Clearing the Smoke on Misconceptions of Medical Marijuana: A focus on older adults

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Abstract

   Older adults tend to suffer from a number of ailments for which medical marijuana could provide some relief, with fewer side effects, compared to existing treatments. Despite its potential medicinal use, marijuana is currently labeled by the DEA as schedule 1 drug – indicating that is has no medical value and is a danger to public health, making the progression of research very difficult. This article begins with a brief history of cannabis in the U.S. medical system, its properties, and methods of administration. The following section discusses the problems with polypharmacy in the aging population. Next, we provide examples from research findings of medical marijuana's effects on conditions that are likely to affect older adults, including: Alzheimer's and Parkinson's disease, arthritis, cancer, osteoporosis, glaucoma, depression, and methicillin-resistant staphylococcus aureus (MRSA) in nursing homes. We conclude by discussing the barriers to research on medical marijuana.

Key Words: Medical cannabis, polypharmacy, chronic diseases, legalization

"We didn't have any large double-blind studies of penicillin until the mid-60s, so it was all anecdotal evidence. But it came across as a wonder drug. And it was." – Lester Grinspoon, 87, an Associate Professor Emeritus of Psychiatry at Harvard Medical School

Introduction

An increasing number of states have legalized medical marijuana in the U.S., and use the plant as a possible alternative to pharmaceutical drugs offering relief to those who suffer from chronic conditions (See Table 1). Several studies have shown that medical marijuana is an effective treatment for various illnesses, and many researchers believe that it has great potential to treat several serious disorders such as Alzheimer's disease. However, scholarly research is being blocked by the DEA classification of marijuana as a Schedule I drug, leaving researchers without access to double blind studies and with only mice as test subjects.

This article refutes many of the misconceptions about medical marijuana, such as addiction and harmful side effects, with research findings that focus on chronic diseases most common among the 65 and older population, including: Alzheimer's and Parkinson's disease, arthritis, cancer, osteoporosis, glaucoma, depression, and methicillin-resistant Staphylococcus aureus (MRSA) in nursing homes. We conclude with a discussion of the DEA's opposition to the legalization of marijuana.

A Brief History of Cannabis in the U.S. Medical System

The marijuana plant was introduced to North America in 1611 by the Jamestown settlers. The first known mention of cannabis as treatment for depression was in the mental health book "The Anatomy of Melancholy" in 1621. In the early 1800s, physicians were free to make autonomous

decisions regarding patient care, which often included the use of cannabis as medication. Jacques-Joseph Moreau, a French psychiatrist in the 1840s, found that marijuana suppressed headaches, increased appetites, and helped people to sleep better. By 1850, marijuana was classified as a legitimate medical compound in the United States Pharmacopeia – the official handbook for all prescriptions and over the counter medications. The handbook listed marijuana as a treatment for various illnesses, including: convulsive disorders, gout, neuralgia, tetanus, alcoholism, opiate addiction, anthrax, incontinence, and excessive menstrual bleeding. In 1889, an article by Dr. E. A. Birch in *The Lancet*, defined the ways cannabis could be used for the treatment of opium and chloral hydrate withdrawal symptoms and as an anti-emetic, which eliminates vomiting and nausea.

In 1906, President Roosevelt signed the Food and Drug act. The law required the labeling of products, so that physicians and consumers could make informed decisions about the medications being used or prescribed. Although many states passed marijuana prohibition laws after 1911, by 1918, approximately 60,000 pounds of medical marijuana were being grown annually on pharmaceutical farms. In 1930, there were at least three American companies (Parke-Davis, Eli Lily, and Grimault & Company) selling standardized extracts of marijuana for use as an analgesic, antispasmodic, sedative, and as a remedy for asthma. Several states in 1936 moved to regulate marijuana, and along with the development of aspirin, morphine, and other opium-derived drugs for treatment of pain, this eventually hastened the decline of marijuana use for medical purposes.

In 1937, the Marihuana Tax Act was passed, which criminalized possession of cannabis, except for those with a prescription from a physician. Physicians gradually decreased their

prescriptions of cannabis because of the complex law requirements and ease of obtaining drugs that were produced by pharmaceutical companies. By 1942, marijuana was removed from the U.S. Pharmacopeia, thus losing its therapeutic legitimacy.

Within the next 30 years, the Bureau of Narcotics and Dangerous Drugs and the Controlled Substance Act (drug classification system, which labeled cannabis as a schedule 1 drug – indicating that is has no medical value and is a danger to public health) were established. In 1971, President Nixon declared the war on drugs and marijuana became a key target of the battle against illegal drugs. By 1973, the Bureau of Narcotics and Dangerous Drugs and the Office of Drug Abuse Law Enforcement were merged to form the US Drug Enforcement Agency (DEA) (http://medicalmarijuana.procon.org/view.timeline.php?timelineID=000026).

Cannabinoids: More than just THC

A main concern regarding the use of medical cannabis is the possible psychoactive affect, either euphoria or dysphoria, which comes from one of the cannabinoids (chemical compounds) known as tetrahydrocannabinol (THC). However, THC is only 1 of 85 types of cannabinoids found in cannabis. Other types of cannabinoids, such as cannabidiol (CBD), cannabigerol (CBG), and tetrahydrocannabinolic acid (THCA) are non-psychoactive compounds that have been shown to provide relief for an array of symptoms associated with pain, gastrointestinal disorders, inflammation, and neurological disorders. In addition, cannabinol (CBN) is a mildly psychoactive cannabinoid, which is produced from the degradation of THC. The most evident attribute of CBN is its sedative effect, which is best for people who suffer from sleep disorders. (https://www.leafly.com/news/cannabis-101/cannabinoids-101-what-makes-cannabis-medicine).

However, it can also be used topically as an anti-bacterial to treat methicillin-resistant Staphylococcus aureus (MRSA) and psoriasis (Appendino et al., 2008).

The various cannabinoids have different effects depending on which receptors they bind to in the body. Cannabinoids are not foreign compounds being introduced into the body, rather they imitate compounds that our bodies naturally produce, called endocannabinoids. These compounds, whether endogenously produced by the body or supplied from the cannabis plant, are activated to maintain internal stability and health.

Other concerns are the potential for addiction and harmful side effects from medical cannabis. The results regarding addiction from using marijuana are mixed. The worst side effects come from smoking cannabis that contains THC and include, dry mouth, dry/red eyes, nausea, dizziness, blood pressure problems, hallucinations, increased appetite, and impaired mental functioning (Solowij et al., 2011; WebMD.com). Prescription drugs, on the other hand, can be even more addictive than medical cannabis and are more likely to have many harmful side effects. For example, a prescription drug called Razadyne is used to treat dementia. The list of side effects, precautions, and interactions with other medications can be more serious than the condition being treated (http://www.webmd.com/drugs/2/drug-93285/razadyne-oral/details#uses). Some of the side effects include: seizures, black/bloody stool, vomit that looks like coffee grounds, abdominal pain, severe dizziness, blurred vision, depression, insomnia, loss of appetite, headaches, and various allergic reactions. Although such side effects might not be as serious for a younger, healthier adult, it can be the difference between life and death for a frail older adult. Possible side effects for medical cannabis are mild when compared to many prescription drugs and, as mentioned above, there are compounds other than THC that can be

used for medicinal purposes without even moderately harmful side effects. In addition, options other than smoking are available, including oral ingestion or topical use.

<u>Methods of administration for medical marijuana</u>

There are different ways to obtain the benefits from medical marijuana, including smoking, vaporizing, tinctures, edibles, oils, lotions, and patches. Smoking is the most commonly known method of consumption. One "hit" delivers around 50mg of cannabinoids. The effects can be felt anywhere from instant relief to 15 minutes and can last between 1 and 4 hours. Vaporizing has similar effects to smoking, 95 percent of the vapor is cannabinoids, but is preferable for patients who want to avoid the more toxic elements of smoking.

Medical marijuana can also be taken orally by tinctures (sub-lingual sprays), edibles, or pills. Tinctures are made from alcohol-based cannabis extracts that can either be sprayed into the mouth or applied as drops on or under the tongue. This method is fast acting due to the rapid and effective absorption through the thin tissue of the mouth, which goes directly into the blood stream. Edibles infused with cannabis can be found in various types of foods and drinks. It can take between thirty minutes to an hour to feel the effects because it is broken down in the stomach and absorbed into the intestines. Cannabis oil in a capsule can be swallowed and has similar effects as the edibles.

Cannabis topicals can be administered as a lotion or patch, which are absorbed through the skin. The lotion starts working within minutes. The patch has a controlled release rate and has an onset of action within two hours (https://unitedpatientsgroup.com/resources/methods-of-consumption).

Polypharmacy: The "other" drug problem

Across the nation nearly 50 percent of older adults are taking upwards of 10 different medications to treat chronic illnesses, many of which may not be medically necessary (Maher, Hanlol, and Hajjar, 2014). This phenomenon is known as polypharmacy. Unfortunately, with polypharmacy comes an increased risk for negative health outcomes, such as dangerous drug interactions from lack of geriatric education in medical schools and communication between physicians. For example, many prescription drugs act differently in older patients than younger ones. A drug that has a long half-life will last even longer in the older patient. With only around 7 percent of physicians trained in geriatrics, it can be easily overlooked when prescribing medications to older patients.

Polypharmacy is also a very expensive practice that costs health plans approximately $50 billion annually (Bushardt et al., 2008). It leads to higher healthcare costs due to hospitalization from drug-related complications. The Institute of Medicine study (2006) found that there were at least 400,000 preventable adverse drug events every year in hospitals, which resulted in pushing up health care costs annually by approximately $3.5 billion. The other side of the problem is that prescription drugs can be very expensive and older adults are often unable to afford the medications, thus leading to the under treatment of pain.

So how might medical marijuana help to reduce the number of medications prescribed to older patients? Bradford and Bradford (2016) examined how implementing state-level medical marijuana laws changes prescribing patterns and patient expenditures in Medicare Part D for FDA-approved prescription drugs. The researchers looked at over 87 million prescriptions from the Medicare Part D database enrollees from 2010 to 2013. They focused on conditions where medical marijuana might serve as an alternative treatment, including anxiety, depression,

glaucoma, nausea, pain, psychosis, seizures, sleep disorders, and spasticity. They found that the availability of medical marijuana has a noteworthy effect on prescribing patterns and spending on Medicare Part D. Specifically, in states where medical marijuana was legal, physicians gave out 4,593 fewer prescriptions for all conditions in the study, except for glaucoma, and 1,826 fewer prescriptions specifically for pain medications annually per physician. Other findings show that Medicare Part D spending, for both program and enrollee spending, fell by $104.5 million in 2010. In addition, the cost savings had risen to $165.2 million by 2013. Overall, they suggested that if all states had implemented medical marijuana laws the estimated total savings to Medicare Part D would have been $468.1 million.

<u>Medical Marijuana for various age-related diseases</u>

Alzheimer's and Parkinson's Disease

Currently, there are around 5.2 million Americans age 65 and older diagnosed with Alzheimer's disease (AD) and 1 million diagnosed with Parkinson's. The cost of caring for Alzheimer's patients in the U.S. is estimated to be $236 billion. An estimated $117 billion is spent under Medicare and $43 billion under Medicaid (Alz.org fact sheet, 2016). The projected cost of Parkinson's in the U.S., including treatment, social security payments, and lost income from inability to work, is nearly $25 billion per year.

With multiple states recently passing legislation to legalize marijuana, the potential use of medical marijuana has been reintroduced as an alternative to pharmaceutical drugs on neurological disorders. A review of current scientific studies shows that it is possible for medical cannabis to provide symptomatic relief to patients afflicted with Parkinson's disease (Itay et al.,

2014). Other studies have demonstrated that the use of medical cannabis may moderate the progression of Alzheimer's disease (Watt and Karl, 2017).

Cannabinoid compounds have become potential therapeutic agents against AD and Parkinson's disease because of their known multifaceted neuroprotective properties (Aso, Juves, Maldonado, and Ferrer, 2013). So far, two types of cannabinoid receptors have been isolated for treatment of AD and Parkinson's disease. The CB1 receptor is contained predominantly in the central nervous system, whereas CB2 is found mostly in organs and cells of the immune system (Venderova´, Ru˚zˇicˇka, Vorˇı´sˇek, and Visˇnˇovsky´, 2004). Major attention has been paid to these specific receptors because targeting them may reduce neuro-inflammation and impaired memory without causing psychoactive effects (Campbell and Gowran, 2007).

Multiple studies have examined the effects of cannabinoids on older persons with Alzheimer's disease and found little to no adverse events in regards to safety and falls (Ahmed, van den Elsen, Colbers, van der Marck et. Al 2014; Ahmed, van den Elsen, Colbers, Kramers et.al, 2015; Ahmed, van der Marck, van den Elsen and Rikkert 2015; van den Elsen, Tobben, Ahmed, Verkes, et.al, 2017). Shelef and colleagues (2016) found that medical cannabis oil containing THC helped decrease delusions, agitation/aggression, irritability, apathy, sleep, and caregiver distress.

As mentioned earlier, current AD drugs have a number of unpleasant side effects such as hepatotoxicity and gastrointestinal disturbances. Overall, manipulation of the cannabinoid pathway offers an alternative approach for the treatment of AD that may be more effective than current treatment regimes. However, more research is needed to examine the long-term effects of medical marijuana on these neurological disorders.

Pain Management

Older adults are more likely than younger adults to experience pain due to chronic conditions and many rely on prescription opioids for pain management. More than 1 in 3 adults were given prescription painkillers in 2015, which surpassed tobacco use (SAMHSA, 2016). Prescription opioids can be dangerous or even deadly. Medical marijuana has the potential to help to reduce opioid abuse, mortality, and pain among older adults (Johnson et al., 2010; King, 2015). Older adults are increasingly abusing prescription painkillers and have increasing rates of accidental overdose (SAMHSA.gov, 2012). THC and cannabinoids bind to receptors and block out pain. Almost 10 percent of Americans use marijuana to control pain (Bronstein, Dhaliwal, and Leider, 2011). A 2015 study by the RAND Corporation found that those states with legalized marijuana dispensaries had a reduction in substance abuse treatment for opioids and reductions in opioid-related mortality. Another study of adults age 50 and older found that those living in states where medical marijuana is legal had reduced rates of pain and reduced work interference due to pain (Nichols, 2016).

Arthritis

Arthritis is a medical condition that results in swelling, stiffness, chronic pain, and decreased motion. Osteoarthritis is a type of degenerative arthritis that causes a wearing away of the cartilage between bones, resulting in chronic pain (Arthritis.org, 2016). Joints naturally produce cannabinoids, but over time with arthritis, their ability to do so declines. Injecting cannabinoids can decrease some of the pain, inflammation, and degeneration caused by arthritis and joint damage cause by osteoarthritis (Biro 2016; Ruhaak, et. al, 2011). Oral cannabinoids have been found to give minimal to moderate relief compared to placebo in those with musculoskeletal pain

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including rheumatoid arthritis and fibromyalgia (Biro, 2016). A review of 18 studies of the medical use of cannabinoids found that it was safe and modestly effective for rheumatoid arthritis and fibromyalgia (Lynch and Campbell, 2011). Medical marijuana has also been found to improve sleep, which is a common issue among those with arthritis.

Cancer

Cancer is the leading cause of death of both men and women aged 55-64 (CDC, 2014) and treatments often have several side effects including pain, nausea, and decreased appetite. Several drugs exist to help alleviate cancer treatment side effects including Marinol, which the DEA describes as the existing legal form of medical marijuana. Marinol is a delta-9-THC compound. Although somewhat effective, Marinol is metabolized by the body very quickly and only 10-20 percent of the oral dose actually reaches systemic circulation. By contrast, medical marijuana that is smoked is rapidly absorbed by the body and more of the medicinal compounds actually reach the body's systemic circulation. Marinol also has several precautions and side effects including seizure disorders, increased fall risk, problems with patients who have had heart problems, mental health problems, and issues with substance abuse (Mirinol.com, 2016). Trial studies have indicated that medical marijuana increases appetite and reduces nausea with few side effects (Koch et al., 2015). In a review of 28 studies, for example, medical marijuana was found to reduce nausea and vomiting compared to either active treatments or placebo although the results in some of the studies did not reach statistical significance (Whiting et al., 2015).

Osteoporosis

Osteoporosis occurs when the body makes too little bone, the body loses bone, or both

(NOF.org, 2016). One in two women and one in four men will break a bone by age 50 due to

osteoporosis (NOF.org, 2016). Cannabinoids play a key role in the metabolism of bone (Idris and

Ralston, 2010). Medical marijuana injections could help stop bone loss due to osteoporosis, but

few trials or research studies on its effectiveness exist.

Glaucoma

Glaucoma is a medical condition that causes damage to the optic nerve due to increased eye

pressure. Glaucoma primarily affects older adults (National Eye Institute, 2016). Studies have

found that medical marijuana reduces pressure inside eye reliving discomfort for three to four

hours (Tomida, Pertwee, and Azuara-Blanco, 2004; also see The National Academies of

Sciences, Engineering, Medicine, 2017 for a review). However, one small trial study (n=6;

Tomida et al., 2006) found no difference in intraocular pressure between glaucoma patients who

received cannabinoids versus a placebo and other drugs currently available might relieve pain for

longer.

Depression

Between 1 percent and 5 percent of older adults are depressed. That number rises among those

who receive home healthcare (13.5%) and for those who live in facilities (11.5%; CDC, 2016).

Depression is also common among older adults who have multiple health problems.

The research on medical marijuana and depression is still in the early stages and most

studies are based on non-human subjects. Medical marijuana has been found to reintroduce

cannabinoids into the brain of rats, which helps to replenish depletion and reduce chronic stress and depression.

Views are mixed whether medical marijuana leads to depression or if it treats depression (Lev-Ran, 2014). Mechoulam and Parker (2013) suggested that synthetic endocannabinoid-like compounds, such as cannabis, may be developed as a novel type of antidepressant. A concern about using medical marijuana to treat depression is that it may trigger schizophrenia, anxiety, depression, or psychosis in people at a higher risk of these conditions (Baker, 2010; Degenhardt et al., 2003; Large et al., 2011; van Laar et al., 2007). For example, a recent review of the relevant research literature revealed some association between the use of marijuana and psychosis, schizophrenia, suicidal thoughts, and social anxiety (see The National Academies of Sciences, Engineering, Medicine, 2017 for a review). More research is needed to determine if the benefits outweigh the risks and how to avoid high-risk populations.

MRSA in Nursing Homes

Methicillin-resistant staphylococcus aureus is a type of staph bacteria that can cause bloodstream infections, pneumonia, surgical site infections, sepsis, and even death (CDC.gov, 2016). The risk of contracting MRSA in nursing home facilities is high because it is spread by direct contact with infected skin or objects that were exposed to the bacteria. The most problematic issue with MRSA is that it has become resistant to many antibiotics, which makes it a serious threat to residents in nursing homes. Appendino and colleagues (2008) examined the effects of the five most common cannabinoids (THC, CBD, CBG, CBC, and CBN) on MRSA and found that all of the compounds showed potent antibacterial activity. Topical application was the most effective in reducing skin colonization from MRSA.

What's Blocking Research That Could Help Older Adults with Chronic Conditions?

Several organizations support medical marijuana including the American Nurses Association, American Osteopathic Association, Lymphoma Foundation of America, National Academy of Sciences, Institute of Medicine, New England Journal of Medicine, Florida Medical Association, American Cancer Society, and the American Medical Association. Additionally, in a 2015 Gallop poll, 70 percent favored making it legal for doctors to prescribe marijuana in order to reduce pain and suffering. With reputable organizations and a majority of people favoring making medical marijuana legal, why has opposition to legalization continued to be effective in most states?

One reason is due to fear and misunderstanding about the consequences of allowing medical marijuana, including making it easier for kids and teens to access the drug, driving while under the influence, and abuse. Studies in Colorado and Washington have shown that since medical marijuana was legalized, teen rates of use have been unchanged (Monitoring the Future Survey, 2015). In Colorado, there has been a slight increase in ER visits of children under 9 from accidental ingestion, but ERs and poison control centers are far more likely to see children who have ingested other substances like laundry detergent or crayons (Washington Post, 2016). Safety precautions can keep kids away from medical marijuana much like parents keep children away from gummy vitamins and flavored over-the-counter medicine. Furthermore, arrests in those states for marijuana have declined significantly for whites (saving the system millions of dollars), but not for racial/ethnic minorities. Traffic fatalities have also remained largely unchanged since medical marijuana was legalized, and one study found a 9 percent decrease after the legalization of medical marijuana (Anderson and Rees, 2011). Regarding the potential

for abuse, Wallace (2015) recommends that patients should be given a substance abuse evaluation before being prescribed medical marijuana if it is to be combined with opioids for pain management, and monitored through routine follow-ups to assess progress with treatment, side effects, compliance, and a treatment plan revision.

On the other hand, prescription opioids can be dangerous or even deadly for people of all ages. Currently, there are enough opioids prescribed each year to put a bottle in every household. Opioids can be dispensed as pills, patches or a flavored lollipop. The rate of children hospitalized for opioid poisoning increased 165 percent from 1997 to 2012, and the rate of toddlers being hospitalized has more than doubled (NPR, 2016). In general, opioid-related fatal poisonings have quadrupled over the last two decades (CDC, 2011). In 2010, prescription opioids were responsible for almost 60 percent (16,651) of all deaths due to drug overdoses in the U.S. (Jones, Mack, and Paulozzi, 2013). By contrast, there has never been a reported overdose due to marijuana (medical or otherwise). In addition, states that have instituted medical marijuana have a 24.8 percent lower annual opioid mortality rate than states without access to medical marijuana (Bachhuber et al., 2014; Hayes and Brown, 2014).

Another barrier is marijuana's classification. Marijuana is classified as a Schedule I drug—in the same class as heroin. This classification puts it as highly addicting with no medicinal value at all, which is contrary to the science and research available on the drug. Furthermore, this classification makes it difficult for any research to be conducted on the drug. In August of this year, the DEA once again rejected the opportunity to reschedule marijuana to a Schedule II drug—a classification that would allow for more research. The decision was largely based on the FDA's assertion that marijuana "does not have a currently accepted medical use in

treatment in the United States" (US DEA, 2016). As Ingraham of the Washington Post explains, "The FDA has never approved whole-plant marijuana as a drug… most drugs the FDA approves of are individual chemical compounds, not plants. Penicillin is an FDA-approved drug, for instance. The mold it's derived from is not." He goes on to say that, "… the DEA cannot change the legal status of marijuana unless the FDA determines it has a medical use. The FDA cannot determine it has a medical use in part because of the highly restrictive legal status of the drug." Pharmaceutical companies also stand to profit from marijuana's classification. Insys Therapeutics, for example, is the maker of a synthetic THC drug and has recently contributed $500,000 to oppose legislation in Arizona that would allow for full legalization (Washington Post, 2016).

Some states have enacted their own laws regarding marijuana that largely support physicians' standpoints that medical marijuana is beneficial to their patients. Other suggestions include keeping marijuana as a Schedule I drug, but allow for a caveat that it can be used for research or amend the Controlled Substances Act.

Conclusion

The miseducation about medical marijuana over the last 50 years has been detrimental to the progression of research regarding the effects it may have on countless diseases. With a rapidly aging population comes an increase in chronic disease. If medical marijuana is as effective and inexpensive as some of the recent studies have shown, and able to provide relief from the national epidemic of prescription painkiller overdoses, then the people with these debilitating diseases deserve an alternative. However, until the DEA changes medical marijuana from a

Schedule I drug, researchers will continue to face multiple hurdles in trying to understand its

benefits.

Table 1. States that Allow Medical Marijuana and Recreational Use

State	Medical Use Only	Medical and Recreational
Alaska		X
Arizona	X	
Arkansas	X	
California		X
Colorado		X
Connecticut	X	
Delaware	X	
Washington D.C.		X
Florida	X	
Hawaii	X	
Illinois	X	
Louisiana	X	
Maine		X
Maryland	X	
Massachusetts		X
Michigan	X	
Minnesota	X	
Montana	X	
Nevada		X
New Hampshire	X	
New Jersey	X	
New Mexico	X	
New York	X	
North Dakota	X	
Ohio	X	
Oregon		X
Rhode Island	X	
Pennsylvania	X	
Vermont	X	
Washington		X

References

Ahmed, A., van den Elsen, G., Colbers, A., van der Marck, M., Burger, D., Feuth, T., Rikkert, M., and Kramers, C. (2014). "Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: A randomized controlled trial." *European Neuropsychopharmacology*, 24, 1475–1482.

Ahmed, A., van den Elsen, G., Colbers, A., Kramers, C., Burger, D., van der Marck, M., and Rikkert, M. (2015). "Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia." *Psychopharmacology*, 232, 2587–2595. doi:10.1007/s00213-015-3889-y

Ahmed, A., van der Marck, M., van den Elsen, G., and Rikkert, M. (2015). "Cannabinoids in Late-Onset Alzheimer's Disease." *Clinical Pharmacology & Therapeutics*, 97(6), 597-606.

Anderson, D., & Rees, D. (2011). Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption. IZA Discussion Paper No. 6112. Retrieved from http://medicalmarijuana.procon.org/view.timeline.php?timelineID=000026

Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., Smith, E., & Rahman, M. (2008). "Antibacterial Cannabinoids from Cannabis sativa: A Structure-Activity Study." *Journal of Natural. Products*, 71(8), 1427-1430. doi:10.1021/np8002673

Aso, E., Juves, S., Maldonado, R., & Ferrer, I. (2013). CB2 Cannabinoid Receptor Agonist

    Ameliorates Alzheimer-Like Phenotype in AβPP/PS1 Mice. *Journal of Alzheimer's*

    Disease 35, 847–858. doi:10.3233/JAD-130137

Bachhuber, M., Saloner, B., Cunningham, C., & Barry, C. (2014). Medical Cannabis Laws

    and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. *JAMA Intern*

    Med., 174(10), 1668-1673. doi:10.1001/jamainternmed.2014.4005

Baker, A., Hides, L., & Lubman, D. (2010). Treatment of Cannabis Use Among People with

    Psychotic or Depressive Disorders: A Systemic Review. *Journal of Clinical Psychiatry*

    71(3), 247-254. doi:10.4088/JCP.09r05119gry

Biro, T. (2016). SP0107 Cannabinoids and Inflammation: Focus on the Joint. *Annals of the*

    Rheumatic Diseases 75, 26. doi:10.1136/annrheumdis-2016-eular.6417

Bradford, A. & Bradford, D. (2016). Medical Marijuana Laws Reduce Prescription

    Medication Use in Medicare Part D. *Health Affairs* 35 (7), 1230-1236.

    doi:10.1377/hlthaff.2015.1661

Bronstein, K., Dhaliwal, J., & Leider, H. (2011). Rates of Inappropriate Drug Use in the

    Chronic Pain Population: An Update. *The Journal of Pain* 12(4), P5.

    doi:10.1016/j.jpain.2011.02.020

Bushardt, R., Massey, E., Simpson, T., Ariail, J., & Simpson, K. (2008). Polypharmacy: Misleading, but Manageable. *Clinical Interventions in Aging* 3(2), 383-389

Campbell, V.A. & Gowran, A. (2007) Alzheimer's disease: taking the edge off with cannabinoids? *British Journal of Pharmacology* 152, 655–662. doi:10.1038/sj.bjp.0707446

Centers for Disease Control. (2016). Depression is Not a Normal Part of Growing Older. Retrieved from http://www.cdc.gov/aging/mentalhealth/depression.htm

Centers for Disease Control. (2014). Leading Causes of Death. Retrieved from http://www.cdc.gov/injury/wisqars/leadingcauses.html

Centers for Disease Control. (2011). Vital Signs: Overdoses of prescription Opioid Pain Relievers—United States, 1999-2008. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm

Degenhardt, L., Hall, W. & Lynskey, M. (2003). Exploring the association between cannabis use and depression. *Addiction*, 98, 1493–1504. doi:10.1046/j.1360-0443.2003.00437.x

Hayes, M., & Brown, M. (2014). Legalization of Medical Marijuana and Incidence of Opioid Mortality. *JAMA Internal Medicine*, 174(10), 1673-1674. doi:10.1001/jamainternmed.2014.2716.

Idris, A., & Ralston, S. (2010). Cannabinoids and Bone: Friend or Foe? *Calcification Tissue*

    Int. 87(4), 285-297. doi:10.1007/s00223-010-9378-8

Institute of Medicine. (2006). Medication Errors: IOM Report.

    https://themgo.com/MGOPublications/QualityMatters/MedicationErrorsIOMReportFall2

    006.aspx

Itay, L., Treves, T., Roditi Y., & Djaldetti, R. (2014). Cannabis (Medical Marijuana)

    Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label

    Observational Study. *Clinical Neuropharmacology*, 37(2), 41-44.

    doi:10.1097/WNF.0000000000000016

Johnson, J., Burnell-Nugent, M., Lossignol, D., Ganae-Moton, E., Potts, R., & Fallon, M.

    (2010). Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group

    Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in

    Patients with Intractable Cancer-Related Pain. *Journal of Pain and Symptom*

    Management, 39(2), 167-179. doi:10.1016/j.jpainsymman.2009.06.008

Jones, C., Mack, K., & Paulozzi, L. (2013). Pharmaceutical Overdose Deaths, United States,

    2010. *Journal of the American Medical Association* 309 (7), 657-659.

    doi:10.1001/jama.2013.272

King, S. (2015). Medical marijuana for pain: what the evidence shows. *Psychiatric Times*, 32(8), 4.

Koch, M., Varela, L., Kim, J., Kim, J., Hernandez-Nuno, F., Simonds, S., Castorena, C., et al. (2015). Hypothalamic POMC neurons promote cannabinoid-induced feeding. *Nature*, 519, 45-50. doi:10.1038/nature14260

Large M., Sharma S., Compton MT., Slade T., & Nielssen O. (2011). Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-analysis. *Arch Gen Psychiatry*, 68(6), 555-561. doi:10.1001/archgenpsychiatry.2011.5

Lev-Ran, S., Roerecke, M., Le Foll, B., George, T., McKenzie, K., & Rehm, J. (2014). The Association Between Cannabis Use and Depression: A Systemic Review and Meta-Analysis of Longitudinal Studies. *Psychology Medicine* 44(4), 797-810. doi:10.1017/S0033291713001438

Lynch, M., & Campbell, F. (2011). Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systemic Review of Randomized Trials. *British Journal of Clinical Pharmacology* 72(5), 735-744. doi:10.1111/j.1365-2125.2011.03970.x

Maher, R., Hanlon, J., & Hajjar, E. (2014). Clinical Consequences of Polypharmacy in Elderly. *Expert Opin Drug Saf.* January, 13(1), 1-11. doi:10.1517/14740338.2013.827660

Mechoulam, R., & Parker, L. (2013). The Endocannabinoid System and the Brain. *Annual Rev. Psychol.*, 64, 21–47. doi:10.1146/annurev-psych-113011-143739

Monitoring the Future Survey. (2015). Retrieved from http://www.monitoringthefuture.org/

National Academies of Sciences, Engineering, and Medicine. (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press. doi:10.17226/24625.

National Eye Institute. (2016). Facts About Glaucoma. Retrieved from https://nei.nih.gov/health/glaucoma/glaucoma_facts

National Osteoporosis Foundation. (2016). Retrieved from https://www.nof.org/

Nicholas, L. & Maclean, J. (2016). The Impact of Medical Marijuana Laws on the Labor Supply and Health of Older Adults: Evidence from the Health and Retirement Study. NBER Working Paper No. 22688. Retrieved from http://www.nber.org/papers/w22688

Ruhaak, L., Felth, J., Karlsson, Pernilla, Rafter, J., Verpoorte, R., & Bohlin, L. (2011). Evaluation of the Cyclooxygenase Inhibiting Effects of Six Major Cannabinoids Isolated from Cannabis Sativa. *Biological and Pharmaceutical Bulletin* 34(5), 774-778. doi:10.1248/bpb.34.774

Shelef, A., Barak, Y., Berger, U., Paleacu, D., Tadger, S., Plopsky, I., & Baruch, Y. (2016).

Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological

Symptoms of Dementia: An-Open Label, Add-On, Pilot Study. *Journal of Alzheimer's*

Disease 51, 15–19. doi:10.3233/JAD-150915

Solowij, N., Jones, K., Rozman, M.,Davis, S., Ciarrochi, J., Heaven, P., Lubman, D., & Yucel,

M. (2011). Verbal learning in memory in adolescent cannabis users, alcohol users and

non-users. *Psychopharmacology* 216, 131–144. doi:10.1007/s00213-011-2203-x

Substance Abuse and Mental Health Services Administration. (2012)." Results from the 2012

National Survey on Drug Use and Health: Summary of National Findings." Retrieved

from

https://www.samhsa.gov/data/sites/default/files/NSDUHnationalfindingresults2012/NSD

UHnationalfindingresults2012/NSDUHresults2012.htm#ch8.3

Substance Abuse and Mental Health Services Administration. (2016). "Specific Populations and

Prescription Drug Misuse and Abuse." Retrieved from

http://www.samhsa.gov/prescription-drug-misuse-abuse/specific-populations

Tomida, I., Pertwee, R., & Azuara-Blanco, A. (2004). Cannabinoids and glaucoma. *Br J*

Ophthalmol 88, 708-713. doi:10.1136/bjo.2003.032250

Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. (2006). "Effect of

sublingual application of cannabinoids on intraocular pressure: a pilot study." *J Glaucoma*. 15, 349-353.

U.S. Drug Enforcement Agency. (2016). Retrieved from https://www.dea.gov/druginfo/ds.shtml

Van den Elsen, G., Tobben, L., Ahmed, A., Verkes, R., Kramers, C., Marijnissen, R., Rikkert, M., and van der Marck, M. (2017). "Effects of tetrahydrocannabinol on balance and gait in patients with dementia: A randomized controlled crossover trial." *Journal of Psychopharmacology*, 31(2), 184-191. doi: 10.1177/0269881116665357

Van Laar, M., Van Dorsselaer, S., Monshouwer, K. & De Graaf, R. (2007). Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction*, 102, 1251–1260. doi:10.1111/j.1360-0443.2007.01875.x

Venderovaˊ, K., Ru˚zˇicˇka, E., Vorˇıˊsˇek, V., & Visˇnˇovskyˊ, P. (2004). Survey on Cannabis Use in Parkinson's Disease: Subjective Improvement of Motor Symptoms. *Movement Disorders,* 19 (9), 1102-1106. doi:10.1002/mds.20111

Wallace, M. & Furnish, T. (2015). What Steps Should be Taken to Integrate Marijuana into Pain Regimens? *Pain Management* 5(4), 225-227. doi:10.2217/pmt.15.20

Washington Post. (2016). Colorado Gives Marijuana Candy a New Look to Avoid Confusion.

Retrieved from https://www.washingtonpost.com/national/health-science/colorado-gives-marijuana-candy-a-new-look-to-avoid-confusion/2016/09/30/34478cae-86e9-11e6-b57d-dd49277af02f_story.html

Washington Post. (2016). A maker of deadly painkillers is bankrolling the opposition to legal marijuana in Arizona. Retrieved from https://www.washingtonpost.com/news/wonk/wp/2016/09/09/a-maker-of-deadly-painkillers-is-bankrolling-the-opposition-to-legal-marijuana-in-arizona/?utm_term=.bdec569e7654

Watt, G. and Karl, T. (2017). "In vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease." *Frontiers in Pharmacology*, 8, 1-7. doi:10.3389/fphar.2017.00020

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. (2015). "Cannabinoids for Medical UseA Systematic Review and Meta-analysis." *JAMA*. 313, 2456-2473. doi:10.1001/jama.2015.6358.