CLINICAL DECISIONS
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Medical Marijuana for Chronic Pain

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Woman with Chronic Pain

Lisa Caulley, M.D., M.P.H.

Ms. Rothstein is a 31-year-old woman who comes to your office to consult with you regarding a long-standing history of complex regional pain syndrome in her right leg and foot. She is a graduate student and former varsity soccer player who became disabled 7 years ago after having a hairline fracture in the right fibula. Since several weeks after her injury, she has had intractable pain in her foreleg and foot even though the fracture has healed. She describes spontaneous, excruciating pain — mainly burning and deep aching — in her right lower leg, as well as allodynia and hyperalgesia. Three-phase bone scintigraphy has shown findings associated with complex regional pain syndrome type 1. Her affected right foot and lower leg are warmer than her left foot and lower leg; in addition, the skin is shiny and thin, and the nails are opaque. She has tried a number of treatments for pain relief, including several opioids, regional and sympathetic nerve blocks, transcutaneous nerve stimulation, lidocaine and compounded salves, behavior modification, and acupuncture, as well as alendronate infusions. All these treatments have had an insufficient effect. She is currently receiving gabapentin, at a dose of 600 mg orally three times a day, and oxycodone, at a daily dose of 20 mg orally, but has had little alleviation of her pain. She is frustrated by the drowsiness, fatigue, and constipation associated with use of the medications. She reports that her pain has made it difficult to concentrate, and she is motivated to find alternative treatment regimens. She is also concerned about the risk of opioid dependence. She inquires about a prescription for medical marijuana for her chronic pain.

TREATMENT OPTIONS

Which one of the following approaches would you recommend for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

1. **Prescribe medical marijuana.**
2. **Discourage the use of medical marijuana.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field of pain management. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

Disclosure forms provided by the author are available at NEJM.org.

From the Ear, Nose, and Throat Department, Guy's Hospital, London.

OPTION 1

Prescribe Medical Marijuana

Benjamin Caplan, M.D.

The efficacy of cannabis, particularly when it is used as a component of a treatment plan for chronic pain and allodynia, makes it a strong choice for Ms. Rothstein. Its potential as a replacement for opioids is especially appealing. The chronic pain and complex regional pain syndrome that Ms. Rothstein is experiencing are multidimensional. The long-term, spontaneous, disabling allodynia and hyperalgesia are worsened by frustrating results of therapy, difficulty sleeping, and psychological stress. Trials of opioids, nerve blocks, and analgesics suggest persistently disappointing efforts to find relief for this otherwise healthy young woman. These experiences should be viewed as interacting and self-regenerating. Cannabis added to her regimen could alleviate emotional distress and provide a more direct route to pain relief.[1] Cannabis can cause a shift

in a patient's psychological orientation from stimuli that have a negative effect toward stimuli that have a positive effect.[2]

Cannabis has been shown to contribute, through cannabinoid-receptor and non–cannabinoid-receptor mechanisms, to antiinflammatory and neuroprotective effects that may alleviate chronic pain.[3] These effects appear to be dose-dependent with respect to synaptic transmission within the dorsal horn of the spinal cord, and inhibition of this communication may play a role in the development of chronic pain associated with local inflammation or nerve injury.[4] For example, in a murine model of neuropathic pain, administration of cannabis significantly reduced allodynia in a dose-dependent manner.[5] Furthermore, in a recent study of refractory pain, cannabis showed efficacy in patients for whom traditional treatment options had failed.[6]

Certain plants, as well as products made from their derivatives, yield a variety of cannabinoid alkaloids that have diverse functions and uses. Different formulations can be administered orally, topically, or by vaporization, in measured doses that avoid potential toxins associated with smoke from combustion of the plant. High-quality evidence is limited, but the evidence that is available suggests no lasting illness from cannabinoid use or, at worst, temporary discomfort associated with excessive or extreme doses.[7] There are, however, few clinical trials focused on pain control in humans that quantify adverse effects of medical marijuana. Despite decades of campaigns that have limited the ability to conduct research in the field and federal restrictions on cannabis, trials in humans have shown measurable effects of cannabinoids in alleviating chronic pain, with an acceptable safety profile.[1] Experimental research and research in animals provide reassuring support on safety.[7]

In Ms. Rothstein's case, cannabis is an appealing option to address the frustration she has expressed with the inefficacy, side effects, and addictive nature of opioids. Although many people use cannabis for pain relief, the prevalence of addiction and the risk of overdose are low. Trials of agents that inhibit the enzymatic degradation of cannabinoids have shown opioid-sparing effects in a dose-dependent manner, with reversal of allodynia and hyperalgesia, diminished tolerance of the opioids (i.e., less need for increased doses of the opioids to achieve the same analgesic effect), and no reduction in gastric motility or other problems that are common with opioids.[8]

On the basis of a number of experimental studies and a few adequate trials in humans, cannabis or oral formulations of cannabinoids would be safe for Ms. Rothstein and would be likely to offer effective pain control. Provided that the patient is informed about the risks of combustion-related toxins and educated about how to abate the potential discomfort of inadvertent overexposure to tetrahydrocannabinol (e.g., by administering cannabidiol), her trying this treatment carries negligible risk. At a minimum, Ms. Rothstein can expect moderate analgesia, reduced allodynia, muscle relaxation, a reduced stress response to her disability, and an empowering level of control over mood in coping with her illness.

Disclosure forms provided by the author are available at NEJM.org.

From CED Foundation, CED Clinic, and solo sciences — all in Boston.

OPTION 2

Discourage the Use of Medical Marijuana

Edgar Ross, M.D.

Medical marijuana has received widespread attention as a treatment for various chronic medical conditions, including pain. Although the growing support for state legalization has led to its approval for medical use in most of the 50 states, enthusiasm for medical marijuana has been based largely on anecdotal information. Ms. Rothstein, a 31-year-old woman with complex regional pain syndrome type 1, is inquiring about medical marijuana. She reports that she has tried multiple (but not all) therapies that would be considered to be evidence-based for her chronic, disabling pain but has not had improvement and has had substantial side effects.

Medical marijuana contains many compounds, of which approximately 60 are cannabinoids.[9] The two principal cannabinoid receptors are receptor 1 (CB_1) and receptor 2 (CB_2). CB_1 is found primarily in the central nervous system and is considered to regulate central nervous system excitability through presynaptic inhibition of excitatory neurotransmitters. CB_2 is expressed predominantly in hematologic systems, where it exerts an immunomodulatory effect.[10]

Literature reviews on the efficacy of medical marijuana are cautionary about effectiveness and side effects. Although the cannabinoid compounds are almost certainly safer than long-term opioid therapy, studies in humans that suggest efficacy are limited in quality and scope. Various studies suggest that the analgesic potency of cannabinoids is roughly similar to that of codeine. However, commonly reported side effects of cannabinoids include sedation, dizziness, dry mouth, dysphoria, appetite stimulation, and short-term memory loss, all of which can interfere with established treatments such as rehabilitation and psychological therapies.[9] Long-term exposure to cannabis has also been associated with a risk of psychotic disorders, including the emergence of latent schizophrenia in a dose-dependent manner, particularly in persons with a preexisting vulnerability.[11,12] Since the mechanism underlying cannabis-associated psychosis is unknown, establishing a safe dose for routine use is difficult.[11] Controversy about the addictive potential of cannabis and the risk of cannabis withdrawal syndrome is also ongoing.[12]

Delivery systems for cannabinoids are problematic. Oral cannabidiol bioavailability varies, ranging between 13 and 19%, and the drug can take up to 3 hours to reach peak concentrations.[9] Although smoking marijuana has better bioavailability than oral formulations, the smoke itself is a risk factor for chronic obstructive pulmonary disease. The risk of lung cancer from marijuana smoke is unknown, but an elevated risk seems possible with long-term use.[13] Since there is no regulatory oversight or standardization of cannabinoids, the types and concentrations of cannabinoids found in medical marijuana are unknown and vary widely.[14]

Multidisciplinary treatment programs based on a modern rehabilitation model are considered to be highly effective for the management of chronic pain of all types. The model uses concurrent treatment by a team specializing in psychological therapies, rehabilitation, and pain specialty care. This model has not yet been tried in an organized fashion in this patient.[15] In addition, other proven therapies that are known to be effective for neuropathic pain, which include antiepileptic drugs (only gabapentin has been tried), antidepressants, and even spinal cord stimulation, have not been implemented. Ms. Rothstein has a chronic pain condition that is unlikely to resolve. Instead of the serial and uncoordinated approach to pain control such as that described in the vignette, a multidisciplinary program should be tried; this approach is more likely to be beneficial in the long term than medical marijuana, which is an unproven treatment with poorly defined toxic effects, safety, and efficacy. In addition, the likely side effects of medical marijuana use are exactly the ones that the patient is hoping to avoid.

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From the Department of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital, and Harvard Medical School — both in Boston.

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