Alternative Solutions Plus
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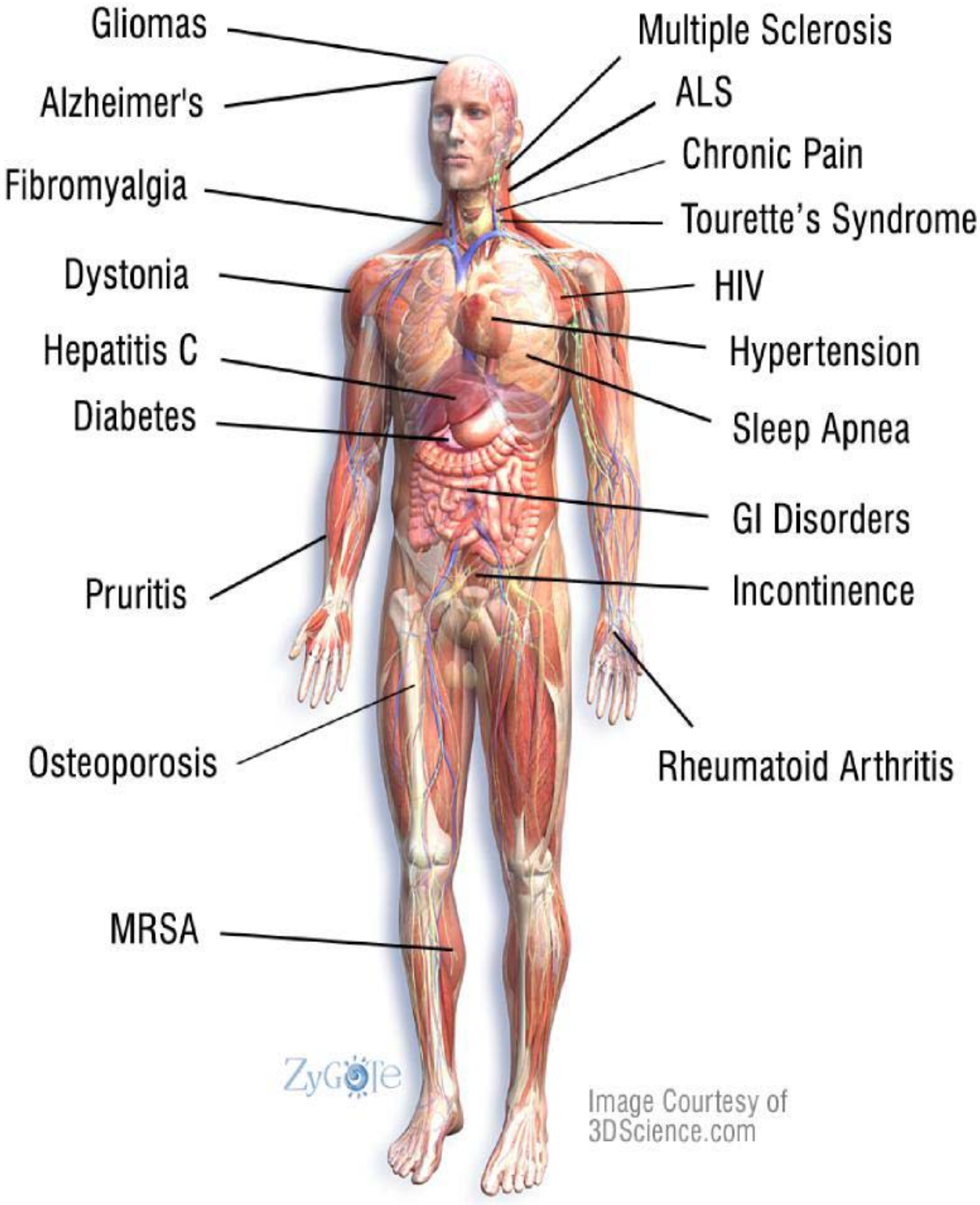

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Introduction

Despite the ongoing political debate regarding the legality of medical marijuana, clinical investigations of the therapeutic use of cannabinoids are now more prevalent than at any time in history.

For example, in February 2010 investigators at the University Of California Center for Medicinal Cannabis Research publicly announced the findings of a series of randomized, placebocontrolled clinical trials on the medical utility of inhaled cannabis. The studies, which utilized the so called 'gold standard FDA clinical trial design, concluded that marijuana ought to be a first line treatment for patients with neuropathy and other serious illnesses.

Among the studies conducted by the Center, four assessed smoked marijuanas ability to alleviate neuropathic pain, a notoriously difficult to treat type of nerve pain associated with cancer, diabetes, HIV/AIDS, spinal cord injury and many other debilitating conditions. Each of the trials found that cannabis consistently reduced patients pain levels to a degree that was as good as or better than currently available medications.

Another study conducted by the Centers investigators assessed the use of marijuana as a treatment for patients suffering from multiple sclerosis. That study determined that smoked cannabis was superior to placebo in reducing spasticity and pain in patients with MS, and provided some benefit beyond currently prescribed treatments.

Around the globe, similarly controlled trials are also taking place. A 2010 review by researchers in Germany reports that since 2005 there have been 37 controlled studies assessing the safety and efficacy of marijuana and its naturally occurring compounds in a total of 2,563 subjects. By contrast, most FDAapproved drugs go through far fewer trials involving far fewer subjects.

While much of the renewed interest in cannabinoid therapeutics is a result of the discovery of the endocannabinoid regulatory system (which we describe in detail later in this booklet), some of this increased attention is also due to the growing body of testimonials from medical cannabis patients and their physicians. Nevertheless, despite this influx of anecdotal reports, much of the modern investigation of medical cannabis remains limited to preclinical (animal) studies of individual cannabinoids (e.g. THC or cannabidiol) and/or synthetic cannabinoid agonists (e.g., dronabinol or WIN 55,2122) rather than clinical trial investigations involving whole plant material.

Because of the US government's strong public policy stance against any use of

cannabis, the bulk of this modern cannabinoid research is predictably taking place outside the United States.

As clinical research into the therapeutic value of cannabinoids has proliferated – there are now an estimated 20,000 published papers in the scientific literature analyzing marijuana and its constituents — so too has investigators' understanding of cannabis' remarkable capability to combat disease. Whereas researchers in the 1970s, 80s, and 90s primarily assessed cannabis' ability to temporarily alleviate various disease symptoms — such as the nausea associated with cancer chemotherapy — scientists today are exploring the potential role of cannabinoids to modify disease.

Of particular interest, scientists are investigating cannabinoids' capacity to moderate autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, as well as their role in the treatment of neurological disorders such as Alzheimer's disease and amyotrophic lateral sclerosis (a.k.a. Lou Gehrig's disease.) In fact, in 2009, the American Medical Association (AMA) resolved for the first time in the organization's history "that marijuana's status as a federal Schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines."

Investigators are also studying the anti-cancer activities of cannabis, as a growing body of preclinical and clinical data concludes that cannabinoids can reduce the spread of specific cancer cells via apoptosis (programmed cell death) and by the inhibition of angiogenesis (the formation of new blood vessels). Arguably, these latter findings represent far broader and more significant applications for cannabinoid therapeutics than researchers could have imagined some thirty or even twenty years ago.

THE SAFETY PROFILE OF MEDICAL CANNABIS

Cannabinoids have a remarkable safety record, particularly when compared to other therapeutically active substances. Most significantly, the consumption of marijuana – regardless of quantity or potency -- cannot induce a fatal overdose. According to a 1995 review prepared for the World Health Organization, “There are no recorded cases of overdose fatalities attributed to cannabis, and the estimated lethal dose for humans extrapolated from animal

studies is so high that it cannot be achieved by … users."

In 2008, investigators at McGill University Health Centre and McGill University in Montreal and the University of British Columbia in Vancouver reviewed 23 clinical investigations of medical cannabinoid drugs (typically oral THC or liquid cannabis extracts) and eight observational studies conducted between 1966 and 2007. Investigators "did not find a higher incidence rate of serious adverse events associated with medical cannabinoid use" compared to non-using controls over these four decades.

That said, cannabis should not necessarily be viewed as a 'harmless' substance. Its active constituents may produce a variety of physiological and euphoric effects. As a result, there may be some populations that are susceptible to increased risks from the use of cannabis, such as adolescents, pregnant or nursing mothers, and patients who have a family history of mental illness.

Patients with hepatitis C, decreased lung function (such as chronic obstructive pulmonary disease), or who have a history of heart disease or stroke may also be at a greater risk of experiencing adverse side effects from marijuana. As with any medication, patients should consult thoroughly with their physician before deciding whether the medical use of cannabis is safe and appropriate.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurological disorder of unknown origin that is characterized by a progressive loss of memory and learned behavior. Patients with Alzheimer's are also likely to experience depression, agitation and appetite loss, among other symptoms. Over 4.5 million Americans are estimated to be afflicted with the disease. No approved treatments or medications are available to stop the progression of AD, and few pharmaceuticals have been FDA-approved to treat symptoms of the disease.

A review of the recent scientific literature indicates that cannabinoid therapy may provide symptomatic relief to patients afflicted with AD while also moderating the progression of the disease.

Writing in the February 2005 issue of the *Journal of Neuroscience*,

investigators at Madrid's Complutense University and the Cajal Institute in Spain reported that the intracerebroventricular administration of the synthetic cannabinoid WIN 55,212-2 prevented cognitive impairment and decreased neurotoxicity in rats injected with amyloidbeta peptide (a protein believed to induce Alzheimer's). Additional synthetic cannabinoids were also found to reduce the inflammation associated with Alzheimer's disease in human brain tissue in culture. "Our results indicate that ... cannabinoids succeed in preventing the neurodegenerative process occurring in the disease," investigators concluded. Follow up studies by investigators demonstrated that the administration of the nonpsychotropic plant cannabinoid cannabidiol (CBD) also mitigated memory loss in a mouse model of the disease.

Investigators at The Scripps Research Institute in California in 2006 reported that THC inhibits the enzyme responsible for the aggregation of amyloid plaque — the primary marker for Alzheimer's disease — in a manner "considerably superior" to approved Alzheimer's drugs such as donepezil and tacrine. "Our results provide a mechanism whereby the THC molecule can directly impact Alzheimer's disease pathology," researchers concluded. "THC and its analogues may provide an improved therapeutic [option] for Alzheimer's disease [by]... simultaneously treating both the symptoms and the progression of [the] disease."

More recently, investigators at Ohio State University, Department of Psychology and Neuroscience, reported that older rats administered daily doses of WIN 55,212-2 for a period of three weeks performed significantly better than non-treated controls on a water-

maze memory test. Writing in the journal *Neuroscience* in 2007, researchers reported that rats treated with the compound experienced a 50 percent improvement in memory and a 40 to 50 percent reduction in inflammation compared to controls.

Previous preclinical studies have demonstrated that cannabinoids can prevent cell death by anti-oxidation. Some experts believe that cannabinoids' neuroprotective properties could also play a role in moderating AD. Writing in the September 2007 issue of the *British Journal of Pharmacology*, investigators at Ireland's Trinity College Institute of Neuroscience concluded, "[C]annabinoids offer a multi-faceted approach for the treatment of

Alzheimer's disease by providing neuroprotection and reducing neuroinflammation, whilst simultaneously supporting the brain's intrinsic repair mechanisms by augmenting neurotrophin expression and enhancing neurogenesis. ... Manipulation of the cannabinoid pathway offers a pharmacological approach for the treatment of AD that may be efficacious than current treatment regimens."

In addition to potentially modifying the progression of AD, clinical trials also indicate that cannabinoid therapy can reduce agitation and stimulate weight gain in patients with the disease. Most recently, investigators at Berlin Germany's Charite Universitatmedizin, Department of Psychiatry and Psychotherapy, reported that the daily administration of 2.5 mg of synthetic THC over a two-week period reduced nocturnal motor activity and agitation in AD patients in an open-label pilot study.
Clinical data presented at the 2003 annual meeting of the International Psychogeriatric Association previously reported that the oral administration of up to 10 mg of synthetic THC reduced agitation and stimulated weight gain in late-stage Alzheimer's patients in an open-label clinical trial.[9] Improved weight gain and a decrease in negative feelings among AD patients administered cannabinoids were previously reported by investigators in the *International Journal of Geriatric Psychiatry* in 1997.[10] Additional study of the use of cannabinoids and Alzheimer's would appear to be warranted.

Additional study assessing the use of cannabinoids for Alzheimer's would appear to be warranted.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a fatal neurodegenerative disorder that is characterized by the selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. An estimated 30,000 Americans are living with ALS, which often arises spontaneously and afflicts otherwise healthy adults. More than half of ALS patients die within 2.5 years following the onset of symptoms.

A review of the scientific literature reveals an absence of clinical trials investigating the use of cannabinoids for ALS treatment. However, recent

preclinical findings indicate that cannabinoids can delay ALS progression, lending support to anecdotal reports by patients that cannabinoids may be efficacious in moderating the disease's development and in alleviating certain ALS-related symptoms such as pain, appetite loss, depression and drooling.

Writing in the March 2004 issue of the journal *Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders*, investigators at the California Pacific Medical Center in San Francisco reported that the administration of THC both before and after the onset of ALS symptoms staved disease progression and prolonged survival in animals compared to untreated controls.

Additional trials in animal models of ALS have shown that the administration of other naturally occurring and synthetic cannabinoids can also moderate ALS progression but not necessarily impact survival. One recent study demonstrated that blocking the CB1 cannabinoid receptor did extend life span in an ALS mouse model, suggesting that cannabinoids' beneficial effects on ALS may be mediated by non-CB1 receptor mechanisms.

As a result, experts are calling for clinical trials to assess cannabinoids for the treatment of ALS. Writing in the *American Journal of Hospice & Palliative Medicine* in 2010, a team of investigators reported, ″ Based on the currently available scientific data, it is reasonable to think that cannabis might significantly slow the progression of ALS, potentially extending life expectancy and substantially reducing the overall burden of the disease.″ They concluded, ″ There is an overwhelming amount of preclinical and clinical evidence to warrant initiating a multicenter randomized, double-blind, placebo-controlled trial of cannabis as a disease-modifying compound in ALS.″

Chronic Pain

As many as one in five Americans live with chronic pain. Many of these people suffer from neuropathic pain (nerve-related pain) -- a condition that is associated with numerous diseases, including diabetes, cancer, multiple sclerosis, and HIV. In most cases, the use of standard analgesic medications such as opiates and NSAIDS (non-steroidal anti- inflammatory drugs) is ineffective at relieving neuropathic pain.

Survey data indicates that the use of cannabis is common in chronic pain

populations [2] and several recent FDA-designed clinical trials indicate that inhaled marijuana can significantly alleviate neuropathic pain. These include a pair of randomized, placebo-controlled clinical trials demonstrating that smoking cannabis reduces neuropathy in patients with HIV by more than 30 percent compared to placebo. (Additional details on these studies appear in the HIV section of this book.) In addition, a 2007 University of California at San Diego
double-blind, placebo-controlled trial reported that inhaled cannabis significantly reduced capsaicin-induced pain in healthy volunteers. A 2008 University of California at Davis
double-blind, randomized clinical trial reported both high and low doses of inhaled cannabis reduced neuropathic pain of diverse causes in subjects unresponsive to standard pain therapies. Finally, a 2010 McGill University study finding that smoked cannabis significantly improved measures of pain, sleep quality and anxiety in participants with refractory pain for which conventional therapies had failed.

Preclinical data indicates that cannabinoids, when administered in concert with one another, are more effective at ameliorating neuropathic pain than the use of a single agent. Investigators at the University of Milan reported in 2008 that the administration of single cannabinoids such as THC or CBD produce limited relief compared to the administration of plant extracts containing multiple cannabinoids, terpenes (oils), and flavonoids (pigments).

Researchers concluded: ″ The use of a standardized extract of Cannabis sativa ... evoked a total relief of thermal hyperalgesia, in an experimental model of neuropathic pain ... ameliorating the effect of single cannabinoids, ″ investigators concluded. ... ″ Collectively, these findings strongly support the idea that the combination of cannabinoid and non- cannabinoid compounds, as present in [plant-derived] extracts, provides significant advantages in the relief of neuropathic pain compared with pure cannabinoids alone.″

In 2009, an international team of investigators from the United Kingdom, Belgium and Romania affirmed these preclinical findings in a clinical study of intractable cancer pain patients. They concluded: ″ In this study, the THC/CBD extract showed a more promising efficacy profile than the THC extract alone. This finding is supported by evidence of additional synergy between THC and CBD. CBD may enhance the analgesic potential of THC

by means of potent inverse agonism at CB2 receptors, which may produce anti- inflammatory effects, along with its ability to inhibit immune cell migration. ... These results are very encouraging and merit further study."

Diabetes Mellitus

Diabetes mellitus is a group of autoimmune diseases characterized by defects in insulin secretion resulting in hyperglycemia (an abnormally high concentration of glucose in the blood). There are two primary types of diabetes. Individuals diagnosed with type 1 diabetes (also known as juvenile diabetes) are incapable of producing pancreatic insulin and must rely on insulin medication for survival. Individuals diagnosed with type 2 diabetes (also known as adult onset diabetes) produce inadequate amounts of insulin. Type 2 diabetes is a less serious condition that typically is controlled by diet. Over time, diabetes can lead to blindness, kidney failure, nerve damage, hardening of the arteries and death. The disease is the third leading cause of death in the United States after heart disease and cancer.

A search of the scientific literature reveals no clinical investigations of cannabis for the treatment of diabetes, but does identify a small number of preclinical studies indicating that cannabinoids may modify the disease's progression and provide symptomatic relief to those suffering from it. A 2006 study published in the journal *Autoimmunity* reported that injections of 5 mg per day of the non-psychoactive cannabinoid CBD significantly reduced the incidence of diabetes in mice. Investigators reported that 86% of untreated control mice in the study developed diabetes. By contrast, only 30% of CBD-treated mice developed the disease.[3] In a separate experiment, investigators reported that control mice all developed diabetes at a median of 17 weeks (range 15-20 weeks), while a majority (60 percent) of CBD- treated mice remained diabetes-free at 26 weeks.

Other preclinical trials have demonstrated cannabinoids to possess additional beneficial effects in animal models of diabetes. Writing in the March 2006 issue of the *American Journal of Pathology*, researchers at the Medical College of Virginia reported that rats treated with CBD for periods of one to four weeks experienced significant protection from diabetic retinopathy. This condition, which is characterized by retinal oxygen deprivation and a breakdown of the blood-retinal barrier, is the leading cause of blindness in working-age adults.

Cannabinoids have also been shown to alleviate neuropathic pain associated with the disease. A pair of studies published in the journal *Neuroscience Letters* in 2004 reported that mice administered a cannabis receptor agonist experienced a reduction in diabetic-related tactile allodynia (pain resulting from non-injurious stimulus to the skin) compared to non-treated controls. The findings suggest that ″ cannabinoids have a potential beneficial effect on experimental diabetic neuropathic pain.″

A 2001 trial demonstrated that delta-9-THC could moderate an animal model of the disease by reducing artificially-elevated glucose levels and insulitis in mice compared to non-treated controls. Most recently, an international team of researchers from the United States, Switzerland and Israel reported in the Journal of the American College of Cardiology that the administration of CBD reduces various symptoms of diabetic cardiomyopathy (weakening of the heart muscle) in a mouse model of type 1 diabetes. Authors concluded, "These results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications. With the incidence of diabetes steadily increasing in both the adult and juvenile population, it would appear that further cannabinoid research is warranted in the treatment of this disease.

Dystonia

Dystonia is a neurological movement disorder characterized by abnormal muscle tension and involuntary, painful muscle contractions. It is the third most common movement disorder after Parkinson's disease and tremor, affecting more than 300,000 people in North America.

A small number of case reports and preclinical studies investigating the use of cannabis and cannabinoids for symptoms of dystonia are referenced in the recent scientific literature. A 2002 case study published in the July issue of the *The Journal of Pain and Symptom Management* reported improved symptoms of dystonia after smoking cannabis in a 42-yearold chronic pain patient. Investigators reported that subject's subjective pain score fell from 9 to zero (on a zero-to-10 visual analog scale) following cannabis inhalation, and that the subject did not require any additional analgesic medication for the following 48 hours. "No other treatment intervention to date had resulted

in such dramatic overall improvement in [the patient's] condition," investigators concluded.

A second case study reporting "significant clinical improvement" following cannabis inhalation in a single 25-year-old patient with generalized dystonia due to Wilson's disease was documented by an Argentinian research team in the August 2004 issue of the journal *Movement Disorders*.

Also in 2004, a German research team at the Hannover Medical School reported successful treatment of musician's dystonia in a 38-year-old professional pianist following administration of 5 mg of THC in a placebo-controlled single-dose trial. Investigators reported "clear improvement of motor control" in the subject's affected hand, and noted, "[Two] hours after THC intake, the patient was able to play technically demanding literature, which had not been possible before treatment." Prior to cannabinoid treatment, the subject had been unresponsive to standard medications and was no longer performing publicly. "The results provide evidence that ... THC intake ... significantly improves [symptoms of] ... focal dystonia," investigators concluded.

By contrast, a 2002 randomized, placebo-controlled study investigating the use of the synthetic oral cannabinoid naboline (Cesamet) in 15 patients afflicted with generalized and segmental primary dystonia did not show a significant reduction in dystonic symptoms. Investigators speculated that this result may have been dose-related, and that administration of a higher dosage may have yielded a different outcome.

At least one recent preclinical trial indicates that both synthetic cannabinoids as well as high doses of the natural non-psychoactive cannabinoid cannabidiol (CBD) could moderate the disease progression of dystonia in animals. Limited references regarding the use of cannabinoids for dystonia in humans and animals in the 1980s and the 1990s also appear in the scientific literature. It would appear that additional, larger clinical trials are warranted to investigate the use of cannabis and cannabinoids for this indication.

Fibromyalgia

Fibromyalgia is a chronic pain syndrome of unknown etiology. The disease is characterized by widespread musculoskeletal pain, fatigue and multiple tender points in the neck, spine, shoulders and hips. An estimated 3 to 6 million

Americans are afflicted by fibromyalgia, which is often poorly controlled by standard pain medications.

Fibromyalgia patients frequently self-report using cannabis therapeutically to treat symptoms of the disease, and physicians – where legal to do so – often recommend the use of cannabis to treat musculoskeletal disorders. To date however, there are few clinical trials assessing the use of cannabinoids to treat the disease.

Writing in the July 2006 issue of the journal *Current Medical Research and Opinion*, investigators at Germany's University of Heidelberg evaluated the analgesic effects of oral THC in nine patients with fibromyalgia over a 3-month period. Subjects in the trial were administered daily doses of 2.5 to 15 mg of THC and received no other pain medication during the trial. Among those participants who completed the trial, all reported a significant reduction in daily recorded pain and electronically induced pain.

A 2008 study published in the *The Journal of Pain* reported that the administration of the synthetic cannabinoid nabilone significantly decreased pain in 40 subjects with fibromyalgia in a randomized, double-blind, placebo-controlled trial. "As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia," investigators concluded. A separate 2010 trial performed at McGill University in Montreal reported that low doses of nabilone significantly improved sleep quality in patients diagnosed with the disease.

Previous clinical and preclinical trials have shown that both naturally occurring and endogenous cannabinoids hold analgesic qualities, particularly in the treatment of pain resistant to conventional pain therapies. (Please see the 'Chronic Pain' section of this book for further details.) As a result, some experts have suggested that cannabinoids are applicable for the treatment of chronic pain conditions such as fibromyalgia, and have theorized that the disease may be associated with an underlying clinical deficiency of the endocannabinoid system.

Gastrointestinal Disorders

Gastrointestinal (GI) disorders, including functional bowel diseases such as irritable bowel syndrome (IBS) and inflammatory bowel diseases such as

Crohn's disease and colitis, afflict more than one in five Americans, particularly women. While some GI disorders may be controlled by diet and pharmaceutical medications, others are poorly moderated by conventional treatments. Symptoms of GI disorders often include cramping, abdominal pain, inflammation of the lining of the large and/or small intestine, chronic diarrhea, rectal bleeding and weight loss.

Although several anecdotal reports and a handful of case reports exist in the scientific literature supporting the use of cannabinoids to treat symptoms of GI disorders, virtually no clinical trial work has been performed in this area, aside from a 2007 clinical study assessing the impact of oral THC on colonic motility.

However, numerous preclinical studies demonstrate that activation of the CB1 and CB2 cannabinoid receptors exert biological functions on the gastrointestinal tract. Effects of their activation in animals include suppression of gastrointestinal motility, inhibition of intestinal secretion, reduced acid reflux and protection from inflammation, as well as the promotion of epithelial wound healing in human tissue. As a result, many experts now believe that cannabinoids and/or modulation of the endogenous cannabinoid system represents a novel therapeutic approach for the treatment of numerous GI disorders — including inflammatory bowel diseases, functional bowel diseases, gastro-oesophagael reflux conditions, secretory diarrhea, gastric ulcers and colon cancer.

Gliomas/Cancer

Gliomas (tumors in the brain) are especially aggressive malignant forms of cancer, often resulting in the death of affected patients within one to two years following diagnosis. There is no cure for gliomas and most available treatments provide only minor symptomatic relief.

A review of the modern scientific literature reveals numerous preclinical studies and one pilot clinical study demonstrating cannabinoids' ability to act as antineoplastic agents, particularly on glioma cell lines.

Writing in the September 1998 issue of the journal *FEBS Letters*, investigators at Madrid's Complutense University, School of Biology, first reported that delta-9-THC induced apoptosis (programmed cell death) in glioma cells in

culture. Investigators followed up their initial findings in 2000, reporting that the administration of both THC and the synthetic cannabinoid agonist WIN 55,212-2 "induced a considerable regression of malignant gliomas" in animals. Researchers again confirmed cannabinoids' ability to inhibit tumor growth in animals in 2003.

That same year, Italian investigators at the University of Milan, Department of Pharmacology, Chemotherapy and Toxicology, reported that the non-psychoactive cannabinoid, cannabidiol (CBD), inhibited the growth of various human glioma cell lines *in vivo* and *in vitro* in a dose dependent manner. Writing in the November 2003 issue of the *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, researchers concluded, "Non-psychoactive CBD ... produce[s] a significant anti-tumor activity both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as an antineoplastic agent."

In 2004, Guzman and colleagues reported that cannabinoids inhibited glioma tumor growth in animals and in human glioblastoma multiforme (GBM) tumor samples by altering blood vessel morphology (e.g., VEGF pathways). Writing in the August 2004 issue of *Cancer Research*, investigators concluded, "The present laboratory and clinical findings provide a novel pharmacological target for cannabinoid-based therapies." More recently, investigators at the California Pacific Medical Center Research Institute reported that the administration of THC on human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced cell death more rapidly than did the administration of WIN 55,212-2. Researchers also noted that THC selectively targeted malignant cells while ignoring healthy ones in a more profound manner than the synthetic alternative.

Most recently, Guzman and colleagues reported that THC administration decreases recurrent glioblastoma multiforme tumor growth in patients diagnosed with recurrent GBM. In the first ever pilot clinical trial assessing the use of cannabinoids and GBM, investigators found that the intratumoral administration of THC was associated with reduced tumor cell proliferation in two of nine subjects. "The fair safety profile of THC, together with its possible anti-proliferative action on tumor cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids," investigators concluded. Several additional investigators have also recently called for

further exploration of cannabis-based therapies for the treatment of glioma.

In addition to cannabinoids' ability to moderate glioma cells, separate studies demonstrate that cannabinoids and endocannabinoids can also inhibit the proliferation of other cancer cell lines, including breast carcinoma, prostate carcinoma, colorectal carcinoma, gastric adenocarcinoma, skin carcinoma, leukemia cells, neuroblastoma, lung carcinoma, uterus carcinoma, thyroid epithelioma, pancreatic adenocarcinoma, cervical carcinoma, oral cancer, biliary tract cancer (cholangiocarcinoma)and lymphoma.
Studies also indicate that the administration of cannabinoids, in conjunction with conventional anti-cancer therapies, can enhance the effectiveness of standard cancer treatments. Most recently, investigators at the University of California, Pacific Medical Center reported that cannabinoids possess synergistic anti-cancer properties -- finding that the administration of a combination of the plant's constituents is superior to the administration of isolated compounds alone.

Consequently, many experts now believe that cannabinoids "may represent a new class of anticancer drugs that retard cancer growth; inhibit angiogenesis and the metastatic spreading of cancer cells."

Hepatitis C

Hepatitis C is a viral disease of the liver that afflicts an estimated four million Americans. Chronic hepatitis C is typically associated with fatigue, depression, joint pain and liver impairment, including cirrhosis and liver cancer.

Patients diagnosed with hepatitis C frequently report using cannabis to treat both symptoms of the disease as well as the nausea associated with antiviral therapy. An observational study by investigators at the University of California at San Francisco (UCSF) found that hepatitis C patients who used cannabis were significantly more likely to adhere to their treatment regimen than patients who didn't use it. Nevertheless, no clinical trials assessing the use of cannabinoids for this indication are available in the scientific literature.

Preclinical data indicates that the endocannabinoid system may moderate aspects of chronic liver disease and that cannabinoids may reduce inflammation in experimental models of hepatitis. However, other clinical reviews have reported a positive association between daily cannabis use and the progression of liver fibrosis (excessive tissue build up) and steatosis (excessive fat build up) in select hepatitis C patients.

As a result, experts hold divergent opinions regarding the therapeutic use of cannabinoids for hepatitis C treatment. Writing in the October 2006 issue of the *European Journal of Gastroenterology*, investigators from Canada and Germany concluded that cannabis' "potential benefits of a higher likelihood of treatment success [for hepatitis c patients] appear to outweigh [its] risks." By contrast, other experts discourage the use of cannabis in patients with chronic hepatitis until further studies are performed.

Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus is a retrovirus that invades cells in the human immune system, making it highly susceptible to infectious diseases. According to the World Health Organization, over 500,000 Americans have died from HIV/AIDS and over one million US citizens are living with the disease.

Survey data indicates that cannabis is used by as many one in three North American patients with HIV/AIDS to treat symptoms of the disease as well as the side-effects of various antiretroviral medications. One recent study reported that more than 60 percent of HIV/AIDS patients self-identify as "medical cannabis users. Patients living with HIV/AIDS most frequently report using cannabis to counter symptoms of anxiety, appetite loss and nausea, and at least one study has reported that patients who use cannabis therapeutically are 3.3 times more likely to adhere to their antiretroviral therapy regimens than non-cannabis users.

Clinical trial data indicates that cannabis use does not adversely impact CD4 and CD8 T cell counts and may even improve immune function.

In 2007, investigators at Columbia University published clinical trial data in 2007 reporting that HIV/AIDS patients who inhaled cannabis four times daily experienced "substantial ... increases in food intake ... with little

evidence of discomfort and no impairment of cognitive performance." They concluded, "Smoked marijuana ... has a clear medical benefit in HIV-positive [subjects]."

That same year, investigators at San Francisco General Hospital and the University of California's Pain Clinical Research Center reported in the journal *Neurology* that inhaling cannabis significantly reduced HIV-associated neuropathy compared to placebo. Researchers reported that inhaling cannabis three times daily reduced patients' pain by 34 percent. They concluded, "Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated neuropathy [in a manner] similar to oral drugs used for chronic neuropathic pain.

In 2008, researchers at the University of California at San Diego reported similar findings. Writing in the journal *Neuropsychopharmacology*, they concluded: "Smoked cannabis... significantly reduced neuropathic pain intensity in HIV-associated ... polyneuropathy compared to placebo, when added to stable concomitant analgesics. ... Mood disturbance, physical disability and quality of life all improved significantly during study treatment. ... Our findings suggest that cannabinoid therapy may be an effective option for pain relief in patients with medically intractable pain due to HIV."

As a result, many experts now believe that "marijuana represents another treatment option in [the] health management" of patients with HIV/AIDS.

Hypertension

High blood pressure, or hypertension, afflicts an estimated one in four American adults. This condition puts a strain on the heart and blood vessels and greatly increases the risk of stroke and heart disease.

Emerging research indicates that the endogenous cannabinoid system plays a role in regulating blood pressure, though its mechanism of action is not well understood. Animal studies demonstrate that anandamide and other endocannabinoids profoundly suppress cardiac contractility in hypertension and can normalize blood pressure, leading some experts to speculate that the manipulation of the endocannabinoid system ″ may offer novel therapeutic

approaches in a variety of cardiovascular disorders."

The administration of natural cannabinoids has yielded conflicting cardiovascular effects on humans and laboratory animals. The vascular response in humans administered cannabis in experimental conditions is typically characterized by a mild increase in heart rate and blood pressure. However, complete tolerance to these effects develops quickly and potential health risks appear minimal.

In animals, cannabinoid administration in animals is typically associated with vasodilation, transient bradycardia and hypotension, as well as an inhibition of atherosclerosis (hardening of the arteries) progression. The administration of synthetic cannabinoids have also been shown to lower blood pressure in animals and have not been associated with cardiotoxicity in humans.

At this time, research assessing the clinical use of cannabinoids for hypertension is in its infancy though further investigation appears warranted.

Incontinence

Urinary incontinence is defined as a loss of bladder control. Incontinence can result from several biological factors, including weak bladder muscles and inflammation, as well as from nerve damage associated with diseases such as multiple sclerosis (MS) and Parkinson's disease. More than one in ten Americans over age 65 is estimated to suffer from incontinence, particularly women.

Several recent clinical trials indicate that cannabinoid therapy may reduce incidents of incontinence. Writing in the February 2003 issue of the journal *Clinical Rehabilitation*, investigators at Oxford's Centre for Enablement in Britain reported that self-administered doses of whole-plant cannabinoid extracts improved bladder control compared to placebo in patients suffering from MS and spinal cord injury.

Investigators at London's Institute for Neurology followed up these initial findings in an open-label pilot study of cannabis-based extracts for bladder dysfunction in 15 patients with advanced multiple sclerosis. Following cannabinoid therapy, "urinary urgency, the number of and volume of incontinence episodes, frequency and nocturia all decreased significantly,"

investigators determined. "Cannabis-based medical extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS."

These findings were confirmed in 2006 in a multi-center, randomized placebo-controlled trial involving 630 patients administered oral doses of cannabis extracts or THC. Researchers reported that subjects administered cannabis extracts experienced a 38 percent reduction in incontinence episodes from baseline to the end of treatment, while patients administered THC experienced a 33 percent reduction, suggesting a "clinical effect of cannabis on incontinence episodes.

Most recently, preclinical data presented at the 2006 annual meeting of the American Urological Association indicated that cannabis analogs can reduce bladder inflammation and bladder over-activity in animals.

In light of these findings, experts have recommended the use of cannabinoids as potential 'second-line' agents for treating incontinence.

Methicillin-resistant *Staphyloccus aureus* (MRSA)

Many bacterial infections possess multi-drug resistance. Arguably the most significant of these bacteria is methicillin-resistant *Staphyloccus aureus*, more commonly known as MRSA or ′ the superbug.′ This bacterium is resistant to standard antibiotics, including penicillin. According to the *Journal of the American Medical Association*, MRSA is responsible for nearly 20,000 hospital-stay related deaths annually in the United States.

Published data demonstrates that cannabinoids possess strong antibacterial properties. In 2008, investigators at Italy's Universita del Piemonte Orientale and Britain's University of London, School of Pharmacy assessed the germ-fighting properties of five separate cannabinoids against various strains of multidrug-resistant bacteria, including MRSA. They reported that all of the compounds tested showed "potent antibacterial activity" and that cannabinoids were "exceptional" at halting the spread of MRSA.

A second study published that same year reported that non-cannabinoid constituents in the plant also possess antibacterial properties against MRSA and malaria.

Clinical trials regarding the use of cannabinoids for MRSA have been recommended, with some experts stating, “Cannabis sativa ... represents an interesting source of antibacterial agents to address the problem of multidrug resistance in MRSA and other pathogenic bacteria.”

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system that causes inflammation, muscular weakness and a loss of motor coordination. Over time, MS patients typically become permanently disabled and, in some cases the disease can be fatal. According to the US National Multiple Sclerosis Society, about 200 people are diagnosed every week with the disease — often striking those 20 to 40 years of age.

Clinical and anecdotal reports of cannabinoids' ability to reduce MS-related symptoms such as pain, spasticity, depression, fatigue, and incontinence are plentiful in the scientific literature. Most recently, investigators at the University of California at San Diego reported in 2008 that inhaled cannabis significantly reduced objective measures of pain intensity and spasticity in patients with MS in a placebo-controlled, randomized clinical trial. Investigators concluded that "smoked cannabis was superior to placebo in reducing spasticity and pain in patients with multiple sclerosis and provided some benefit beyond currently prescribed treatment." Not surprisingly, patients with multiple sclerosis typically report engaging in cannabis therapy, with one survey indicating that nearly one in two MS patients use the drug therapeutically.

Other recent clinical and preclinical studies suggest that cannabinoids may also inhibit MS progression in addition to providing symptom management. Writing in the July 2003 issue of the journal *Brain*, investigators at the University College of London's Institute of Neurology reported that administration of the synthetic cannabinoid agonist WIN 55,212-2 provided "significant neuroprotection" in an animal model of multiple sclerosis. "The results of this study are important because they suggest that in addition to symptom management ... cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in multiple sclerosis and probably other disease," researchers concluded.

Investigators at the Netherland's Vrije University Medical Center,

Department of Neurology, also reported for the first time in 2003 that the administration of oral THC can boost immune function in patients with MS. "These results suggest pro-inflammatory disease-modifying potential of cannabinoids [for] MS," they concluded.

Clinical data reported in 2006 from an extended open-label study of 167 multiple sclerosis patients found that use of whole plant cannabinoid extracts relieved symptoms of pain, spasticity and bladder incontinence for an extended period of treatment (mean duration of study participants was 434 days) without requiring subjects to increase their dose.

Osteoporosis

Osteoporosis is a degenerative skeletal disease characterized by a deterioration of bone tissue. Patients with osteoporosis are at risk for suffering multiple fractures and other serious disabilities. Approximately 10 million Americans over age 50 suffer from osteoporosis, according to the US Surgeon General's office, and another 34 million are at risk for developing the disease.

Initial references regarding the potential use of cannabinoids to protect against the onset of osteoporosis are available in the scientific literature beginning in the early 1990s. To date, however, no clinical work has taken place investigating the use of cannabis for this indication.

Writing in the January 2006 issue of the *Proceedings of the National Academy of Sciences*, investigators at the Bone Laboratory of the Hebrew University in Jerusalem reported that the administration of the synthetic cannabinoid agonist HU-308 slowed the development of osteoporosis, stimulated bone building and reduced bone loss in animals. Follow up research published in the *Annals of the New York Academy of Sciences* in 2007 reported that the activation of the CB2 cannabinoid receptor reduced experimentally-induced bone loss and stimulated bone formation. Investigators have previously reported that mice deficient in the CB2 cannabinoid receptor experienced age-accelerated bone loss reminiscent of human osteoporosis.

Scientists now speculate that the main physiologic involvement of specific endocannabinoid receptors (CB2 receptors) is to maintain "bone remodeling

at balance, thus protecting the skeleton against age-related bone loss," leading some experts to believe that cannabinoids may be "a promising target novel target for anti-osteoporotic drug development."

Pruritus

Itching (pruritus) is a common symptom associated with numerous skin diseases, as well as a secondary symptom of numerous serious conditions such as renal failure and liver disease. Itching, unlike other skin sensations, is generally a result of CNS activities and typically goes untreated by standard medical therapies.

A review of the scientific literature reveals three clinical trials investigating the use of cannabinoids in the treatment of pruritus. Writing in the August 2002 issue of the *American Journal of Gastroenterology*, investigators from the University of Miami Department of Medicine reported successful treatment of pruritus with 5 mg of THC in three patients with cholestasis liver disease. Prior to cannabinoid therapy, subjects had failed to respond to standard medications and had lost their ability to work. Following evening cannabinoid administration, all three patients reported a decrease in pruritus, as well as "marked improvement" in sleep and were eventually able to return to work. Resolution of depression was also reported in two out of three subjects. "Delta-9-tetrahydrocannabinol may be an effective alternative in patients with intractable cholestatic pruritus," investigators concluded.

The following year, British researchers reported in the June 2003 issue of the journal *Inflammation Research* that the peripheral administration of the synthetic cannabinoid agonist HU-211 significantly reduced experimentally-induced itch in 12 subjects. Investigators had previously reported that topical application of HU-210 on human skin reduced experimentally-induced pain and acute burning sensations.

Most recently, researchers at Wroclaw, Poland's University of Medicine, Department of Dermatology, reported that application of an endocannabinoid-based topical cream reduced uremic pruritus and xerosis (abnormal dryness of the skin) in hemodialysis patients. Three weeks of twice-daily application of the cream "completely eliminated" pruritus in

38 percent of trial subjects and "significantly reduced" itching in others. Eighty-one percent of patients reported a "complete reduction" in xerosis following cannabinoid therapy.

In light of these encouraging preliminary results, some dermatology experts now believe that cannabinoids and the cannabinoid system may represent "promising new avenues for managing itch more effectively."

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory disease of the joints characterized by pain, stiffness, and swelling, as well as an eventual loss of limb function. Rheumatoid arthritis is estimated to affect about one percent of the population, primarily women.

Use of cannabis to treat symptoms of RA is commonly self-reported by patients with the disease. In a 2005 anonymous questionnaire survey of medical cannabis patients in Australia, 25 percent reported using cannabinoids to treat RA. A survey of British medical cannabis patients found that more than 20 percent of respondents reported using cannabis for symptoms of arthritis. Nevertheless, few clinical trials investigating the use of cannabis for RA appear in the scientific literature.

In January 2006, investigators at the British Royal National Hospital for Rheumatic Disease reported successful treatment of arthritis with cannabinoids in the first-ever controlled trial assessing the efficacy of natural cannabis extracts on RA. Investigators reported that administration of cannabis extracts over a five week period produced statistically significant improvements in pain on movement, pain at rest, quality of sleep, inflammation and intensity of pain compared to placebo. No serious adverse effects were observed. Similar results had been reported in smaller Phase II trials investigating the use of orally administered cannabis extracts on symptoms of RA.

Preclinical data also indicates that cannabinoids can moderate the progression of RA. Writing in the August 2000 issue of the *Journal of the Proceedings of the National Academy of Sciences*, investigators at London's Kennedy Institute for Rheumatology reported that cannabidiol (CBD) administration suppressed progression of arthritis *in vitro* and in animals.

Administration of CBD after the onset of clinical symptoms protected joints against severe damage and "effectively blocked [the] progression of arthritis," investigators concluded. Daily administration of the synthetic cannabinoid agonist HU-320 has also been reported to protect joints from damage and to ameliorate arthritis in animals.

Summarizing the available literature in the September 2005 issue of the *Journal of Neuroimmunology*, researchers at Tokyo's National Institute for Neuroscience concluded, "Cannabinoid therapy of RA could provide symptomatic relief of joint pain and swelling as well as suppressing joint destruction and disease progression."

Sleep Apnea

Sleep apnea is a medical disorder characterized by frequent interruptions in breathing of up to ten seconds or more during sleep. The condition is associated with numerous physiological disorders, including fatigue, headaches, high blood pressure, irregular heartbeat, heart attack and stroke. Though sleep apnea often goes undiagnosed, it is estimated that approximately four percent of men and two percent of women ages 30 to 60 years old suffer from the disease.

One preclinical study is cited in the scientific literature investigating the role of cannabinoids on sleep-related apnea. Writing in the June 2002 issue of the journal of the American Academy of Sleep Medicine, researchers at the University of Illinois (at Chicago) Department of Medicine reported "potent suppression" of sleep-related apnea in rats administered either exogenous or endogenous cannabinoids. Investigators reported that doses of delta-9-THC and the endocannabinoid oleamide each stabilized respiration during sleep and blocked serotonin-induced exacerbation of sleep apnea in a statistically significant manner. No follow up investigations have taken place assessing the use of cannabinoids to treat this indication. However, several recent preclinical and clinical trials have reported on the use of THC, natural cannabis extracts and endocannabinoids to induce sleep and/or improve sleep quality.

Tourette's Syndrome

Tourette's syndrome (TS) is a complex neuropsychiatric disorder of unknown etiology that is characterized by involuntary vocal tics. Severity of this condition varies widely among patients. Though there is no cure for Tourette's syndrome, the condition often improves with age. Experts estimate that 100,000 Americans are afflicted with TS.

A review of the scientific literature reveals several clinical trials investigating the use of cannabinoids for the treatment of TS. Writing in the March 1999 issue of the *American Journal of Psychiatry*, investigators at Germany's Medical School of Hanover, Department of Clinical Psychiatry and Psychotherapy, reported successful treatment of Tourette's syndrome with a single dose of 10 mg of delta-9-THC in a 25-year-old male patient in an uncontrolled open clinical trial. Investigators reported that the subject's total tic severity score fell from 41 to 7 within two hours following cannabinoid therapy, and that improvement was observed for a total of seven hours. "For the first time, patients' subjective experiences when smoking marijuana were confirmed by using a valid and reliable rating scale," authors concluded.

Investigators again confirmed these preliminary results in a randomized, double-blind, placebo-controlled, crossover, single dose trial of THC in 12 adult TS patients. Researchers reported a "significant improvement of tics and obsessive-compulsive behavior (OCB) after treatment with delta-9-THC compared to placebo." Investigators reported no cognitive impairment in subjects following THC administration and concluded, "THC is effective and safe in treating tics and OCB in TS."

Investigators confirmed these results in a second randomized, double-blind, placebo-controlled trial involving 24 patients administered daily doses of up to 10 mg of THC over a six-week period. Researchers reported that subjects experienced a significant reduction in tics following long-term cannabinoid treatment, and suffered no detrimental effects on learning, recall or verbal memory. A trend toward significant improvement of verbal memory span during and after therapy was also observed.