UMHS Information for Clinicians on the Michigan Medical Marijuana Program

I. Objectives

- To inform patients and clinicians of the evidence and potential benefits and harms of marijuana.
- To provide information on the State of Michigan's process for obtaining certification for the use of marijuana for medical purposes.

II. Key Points

- Patients who wish to use marijuana for medical purposes need to ask their physician for written certification that they have a qualifying debilitating condition that meets the criteria under the law.
- The physician must also certify that, in the physician's professional opinion, the patient is likely to receive therapeutic or palliative benefit from the medical use of marijuana to treat or alleviate the patient's debilitating medical condition or symptoms associated with the debilitating medical condition.
- Physicians are not obligated to provide this certification even if the patient's medical condition meets the legal criteria.
- There are many other classes of analgesics and many nonpharmacological therapies that either have greater effectiveness than marijuana or have less side effects, and these treatments should generally be tried prior to using marijuana.
- It is important to counsel patients not to substitute marijuana for their prescription medications.
- Patients with dependence/addiction issues would not be appropriate candidates for marijuana, particularly chronic pain patients who are at high risk for medication misuse or diversion. The use of marijuana or other illicit drugs is generally considered a violation of controlled substance prescribing contracts.
- For more details on the State of Michigan laws, go to http://www.michigan.gov/mmp.

III. Patient Population

- Patients under 18 must have consent of parent or guardian to enroll in the program and written certification from 2 physicians
- Patients must have certification from a physician noting they have one of the following "qualifying debilitating conditions":
  - **Chronic debilitating disease causing**
    - **cachexia or wasting syndrome**
    - **severe or chronic pain**
    - **severe nausea**
    - **seizures (including but not limited to those caused by epilepsy)**
    - **severe or persistent muscle spasms, including but not limited to multiple sclerosis (MS).**
  - **Amyotrophic lateral sclerosis (ALS)**
  - **Alzheimer's agitation**
  - **Cancer**
  - **Crohn's disease**
  - **Glaucoma or nail-patella syndrome (increased risk for glaucoma)**
  - **Hepatitis C**
  - **HIV/AIDS**

IV. Instructions for Medical Marijuana Use in Michigan

1) The law does NOT permit:

- possessing or using marijuana
  - in a school bus, or
  - on the grounds of primary or secondary schools, or
  - in any correctional facility.
- smoking marijuana
  - on any form of public transportation, or
  - in any public place. *(Note: The University of Michigan Hospital and Health Centers is a smoke-free public institution.)*
- operating, navigating, or being in physical control of any motor vehicle, aircraft, or motorboat while under the influence,

2) Qualification of Caregivers

- A caregiver agrees to assist a specific patient, must be aged 21 years or older, and has not been convicted of a felony involving illegal drugs.
- Registered patients/caregivers are allowed to grow up to 12 plants in an enclosed, locked facility, and to possess up to 2.5 ounces of usable marijuana without arrest and prosecution by state law enforcement.

3) Certification Process

- Patients obtain written certification from physician verifying that one of the qualifying medical conditions exist

    - MD or DO only; must have established patient/physician relationship
    - Signed and dated Physician Statement must be current within 3 months of the new or renewal application
  - Application is made by the patient (available after April 4, 2009)
  - Michigan Department of Community Health has 15 days to verify information on application, plus an additional 5 days to issue identification card
  - Patient must pay an annual application fee of $100 or $25 if enrolled in Medicaid or recipient of current Supplemental Security Income benefits
  - No actual "prescription" from the physician
  - A physician may not be arrested, prosecuted, or penalized in any manner for discussing marijuana for medical purposes
  - No legal distribution process (patient must grow or acquire from their own sources)
  - A person with an ID card is exempt from criminal laws of the State of Michigan for marijuana use for a qualifying debilitating medical condition

4) Other Legal Issues

- Federal authorities may still pursue enforcement of federal controlled substance laws.

V. Definition of Marijuana and Related Information

- Marijuana is defined as "a mixture of the dried, shredded leaves, stems, seeds, and flowers of Cannabis sativa." The main psychoactive substance in marijuana is delta-9-tetrahydrocannabinol (THC).
- Marijuana has a strong potential for abuse and is regulated as a Schedule I controlled substance under the Controlled Substances Act.
- Marijuana appears to have antiemetic and analgesic effects.
- Marijuana is usually used in cigarette form and inhaled. When inhaled, THC is rapidly absorbed and distributed throughout the body.
- Marijuana can be harmful to the heart, lungs, brain, endocrine system, and eyes. In particular, inhalation of marijuana can result in impaired lung function.
  - Chronic use may lead to restrictive lung disease, such as interstitial fibrosis. One study indicates that smoking less than one marijuana cigarette a day diminished vital capacity as much as smoking 16 tobacco cigarettes.
  - Marijuana is frequently contaminated with aspergillus mold and can result in fungal sensitization, which can be particularly harmful in immunocompromised patients.
- There are two drugs approved by the Food and Drug Administration (FDA) that contain, in part, similar active constituents as marijuana.
  - Dronabinol (Marinol®), a Schedule III controlled substance, is the synthetic version of THC and is FDA approved for anorexia in

patients with HIV and in those with nausea and vomiting associated with cancer chemotherapy.

- Nabilone (Cesamet®) is a synthetic cannabinoid that is not found in botanical marijuana, but is similar to THC. It is a Schedule II controlled substance and is FDA approved for the treatment of chemotherapy-induced emesis.

VI. Medical Marijuana Use in Specific Conditions

1. Severe/Chronic Pain

a) Overview. THC is one of many chemicals called cannabanoids that bind to specific receptors in the brain and other regions of the body to cause a variety of effects. In addition to cannabanoids that can be smoked or ingested, there are also cannabanoids that your body makes internally that bind to these same cannabanoid receptors. These internally produced chemicals are termed endocannabanoids. This is analogous to the fact that the body produces endogenous opioids, such as endorphins and enkephalins, that bind to the same receptors as opioid analgesics (e.g., morphine) that are used to treat pain. Like any compound that is used as a drug, cannabanoids have both side effects and some potential beneficial effects.

b) Evidence. THC and other cannabanoids can be effective analgesics in some individuals. They are probably as potent as weak or moderate strength opioids.

c) Harms. Some of the specific side effects of THC are due to the fact that marijuana is smoked rather than administered orally or via other methods. Smoking marijuana can cause side effects to the lung, such as chronic cough and emphysema, interstitial fibrosis and might be associated with an increased risk for cancer (although this increase in risk appears to be less than that caused by smoking cigarettes).

d) Preferred Treatment. The following drugs generally would have a better side effect profile than marijuana for treating chronic pain:

(1) Typical analgesics (e.g., acetaminophen [Tylenol], ibuprofen [Motrin®], naproxen [Aleve®]; (2) tramadol (Ultram®); (3) narcotic-containing compounds; (4) dual reuptake inhibitors including tricyclic drugs (e.g., amitriptyline [Elavil®], cyclobenzaprine [Flexeril®]) and serotonin-norepinephrine re-uptake inhibitors (e.g., duloxetine [Cymbalta®], milnacipran [Savella®]); and (5) alpha-2-delta ligands (e.g., gabapentin [Neurontin®], pregabalin [Lyrica®]).

(2) The following nonpharmacological therapies have been shown to be very effective for treating many types of chronic pain and should generally be used prior to using marijuana: (1) education, (2) exercise and physical therapy, and (3) cognitive behavioral therapy.

2. Severe Nausea

a) **Overview,** Cannabinoids, both as plant extracts (e.g., dronabinol) and as semisynthetic agents (e.g., nabilone), have been found to have antiemetic activity when used alone or in combination with other agents. The activity of dronabinol (given in oral doses varying from 2.5 mg per dose to 10 mg/m^2) has been shown to be significantly less than that of metoclopramide (Reglan®) in a randomized, double-blinded trial with patients receiving cisplatin. Activity reported for dronabinol in patients receiving methotrexate (Rheumatrex®) was not seen by the same investigator testing the agent in patients receiving cyclophosphamide (Cytoxan®) and doxorubicin (Doxil®).

b) **Evidence.** Inhalant marijuana has been compared with dronabinol in only one randomized, double-blind trial with patients receiving chemotherapy of intermediate emetic risk. The inhalant and the oral cannabinoids were not effective in either arm of the study. There was no efficacy, side effect, or pharmacologic advantage for either agent or route; however, there was a modest patient preference for dronabinol in this cross-over, blinded trial.

c) **Harms.** These agents cause frequent dizziness, sedation, hypotension, and dysphoria, especially in older adults.

d) **Preferred Treatment.** The American Society of Clinical Oncology Guideline Panel for Antiemetics in Oncology, in their 2006 update, addressed antiemetic agents of lower therapeutic index, including the cannabinoids: *Lower Therapeutic Index—Metoclopramide, Butyrophenones, Phenothiazines, and Cannabinoids* For persons receiving chemotherapy of high emetic risk, there is no group of patients for whom agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT_3 serotonin receptor antagonists, NK_1 receptor antagonists, and dexamethasone.

3. Epilepsy

a) **Overview**. Surveys suggest that up to a quarter of epilepsy patients were actively using marijuana.

b) **Evidence**. There have been no large-scale, controlled clinical trials to examine the effects of cannabinoids in various forms of epilepsy.

c) **Harms**. In epilepsy patients using marijuana, both increases and decreases in seizure frequency have been reported.

d) **Preferred Treatment**. Traditional antiepileptic medications provide good seizure reduction with acceptable side effects in a majority of patients with epilepsy. These medications include lorazepam (Ativan®), carbamazepine (Tegretol®), clonazepam (Klonopin®), gabapentin, lamotrigine (Lamictal®), levetiracetam (Keppra®), phenytoin (Dilantin®), tiagabine (Gabitril®), topiramate (Topamax®), and valproic acid (Depakene®).

4. Multiple Sclerosis (MS)

a) **Overview**. There are no good studies have evaluated marijuana in MS.

b) **Evidence**. Anecdotal reports and patient surveys describing the effectiveness of marijuana in relieving symptoms of MS were supported by the results of early open or single-blind observations involving small numbers of patients. The most consistent finding was a subjective improvement in spasticity, but benefits for mobility, tremor, nystagmus, mood, and bladder control were also reported.

A large multicenter study involving 33 clinical centers and 660 MS patients in the United Kingdom and United States explored the effects of cannabis extract (Cannador®) or dronabinol versus placebo on spasticity, pain, tremor, bladder function, and cognitive function (the CAMS study). After 15 weeks of treatment with dronabinol or cannabis extract, there was no change in the Ashworth score of spasticity, tremor, irritability, depression, or tiredness. There were significant improvements in patient reported spasticity, pain, and sleep quality. In the 12-month follow-up of the original CAMS study of 657 patients, muscle spasticity measured by the Ashworth scale was significantly improved in the THC-treated group. Adverse side effects were generally minor and similar to those with placebo.

Based on evidence that THC may have anti-inflammatory effects, may promote synaptogenesis, and may promote repair through stimulation of neuronal progenitor production, as well as results from the CAMS study suggesting that THC may have an effect on disease progression, a large scale trial investigating the effect of long-term oral THC on MS progression is ongoing, Cannabinoid Use in Progressive Inflammatory Brain Disease (CUPID).

c) **Harms**. Although the results of the above clinical studies are somewhat equivocal, patients treated with cannabis experienced improvements in the disturbing symptoms including pain and spasticity compared with those receiving placebo, without experiencing significant side effects.

d) **Preferred Treatment**. Immunomodulatory agents in multiple sclerosis include: (1) corticosteroids for acute MS flares, and (2) interferon beta-1b (Betaseron®), interferon beta-1a (Rebif®, Avonex®), and glatiramer (Copaxone®) in the treatment of relapsing remitting MS. Supportive care for MS patients includes speech therapy, physical therapy, baclofen (Lioresal®) use to treat muscle cramps, amantadine (Symmetrel®) and modafinil (Provigil®) can be effective for MS related fatigue.

5. Alzheimer's Disease (AD)

a) **Evidence**. No good studies have investigated marijuana in AD. In an open-label pilot study of six patients in the late stages of dementia (five patients with AD and one patient with vascular dementia), treatment with 2.5 mg of dronabinol daily for 2 weeks significantly improved the neuropsychiatric inventory total score and the subscores for agitation and aberrant motor and nighttime behaviors.

b) **Harms**. The potential for negative cognitive and psychoactive effects is a major concern in this patient population.

c) **Preferred Treatment**. In addition to supportive care that can be provided in an AD multi-specialty clinic, several medications have been approved for use as cognitive enhancers in the treatment of mild to moderate Alzheimer disease include the acetylcholinesterase inhibitors (e.g., donepezil [Aricept®], galantamine [Razadyne®], and rivastigmine [Exelon®]). Donepezil and the NMDA-receptor antagonist, memantine (Namenda®), are approved for use in moderate to severe Alzheimer disease.

Treatment of agitation in AD is especially problematic. Nonpharmacologic approaches to care include increased socialization and improved sleep hygiene. Pharmacologic therapy of agitation, mood, and undesirable behaviors has included neuroleptics, antidepressants, and anxiolytics.

6. Amyotrophic Lateral Slerosis (ALS)

a) **Overview**. Based on potential protective effect of cannabinoids against oxidative cell damage and excitotoxicity, marijuana has been proposed for the pharmacological management of neurodegenerative diseases including ALS.

b) **Evidence**. No good studies have investigated marijuana in ALS. In a pilot study of the safety and tolerability of THC in ALS patients, symptomatic benefits for spasticity, insomnia, and appetite were reported.

c) **Harms**. The potential respiratory side effects of marijuana, in a disease that in late stages causes respiratory difficulties is a concern.

d) **Preferred Treatment**. In addition to supportive care that can be provided in an ALS mutli-specialty clinic, only one medication has been FDA approved for treatment of ALS, riluzole (Rilutek®). Riluzole appears to be reasonably safe and probably prolongs survival by about 2 months in patients with ALS. The Quality Standards Subcommittee of the American Academy of Neurology has recommended that the drug should be offered to patients. Supportive care for ALS patients includes speech therapy and physical therapy. Diazepam (Valium®)and baclofen can be used to treat muscle cramps.

7. Cancer

a) **Overview.** Cancer patients may have beneficial effects on pain, depression, nausea, vomiting, and weight loss if placed on THC, however results are inconclusive.

b) **Evidence.** Advanced cancer patients tend to maintain weight and be mildly euphoric and tranquilized by THC. Antineoplastic effects have been demonstrated in vitro but several in vivo studies have not shown benefit.

c) **Harms.** Can cause dizziness, sedation, hypotension, and dysphoria, especially in older adults.

8. Crohn's Disease

a) **Overview**. The endocannabinoids, as well as THC and marijuana, have a variety of effects on the enteric nervous system and immune cells in rodents, likely via the CB1 and CB2 receptors. Therefore, it is biologically plausible that cannabinoids might have significant effects (positive or negative) on Crohn's disease. In the absence of clinical trial evidence to support the use of marijuana in Crohn's disease, and the known potential gastrointestinal adverse effects of marijuana use, and the availability of many RCT-proven therapies for Crohn's disease, neither marijuana nor THC can be recommended as a therapy for Crohn's disease at this time.

b) **Evidence**. While patients with Crohn's disease have been reported to be frequent users of marijuana, there is no evidence of any therapeutic benefit. There are no prospective studies or randomized controlled trials of marijuana (or THC) for the treatment of Crohn's disease. There are no retrospective studies suggesting any benefit of marijuana or THC for the treatment of Crohn's disease.

c) **Harms**. There is strong prospective data supporting the negative effects of smoking on both outcomes and the efficacy of therapies in Crohn's disease. There is solid retrospective data demonstrating an association between Crohn's disease and pulmonary dysfunction.

   It is known that chronic use of cannabinoids by humans can produce gastrointestinal dysmotility, resulting in a severe, disabling cannabinoid vomiting syndrome. Given the association of Crohn's disease with pulmonary dysfunction, and the known hazards of smoking in Crohn's disease, smoking appears to be a potentially dangerous drug delivery mechanism for Crohn's disease.

d) **Preferred treatment**. RCT-proven therapies for Crohn's disease include methotrexate, azathioprine (Imuran®), infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), and tacrolimus (Prograf®).

9. Glaucoma/nail-patella syndrome

a) **Overview**. The Glaucoma Service of the University of Michigan Kellogg Eye Center does not intend at this time to prescribe medical marijuana for our patients with glaucoma, in keeping with the current recommendations of the Institute of Medicine, the National Eye Institute, the American Academy of Ophthalmology, and the American Medical Association, all of which are based on the best scientific evidence available.

b) **Evidence**. Although marijuana use can indeed reduce intraocular pressure, to achieve the antiglaucoma-related effects marijuana must be taken in high doses and the beneficial effects are short-lived. Thus, patients would need to take the drug numerous times daily to achieve long-term treatment benefit.

c) **Harms.** At frequent high doses, use of the drug has considerable adverse effects, such as temporary mind alteration and overall blood-pressure reduction.

d) **Preferred Treatment**. Numerous safer and more effective treatment options are available. Pharmaceutical products (typically eye drops) registered with the FDA for use in patients with glaucoma have long-term effectiveness if taken consistently as prescribed, and their side effects generally are considerably more mild than those associated with high-dose medical marijuana use. If the antiglaucoma effects achieved by the use of FDA-approved eye drops alone are inadequate, various surgical procedures can be performed to further reduce the intraocular pressure.

10. Hepatitis C

a) **Overview**. It is thought that marijuana use, like alcohol use, will increase the rate of developing cirrhosis of the liver in patients with hepatitis C. Thus regular use of marijuana by persons who are infected with the hepatitis C virus is strongly discouraged.

b) **Evidence**. Studies of quality of life of patients with hepatitis C have shown that hepatitis C patients report, on average, lower quality of life, but their scores overlap considerably with those of patients with no known disease. There are no studies to show whether any of these symptoms are improved by use of marijuana.

Several small retrospective studies have suggested that for persons who smoke marijuana regularly, continuing its use during hepatitis C treatment might help them tolerate treatment and its side effects. However, some of the side effects of marijuana withdrawal may mimic some of the treatment side effects of hepatitis C and therefore these studies do not provide any information about whether new use of marijuana during hepatitis C treatment would be beneficial.

c) **Harms**. Marijuana has effects on the human mind and body through cannabinoid receptors on nerves and other tissues, including the liver. There are two main receptors, CB1 and CB2. The compounds in marijuana act on both of these receptors, but the effects on CB1 may predominate in the liver. Activation of the CB1 receptor has been shown in many experimental studies to increase development of fibrosis (scarring) in the liver and to increase the development of fatty liver. Use of marijuana and activation of the CB1 receptor has been shown to increase liver fat both in hepatitis C patients and in those with obesity. This can lead to an additional liver disease, fatty liver hepatitis, which can itself lead to cirrhosis.

Studies in patients with hepatitis C from several large centers have shown that persons who smoke marijuana regularly have, on average, much higher amounts of fibrosis in their livers than matched patients who do not use marijuana regularly. In one recent study, the risk of having a high level of fibrosis was increased seven times. Other studies show that some of the complications of cirrhosis (cardiac abnormalities, dilation of blood vessels leading to complications such as ascites, renal dysfunction, varices) may be promoted by cannabinoids through the CB1 receptor.

d) **Preferred Treatment**. For fatigue, exercise, good sleep habits, and possibly antidepressants may have some value. For treatment of side effects of hepatitis C

treatment with interferon therapy, other antiemetics, appetite stimulants and antidepressants and sleep aids have been useful. For prevention of progression of hepatitis C fibrosis, abstention from alcohol and marijuana is helpful. Treatments to eradicate the virus, although difficult, is the best method to prevent fibrosis, cirrhosis and complications. Many randomized studies have identified interferon and ribavirin as good (although not ideal) curative treatments. Other drugs are currently undergoing clinical trials.

11. HIV/AIDS

a) **Overview.** THC has been shown in cancer patients to be beneficial to treat nausea and stimulate appetite however, such treatment is not considered first line therapy. By extension, many patients with HIV infection and AIDS wasting syndrome have used marijuana to help gain weight via appetite stimulation and through the management of nausea. Marinol (dronabinol), which contains the active ingredient of marijuana (THC), has been FDA approved for AIDS wasting syndrome since 1992 and is often used for appetite stimulation and to treat nausea. Smoked marijuana is a potential alternative to oral dronabinol. Other uses for cannabinoids include the management of neuropathic pain.

b) **Evidence.** Clinical trials have demonstrated the benefit of smoked marijuana on appetite stimulation and suppression of nausea and vomiting, however, clinical studies to demonstrate the usefulness of marijuana in the setting of AIDS wasting syndrome have been blocked by the Federal Government and thus have not been performed.

c) **Harms.** The adverse effects associated with inhaled marijuana include cough, bronchospasm, alterations in consciousness and mood, tachycardia, euphoria, drowsiness, and an increased risk of respiratory illness. In laboratory studies marijuana has been shown to have negative effects on immune function. No human studies have shown this to be clinically relevant to date however. Some studies have shown that the use of marijuana in adolescence can potentially lead to certain neuropsychiatric conditions

d) **Preferred Treatment.** Drugs which have been FDA approved and are considered to be standard to treat AIDS wasting syndrome include: dronabinol, oxandralone (Oxandrin®), megestrol (Megace®), and human growth hormone.

VII. References

http://www.michigan.gov/mmp
www.procon.org

VIII. Authorship

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