CLINICAL DECISIONS
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Medicinal Use of Marijuana

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at NEJM.org, *readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

CASE VIGNETTE

Marilyn is a 68-year-old woman with breast cancer metastatic to the lungs and the thoracic and lumbar spine. She is currently undergoing chemotherapy with doxorubicin. She reports having very low energy, minimal appetite, and substantial pain in her thoracic and lumbar spine. For relief of nausea, she has taken ondansetron and prochlorperazine, with minimal success. She has been taking 1000 mg of acetaminophen every 8 hours for the pain. Sometimes at night she takes 5 mg or 10 mg of oxycodone to help provide pain relief. During a visit with her primary care physician she asks about the possibility of using marijuana to help alleviate the nausea, pain, and fatigue. She lives in a state that allows marijuana for personal medicinal use, and she says her family could grow the plants. As her physician, what advice would you offer with regard to the use of marijuana to alleviate her current symptoms? Do you believe that the overall medicinal benefits of marijuana outweigh the risks and potential harms?

Which one of the following approaches do you find appropriate for this patient? Base your choice on the published literature, your clinical experience, recent guidelines, and other sources of information.

1. **Recommend the medicinal use of marijuana.**
2. **Do not recommend the medicinal use of marijuana.**

Choose an option and comment on your choice at NEJM.org

To aid in your decision making, each of these approaches is defended in the following short essays by experts in the field. Make your choice and make recommendations for the patient at NEJM.org.

OPTION 1

Recommend the Medicinal Use of Marijuana

J. Michael Bostwick, M.D.

Within established doctor–patient relationships, I endorse thoughtful prescription of medicinal marijuana for patients in situations similar to Marilyn's. A largely anecdotal but growing literature supports its efficacy, particularly for pain or nausea that is unresponsive to mainstream treatments.[1] In 1970, marijuana was designated a Schedule I drug under the Controlled Substances Act, a classification indicating a high potential for abuse and a lack of medical value.[2] But physicians face a catch-22: although 18 states have legalized medicinal marijuana, physicians in those states who write prescriptions violate the law of the land.

Federal policy has failed to keep pace with recent scientific advances. Laboratory research has elucidated the far-flung endocannabinoid system that modulates neurotransmitter networks throughout the body through cannabinoid-1 (CB_1) receptors that are preferentially distributed in the brain and cannabinoid-2 (CB_2) receptors that are prominent in gut and immune tissues. Among dozens of cannabinoids in raw marijuana, two show medicinal promise. The first, Δ^9-tetrahydrocannabinol (Δ^9-THC), is the CB_1 ligand that recreational users prize. The second, cannabidiol (CBD), acting on CB_2, lacks psychoactivity but works synergistically with Δ^9-THC to minimize "highs" and maximize analgesia.[2,3]

Arguments for and against medicinal marijuana are manifold. Under federal law, the drug is illegal. However, given widespread state defiance, the cannabis horse long ago burst from

the federal jurisdictional barn. In Colorado, a handful of physicians write half the state's prescriptions for medicinal marijuana, for questionable indications.[4] Just because a few rogue doctors flout lax legislation to abet pot-mill commerce, that doesn't justify depriving all physicians of the right to prescribe medicinal marijuana. No trials under the auspices of the Food and Drug Administration (FDA) have compared medicinal marijuana with traditional analgesics.[5] Because of marijuana's Schedule I status, industry is thwarted in its attempts to develop compounds with endocannabinoid agonist or antagonist qualities that might have analgesic, appetite-modulatory, immunosuppressant, antiemetic, neuroleptic, or antineoplastic effects, among other possibilities.[2] Some people may contend that dose determination by patients deviates from modern medical practice,[3,6] but adjustment of medications by patients is ubiquitous in hospitals through patient-controlled analgesia pumps. Some people argue that as a drug of abuse, marijuana has no business being used for clinical purposes. Yet, several Schedule I drugs have close cousins with legitimate medical applications. Heroin and morphine derivatives have an illicit–licit kinship, as do "ecstasy" (3,4-methylenedioxymethamphetamine) and stimulant drugs central to the treatment of attention deficit–hyperactivity disorder, as well as phencyclidine and ketamine, an anesthetic agent.[2]

Meanwhile, Marilyn seeks relief from the consequences of metastatic breast cancer. Neither acetaminophen nor oxycodone has proven to be effective against the serious pain of spinal and visceral metastases. Neither ondansetron nor prochlorperazine has relieved the nausea, which may have been induced by doxorubicin. More aggressive narcotics could be prescribed (risking the worsening of gastrointestinal symptoms), but Marilyn asks her doctor whether medicinal marijuana might offer the singular advantage of reducing pain and nausea simultaneously.

Inhaled pharmaceuticals are commonplace, but in the United States no vaporized inhalant is currently available as an alternative to medicinal marijuana, pending FDA approval of nabiximols, currently in phase 3 trials (ClinicalTrials.gov number, 01337089).[6] With slow onset and unreliable bioavailability, oral cannabinoids are ill suited to relieving Marilyn's acute distress.[2] If she had no recreational experience with marijuana, Marilyn could find medicinal marijuana's psychoactive effects unacceptable, although noxious psychoactivity also limits opiate use. Should Marilyn experience benefit, however, she would channel 5000 years of medical history, including the century when cannabis derivatives routinely resided in American doctors' black bags.[1]

In sum, I believe that physicians who prescribe medicinal marijuana should do so only when conservative options have failed for fully informed patients treated in ongoing therapeutic relationships. As federal gridlock prevents much-needed research, patients such as Marilyn deserve the potential relief that medicinal marijuana affords.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend against the Medicinal Use of Marijuana

Gary M. Reisfield, M.D., and Robert L. DuPont, M.D.

Marilyn's query should be recognized both for the words — a straightforward question about medicinal marijuana use — and for the music — a plea for symptom relief. Both must be addressed. Although marijuana probably involves little risk in this context, it is also unlikely to provide much benefit. Simply to allow a patient with uncontrolled symptoms of metastatic breast cancer to leave the office with a recommendation to smoke marijuana is to succumb to therapeutic nihilism.[6]

There is burgeoning interest in the therapeutic potential of targeting the endocannabinoid system. Although most of the research into this system involves the use of specific cannabinoids, a small body of high-quality research shows evidence of clinically significant analgesia from smoked marijuana, primarily for neuropathic pain. There is little evidence to support the use of smoked marijuana for Marilyn's nociceptive pain, and less still for her other symptoms.

Smoked marijuana is a nonmedical, nonspecific, and potentially hazardous method of drug delivery. The cannabis plant contains hundreds of pharmacologically active compounds, most of

which have not been well characterized. Each dispensed quantity of marijuana is of uncertain provenance and of variable and uncertain potency and may contain unknown contaminants.

There are other questions to consider in Marilyn's case. Could marijuana's cognitive side effects, particularly its effects on memory, promote or exacerbate chemotherapy-induced cognitive dysfunction? If Marilyn's pulmonary disease includes lymphangitic spread, could smoking cause hypoxemia? What effects will marijuana's potential immunologic hazards (e.g., chemical constituents, pyrolized gases, viable fungal spores, or pesticide residues) have on her health during periods of immunocompromise?[7] How will marijuana, alone or in combination with other medications associated with potential cognitive and psychomotor impairment, affect her ability to safely operate a motor vehicle?[8] What are the possible effects of marijuana on tumor progression? The putative cannabinoid receptor GPR55 (G-protein–coupled receptor 55) is expressed in human breast cancers, with higher levels of expression correlated with more aggressive phenotypes.[9] The marijuana constituent Δ^9-THC has been shown in some studies to act as a GPR55 agonist, raising the possibility that it can promote cancer-cell proliferation.[10]

Two prescription cannabinoids are available, dronabinol (Marinol) (a synthetic Δ^9-THC) and nabilone (Cesamet) (a Δ^9-THC congener), which are FDA-approved for the treatment of chemotherapy-induced nausea and vomiting. These medications have shown efficacy in the management of pain and distress. In contrast to smoked marijuana, they feature oral administration, chemical purity, precise dosages, and a slower onset but sustained duration of action. They may be less likely than smoked marijuana to induce anxiety, panic, and negative mood states,[11] but they have otherwise similar side-effect profiles.

Cannabinoids, however, should be used only as lower-tier therapies for chemotherapy-induced nausea and vomiting, since other medications, such as 5-hydroxytryptamine$_3$-receptor antagonists, dexamethasone, and aprepitant, have superior efficacy and fewer side effects.[12]

Assure Marilyn — and follow through on the assurance — that throughout her illness she will be accompanied, cared for, and helped to live as well and as long as possible. Reassure her that meticulous attention will be paid to symptom relief. Discuss the patient-specific potential risks and benefits of smoked marijuana and of the administration of pharmaceutical cannabinoids. There is little scientific basis for recommending that she smoke marijuana for symptom control. As Bernard Lown remarked, "Caring without science is well-intentioned kindness, but not medicine."[13]

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