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Scientific Evidence Concerning Medical Marijuana Use

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1 Scientific Evidence Concerning Medical Marijuana Use

12 CE Assessment Questions

Learning Objectives

1. Describe the history of the medical use of marijuana.
2. Identify three of the active substances within cannabis that have been evaluated for medical use.
3. Describe several safety concerns with the use of marijuana.
4. Identify three proposed medical uses of marijuana that have evidence to support its use.
5. Explain why further research is needed for two proposed uses.

Marijuana, cannabis, and hashish are terms for different forms of a naturally occurring substance that generates all kinds of connotations and emotions. Historically this substance has been used recreationally and medicinally. Medical use of marijuana has generated much public interest in recent years. This report will assess the current knowledge on the therapeutic potential of cannabinoids. The history of medical marijuana use, its pharmacologic potential, untoward effects and common uses are reviewed with a summary of the scientific evidence that is currently available.

History

Originating from Central Asia, cannabis is one of the oldest psychotropic drugs known. According to archeological discoveries, cannabis has been known in China at least since the Neolithic period, around 4000 BC.[1] In 2737 BC the Emperor of China, Shen Nung, described the properties and therapeutic uses of cannabis in his compendium.[2] Soon thereafter, the plant was cultivated for its fiber, seeds, recreational consumption and use in medicine. From China, cannabis spread to India, where in 1839 William O'Shaughnessy, a British physician and surgeon working in India discovered the analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties of cannabis. The medical use of cannabis expanded quickly from there.[3] It was in 1854 that cannabis was listed in the United States Dispensatory and sold freely in pharmacies of Western countries.[4] However, over the next several decades the use of cannabis became reportedly associated with mental health issues, moral and intellectual deterioration, violence and various crimes. The American authorities condemned its use after the prohibition of alcohol was lifted. Thus, in 1937, under pressure from the Federal Bureau of Narcotics, and against the advice of the American Medical Association, the U.S. Government introduced the *Marihuana Tax Act:* a tax of $1 per ounce was collected when marijuana was used for medical purposes and $100 per ounce when it was used for unapproved purposes.[5] Cannabis was removed from the United States Pharmacopoeia in 1942, thus losing its therapeutic legitimacy. Despite its illegality, patients have continued to obtain cannabis for self-medication.

Chemistry

Cannabis is a leafy annual, with some species attaining heights of more than 10 feet. Each leaf has 5 to 10 leaflets radiating from the top of the stalk. These leaflets are soft textured, roughly 7 – 10 inches long, with regular dentations like a saw blade.

The University of Iowa

The glandular hairs on the leaflets produce a resin mixture.[6] The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco but referring today to dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant. There are several species of cannabis, with the most relevant being *Cannabis sativa, Cannabis indica* and *Cannabis ruderalis.*[7] Cannabis contains more than 460 known isolated chemicals, greater than 60 of which are grouped under the name cannabinoids. Delta-9-tetrahydrocannabinol, a cannabinoid known as THC, is the major psychoactive ingredient of cannabis. It has been synthetically prepared and is available under the name dronabinol. Other cannabinoids include delta-8-tetrahydrocannabinol, cannabinol, and cannabidiol (CBD), but they are present in small quantities and have no significant psychotropic effects compared to THC.[1] In addition to these compounds, marijuana contains alkaloids, steroidal compounds and mixtures of volatile components.[6]

Uses and Pharmacology

Marijuana exerts its action in the body following inhalation of the smoke or oral ingestion.[6] Once inhaled, THC and many more of the chemical components are rapidly absorbed and distributed throughout the tissues of the body, particularly to tissues with high lipid content. The THC and some of the other cannabinoids exert their action by binding to specific CB_1 and CB_2 cannabinoid receptors. The medical use of marijuana had been looked down upon since 1942, but interest began to rise again in 1978 when Robert Randal, a glaucoma patient, began treating himself by smoking marijuana.[8] In response to a lawsuit filed by the patient, the U.S. Government created a compassionate program for medical marijuana. Under this program, the U.S. Government supplied marijuana to a limited number of patients with debilitating diseases. In 1991, President Bush closed the program to new candidates due to a surge in new applications from AIDS patients. Seven of the original 20 patients continue to receive their marijuana. During this time there has also been renewed interest in the plant's analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties. These will be reviewed in detail after a brief discussion about the undesirable effects.

Toxicology

Marijuana has a strong potential for abuse and is classified as a schedule I drug.[6] It can be harmful to the heart, lungs, brain, endocrine system, and eyes. The actual toxicity from overdose is very rare. The dose necessary to be lethal to 50% of rats (LD50) is 45 mg/Kg or 30 mg/Kg if they are pregnant.[9;10] The LD50 is the same for either intravenous or inhalation, but would be much higher for oral administration.[10] The authors observed that some of the behavioral and motor side effects occurred at the same mg/Kg dose in both rodents and man so they presumed that the LD50 dose from rats would correspond to approximately 40 mg/Kg in humans. Each cigarette has about 20 mg, so it would take about 2 cigarettes for every Kg a person weighs to be potentially lethal in 50% of humans.

The danger from cannabis is not in its direct toxicity, but after ingestion of marijuana, users may experience many undesirable effects including tachycardia, an increase in blood pressure and several neuro-psychoactive effects. Marijuana impairs reaction time, motor coordination, and visual perception. It can also produce panic attacks, "flashbacks", impaired cognition and other emotional disturbances.[11;12] Reduced sperm counts, sperm structural abnormalities, and motility changes have all been reported. Abnormal menstruation has been associated with long-term marijuana use. Marijuana ingestion may also cause dry mouth, nausea, and vomiting. Some people develop tolerance to these undesirable effects on repeated exposure. It has also been observed that some people seem to be more susceptible to the desirable medical effects while others are more prone to the undesirable physiological consequences.

Current Uses

Considerable research has been conducted over the past 25 years to evaluate the benefits and the risks associated with the use of medical marijuana. Numerous case reports exist of patients testifying to the effectiveness of marijuana in various conditions. But this manuscript will focus on summarizing experimental studies that have been conducted for these various conditions.

Analgesia

Four studies have compared smoked marijuana to a placebo cigarette for pain relief in patients with neuropathic pain.[13-16] Generally they found that the use of marijuana leads to significant improvement in pain assessment compared to placebo, but there were only small numbers of patients (15-50). In two of the studies the placebo response was fairly high (46% treatment response vs 18% placebo response and 52% vs 24% in the other study) calling into question the validity of the difference.[13;14] Wallace and colleagues[15] studied four different cigarettes; a placebo (no THC), a low dose (2% THC), a moderate dose (4% THC) and a high dose (8% THC). They observed pain relief, a reduction of visual analog pain scale scores, at a moderate dose (4% THC), but increased pain at a higher dose (8% THC) following capsaicin-induced pain. Psychoactive side effects including cognitive and memory impairment were present in many of the subjects, but were generally mild. Wilsey and coworkers[16] conducted a placebo-controlled randomized crossover study in 27 patients with neuropathic pain. They found that smoking marijuana with 3.5% or 7% THC significantly reduced pain on a visual analog scale compared to placebo. There were some acute cognitive effects with the marijuana, but they were judged to be well tolerated.

Smoked marijuana may not provide consistent relief of pain without the concurrent presence of undesirable side effects. Consequently, two components of marijuana, THC and cannabidiol (CBD) have both been prepared alone as an oromucosal spray. Two studies[17;18] have shown that THC spray alone and those two studies plus four additional[19-22] have shown that THC combined with CBD as a spray are better than placebo for the relief of pain. Two studies focused on neuropathic pain, two with central pain of multiple sclerosis, one unspecified chronic pain and the other chronic pain of rheumatoid arthritis. Each of the studies demonstrated a statistically significant reduction of pain intensity score compared to placebo. The percent improvement in pain intensity scores from the treatment compared to placebo were 22%,

21%, 10%, 13%, 19% and 8% in the various studies. In addition, four studies showed an improvement in quality of sleep from a quality of life survey. However, adverse events were common and several patients could not complete the study because of these events which included dizziness, sedation, feeling intoxicated and nausea. Of the patients that received active treatments 17 out of 269 (13.75%) discontinued treatment because of the side effects. CBD spray alone was no better than placebo with regard to improvement of pain intensity scores.[17;18] When CBD was administered orally it did not provide significant analgesic relief.[18;23]

Three studies[24-26] indicated that when oral THC (dronabinol 5-20 mg) was administered there was no change in visual analog pain assessments in 12 healthy volunteers, in one patient with chronic gastrointestinal pain, or in 40 patients with post-hysterectomy pain when compared to placebo. Noyes and coworkers[27;28] looked at cancer pain and evaluated analgesic response after a single dose of placebo, 5 mg, 10 mg, 15 mg or 20 mg THC. They reported that a higher dose (15 or 20 mg) of oral THC provided analgesia based on an hourly questionnaire administered by a research nurse in a clinical research center. However, the authors reported that the side effects of somnolence, dizziness, ataxia and blurred vision would not make it a practical choice for analgesia in chronic cancer pain. They reported that the analgesic effect of 10 mg of THC was similar to 60 mg of codeine and the analgesic effect of 20 mg THC was equivalent with 120 mg of codeine, but the side effects were much greater than codeine. Svendsen and coworkers[29] evaluated the analgesic effect of 10 mg of dronabinol daily for 3 weeks compared to placebo in 24 multiple sclerosis patients with neuropathic pain. The estimated relative reduction in pain scores between dronabinol and placebo was -20.5% (95% CI -37.5 to -4.5). The number of patients with adverse effects in the dronabinol group was higher, but no one was withdrawn from the trial due to these effects, which were mostly dizziness and light-headedness. Raft and coworkers[30] evaluated the intravenous administration of THC and found no relief of pain, but it produced bothersome euphoria and dysphoria.

Additional synthetic analogs identified from the cannabis plant have also been studied for the relief of pain. Nabilone is one of those compounds that has been identified and has been approved since 1985 for use as an antiemetic. It is marketed under the brand name Cesamet®, a schedule II controlled substance. Three studies[31-33] have looked at its use in pain in 40 patients with fibromyalgia, 30 patients with unspecified chronic pain and in 13 patients with chronic upper motor neuron syndrome. It was found that from 0.25 to 1 mg, given up to twice a day, is better than placebo as an adjunct for the relief of pain when assessed by visual analog scales and quality of life assessments. A drop of 2.0 points on the visual analog scale was typically seen when the dose was 1 mg twice a day. Side effects that included dry mouth, limb weakness, and drowsiness were generally mild. Only one out of the 83 patients dropped out of the study, and that was due to lower limb weakness. Another synthetic analog, benzopyranoperidine, was investigated for its effect in chronic cancer pain and in one study[34] it was shown to be superior to placebo in 15 patients when measuring pain intensity, and in another[35] in which it was no better than placebo in 35 patients. In a study in 21 patients the analog CT-3 was shown to be effective in reducing chronic neuropathic pain when compared to placebo (11.5% reduction in VAS pain intensity compared to placebo 9.9% reduction, P=0.02), but no further studies have been published.[36] Levonantradol given intramuscularly was also shown to be effective in 56 postoperative or trauma patients, but 67% of the patients had drowsiness or other bothersome side effects.[37] It appears that from all these studies, further research is still needed to identify the specific component of cannabis that is beneficial for providing pain relief, without causing undesirable effects as many of these studies have shown.

Appetite Stimulant

Abrams and coworkers[38] compared smoking marijuana to oral THC and to placebo in adults with HIV. After 21 days the oral group and smoking group had larger weight gains (3.0 Kg and 3.2 Kg) compared to placebo (1.1 Kg). Three of the 46 patients in the two treatment groups dropped out due to neuro-psychiatric troubles. The authors concluded that the treatment was more effective than placebo but they were concerned about how well the treatment would compare to other currently used appetite stimulants. Strasser and coworkers[39] used a plant extract that contained THC (2.5 mg) and CBD (1 mg) and found that in 164 patients that it was no better than placebo as an appetite stimulant.

Jatoi and colleagues[40] compared dronabinol 2.5 mg (oral THC) with megestrol 800 mg and found that megestrol was significantly better in stimulating appetite and weight gain compared to dronabinol and the combination did not provide any additional benefit over megestrol alone. Beal and coworkers[41] showed an increase in appetite, but not in weight gain. In 12 patients Struwe[42] demonstrated a short term benefit for dronabinol. Side effects were generally well tolerated, but occasional severe adverse events included dizziness, drowsiness and confusion. Dronabinol may have some benefit as an appetite stimulant, but it is not free of the neuro-psychiatric adverse effects.

Anti-Emetic

Emesis associated with chemotherapeutic agents is a major problem. Three studies have examined the role of smoking marijuana for relief of chemotherapy induced nausea and vomiting. Chang and coworkers[43] showed that oral THC alone given at 10 mg/m^2 for five doses, or combined with smoking marijuana in 15 patients with low emetogenic chemotherapy resulted in a superior antiemetic effect compared to placebo in reducing the number of vomiting episodes ($P<0.02$), the degree of nausea ($P<0.01$), the duration of nausea ($P<0.01$), and the volume of emesis ($P<0.001$). There was a 72% incidence of nausea in the osteogenic sarcoma patients receiving high dose methotrexate (low emetogenic potential) and on placebo, a 44% incidence when measured plasma THC levels were < 5.0 ng/ml, 21% for levels 5-10 ng/ml and 6% when THC levels were > 10 ng/ml. However, a later study by the same author[44] in 8 patients with soft tissue sarcomas and who receiving cyclophosphamide and doxorubicin (both with moderate emetogenic potential) found that this was no better than placebo in reducing the number of episodes, the degree of nausea, the duration of nausea or the volume of emesis and that there were significant undesired effects, 75% of the patients experiencing euphoria and short episodes of tachycardia. Levitt and colleagues[45] reported that when smoking marijuana was added to 15 mg of oral THC, given for 4 doses in cancer patients receiving highly emetogenic chemotherapeutic agents, that only 25% saw improvement in the rate of emesis, while 35% had adverse effects that included distortions of time or hallucinations.

Oral THC (dronabinol) has been compared to placebo in five studies[43;44;46-48]. The previous paragraph talked about two studies Chang and coworkers conducted with oral THC combined with smoking marijuana. When they looked at just oral THC the results were no different than the combination, which was effective when patients received high dose methotrexate (low emetogenic potential) and ineffective with cyclophosphamide and doxorubicin (moderate emetogenic potential). . Frytak and coworkers[46] compared oral THC (n=38) to placebo (n=37) in patients with gastro-intestinal carcinoma who were receiving moderately emetogenic chemotherapy. After day 1 of the treatment, 42% of the oral THC patients experienced no nausea or vomiting, 5% had nausea only and 53% had nausea and vomiting. In the placebo group 19% had no nausea or vomiting, 16% had nausea alone and 65% had nausea and vomiting (P=0.049). Kluin-Neleman and colleagues[47] in a small group of 9 lymphoma patients that were receiving high emetogenic therapy demonstrated a significant reduction in the incidence of nausea and vomiting but a patient questionnaire indicated that most patients preferred the nausea and vomiting rather than experience the side effects (82% dizziness, 45% hallucinations, 36% euphoria, 36% drowsiness, 18% derealization and 18% concentration disorder). Sallan and coworkers[48] also found the antiemetic effect of THC to be superior to placebo in 20 adults with various tumors who received moderate or highly emetogenic chemotherapy. Oral THC patients who experienced 50% or greater reduction of nausea and vomiting episodes were 14 out of 20, while 0 patients out of 22 who received placebo had a 50% or greater reduction in nausea and vomiting episodes (P<0.001). Euphoria was experienced by 81% of the oral THC patients.

Most of these studies indicated that side effects were common and generally the placebo response was very large so it is important to know how oral THC compares to other antiemetic treatments. Two studies[46;49] have demonstrated that dronabinol is equally effective with prochlorperazine, but that it does have more side effects. Frytak and colleagues[46] compared the occurrence of nausea and nausea plus vomiting on the first day following highly emetogenic therapy and found that in the prochlorperazine group (n=41) that 2% had nausea, 56% had nausea and vomiting and 42% had none while in the dronabinol group (n=38) 5% had nausea, 53% had nausea and vomiting and 42% had none. These differences were not statistically significant. Also on days 2 to 4 when the chemotherapy was not as emetogenic there were also no differences between the two active treatment groups. Sedation and coordination problems were significantly higher in the dronabinol group compared to placebo and to prochlorperazine. Fourteen of the 116 patients refused to continue in the study due to the central nervous system side effects, one in the placebo group, one in the prochlorperazine group and 12 in the dronabinol group. Ungerleider and coworkers[49] evaluated 172 patients with various types of cancer and levels of emetogenic chemotherapy in a randomized double-blind crossover study. They did not find any difference between the two treatment groups with the nausea scale that was utilized. They did document a significant increase in the drug related adverse effects (P<0.05) in the dronabinol group.

Three additional studies[50-52] have demonstrated that dronabinol is superior to prochlorperazine but acknowledged that oral THC does cause significant dysphoria. McCabe and coworkers[50] evaluated 36 patients in a crossover randomized controlled trial with several types of cancers and receiving chemotherapeutic agents with various levels of emetogenic potential. They found that 64% (n=23) of the patients responded to the oral THC at a dose of 15 mg/m^2, while only 1 out of 36 responded to the prochlorperazine based on diaries that recorded all nausea and vomiting episodes. This was significantly better, but all experienced sensorial changes on the dronabinol. Nineteen reported a pleasant "high" and 17 reported an unpleasant dysphoria. This dysphoria included episodes of dizziness, hallucinations, memory-lapses and paranoia. Orr and colleagues[51] also included patients with various types of tumors and chemotherapeutic agents with varying levels emetogenic potential. Dronabinol dosed at 7 mg/m^2 resulted in 40 out of 55 having no nausea while prochlorperazine at 7 mg/m^2 had 8 out of 55 patients nausea-free (P<0.05). The oral THC group had 82% of patients experiencing euphoria, 28% sedated and 21% having a loss of physical or emotional control. The prochlorperazine group had 26% with sedation and 22% with dizziness. Sallan and fellow researchers[52] found that dronabinol provided complete relief of nausea in 36 of 79 cases while prochlorperazine worked in 16 of 78 cases. When asked which drug they preferred, 20 out of 25 respondents preferred the dronabinol. A complete response was reported by 36 of the oral THC patients, and 32 experienced a "high".

Lane and coworkers[53] suggested that when oral THC was added to prochlorperazine the combination was more effective than either agent alone, again there were significant dysphoric effects. A randomized parallel group study of 62 patients with mild to moderate emetogenic chemotherapy reported the results with several outcome measures. Many studies indicate that if a patient has two or fewer episodes of nausea or vomiting then they have adequate antiemetic control. Utilizing this measure, there were no significant differences in the percent of patients achieving adequate control between the dronabinol 10 mg every 6 hours (41%), the prochlorperazine 10 mg every 6 hours (30%) and the combination group that received both drugs (47%). However, when the outcome was the median duration of nausea or vomiting there was a significant decrease (P<0.001) with a 2 minute median duration in the combination group compared to 5 minute median duration in either single agent group. When the severity of the nausea was subjectively assessed using a visual analog scale the severity of the nausea was markedly less for the combination than for either agent alone (P<0.001). Neuropsychotropic side effects were reported in 62% of the dronabinol group, 29% in the prochlorperazine group and 55% in the combination group.

Colls and colleagues[54] reported that dronabinol was no different in efficacy from metoclopramide or thiethylperazine, but that it was not recommended because of the undesirable adverse events. A randomized double-blind crossover was conducted in 35 patients with various solid tumors who were receiving cyclical mild to moderate emetogenic chemotherapy. Treatments consisted of dronabinol 4 mg/0.33 m^2 2 hours before treatment and 2 and 6 hours after treatment or thiethylperazine 2.2 mg/0.33 m^2 2 hours before treatment and 2 and 6 hours afterwards, or metoclopramide 1.5 mg/0.33 m^2 IV just before chemotherapy. Patients all received 6 cycles of chemotherapy and received each therapy twice, assigned in a random order. There was no significant difference in the emetic effect for the three treatment groups (P>0.01), but the side effects, mostly neuropsychiatric, were significantly higher (P<0.01) for the oral THC compared to either the metoclopramide or the thiethylperazine. Patients also recorded their level of distress during the first 6 hours after chemotherapy. Patient distress was

significantly greater for dronabinol compared to both agents (P<0.02). Haloperidol and oral THC were also shown to be equally effective, but that the side effects were more pronounced with THC.[55] There were 52 patients in a randomized controlled cross-over trial where patients received 10 mg of oral THC or 2 mg of haloperidol 2 hours before and 30 minutes before chemotherapy, 1 hour afterwards and every 3-4 hours as needed up to 8 doses. There were no significant differences in the efficacy measurements; 41% of patients (or adult companion) rated oral THC as effective in preventing nausea compared to 37% for haloperidol, 51% rated it as effective in relief of nausea and vomiting for oral THC compared to haloperidol and mean vomiting episodes of 9.9 for dronabinol compared to 13.2 for haloperidol. The authors reported that THC was clearly more likely to produce moderate to severe side effects (25% vs 6%), but indicated that none of them were serious when the patient was under close observation. Gralla and coworkers[56] also showed metoclopramide to be superior to dronabinol with the side effects being similar. The randomized parallel group study in 31 patients receiving highly emetogenic chemotherapy resulted in significantly fewer episodes of vomiting (P<0.02), for patients on metoclopramide compared to the oral THC, but the volume of emesis and the median duration of vomiting was not significantly different (P>0.05). The side effects of dizziness, dry mouth and "high" were more common with the THC than with the metoclopramide. The evidence from all these comparative effectiveness studies suggests that as an antiemetic oral THC may be more effective than prochlorperazine, but not the other agents and that side effects may nullify this potential benefit.

Nabilone, a synthetic cannabinoid, has also been studied as an oral antiemetic in the treatment of refractory chemotherapy-induced nausea/vomiting in patients that have failed to respond to traditional antiemetic therapy.[57] Fifteen studies were conducted during the 1970's and 1980's where nabilone was administered orally as an antiemetic to 600 patients suffering from various types of cancers.[58] Nabilone 2 mg given twice daily demonstrated superiority to: placebo with fewer nausea and vomiting episodes in three randomized controlled trials in patients receiving chemotherapy with various emetogenic potential[59-61]; alizapride that was given as 150 mg three times a day to testicular cancer patients with highly emetogenic chemotherapy where 65% of patients receiving nabilone had complete relief compared to 30% for the alizapride[62]; prochlorperazine where 7 randomized controlled trials with a crossover design demonstrated that nabilone significantly deceased the rate of nausea and vomiting and/or was preferred over prochlorperazine[63-69]; and domperidone where nabilone significantly decreased the number of vomiting episodes in the patients who had all received highly emetogenic chemotherapy[70;71]. It was demonstrated to be equivalent to metoclopramide with no difference in the number of vomiting episodes for each treatment in 32 patients that had received highly emetogenic chemotherapy[72] and chlorpromazine with no difference in the number of vomiting episodes in 20 patients receiving highly emetogenic chemotherapy[73]. Side effects in all of these studies were often evident for nabilone, including drowsiness, dizziness and mood changes, but benefits were judged to outweigh the risks. The results of these randomized controlled studies led to the approval of the drug in 1985. Nabilone, marketed under the brand name Cesamet®, is a schedule II controlled substance with an antiemetic recommended adult dosage of 1 or 2 mg twice daily.[57]

One additional synthetic analog, levonantradol, was evaluated at 0.5, 0.75 and 1 mg IM for 4 doses in a single blind randomized parallel group study of 108 patients who were receiving highly emetogenic chemotherapy and where it was shown to be better than chlorpromazine 25 mg IM, but neither drug was judged to provide adequate emesis relief.[74] Researchers have identified some specific components of cannabis that are effective in suppressing emesis and have been able to minimize the potential for undesirable effects. However, the American Society of Clinical Oncology Guidelines for Antiemetics in Oncology (Updated 2006) do not recommend any cannabinoid or derivative as first line agents to treat chemotherapy induced emesis.[75] They recommend that cannabinoids, and other lower therapeutic index antiemetics, should be reserved for patients intolerant or refractory to 5-HT_3 serotonin receptor antagonists, dexamethasone and aprepitant.

Muscle Relaxant

Numerous disorders have been treated with cannabis based on its proposed effects on relaxing muscles. It has been used to relieve muscle spasms in multiple sclerosis, to relax smooth muscles in patients with glaucoma, to reduce muscle rigidity and spasms in Parkinsonism patients and relieve the involuntary muscle movements in patients with Tourette's Syndrome. Greenberg and coworkers[76] evaluated smoking marijuana compared to placebo to help relieve the muscle spasticity that plagues many multiple sclerosis (MS) patients. In the double-blind randomized placebo controlled study in 10 patients with spastic multiple sclerosis patients reported that they often felt that they were getting better. However, posture measurements were evaluated and clearly demonstrated (P<0.0025) that marijuana smoking further impaired posture and balance in patients with spastic MS when comparisons were made pre- and post-smoking and when compared to placebo. Freeman and colleagues[77] in a randomized placebo controlled parallel group trial of 630 stable MS patients with muscle spasticity (the CAMS study) did show an improvement in bladder spasms in patients with MS [38% decrease in urge incontinence episodes in the cannabis extract group (P=0.005 compared to placebo), 33% decrease in the oral THC group (P=0.039 compared to placebo) and 18% decrease in the placebo group], even though there was no motor improvement following the oral administration of the THC extract [mean reduction in total Ashworth score compared to placebo 0.32 (95% CI -1.04 to 1.67) and for the dronabinol compared to placebo 0.94 (95% CI -0.44 to 2.31)].

Four studies[78-81] have shown a partial effect from oral THC, in a few of the patients, but these were often patient perceived benefits and most authors concluded more research is needed. Clifford[78] in 8 MS patients found subjective improvement in 5 of the 8 patients, but only 2 patients demonstrated objective improvement evidenced by improved handwriting and use of eating utensils. Petro and Ellenberger[79] evaluated 9 MS patients in a pilot study by measuring deep tendon reflexes and muscular resistance to stretch using EMG. The EMG measurements were not helpful in identifying patient response. The change in spasticity score based on deep tendon reflex showed a significant improvement 3 hours after the administration of 5 or 10 mg of dronabinol compared to placebo (P<0.005), however this benefit was short lived, returning to baseline within the next 3 hours. One of the 3 patients that felt better after taking the oral THC did not have any objective improvement in the spasticity scores. Ungerleider and coworkers[80] conducted a double-blind placebo controlled crossover study in 13

MS patients with spasticity. Subjects received escalating doses of oral THC from 2.5 up to 15 mg. At doses greater than 7.5 mg there was significant improvement in patient reported subjective spasticity scores when compared to placebo. Unfortunately no objective outcomes were measured. Wade and colleagues[81] evaluated muscle spasms as one outcome of a randomized double-blind placebo controlled crossover that evaluated plant extracts of THC, CBD and a 1:1 mixture of THC:CBD all administered as sublingual sprays to 24 patients, 18 with MS. Patients were asked to assess both spasms and spasticity using a visual analog scale. The THC and the THC:CBD group both had significant improvement in the spasm assessment (P<0.05) and all three treatment groups had a significant improvement in the spasticity severity rating over placebo (P<0.05). The authors acknowledge that this was a preliminary study and that large well-controlled studies are needed to confirm the results.

Three studies[82-84] clearly showed (P< 0.02) that oral THC did not have any functional improvement of MS associated tremor. Fox and coworkers[82] in a randomized double-blind placebo-controlled crossover in 14 MS patients with upper limb tremors evaluated the effect of oral cannabis extract on a tremor index scale. Patients received 5-10 mg of THC twice a day for 5 days. There was no improvement when compared to placebo for the index or the other secondary outcomes measured. Killestein and colleagues[83] conducted a double-blind randomized placebo-controlled crossover in 16 patients with MS who had severe spasticity. Active treatment with oral THC or with a plant extract did not significantly improve Ashworth spasticity scores (P>0.05). Quality of life assessments were conflicting with some scales showing improvement and other measures like the subject's global impression score worsened on active treatment. Adverse events were more common in the active treatment group, but none were deemed to be serious. Zajicek and coworkers[84] in the largest study to date (the CAMS study) examined 630 MS patients with muscle spasticity in a multicenter randomized placebo-controlled study. There was no motor improvement following the oral administration of the THC extract [mean reduction in total Ashworth score compared to placebo 0.32 (95% CI -1.04 to 1.67) and for the dronabinol compared to placebo 0.94 (95% CI -0.44 to 2.31)] However, they did report a treatment effect on patient-reported spasticity (P=0.003), with a reduction in spasticity 61% (n=121, 95% CI 54.6–68.2) for patients on the cannabis extract, 60% (n=108, 52.5–66.8) for those on the oral THC, and 46% (n=91, 39·0–52·9) for the placebo group. Vaney and coworkers[85] studied oral THC and CBD being used together as an extract in 50 MS patients in a randomized placebo-controlled crossover. The 50 patients in the intent-to-treat analysis had no significant difference in Ashworth spasticity scores when compared to placebo. The authors also reported the results of the subset of patients that received over 90% of the treatment (per protocol analysis) and in these 37 patients they did observe a significant improvement in the number of spasms and the spasticity scores (P=0.013). The authors suggest that when patients are able to tolerate the therapy and receive appropriate doses there may be some benefit for treating spasms in MS patients. In addition to a study already mentioned[81], two other studies have looked at THC and CBD sprays for muscle spasm relief in MS.[86;87] Both were randomized placebo-controlled parallel group studies (n=189 and n=160) and used an oromucosal spray that contained 2.7 mg of THC and 2.5 mg of CBD per spray. When the two agents were combined as sprays, there was a patient reported improvement in spasticity scores compared to placebo (P<0.001 and P<0.05 in the two studies).

The only study that has looked at a synthetic analog is an N of 1 trial in a single patient that took nabilone and did report significant improvement of muscle spasms.[88] The patient used a daily diary to record nocturia, to quantify pain and muscle spasm discomfort using a visual analog scale. The patient alternated between a week of drug therapy and placebo for two cycles. There was a clear improvement in symptoms during the weeks that the patient was receiving the nabilone 1 mg every other day. When all of the studies in MS patients are evaluated, it appears that smoking marijuana will likely make muscle spasms worse. The evidence is unclear about the beneficial effects of THC and CBD; some patients, especially those that can tolerate the side effects, may have an improvement in muscle spasms but further research is needed. A single exposure to a synthetic analog indicates that there may be some potential here. The bottom-line is that much more research is needed for multiple sclerosis patients to identify the role of cannabis treatment.

Decreasing intraocular pressure in glaucoma patients can be achieved by relaxation of smooth muscles in the eye. Merritt and colleagues[89] evaluated smoking marijuana on intraocular pressure in 18 glaucoma patients in a randomized placebo controlled crossover design. They were able to document a decrease in ocular pressure, but cardiovascular effects, including increased heart rate, palpitations and postural hypotension all put the patient at risk and thus the author recommended against this proposed use. A year later an eye drop that contained dronabinol (THC) was tried.[90] Six patients with open-angle glaucoma were given a light mineral oil vehicle that contained either 0%, 0.05% or 0.1% THC. Intraocular pressure, heart rate and blood pressure were measured every hour for 10 hours after 0.1 ml (2 drops) was administered to the eye. Both the treated eye and untreated eye were measured. The pressure was reduced in both the treated and untreated eye, but authors concluded that systemic reductions in blood pressure limits the usefulness of this treatment. The authors planned to evaluate other concentrations and vehicles to deliver topical THC to the eye. Tomida and colleagues[91] also tried sublingual THC and sublingual CBD in a pilot study of 6 glaucoma patients in a randomized double-blind placebo controlled 4-way crossover. The 5 mg sublingual THC had a transient decrease in intraocular pressure (23.5 mm Hg compared to 27.3 mm Hg, P<0.026) but did not change visual acuity. Some patients had bothersome side effects. The CBD at 20 mg did not reduce intraocular pressure and at 40 mg actually increased it (23.2 mm Hg to 25.9 mm Hg). So far there is not sufficient evidence to recommend any cannabis related treatment for glaucoma.

The muscle spasms that are associated with parkinsonism and muscle rigidity that can result from its treatment may benefit from the muscle relaxant activity of cannabis. Carroll and coworkers[92] examined the effects of a cannabis extract that contains oral THC 2.5 mg and CBD 1.25 mg in a capsule in a dose escalating study followed by a randomized double-blind cross-over study in 19 patients with Parkinson disease. The efficacy study did not show any objective or subjective improvement in dyskinesias or parkinsonism (Unified Parkinson Disease Rating Scale, P=0.9). Adverse effects were slightly more common in the patients on the cannabis extract, but were minor and improved on dose reduction.

The synthetic analog nabilone was evaluated in a pilot study in 7 patients in a randomized cross-over design.[93] The authors demonstrated that nabilone significantly reduced levodopa-induced dyskinesias with the mean levodopa-induced dyskinesia score reduced from 22 to 17 ($P<0.05$) when nabilone was used, but several patients experienced adverse effects, including orthostatic hypotension, mild sedation, floating sensation, dizziness and partial disorientation. The authors suggested that larger studies be conducted to clearly identify the potential role for this synthetic analog.

The involuntary movements (tics) associated with Tourette's syndrome have been evaluated in two studies using oral THC (dronabinol) at 5, 7.5 or 10 mg once a day.[94;95] The pilot study, a randomized double-blind cross-over study in 12 adults with Tourette's Syndrome, demonstrated that it was safe and effective according to one measure of tic activity, the Tourette's Syndrome System List (TSSL) but not according to other scales. There were no serious adverse events and there were slightly more mild side effects with dronabinol compared to placebo. A follow-up study in 24 patients gave further evidence for its effectiveness and safety when compared to placebo. During the 6 week treatment there was a significant reduction in tics based on global and detailed examiner ratings, self rating and a video tape based rating. There were no serious side effects and those that occurred improved over time. There is potential based on these two studies, but larger controlled studies need to done and comparative studies to current treatments before the treatment is recommended.

Anticonvulsant

Oral cannabidiol was evaluated in 15 patients who were inadequately controlled with traditional epilepsy drugs.[96] The CBD was given to 8 patients and 8 patients received placebo. Four of the 8 patients that received 200 or 300 mg of CBD daily were seizure free and 3 had slight clinical improvement. Seven of the 8 placebo patients had no improvement in seizure activity. The authors concluded that there was some improvement, but that due to the small numbers, further studies are needed. To date, no additional studies have been done.

Conclusion

Cannabis is one of the oldest psychotropic drugs known to humanity. Its use has risen and fallen throughout the years, dating back to 4000 BC. Currently, research is being performed looking at the medicinal performance of marijuana in a number of diseases. The therapeutic potentials for cannabinoids include treatment of pain, lack of appetite, nausea, glaucoma, asthma, epilepsy, spasticity, and tremors.[78] Tetrahydrocannabinol, the major active ingredient of marijuana, has prominent psychoactive properties that sometimes make it undesirable to the patient or could render the patient potentially dangerous to others during episodes of dysphoria therefore it is difficult to justify its use where there are more specific therapies. Once a potential action of marijuana has been identified, natural and synthetic analogs can be researched and tested to target the useful drug characteristic and reduce the nonspecific, often undesirable, actions. Weighing all the evidence reviewed in this report the following observations are made:

- Smoking marijuana may provide pain relief in some patients, but comparative effectiveness studies still need to be done. If used, patients must be cautioned about the high incidence of neuro-psychoactive adverse effects.
- Oral THC and synthetic cannabis derivatives have also shown potential as analgesics but again comparative effectiveness studies are still needed and patients must be cautioned about the high incidence of neuro-psychoactive adverse effects.
- Smoking marijuana and oral THC (dronabinol) are better than placebo, but not as good as megestrol as an appetite stimulant, therefore it should only be recommended when standard therapy has failed. Again patients should be cautioned about neuro-psychiatric adverse effects.
- Smoking marijuana, oral THC and the synthetic derivative are generally better than placebo and oral THC may be better than prochlorperazine but they are not better than the first line antiemetics or other low therapeutic index antiemetic agents (metoclopramide, thiethylperazine or haloperidol). Therefore the American Society of Clinical Oncology recommends that cannabinoids, and other lower therapeutic index antiemetics, should be reserved for patients intolerant or refractory to 5-HT_3 serotonin receptor antagonists, dexamethasone and aprepitant. These agents can be considered when the standard therapies are not effective. The neuro-psychoactive side effects are more common so patients must be warned of this potential.
- Smoking marijuana, oral THC and synthetic derivatives have been perceived by many MS patients as providing relief from muscle spasms, but the evidence suggests that although patients feel better their muscle tone and their balance actually declined. Additional research is necessary to clearly demonstrate a beneficial effect.
- Smoking marijuana and topically applied THC has shown a temporary reduction in intraocular pressure in glaucoma patients but the systemic reduction in blood pressure and increase in heart rate has made it dangerous to use these agents to treat glaucoma.
- Cannabis extracts have not been demonstrated to be of benefit in Parkinsonism patients but the synthetic analog nabilone has shown some potential benefit, but large scale studies are needed before it can be recommended.
- Two small studies have shown potential benefit for oral THC to treat tics associated with Tourette's syndrome, but large studies and comparative efficacy studies are needed before this can be routinely recommended.
- In a single study in 8 patients oral cannabidiol has shown some benefit in providing additional seizure control in epileptics refractory to standard therapy. Again larger scale studies are necessary before this can be routinely recommended.

It is important to carefully sift through scientific studies already done to determine the superiority or inferiority of marijuana not just in comparison to placebo but also compared to active treatments that are the current standard of care.

When there is inadequate evidence, then additional studies should be done before recommendations are made about the appropriate use of marijuana. It would be wise to make these assessments before the regulatory control related to marijuana possession and use is altered.

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ASSESSMENT QUESTIONS

0107-9999-10-061-H01-P

1. Which event below is not correct regarding the history of medical marijuana use?
   a. Medical use described in Emperor Shen Nung's compendium in 2737 BC
   b. O'Shaughnessy described its use in analgesia, appetite stimulant, antiemetic and muscle relaxant use in 1839 in India.
   c. Immediately following the U.S. Civil War (1865) the U.S. introduced the Marihuana Tax Act
   d. Cannibis was removed from the U.S. Pharmacopeia in 1942.
2. Hashish is a term that refers to:
   a. The stem of the cannabis sativa plant
   b. Dried and ground Indian hemp leaves.
   c. A Mexican term for the hangover-like adverse effect.
   d. The resin mixture collected from the cannabis plant.
3. There are over 460 isolated chemical substances in the cannabis plant. They fall into four major groups. Which one of these groups does most medical research focus on for this substance:
   a. Alkaloids
   b. Cannabinoids
   c. Steroidal compounds
   d. Volatile substances
4. The major psychoactive component of the cannabis plant is:
   a. Delta-8-tetrahydrocannabinol
   b. Delta-9-tetrahydrocannabinol
   c. Cannabinol
   d. Cannabidiol (CBD)
5. An 80 Kg adult who decided to take an overdose with marijuana would need to inhale how many cigarettes in a short period of time?
   a. 5
   b. 20
   c. 40
   d. 160
6. Which one of the following does not occur with marijuana use?
   a. Increased heart rate
   b. Impaired reaction time
   c. Improved cognition
   d. Reduced sperm counts
7. Which proposed use of a marijuana substance has the most evidence to support its use:
   a. Orally administered THC for analgesia.
   b. A synthetic cannabinoid for nausea and vomiting
   c. Smoking marijuana for multiple sclerosis
   d. A dronabinol eye drop for glaucoma
8. An HIV patient of yours comes into the pharmacy and confidentially asks for your advice. A friend has been using marijuana for years and has really been gaining weight. Your patient has been continuing to lose weight and has just started to gain a little after starting on megestrol. The friend has offered your patient a free unlimited supply of marijuana and now the patient is asking your advice on stopping the megestrol and starting to regularly use the marijuana. What advice would give the patient?
   a. It is your life, you can choose but you will pay the consequences.
   b. A study has shown that both oral marijuana and smoking it results in a greater weight gain than placebo, so it may be worth a try.
   c. A study has shown that megestrol is much better than oral marijuana in both increasing appetite and causing weight gain and another study has shown that weight gain with oral THC is transient, therefore it is important not to stop the megestrol
   d. The weight gain in your friend is just because the chronic use of marijuana results in apathy and laziness and if that does not bother you then the marijuana might be an option.
9. For the treatment of chemotherapy induced emesis, nabilone has been shown to be superior to all of the following except:
   a. Domperidone
   b. Metoclopramide
   c. Placebo
   d. Prochlorperazine
10. There is some evidence for the use cannabinoids in epilepsy and in Tourette's syndrome but more research is needed for both of these because:
    a. The efficacy data is from only a small number of patients.
    b. Only smoking marijuana has been evaluated in these patients.
    c. The side effects were greater than the benefits.
    d. The study designs were flawed.

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