Medicine OR Menace?

What we know about medical marijuana

BY HOWARD BELL
At Gillette Children’s Specialty Healthcare in St. Paul, pediatric pain and palliative care specialist Scott Schwantes, M.D., was recently talking with the mother of one of his patients—an 8-year-old boy with cerebral palsy, epilepsy, spasticity, dystonia, dysautonomia, irritability and pain. “I fed my son marijuana brownies and it really helped his dystonia,” the mom said. “Am I crazy for doing this?”

Schwantes and his partners have heard other parents say the same thing. Although he says he cannot tell families to try this approach, he says some studies show marijuana can help relieve symptoms such as those exhibited by the boy. “Anecdotally, in our patient population, marijuana has been helpful,” he says.

It’s also illegal. Physicians can’t prescribe it even in states where medical marijuana is legal because it’s a Schedule I drug deemed to have no medical value. That also means no federal funds are available to study its potential benefits and clear the air for physicians who feel stuck in the middle as more patients turn to marijuana, mostly in desperation, when conventional drugs don’t work or aren’t tolerated. “Most people who smoke it for medical reasons do so because they don’t have an alternative that works well,” says J. Michael Bostwick, M.D., a Mayo Clinic psychiatrist and medical marijuana expert who has written on the subject.

### Medical marijuana timeline

Over the last 5,000 years, medical marijuana has been embraced, then demonized, only to be embraced again.

**2800 B.C.** First reported use of medical marijuana in China.

**1500 B.C.** Earliest written references to medical marijuana in Chinese Pharmacopeia.

**1542** British doctors begin using marijuana as an analgesic, anti-spasmodic and anti-emetic.

**1854** Marijuana added to the U.S. Pharmacopeia. Physicians routinely prescribe marijuana cigarettes and extracts to treat anorexia, headaches, insomnia and sexual dysfunction.

**Early 1900s** Medical use of marijuana begins to decline because of increasing availability of synthetic pharmaceuticals, potency variability and unreliable supply sources.

**1936** The film *Reefer Madness* depicts marijuana smokers as addicted maniacs and killers.

Forty-eight states have laws that regulate marijuana.

**1937** Marijuana Tax Act causes further decline in prescribing medical marijuana. The American Medical Association opposes the Marijuana Tax Act, fearing it would limit research on its benefits for treating a variety of conditions.

**1942** Marijuana removed from the U.S. Pharmacopeia, eliminating its last vestige of legitimacy as a therapeutic drug.

**1964** The principal psychoactive ingredient in cannabis, THC, is identified and synthesized.

**1970** Congress makes marijuana a Schedule I drug, a class reserved for street drugs with abuse potential and “no currently accepted medical use.”

**1976** A man with glaucoma becomes the first American to receive government-supplied marijuana for a medical disorder.

**1978** New Mexico passes the first state law recognizing the medical value of marijuana.

The federal government’s Compassionate Use Program begins supplying free marijuana to seriously ill patients who might benefit from it.

**1980** National Cancer Institute tests dronabinol (Marinol), a synthetic THC, on cancer patients.

**1985** Food and Drug administration approves dronabinol.

**1988** Researchers discover a THC protein receptor located on human nerve cells—cannabinoid receptor 1 (CB1). Soon after, the same researchers discover a cannabinoid receptor 2 (CB2) on white blood cells and immune tissue. The search for cannabinoid-based pharmaceuticals begins.
1991 In an anonymous survey by the American Society of Clinical Oncology, 53 percent of respondents say marijuana should be available by prescription.

The federal government suspends the Compassionate Use Program because it undercuts Bush administration policy against use of illegal drugs.

1992 Israeli researchers discover the brain's first endogenous cannabinoid and call it anandamide, from the Sanskrit word ananda meaning eternal bliss or supreme joy.

1996 California becomes first state to legalize medical marijuana.

1997 *New England Journal of Medicine* publishes editorial calling for marijuana to be reclassified a Schedule II drug to acknowledge it has some medical use.

1999 Institute of Medicine publishes its first meta-analysis on the medical effects of marijuana.

Dronabinol reclassified as a Schedule III drug to increase availability to patients.

Canada begins funding research on medical uses for marijuana.

2003 Institute of Medicine publishes its second meta-analysis listing several medical conditions for which marijuana appears to have benefit.

2004 Drug Enforcement Administration instructs the Department of Health and Human Services to review marijuana for possible rescheduling.

2008 American College of Physicians calls for making marijuana a Schedule II drug, the same classification as opioid narcotics, and supports use of nonsmoked forms of medical marijuana.

2014 20 states plus the District of Columbia have legalized medical use of marijuana, which remains a Schedule I drug “with no currently accepted medical use.”

Sources: Bostwick JM, Blurred boundaries: the therapeutics and politics of medical marijuana, Mayo Clinic Proceedings, February 2012, 172-186; Robson PJ, Therapeutic potential of cannabinoid medicines, Drug Test Analysis, 2014, 6, 24-30; ProCon.org
The human cannabinoid system

In 1988, researchers discovered that the human body produces its own cannabinoids that attach to cannabinoid receptor sites throughout the body. The “endocannabinoid system” (ECS) affects nearly every physiologic function in the body by regulating neurotransmission between synapses.

The cannabinoids in marijuana exert their effects on the body and brain by attaching to these cannabinoid receptor sites. THC, a cannabinoid found in marijuana that produces the high users experience, attaches to cannabinoid receptor 1 (CB1), which is found mostly on cells in the brain, spinal cord and gut. CB1 helps regulate movement, pleasure, learning, memory, processing, attention and appetite. Recreational marijuana smokers may get the munchies when THC attaches to the CB1 receptors that govern food intake, according to J. Michael Bostwick, M.D., a Mayo Clinic psychiatrist and medical marijuana expert.

Another cannabinoid in marijuana called cannabidiol (CBD) attaches to cannabinoid receptor 2 (CB2), which is also found in the brain, but mostly on cells in the gut and on white blood cells. CB2 helps regulate digestion, inflammation and immune response, as well as cardiovascular, reproductive and endocrine function.

The ECS’s widespread influence explains why marijuana has been used for thousands of years to treat many conditions, Bostwick says. “And it’s why discovery of the ECS has ignited interest in cannabis-based medicines and prompted high hopes for developing many new drugs that will eliminate the need for or interest in using smoked cannabis.”

Researchers have found CBD switches off the malignant effects of the virus that causes Kaposi’s sarcoma and regulates movement of white blood cells important in immune defenses. CBD also has anti-seizure effects and reduces anxiety and psychotic symptoms, prompting some to speculate that it could someday be used to treat psychotic disorders.

THC relieves pain, relaxes muscles, prevents nausea, stimulates appetite, reduces intraocular pressure, acts as a bronchodilator and inhibits the growth and spread of lung cancer. CBD does the same for breast cancer. Both have anti-inflammatory effects.

Most of this research is still at the molecular stage or being done in animals. It may lead to the development of cannabinoid pharmaceuticals to treat ileus, inflammatory bowel disease, neuropathic pain, tumor growth and metastasis, hypertension, anxiety, psychosis and immune dysfunction. “We need to figure out how synthetic cannabinoids can modify the function of the ECS with potential implications for helpful treatments in a plethora of diseases,” Bostwick says.

To prevent the cognitive clouding and memory impairment marijuana causes, researchers are trying to create cannabinoid drugs that attach only to CB2 receptors, which are nearly absent from the brain and therefore don’t cause these cognitive side-effects. Another line of research is developing drugs that attach to CB1 receptors, but only those outside of the brain.

Nobody knew about the ECS in 1970 when the federal government banned medical research on marijuana by making it a Schedule I drug. “It’s sad and frustrating that there are so many barriers to translating what we’ve learned about the endocannabinoid system into beneficial pharmaceuticals,” Bostwick says. —H.B.
cantly lowered pain scores as compared with placebo. They also reduced spasticity and improved sleep. A double-blind trial using Sativex for intractable central neuropathic MS pain was so convincing that the results were the primary basis for approving Sativex in the United Kingdom in 2010. (It is not yet approved in the United States.)

For treating PTSD, the evidence is thinner and more anecdotal, but many states include it on their list of authorized conditions. In New Mexico, which created its medical cannabis program in 2007, 42 percent of the enrolled patients smoke marijuana to relieve PTSD symptoms. “We’ve known for years that many PTSD patients smoke marijuana to help them cope with symptoms,” says Steven Jenison, M.D., a medical cannabis expert who directed the program from 2007 to 2009. “Now there’s compelling evidence that supports their experience.”

Clinical and lab studies suggest that cannabinoids may reduce PTSD symptoms by attaching to cannabinoid receptors in the amygdala, the part of the brain that controls fear conditioning, memory storage and retrieval, arousal, mood, sleep, anxiety and depression. A team of investigators from Germany, the United States and the United Kingdom reported in *Drug Test Analysis* in 2012 that marijuana works better than antidepressants for alleviating some symptoms. Last month, the Department of Health and Human Services signed off on a study of marijuana to treat PTSD symptoms in veterans. Researchers from the University of Arizona will evaluate the effects of five different potencies of smoked or vaporized marijuana in 50 veterans, assuming they receive clearance from the DEA.

A thicker stack of studies shows marijuana’s potential for treating epilepsy. Certain cannabinoids in marijuana reduce seizure intensity and frequency in some types of epilepsy. “We’ve known for years that cannabinoids help prevent seizures in research animals,” says Ilo Leppik, M.D., a neurologist who directs the University of Minnesota’s Epilepsy Research and Education Program. “In neuroscience, animal research often translates well to humans.”

Some of Leppik’s patients have told him they sometimes smoke marijuana and it seems to reduce seizure frequency and intensity. “They ask me what I think. I tell them I can’t recommend it. We know there’s a cannabinoid receptor in the brain associated with seizures. But we need to study the potential of specific cannabinoids, not whole marijuana.”

The U.K. drug company that created Sativex is doing just that—testing what it calls Epidiolex, a highly purified liquid cannabidiol extracted from
marijuana plants, to treat pediatric epilepsy syndromes. Unlike THC, cannabidiol doesn’t have psychoactive effects. Robson’s review found that in animal studies, several cannabinoids, especially cannabidiol, have shown significant anti-convulsant properties. The company expects to begin Phase 2 clinical studies of Epidiolex in the latter half of 2014.

Several studies show THC and cannabidiol have anti-inflammatory effects, which may explain why some medical marijuana smokers say it relieves symptoms of inflammatory bowel disease. In the lab, cannabinoids show promise for treating several gastrointestinal conditions. As Mayo Clinic gastroenterologist Michael Camilleri, M.D., wrote in his 2008 review in Gut: “Cannabinoids may benefit patients with irritable bowel syndrome by inhibiting intestinal motility and secretions by docking onto cannabinoid receptors in the gut and acting as a physiological brake.” He qualified that statement by saying “Further clinical trials are required to assess the potential impact on disease.”

Cannabinoids may reverse hepatic fibrosis and have anti-tumor effects in the liver as well. Animal studies show cannabinoids shrink tumors and slow metastasis in colon, liver and pancreatic cancer. “They have been reported to have remarkable growth-inhibiting effects on pancreatic cancer cells,” Camilleri wrote.

Marijuana’s anti-inflammatory effects also may explain why many medical marijuana smokers use it for arthritis pain. In a randomized double-blind trial of 58 rheumatoid arthritis patients comparing Sativex to placebo, most had significant improvements in pain, movement and quality of sleep after only five weeks of treatment. That same study, which was published in Rheumatology in 2006, showed that in many patients the THC and cannabidiol in Sativex actually slowed rheumatoid arthritis progression, based on a standard measure of rheumatoid arthritis disease activity.

Not ready for prime time?
The American Medical Association (AMA), Institute of Medicine and American College of Physicians agree that specific cannabinoids show potential. But that doesn’t mean they support smoking whole marijuana, which many view as an imprecise “shotgun” way to treat anything because it contains 400 different chemicals.

Leppik says smoking marijuana has so many downsides that even if Minnesota legalizes medical marijuana he’d tell his patients not to smoke it. “They’re still going to have seizures, and they’d need to stay high all the time in order to maintain a steady dose. Smoking itself is harmful, and in epilepsy it’s important to minimize side-effects from whatever drugs they’re taking because side-effects can aggravate the condition.” Leppik says he is irritated with the recent flurry of media stories about marijuana as a miracle cure for seizures. “They do a great disservice because they create false hope.”

Another concern is that whole marijuana might increase the risk for earlier and more intense emergence of psychoses, including schizophrenia, especially in susceptible adolescents and young adults. A 2011 meta-analysis by Kuepper published in BMJ looked at the results from three dozen studies of young people in Sweden, New Zealand and the Netherlands and found a strong link between regular marijuana use and later development of schizophrenia.

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found teens who used marijuana to be at a six-fold increased risk for developing schizophrenia. “These are people who did not have signs of the disorder earlier—and after they develop it, there’s no undoing it.”

Gavin Bart, M.D., Ph.D., an internist and addiction medicine specialist at Hennepin County Medical Center who directs their Addiction Medicine Program, recently traveled on a U.S. Embassy-sponsored public health mission to Papua New Guinea, where marijuana grows wild and is freely available. “At the country’s only psychiatric hospital,” Bart says, “the No. 1 reason for admission is marijuana-induced psychosis. It may have to do with a genetic predisposition combined with dose. But if it’s all dose-related, that’s a problem for using marijuana medically.”

Marijuana’s effects differ greatly among individuals. Where it may make one person happy, it may make another sad. Where one person feels relaxed after smoking it, another may feel anxious. Sometimes, it causes all of these in the same person at different times, and its use often makes normal everyday functioning difficult. The American Psychiatric Association’s DSM-5 includes a diagnosis of “cannabis use disorder,” characterized by an inability to fulfill work, school or family responsibilities.

As for addiction, contrary to the 1936 film Reefer Madness, women don’t cry for it and men don’t die for it. Physical addiction is rare; psychological addiction is more common. Bart says the 2013 National Household Survey on Drug Use and Health shows that among regular marijuana users, one in 11 met the criteria for being addicted to it during that year, compared with one in 21 alcohol users and one in eight prescription opioid users. “During the second half of 2013,” he says, “16 percent of all admissions to Twin Cities-area addiction treatment programs were for marijuana addiction.”

More study needed

For all of those reasons and more, Bart believes it’s too early for marijuana to enter the House of Medicine. “We need clinical trials that compare marijuana to approved...
ON THE COVER

**Synthetic cannabinoids**

Minnesotans can prescribe two pills that contain pure THC, the cannabinoid in marijuana that creates the high recreational users seek and is also medically useful. Dronabinol (Marinol) and nabilone (Cesamet) were approved by the FDA in 1985 for preventing chemotherapy-induced nausea and severe weight loss caused by HIV/AIDS. Both are on most hospital formularies.

Thomas Flynn, M.D., an oncologist with Minnesota Oncology in Minneapolis, says he and other oncologists he knows sometimes prescribe dronabinol for cancer-related nausea and anorexia. “It works,” he says, “but usually not as well as the highly effective 5HT3 antagonists like ondansetron, granisetron and palonosetron.”

Dronabinol (Marinol) also has more side effects, including a high or feeling of dysphoria that elderly patients in particular don’t like. For those reasons, dronabinol and nabilone have never been first-choice treatments. “We only use them if the 5HT3 drugs aren’t working or aren’t tolerated,” he says.

Nabilone (Cesamet) is sometimes also used for cancer pain. Flynn says he and his colleagues don’t use it because they have more effective drugs to control pain. A 2014 report by Robson on the therapeutic potential of cannabinoid medicines published in Drug Test Analysis showed nabilone sometimes relieves cancer pain to a degree equivalent to codeine, but that it causes sedation and cognitive clouding in most patients.

Pediatric pain and palliative care specialist Scott Schwantes, M.D., has prescribed dronabinol for his end-of-life patients at St. Paul’s Gillette Children’s Specialty Healthcare to reduce neuropathic pain, anxiety, nausea and spasticity. “It was moderately effective sometimes,” he says. But he agrees that better drugs are available.

Nabiximols (Sativex), a third synthetic cannabinoid, is not yet approved in the United States but has been approved in 22 countries including Canada to treat spasticity caused by multiple sclerosis, as well as cancer pain and neuropathic pain. It’s currently in Phase 3 clinical trials in this country for treating persistent pain that can’t be controlled with other medications.

Sativex is an oral spray containing one part THC and one part cannabidiol (CBD), another compound in marijuana that shows therapeutic promise. Unlike THC, CBD does not cause euphoria, dysphoria, cognitive clouding or sedation. It also reduces anxiety, which pure THC can cause.

Sometimes called “liquid medical marijuana,” nabiximols is an extract made from marijuana plants. The U.K. drug company that makes Sativex grows the plants in its own greenhouses (something that is not allowed in the United States). The drug is absorbed rapidly through the mucosa, offering the same rapid-onset advantage as smoked marijuana but without the side effects or the risk for addiction.

Nabiximols, dronabinol and nabilone are examples of how compounds in marijuana can be turned into therapeutic drugs, according to J. Michael Bostwick, M.D., a Mayo Clinic psychiatrist and medical marijuana expert. “You get a quality-controlled standardized potency without having to inhale a smoke containing hundreds of compounds,” he says. “And there’s little evidence of abuse or addiction because these cannabinoid preparations aren’t much fun to take.” —H.B.

But all medicines have risks, Bostwick points out. Many routinely prescribed drugs cause a long list of adverse effects including mental clouding, memory impairment and mood changes—effects that sometimes are so adverse that patients turn to marijuana instead. States that have legalized medical marijuana have decided that whatever the risks may be, the benefits outweigh them for patients with serious chronic conditions who couldn’t be helped with conventional treatments. Meanwhile, Bostwick says, “the [federal] government is essentially blocking research on the medical benefits of cannabinoids, which could yield an armada of pharmaceuticals to treat many conditions.”

One way to encourage research is to reschedule marijuana. “I think everyone agrees smoking marijuana isn’t good for patients,” Schwantes says. “But if compounds in marijuana help our patients, then we owe it to our patients to study them.” The AMA, the American College of Physicians and the editorial boards of a number of peer-reviewed medical journals have called for changing marijuana to a Schedule II drug so the NIH will fund randomized controlled trials. Until this happens, Leppik says, “the medical marijuana discussion will be based on very little sci-
ence and mostly on anecdotes, politics and sob stories.”

New Mexico’s Jenison agrees that rescheduling marijuana is an important first step, but he says it’s not likely to happen in the foreseeable future. Meanwhile, he says, the public is growing impatient.

“Patients who benefit from medical cannabis find unpersuasive the argument that they should wait for rigorous clinical trials when they know that their government has not only failed to support this promising area of research but has actively obstructed it. Twenty states now protect patients who benefit from medical cannabis from criminal liability. Until better cannabinoid drugs are available by prescription, I consider this a fair and just compromise.”

Howard Bell is a medical writer and frequent contributor to Minnesota Medicine.