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According to a March 2017 publication by the National Conference of State Legislatures, 28 states, the District of Columbia, Guam, and Puerto Rico now have some form of ''comprehensive medical marijuana and cannabis programs.''[1] Meanwhile the U.S. public has expressed growing support for legalization: in an October 2016 Gallup Poll, 60% favored generic legalization,[2] while 89% favored legalization for medical use.[3] These and other data suggest cannabis consumption for medicinal purposes probably takes place nearly everywhere, legal or otherwise.

Also in early 2017, the National Academies of Sciences, Engineering, and Medicine published a comprehensive review, titled The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.[4] This rigorous monograph summarizes safety, efficacy, a research agenda, and other important domains.

Some might suggest that the will of the electorate in supporting legalization has outpaced the science that might most optimally inform public policy and clinical practice. Where does this leave the palliative care clinician?

What Are We Even Talking About?

The marijuana plant contains hundreds of cannabinoid molecules, although THC (tetrahydrocannabinol) and CBD (cannabidiol) are best known and studied. For the purposes of this summary, ''marijuana,'' ''medical marijuana,'' and ''cannabis'' refer to naturally grown plant materials that are (as of April 2017) not U.S. Food and Drug Administration (FDA) approved or regulated. ''Cannabinoids'' are three chemical classes of compounds: plant-derived cannabis, synthesized molecules, and endocannabinoids, which are produced by the mammalian central nervous system. ''Pharmaceutical cannabinoids'' are those that have been approved for production, prescription, and sale by a national regulatory agency such as the FDA.[5]

Most palliative care clinicians are aware that there are currently two FDA-approved pharmaceutical cannabinoid drugs available for prescription by physicians in the United States: dronabinol, a synthetic THC compound, and nabilone, a more potent semisynthetic analog of THC.[6] Dronabinol and nabilone are both approved in pill and injectable form for treatment of chemotherapy-induced nausea and vomiting (CINV); dronabinol is also approved for HIV-associated wasting syndrome. A third THC preparation (an oral liquid version of dronabinol to be marketed as Syndros™) was FDA approved in July 2016 and should be on the U.S. market within a few months.

Nabiximols (Sativex™) is 1:1 racemic mixture of THC:CBD that comes in an oral spray, and is approved in Canada and a number of European countries for treatment-refractory cancer pain and multiple sclerosis (MS)-associated spasticity and central pain. It is in late-phase trials in the United States.

A version of oral liquid CBD known as Epidiolex™ was granted Investigational New Drug status by the FDA in 2013 to facilitate compassionate use in studies of treatment-refractory pediatric epilepsy, and was granted Orphan Drug Status by the European Medicines Agency in early April 2017.

All other medical marijuana ingested by patients in the United States is of unregulated ''products''—the buyer is essentially taking the seller's word for the contents.

Efficacy

Many meta-analyses and reviews have been published in recent years. Studies of cannabinoid efficacy vary greatly: some have tested whole-leaf marijuana (with its naturally occurring varying concentrations of THC, CBD, and other molecules); others assess isolated compounds such as THC, or known/controlled combinations of plant-derived products (such as the nabiximols studies), and some study only synthesized products like nabilone. These differences make comparisons difficult.

A recent Cochrane-style review[7] looked at the quality of evidence supporting the use of cannabinoids in CINV, as appetite stimulant in HIV/AIDS, in chronic pain, spasticity from MS or paraplegia, depression, anxiety, sleep problems, psychosis, glaucoma, or Tourette's syndrome. Seventy-nine randomized trials involving 6462 patients were identified. Moderate quality evidence supports the use of cannabinoids for chronic pain and spasticity. Low quality evidence supports the use of cannabinoids for CINV, wasting, sleep problems, and Tourette's syndrome. Many other uses of cannabinoids are rationalized based on cultural traditions, small case series, open label trials, anecdote, or opinion.

The American Academy of Neurology completed its own recent review and concluded that cannabinoids, particularly nabiximols, provide small benefits for patients with MS-related spasticity, central pain, and urinary symptoms but shows little evidence of efficacy for other neurologic conditions.[8] Orrin Devinsky, a leading U.S. investigator in the use

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of CBD for treatment-refractory pediatric epilepsy, has published an open-label trial showing some efficacy[9] that warrants randomized controlled trials.

The already-mentioned National Academies monograph draws nearly identical conclusions to those above. Readers are referred to it for a comprehensive review of the evidence.

There is also interesting preclinical data suggesting that cannabinoids may have a role in reversing opioid-associated hyperalgesia,[10] may reduce craving and relapse risk in opioid dependence,[11] and could help prevent or treat chemotherapy-induced peripheral neuropathic pain.[12] There is emerging, equivocal data regarding whether cannabinoids improve quality-of-life and reduce symptom burden or disease activity in inflammatory bowel disease.[13,14]

In a recent review[15] of the common indications for use listed in state cannabis regulations, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), cachexia, cancer, Crohn's/inflammatory bowel disease (IBD), epilepsy, severe/chronic pain, glaucoma, hepatitis C, HIV/AIDS, MS, and post-traumatic stress disorder (PTSD) appear regularly. This listing suggests the degree to which state guidelines depart from, and generally exceed, evidence-based uses, and in turn the degree to which lawmaking may be influenced by popular beliefs or political processes. To review the guidelines in your state, readers may wish to consult local code or go to www.leafly.com/news/health/qualifying-conditions-for-medical-marijuana-by-state.

For the palliative care practitioner, these efficacy data are complicated not just by the generally low volume of only moderate quality evidence, and by state regulations that regularly depart from that evidence, but also increasingly by the growing reach of our field beyond cancer and HIV into the realms of adult degenerative diseases of the central nervous system, heart, lung, liver, digestive tract, and to serious noncancer childhood disorders.

Safety

As the National Academies monograph and other recent excellent reviews suggest,[16] recreational (and perhaps medical) use of cannabinoids is particularly concerning in young people with still-developing brains, persons with preexisting (particularly psychosis) mental illness, and those with existing substance abuse problems. In these populations regular cannabis use can unmask or hasten the onset of psychotic illness, is associated with reduced IQ, addiction/dependence, and a withdrawal syndrome. Other widely recognized sequela of regular/chronic use include dropping out of school, decreased motivation, socialization, and life-satisfaction, and chronic bronchitis.

Other than bronchitis, the data regarding respiratory consequences of cannabis consumption (mostly via inhalation of marijuana cigarettes) are equivocal. Inhaled cannabis does NOT appear to confer increased risk for lung cancer or head and neck cancer. The data on marijuana use and cardiac disease have not shown compelling evidence for concern. One recent 20-year comparison of daily tobacco versus marijuana smokers showed only increased risk for periodontal disease with cannabis, whereas tobacco users had expected increases in lung, cardiac, and metabolic (wait circumference, lipid profile, HgA1C, body weight)[17] risk factors. Cannabis appears to have some anti-inflammatory properties; according to the National Academies report, there is insufficient evidence to support any conclusions about the impacts of cannabis on other immune functions.

Interesting public health data suggest that there may be significant trends toward decreases in opioid overdose deaths in states with legalized cannabis,[18] fewer overall traffic deaths (though more cannabis-positive tox screens in those net fewer deaths) after legalization,[19] and reductions in pre-versus-post legalization Medicare expenditures on prescription analgesics, sedative-hypnotics, anxiolytics, and other agents.[20]

A separate but important consideration is whether a standard risk-benefit analysis makes sense for palliative care patients when contemplating cannabis. Risks of overgeneralization aside, most palliative care patients are NOT young people with unlimited life prospects who are early in their school years or social developmental trajectories, are NOT climbing career ladders, are NOT parenting small dependent children, or operating heavy industrial machinery. Thus, I would argue that this brief summary of safety risks should, in the palliative care clinical setting, be balanced against the exigencies of attempting to help patients achieve symptom relief in the context of serious (and often life-limiting) illness, particularly if they are facing difficult symptoms not responsive to conventional treatments.

Uncertainties

In addition to those scientific and public policy matters outlined above, there are many other uncertainties facing the palliative care clinician and his/her patient contemplating cannabis. Chief among them is what the patient actually receives when he/she purchases medical marijuana at a dispensary: a recent small study of marijuana edibles (75 products randomly purchased form dispensaries in San Francisco, Los Angeles, and Seattle) showed accurate labeling in only 17%.[21] The majority of products were ''overlabeled'' (at least 10% less cannabinoid content than claimed), while 23% were ''underlabeled'' (at least 10% more content). Geographic differences were noted as well, with Los Angeles dispensaries showing a significant ($p = 0.01$) inclination to underlabel. FDA has recently published a report of its analysis of CBD products purchased over the internet, which showed most of the products to contain little or no active ingredient.[22] These findings undermine a fundamental element of physician practice, namely the ability to identify and recommend (or prescribe) specific, reliable doses of compounds.

It should also be noted that under most of the state laws, physicians are not prescribing medical marijuana at all. Instead, they are asked to endorse, attest, or certify that in their professional judgment the patient has a disorder for which medical marijuana may have efficacy. This, too, is unfamiliar territory for many of us.

Brass Tacks

1. There is reasonable evidence that cannabinoids can help with some forms of chronic pain, CINV, MS-related spasticity, and central pain. Other uses are not well supported but clearly happen anyway.
2. There are FDA-approved pharmaceutical cannabinoids that may be worthy of clinical trial in patients with difficult to manage, potentially cannabinoid-responsive symptoms.

3. There is considerable uncertainty about the chemical composition and purity of dispensary-purchased products; it is wise for palliative care clinicians to know this and counsel their patients about it.
4. Patients should be counseled about the known risks of cannabinoid use, including inadvertent exposure of others, particularly to children, in the patient's environment. Medical marijuana should be safeguarded in the same ways that we instruct our palliative care patients to store opioids and other controlled substances. We should offer similar counsel regarding caution with *de novo* exposures as they pertain to fall risk, driving safety, and others.
5. It is worthwhile for palliative care clinicians who may be endorsing cannabinoid use by their patients to familiarize themselves with the clinical picture of intoxication, abuse, dependence, and withdrawal states, and to encourage their patients to allow themselves to be clinically monitored as we might do for any other new course of treatment.

David Casarett, MD, a palliative care physician at the University of Pennsylvania, has recently published a book that encompasses many of the topics in this brief review[23] and is well suited to lay readers as well as professionals.

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