia	Amar, 2006[2]*; Hazekamp and Grotenhermen, 2010[13]*; Grotenhermen, and Müller-Vahl, 2012[11]*	9 (N=12-469)	United States (8), Canada (1)		
Glaucoma	Jampel, 2010[15]; Amar, 2006[2]*	3 (N=8-18)	United States (2), Great Britain (1)		
Anxiety Disorders; Posttraumatic Stress Disorder	Greer, Grob, and Halberstadt, 2014[16]; Korem and Akirav, 2014[17]; Fraser, 2009[18]; Bonn-Miller, 2011[19]; Trezza and Campolongo, 2013[20]	3 (N=47-60)	United States (1), Canada (1), Germany (1)		
Intestinal Dysfunction	Hazekamp and Grotenhermen, 2010[13]*	2 (N=30-52)	United States (2)		

Schizophrenia	Hazekamp and Grotenhermen, 2010[13]*	2 (N=13-42)	United States (1), Germany (1)		
Clinical Condition Or Symptom	**Articles[a]**	**Clinical Trial and Size**	**Country of Clinical Trial**	**Animal Trial[a]**	**Observational**
Epilepsy	Amar, 2006[2]*; Porter and Jacobson, 2013[21]; Hill *et al.*, 2013[22]; Hill, Hill, and Whalley, 2013[23]*	1 (N=15)	Brazil (1)		
Hepatitis C	Hazekamp and Grotenhermen, 2010[13]*	1 (N=71)	United States (1)		
Sleep	CMCR, 2015[24];	1 (N=15)	United States (1)		
Diabetes	Rajavashisth *et al.*, 2012[25]; Muniyappa *et al.*, 2013[26]	1 (N=60)	United States (1)		
Cancer **Breast** **Prostate** **Lung** **Skin** **Pancreatic** **Bone** **Glioma** **Lymphoma** **Oral** **Head and Neck** **Thyroid**	Sarfaraz *et al.*, 2008[27]*; Alexander, Smith, and Rosengren, 2009[28]*; Chakravarti, Ravi, and Ganju, 2014[29]*	1 (N=177)[a]		>10 >10 <5 1 <5 >10 >10 <5 1 0 <5	1
Addiction and Dependence	Reiman, 2009[30]; Hurd *et al.*, 2015[31]*	<5		>5	>5
Neuroprotection **Alzheimer's** **Amyotrophic Lateral Sclerosis (ALS)** **Parkinson Disease**	Russo and Guy, 2006[32]*; Carter and Rosen, 2001[33]	0		<5 <5 <5 <5	1
Inflammation **Rheumatoid Arthritis** **Inflammatory Bowel Diseases; Ulcerative colitis** **Crohn's Disease**	Zuardi, 2008[6]* Esposito *et al.*, 2013[34]*	0		>10	
BMI and Waist Circumference	Rodondi *et al.*, 2006[35]; Penner *et al.*, 2013[36]; Le Strat and Le Foll, 2011[37]; Le Foll *et al.*, 2013[38];	0			>5

	Hayatbakhsh *et al.*, 2010[39]				

Notes: * Indicates a review article. No animal, observational, or pre-clinical trials were reported if a clinical condition or symptom was evaluated using clinical trials. a. Randomized controlled trial on cancer pain.

State-Level Medical Cannabis Research Programs

Though many states have recognized the medicinal benefits of cannabis by enacting expansive medicinal cannabis programs, others have enacted limited access therapeutic research programs. Beginning in the 1980s, states began allowing access to cannabis for patients suffering from a more limited number of conditions, generally seizure disorders, and for whom other therapies were not effective. Though called "research" programs and requiring submission of some observational data to the state, these programs were intended to provide access to cannabis as a drug of last resort rather than to support evaluation of its effectiveness. According to the National Conference of State Legislatures, 16 states currently run these types of expanded access programs, several with explicit evaluative research expectations.[40] Table 2 lists the three states that are currently supporting broader research programs on the therapeutic properties of cannabis. Each of these programs is varied in its structure, funding, and type and focus of research supported. All programs require funded researchers to adhere to all current federal laws relating to cannabis supply and human subjects research.

Table 2: Comparison of California, Colorado, and Minnesota Clinical Research Programs

	California[a]	Colorado[b]	Minnesota
Administered by	University System	Colorado Department of Health	Minnesota Department of Health
Year Established	1999, 2003	May 2014	July 2015
Amount of Funding	$8.7 million	$9 million	
Source of Funding	State Funding*	State Funding*	Initially state funded, ongoing funding will come from manufactures' enrollment and from fees
Studies (raw number)	13	9	1
Types of Studies	Clinical trials	Observational and clinical trials	Observational only

Notes: *Authorized to accept private donations
a: Completed studies

b: Approved studies

***California*.** In 1999, California legislature passed Senate Bill 847, establishing the University of California Center for Medicinal Cannabis Research (CMCR).[41] CMCR, established in 2000, is housed within the University of California, San Diego and conducts clinical and pre-clinical trials researching the therapeutic value of cannabis.[24] The institute is the sole recipient of funding from the state of California for medicinal cannabis research. In 2003, the state-funded research center was reauthorized to continue indefinitely, and in 2010, CMCR issued a report to the California legislature on their completed scientific findings. Areas of emphasis for the Center's 13 research studies were severe appetite suppression and weight loss due to HIV, chronic pain (particularly neuropathic pain), severe nausea associated with cancer, and severe muscle spasticity. CMCR's legislative report concludes that "they have reasonable evidence" that cannabis is a promising treatment for pain caused by nervous system disorders and painful muscle spasticity due to multiple sclerosis.[41] Currently, CMCR has a pending study on neuropathic low back pain.

***Colorado*.** Colorado established the Medical Marijuana Research Grant Program in May 2014.[42] The program is supported by Colorado's Medical Marijuana Scientific Advisory Council and the Board of Health and administered by the state health department. In 2015, the council approved nine research grants using a surplus of nine million dollars in medical cannabis tax revenue (See Table 2). Similar to California, the state of Colorado issued calls for applications from researchers. Areas of research emphasis include PTSD, pediatric epilepsy, and pediatric brain tumors, among others. All nine studies are in the beginning stages of research. Both California and Colorado require individual researchers to obtain necessary federal and state approvals to conduct their proposed research.

***Minnesota*.** Minnesota has one of the United States' most limiting medical cannabis policies in that medical patients are permitted to use a liquid or vaporized form of cannabis but not smoked cannabis or edible cannabis products. In comparison to Colorado and California who recruited participants for clinical studies, the state of Minnesota researchers survey every medical cannabis patient in the registry, 662 patients to-date, as part of one ongoing observational study.[43] (The University of Minnesota also is home to one of only two labs licensed by the DEA to conduct plant research on cannabis until 2015).

***Expanded Access Research Programs*.** Several states established new therapeutic cannabis research programs in 2014-2015 that authorized clinical and/or observational studies. In

comparison to California and Colorado, which allowed researchers to submit abstracts, these states specified a limited number of specific conditions (mainly pediatric seizures) and a specific cannabis product to evaluate potential benefits of cannabis and its derivatives. See Table 3 for a list of cannabis-based pharmaceuticals.

- Georgia, after a high profile case involving a toddler suffering from severe epileptic seizures, now authorizes the use of low THC oil for treatment of several medical conditions under a state registry administered by the Georgia Commission on Medical Cannabis.[44] The law also authorized the University of Georgia system to create a research program using low THC oil in treating medication resistant epilepsy for children under age 18. The Georgia Cannabidiol Study now underway expects to enroll approximately 50 children in the state and will utilize pharmaceutical grade cannabis derivative, Epidiolex, already FDA approved for treatment of Dravet Syndrome. This expanded access study has cost an initial $4.8 million in state funding and is receiving Epidiolex free of charge from the manufacturer, GW Pharmaceuticals which is administering the study in several states.
- Alabama Legislature passed Carly's Law, named after a four year old suffering from pediatric seizures not controlled by existing treatments, in 2014.[45] The law approved a $1 million expanded access study. Researchers expect to enroll 50 children and 50 adults. Similar to Georgia, this study is receiving a pharmaceutical cannabis derivative from GW Pharmaceuticals at no charge.
- North Carolina similarly permits the use of hemp extract for treatment of "intractable" epilepsy.[46] North Carolina's Department of Health and Human Services is now authorized to approve pilot studies evaluating the effectiveness of hemp extract for epilepsy, although there is no indication that trials have begun.

Current Federal Government Funded Studies

As of January 31, 2014, NIH funded 30 studies addressing the therapeutic use of cannabis for six categories of medical conditions including seizures, substance use disorders, psychiatric disorders, autoimmune diseases, inflammation, and pain.[47] The portfolio analysis was conducted by internally searching the NIH database for active grants using the text word string "cannabinoid OR cannabis OR marijuana." Over 300 grants were then manually screened to

identify studies in which at least one specific aim included a therapeutic focus. Thirty projects were identified (27 projects and 3 supplements) listed in Appendix C.

Table 3: Cannabis and Cannabis Based Pharmaceuticals

Substance	Schedule Designation	Notes
Medical Cannabis (whole plant) • THC delta-9-tetrahydrocannabinol • CBD cannabidiol	Schedule I	Federally legal supplies (DEA Approved) only available through NIDA.
Artisanal Cannabidiol (CBD) purified oil or liquid	Schedule I	
Industrial Hemp extract	Schedule I but with exceptions	2014 Agricultural Act allows colleges and state agencies to grow and conduct research on hemp if otherwise legal under state law. (Legal in Oregon)
Epidiolex (Pharmaceutical Grade CBD)	Schedule I	FDA Orphan Drug Approval
Cesamet (synthetic Nabilone)	Schedule II	FDA approved for nausea and vomitir with chemotherapy
Marinol® (synthetic Dronabinol)	Schedule III	FDA approved for weight loss due to AIDS/Anorexia
Sativex®		United Kingdom approved. Received FDA "Fast Track Designation" in 2014
Cannador®		Germany Not FDA approved

Task Force Progress and next steps

The Task Force met on December 15, 2015 and discussed the status of current research on the medical and public health benefits of cannabis. The Task Force discussed the need for, and the benefits of, Oregon establishing a program to evaluate the medical and public health properties of cannabis. The task force's next meeting will focus on summarizing the legal barriers to the full range of research in the area as well as identifying any available solutions involving state and/or private entities, including, but not limited to, the following types of research:

1. Clinical research involving human subjects
2. Observational studies

3. Public health research
    a. Impact of medical and/or recreational cannabis policies on population health
    b. Safety and quality of cannabis products in the state
4. Agricultural research

Following those discussions, the Task Force will identify specific legislative recommendations.

Appendix A: Clinical Conditions and Symptoms Treated by Cannabinoids

Nausea and Appetite Stimulation

Cannabis is used to alleviate the treatment side effects of two leading causes of death globally, cancer and HIV. One of the first therapeutic uses of cannabis in an evaluated clinical trial successfully treated patients' nausea and vomiting induced by cancer chemotherapy. Results from studies using rat and mice models also support claims that cannabis suppresses nausea in patients undergoing chemotherapy.[6] Similarly, smoking or ingesting cannabis is used by patients experiencing AIDS-related wasting syndrome and anorexia. Longitudinal cohort studies report patients using cannabis to alleviate antiretroviral therapy (ART) side effects by stimulating their appetite leading to weight gain and improving their mood and quality of life.

Chronic Pain

Cannabis has been used to treat chronic pain for centuries in traditional medicine A meta-analysis of eighteen clinical trials suggests that cannabis is moderately efficacious for treating chronic pain.[12] Neuropathic pain–a chronic pain state caused by chemotherapy, diabetes, HIV, Multiple sclerosis, amputation, alcoholism, shingles, or spinal cord injuries, among other causes–is also alleviated with cannabis.

Inflammation

Rheumatoid arthritis is an autoimmune disease associated with chronic inflammation. Cannabinoids have anti-inflammatory properties due to a combination of immunosuppressive and anti-inflammatory responses.[6] Animal models have shown promise that cannabis is an effective treatment for rheumatoid arthritis[6] and inflammatory bowel diseases, namely ulcerative colitis and Crohn's disease.[34]

Glaucoma

Glaucoma is a disease of the optic nerve caused by increased levels of intraocular pressure. Cannabis has definitively demonstrated a reduction in intraocular pressure in the general population and glaucoma patients who use cannabis.[15] Patients smoke cannabis, ingest pills containing the active ingredient in cannabis, or use eye drops with tetrahydrocannabinol to reduce and slow the progression of optic nerve damage. However, due to cannabis' short period of relief, cannabis would have to be ingested every few hours every day for the patient's life, and thus, the American Glaucoma Society does not support cannabis to treat glaucoma.[15]

Epilepsy

Possibly the most publicized therapeutic treatment of cannabis is for children with epileptic seizures. The media has followed many stories of children whose families moved to states with legalized medical cannabis in order to reduce their children's seizures out of desperation**.** Many of these children were having up to 200 seizures per day with no prior effective treatment. According to parental surveys, the seizures slowed and reduced in number after using special strains of cannabis that contain high levels of cannabidiol (the primary non psychoactive constituent of the cannabis plant) and low levels of tetrahydrocannabinol (the primary psychoactive part of the plant).[21] In addition to the anecdotal stories

and surveys, there is also support of cannabis as an effective treatment of epileptic seizures using animal models.[22] Colorado is in the process of beginning two observational studies reviewing the effect of cannabis on pediatric epilepsy.

Spasms and Tics

Spasticity–one of the most common side effects of Multiple sclerosis–is an involuntary muscle spasm alleviated by using a cannabinoid mouth spray. A review article evaluated six randomized human studies and noted a reduction in spasms of patients with multiple sclerosis following the use of cannabis. Studies on the effectiveness of cannabis and Tourette's syndrome produced similar results. Two German controlled trials observed significant decreases in tics after Tourette's patients received oral tetrahydrocannabinol.

Tumor Reduction

Cancer is a disease characterized by the division and multiplication of cells with damaged DNA. Mechanisms that interrupt the signaling involved in cell proliferation are needed for the management of cancer. Although there is some contradictory evidence of the effectiveness of cannabis on cancer growth, cannabinoids have been shown to inhibit tumor cell growth and prolong life since the early 1970s.[27] Three recent review articles demonstrate the anti-proliferative action of cannabinoids in brain, prostate, breast, lung, skin, pancreatic, uterine, thyroid, and lymphoma cancer cells.[27] [29] [28]

Neuroprotection

Humans have two types of cannabis receptors in their body, CB_1 and CB_2. The preceding section described the ability of cannabinoids to bind to these receptors discouraging cancer cell proliferation. The same binding occurs for patients with Alzheimer's disease slowing the progression Alzheimer's and reducing neuroinflammation. The neuroprotective roles of cannabidiol and tetrahydrocannabinol are effective treatment for migraines, anxiety, Alzheimer's, amyotrophic lateral sclerosis (ALS), Parkinson disease, and Multiple sclerosis.[32]

Anxiety Disorders

A current hot topic in the popular media is the therapeutic potential of cannabis to relieve anxiety for people suffering with post-traumatic stress disorder (PTSD). New studies have led some scientists to recommend cannabis as a treatment of PTSD symptoms in veterans. In 2014, two studies described the reduction of PTSD symptoms using surveys[16] and in vivo utilizing synthetic cannabis.[17] Two studies are underway in Colorado examining the effects of medicinal cannabis on PTSD.

Additional Benefits

Additional health benefits of cannabis use include lowering the risk of diabetes in cannabis users compared to non-users,[25] maintaining smaller waist circumferences and lowering BMI in cannabis users compared to non-users,[36] and helping those suffering from other forms of addiction such as alcoholism and opiate addiction.[30] These therapeutic benefits lack the epidemiologic and scientific evidence than those presented above. Further studies are warranted to substantiate the pilot studies' therapeutic claims.

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Appendix B: State Specific Qualifying Medical Conditions for Medical Cannabis Cardholders[48]

States	AK	AR	CA	CO	CT	DE	DC	HI	IL	ME	MD	MA
Cancer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glaucoma	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓
AIDS/HIV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Crohn's Disease		✓	✓		✓				✓	✓		✓
Hepatitis C		✓	✓						✓	✓		✓
Multiple Sclerosis			✓		✓				✓			✓
Amyotrophic Lateral Sclerosis		✓	✓			✓	✓		✓	✓		✓
Post Traumatic Stress Disorder			✓		✓	✓				✓		✓
Cachexia, Anorexia, or Wasting Away Syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Severe or Chronic Pain	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓
Severe or Chronic Nausea	✓	✓	✓	✓		✓		✓		✓	✓	✓
Seizure Disorders	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓
Muscle Spasticity Disorders	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Agitation of Alzheimer's		✓	✓			✓			✓	✓		✓
Other (arthritis, Parkinson's, hospice)			✓		✓	✓	✓		✓			✓
Allows Addition of Diseases or Conditions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

States	MI	MN	MT	NV	NH	NJ	NM	NY	OR	RI	VT	WA[49]
Cancer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glaucoma	✓		✓	✓	✓	✓	✓		✓	✓		
AIDS/HIV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Crohn's Disease	✓	✓	✓		✓	✓	✓	✓				
Hepatitis C	✓				✓		✓			✓		
Multiple Sclerosis			✓		✓	✓	✓	✓			✓	✓
Amyotrophic Lateral Sclerosis	✓	✓			✓	✓	✓	✓				
Post Traumatic Stress Disorder	✓			✓			✓		✓			
Cachexia, Anorexia, or Wasting Away Syndrome	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Severe or Chronic Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Severe or Chronic Nausea	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Seizure Disorders	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Muscle Spasticity Disorders	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓
Agitation of Alzheimer's	✓				✓				✓	✓		
Other (arthritis, Parkinson's, hospice)		✓	✓		✓			✓				
Allows Addition of Diseases or Conditions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓

Appendix C. National Institute of Health Sponsored Studies Since January 31, 2014

Project Title	Cannabinoid	Study Model
Seizures		
New Drugs to Enhance Endocannabinoid Responses for Treating Excitotoxicity, Phase	Endogenous (AE via FAAH inhibitors)	Animal
SUD, Withdrawal, and Dependence		
Cannabinergic Medications for Methamphetamine Addiction	Synthetic (CB1 agonists and antagonists, proprietary)	Animal
Efficacy and Safety of Dronabinol (Oral THC) for treating Cannabis Dependence	Synthetic (Dronabinol)	Human
Evaluation of Novel Pharmacotherapies for the treatment of Opioid Dependence	Synthetic (Dronabinol, Nabilone)	Human
FAAH- Inhibitor for Cannabis Dependence	Endogenous (AE via PF-04457845 FAAH inhibitor)	Human
Marijuana Relapse: Influence of Tobacco Cessation and Varenicline	Sythetic (Dronabinol)+/- the noncannabinoid varenicline	Human
Medications Development for Cannabis-Use Disorders: Clinical Studies	Purified (THC) and non-cannabinoids: Gabapentin & Tiagabine	Human
Monoacylglycerol Lipase Inhibitors for treating Opioid Use Disorders and Supplement	Endogenous (2-AG via JZL184 MAGL inhibitor)	Animal
Nabilone For Cannabis Dependence: Imaging and Neuropsychological Performance and Supplement	Synthetic (Nabilone)	Human
Novel Medications Approaches for Substance Abuse	Synthetic (Dronabinol, Project4)+noncannabinoid lofexidine	Human
Novel Medications for Cannabis Dependence	Synthetic (Modify THC and nabilone to create new cannabinoids)	Animal
Sativex Associated with Behavioral Prevention Relapse Strategy as Treatment for and Supplement	Purified (Sativex) +/- behavioral therapy	Human
Stress-Induced Marijuana Self-Administration: role of Sex and Oxytocin	Plant (cannabis cigarettes)	Human
Treatment of Cannabinoid Withdrawal in Rhesus Monkeys	Purified (THC) and Endogenous (via AEA via FAAH inhibitors)	Animal
Psychiatric Disorder		

Cannabinoid Regulation of Cognition	Purified (Cannabidiol)	Animal
Cannabidiol Modulation of THC'S Psychotomimetic Effects in Healthy Humans	Purified (Cannabidiol)	Human
Cannabinoid Regulation of Cognition	Purified (Cannabidiol)	Animal
Cannabis, Schizophrenia and Reward: Self-Medication and Agonist Treatment	Synthetic and Plant (Dronabinol & cannabis cigarettes)	Human
Autoimmune disease		
Endocannabinoids, Cannabis, and Neurocognitive Deficits in HIV	Plant (cannabis cigarettes)	Human
Transdermal Delivery of 2-Arachidonoyl Glycerol (2-AG) For the Treatment of Arthr	Endogenous (2-AG)	Animal
Inflammation		
Cannabinoid Epigenomic and Mirna Mechanisms Impact HIV/SIV Disease Progression	Purified (THC)	Animal
Cannabinoid Modulation of Microglial Response to the HIV Protein TAT	Purified and Synthetic (THC and CP55940)	Cell culture and animal models
Pain		
A Randomized, Cross-Over Controlled Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain	Synthetic (Drobinol), Plant (cannabis, vaporized	Human
Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients	Plant (cannabis cigarettes)	Human
Cannabinoid Modulation of Hyperalgesia	Endogenous (AE and 2-AG via URB597 FAAH inhibitor and JZL184 MAGL inhibitor)	Animal
Cannabinoid Receptor Agonists for Treatment of Chronic Pain	Synthetic (CB2 agonist, proprietary)	Animal
Neurogensis and Chronic Cannabinoid Exposure	CB1 Antagonist	Animal
Optimizing Analgesia by Exploiting CB2 Agonist Functional Selectivity	Synthetic (CB2 agonists, proprietary)	Animal
Peripheral FAAH as a Target for Novel Analgesics	Endogenous (AE via FAAH inhibitor (URB937))	Animal
The Effect of Vaporized Cannabis on Neuropathic Pain in Spinal Cord Injury	Plant (cannabis, vaporized)	Human

Note: The analysis was conducted using the internal NIH database (QVR) and was searched using the following: TEXT word string "cannabinoid OR cannabis OR marijuana"; active grants. Grants were manually screened to identify studies in which at least one specific aim included a therapeutic focus.

Appendix D: Recommended Resources and Online Information

For more information regarding CMCR completed studies, visit:
http://www.cmcr.ucsd.edu/index.php?option=com_content&view=category&id=41&Itemid=135

For more information regarding Colorado approved grants, visit:
https://www.colorado.gov/pacific/cdphe/approved-medical-marijuana-research-grants

For more information regarding Minnesota medical cannabis program, visit:
http://www.health.state.mn.us/topics/cannabis/

For more information about NIDA approved studies, visit:
http://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-therapeutic-benefits-cannabis-cannabinoids

For more information regarding NIH sponsored studies, visit:
https://era.nih.gov/nih_and_grantor_agencies/other/query_view_and_report.cfm

For more information regarding the National Center for Natural Research, visit:
http://pharmacy.olemiss.edu/ncnpr/research-programs/cannabis-research/

For more information about the process of getting FDA approval, visit:
http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421173.htm

For more information about NIDA's position, visit:
http://www.drugabuse.gov/drugs-abuse/marijuana/marijuana-research-nida

For more information about the DEA's position, visit:
http://www.dea.gov/docs/marijuana_position_2011.pdf

For more information about federal government policies that limit medical cannabis research, visit:
http://www.brookings.edu/~/media/research/files/papers/2015/10/20-war-on-marijuana-research-hudak-wallack/ending-the-us-governments-war-on-medical-marijuana-research.pdf

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