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Abstract

Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.

Keywords

cannabis, medical marijuana, opioids, hospice, chronic pain, palliative medicine

Introduction

Palliative care medicine is a relatively new subspecialty, arising out of a need for better ways to treat patients with advanced, potentially “life-limiting” conditions. As palliative medicine emerges as a sovereign entity, distinctly different from hospice care, more practitioners are broadening the scopes of their practice to include these services. However, this will require a distinct paradigm shift, away from the “hospice mindset” with respect to the way drugs are prescribed, with drug safety becoming an increasingly important issue. When treating pain in a terminal cancer patient, using opioid drugs will typically provide good relief.¹ However, in hospice, mortality is a forthcoming and expected outcome. This may not be the case in palliative medicine where the patients seek aggressive treatment for pain yet death may not occur for some time. Here, the successful use of opioids will warrant more frequent patient reassessments and significant pharmacovigilance.

This growth in palliative medicine comes at a time when there have been near epidemic increases in deaths related to prescription of opioid analgesics.²⁻¹³ A number of studies have now clearly linked risk of fatal and nonfatal opioid overdose to prescription use, with the risk increasing with the prescribed dosages.¹²⁻¹⁴ According to the Centers for Disease Control and Prevention (CDC), from the years 1999 to 2006, the number of prescription opioid poisoning deaths in the United States (US) nearly doubled, from approximately 20 000 to 37 000.¹⁵

This increase coincided with a nearly 4-fold increase in the use of prescription opioids nationally.

In 2006, Washington State had a rate of poisoning involving opioid painkillers significantly higher than the national rate.¹⁵ A subsequent analysis of overdose deaths involving prescription opioids from 2004 to 2007 revealed that 1668 persons died from prescription of opioid-related overdoses during that time period.¹⁵ Nearly 60% of decedents were male, with most deaths occurring in the 45 to 54 years of age range.¹⁵ A 7-fold higher death rate was noted among persons enrolled in Medicaid programs, compared to those not enrolled. The opioids most commonly involved in the deaths were methadone (64%),

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oxycodone (23%), and hydrocodone (14%), which highlights the particular toxicity of methadone.¹⁵

Contrast these morbid trends with this well-documented fact: no one has ever died from an overdose of cannabis.¹⁶⁻²⁰ Cannabis has no known lethal dose.¹⁶⁻²⁰ If cannabis-based medicines were more widely used to treat pain, potentially thousands of deaths from opioid toxicity may have been prevented. In the past decade, many states have relegalized cannabis for medicinal purposes.²¹ This is based on a continually growing body of evidence demonstrating the efficacy of cannabis in treating neuropathic pain, muscle spasms, fibromyalgia, cacechxia, among others conditions.²¹⁻³⁶ Yet, the laws differ considerably from state to state, with considerable ambiguity what constitutes acceptable medical use.²³ Despite state laws, the Federal United States Drug Enforcement Agency (DEA) laws, as determined by the Controlled Substances Act (CSA), still classify cannabis as a Schedule I drug, the most tightly restricted category, reserved for drugs that have no currently accepted medical use. Thus, there is uniform set of quality control standards in place to assure the quality, consistency, and availability of medicinal cannabis for patients receiving palliative care.

How Did We Get Here?

Against the advice of the American Medical Association, the use of cannabis for any purpose, including medicinal, was criminalized in the United States by 1942.³⁷⁻⁴⁰ Prior to then, there were many cannabis-based medications commercially manufactured by companies including Eli-Lilly, Parke Davis, and Sharp Dohme (now Merck Sharp Dohme).¹ Cannabis was criminalized largely due to the actions of Harry Anslinger, head of the Federal Bureau of Narcotics in the 1930s, who was a notoriously strong opponent of cannabis.³⁸ Multiple government-sponsored panels, including the National Commission on Marijuana and Drug Abuse (the Shafer Commission), appointed by the then President Richard Nixon have recommended that possession of cannabis for personal use no longer be an offense and that casual distribution of small amounts of cannabis for no remuneration or insignificant remuneration no longer be an offense.⁴⁰ The commission further concluded that neither the cannabis user nor the drug itself can be said to constitute a danger to public safety.⁴⁰ Despite the commission's recommendations, an infuriated Nixon and Congress ignored the report. Since then, almost 15 million Americans have been arrested on cannabis charges, with little evidence of any impact on cannabis use in either adults or youths.⁴¹⁻⁵³

Thus, over the past 75 years, there have been further developments in opioid-based medicine, while research in cannabinoid-based medicines has grounded nearly to a halt. Today, opioids are available in a multitude of strengths, in pills, patches, injectables, implantables, etc, while the only form of a cannabinoid-based medicine available in the United States is dronabinol (Marinol). Dronabinol is 100% Delta-9 tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis.⁵⁴ Natural cannabis contains, at most, 20% THC.⁵⁵⁻⁵⁷

Opioids versus Cannabinoids: A Brief Overview

Opioids and cannabinoids have many things in common. They are both among the world's oldest-known class of drugs, with documentation of usage dating back many thousands of years. They both produce their pharmacological effect via actions at specific receptors, found throughout the body.^{1,21} Both of these classes of compounds are also made endogenously in the human body and are part of the normal regulatory, homeostatic processes necessary for life.⁵⁸⁻⁶¹ Without endorphins (opioids) and endocannabinoids (cannabinoids), our bodies would not function properly.

Opioids

Any chemical that works by binding to opioid receptors is considered an opioid.^{62,63} Opioid receptors are found principally in the central and peripheral nervous system and the gastrointestinal tract.⁶³ The receptors in these organ systems mediate both the beneficial and untoward side effects of opioids.^{63,64}

In hospice and palliative care, opioids are the "gold standard" for analgesic medications, being cost- and clinically effective, and generally well-tolerated for treating moderate-to-severe pain. However, in a recent study of 50 641 persons receiving hospice services, approximately 20% had moderate or severe constipation due to morphine use.⁶⁵ However, long-term toxicity is not an issue in hospice but becomes a major problem in the management of chronic pain.

Cannabinoids

There are 2 known cannabinoid receptor subtypes. Subtype 1 (CB1) is expressed primarily in the brain, whereas subtype 2 (CB2) is expressed primarily in the periphery.^{61,66-70} Dense CB1 receptor concentrations have been found in the cerebellum, basal ganglia, and hippocampus, accounting for the effects of cannabis on motor tone, coordination, and mood state.⁷¹⁻⁸¹ Low concentrations are found in the respiratory centers of the brainstem, accounting for the remarkably low toxicity of cannabis.⁸¹ Lethal doses for cannabis in humans have not been described.¹

A detailed biochemical discussion of the remarkably complex cannabis genus is beyond the scope of this article. There are at least 3 species: cannabis sativa, cannabis indica, and cannabis ruderalis, with each containing over 400 distinct chemical moieties.⁸²⁻⁸⁵ There are at least 85 known cannabinoids that have been isolated from the cannabis plant.⁸²⁻⁸⁵ The cannabinoids are lipophilic, 21 carbon terpenes, and include delta-9 THC and delta-8 THC, which produce the majority of psychoactive effects.⁵⁴ Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which significantly modify the effects THC and have distinct effects of their own. CBD appears to modulate and reduce any untoward effects of THC.⁸³⁻⁹⁰ Much less is known about CBN, although it appears to have distinct pharmacological properties that are quite different from CBD.⁸³ Cannabidiol has significant

anticonvulsant, sedative, and other pharmacological activities likely to interact with the effects of THC.⁸³ Cannabidiol may induce sleep and may provide some protection against seizures for epileptics.⁸³ Of relevance for pain management, in addition to analgesia, the following dose-dependent pharmacologic actions have been observed in studies: muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, and anxiolysis.¹⁻⁴ The ratios of the various cannabinoids differ according to the plant strain, and, to some extent, how the plant is grown.⁸²

Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels.⁸⁷⁻⁹⁰ There are strong data indicating that neurons in the rostro-ventral medulla and periaqueductal grey are involved in the brain-mediated analgesic effects of cannabinoids.⁹¹ There are also spinal mechanisms of analgesia, including cannabinergic inhibition of gamma amino butyric acid (GABA), glycine, and glutamate release.^{66,71,72} There is also a growing body of evidence showing a peripheral analgesic action of cannabinoids, particularly if inflammation is present.⁷⁶ Animal studies have demonstrated analgesic effects of locally delivered cannabinoids at doses that would not be systemically effective.⁶⁰ The mechanisms of these peripheral analgesic actions are not completely understood, but appear to be related to the anti-inflammatory effects of cannabinoids.^{59,61} Cannabinoids have profound effects on cytokine production, although the direction of such effects is variable and not always mediated by cannabinoid receptors.⁸¹ Another proposed mechanism for the anti-inflammatory actions is cannabinoid-induced increased production of eicosanoids that promote the resolution of inflammation. This differentiates cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.^{92,93}

The Argument Against Dronabinol

Dronabinol is 100% delta-9 THC, the most psychoactive ingredient in cannabis.⁵⁴ Natural cannabis contain, at best, 20% THC.^{55,56} There are varying physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material.⁹⁴ The Food and Drug Administration first licensed and approved dronabinol in 1986 for the treatment of nausea and vomiting associated with chemotherapy and expanded this in 1992 for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS) wasting.⁹⁴ Most patients find dronabinol too sedating and associated with too many psychoactive effects.^{2,14} Dronabinol is not an appropriate substitute for natural cannabis.

Re-scheduling Cannabis

As previously noted, drugs are categorized (scheduled) by the DEA, as determined by the CSA. Schedule I is a category of drugs not considered legitimate for medical use because of

limited utility and a high potential for dependence. Sharing this schedule with cannabis are heroin, lysergic acid, and methamphetamine. Schedule II is a category of drugs considered to have a strong potential for abuse or addiction, but that also have legitimate medical use. Included here are opium, morphine, cocaine, and oxycodone. Schedule III drugs are felt to have even less abuse or addiction potential than Schedule I or II drugs and have a beneficial medical use. Included here are dronabinol, hydrocodone, amphetamine-based stimulants, and short-acting barbiturates. Schedule IV and V drugs are felt to have even less risks. Schedule IV drugs include benzodiazepines, while Schedule V drugs include antidiarrheals and anti-tussives that contain opioid derivatives.

For further perspective, while the DEA considers cannabis a Schedule I drug, it does not schedule carisoprodol (Soma) at all, implying that this agency does not consider it a dangerous drug. Carisoprodol is a widely used muscle relaxant whose active metabolite is the barbiturate meprobamate. Carisoprodol also shows serotonergic activity at higher levels and has produced overdose in humans.^{95,96} Abrupt cessation in patients taking large doses of carisoprodol will produce withdrawal, characterized by vomiting, insomnia, tremors, psychosis, and ataxia.^{95,96}

Given that dronabinol, being 100% THC and highly psychoactive, is Schedule III, and the potentially addictive drug carisoprodol is unscheduled, it is perplexing how cannabis remains a Schedule I drug. In our opinion, ideally cannabis should be unscheduled. At the very least, it should be reclassified to Schedule III or higher.

Debunking the Smoking Argument

Cannabis does not need to be smoked to be effectively used as medicine. While cannabis smoke does not cause lung cancer, it can potentially irritate bronchial mucosal membranes. However, cannabinoids are volatile and will vaporize at temperatures in the range of 250°F, much lower than actual combustion.⁹⁷⁻⁹⁹ Heated air is drawn through cannabis and the active compounds vaporize, which are then inhaled. This rapid delivery of the cannabinoids allows for easy titration to desired effect, much as with smoking yet without health risks.⁹⁷⁻⁹⁹ Additionally, cannabis can be ingested orally or applied topically in a liniment.¹

Side Effects of Cannabis

As with any drug, cannabis is not without side effects. Medical use of cannabis is also distinctly different from recreational use. A patient does not need to be intoxicated to get a beneficial medical effect.^{100,101} Cannabis may induce euphoria and, as such, may be psychologically addictive. There is no severe physical withdrawal syndrome associated with cannabis. Cannabis addiction is amenable to treatment.⁴⁶ Cannabis may induce paranoia and disorientation in novice users. Many of the undesired psychoactive effects of cannabis are due to THC, which is among the reasons that dronabinol is not a suitable alternative.

However, newer medicinal strains of cannabis are lower in THC and higher in the nonpsychoactive, more therapeutic cannabinoids, such as CBD and CBN. These compounds further improved the efficacy of cannabis.¹⁰²⁻¹⁰⁴ With simple trial and error, most patients are able to get the right combination of cannabinoids that meet their needs. Dosing paradigms for medicinal cannabis have been previously described.^{17,18}

Conclusion

Despite being hampered by legal restrictions, the available medical research on cannabis indicates that cannabis is effective in treating a number of problems commonly encountered in palliative medicine. Many patients in a palliative care setting who are currently on long-term opioids for chronic pain could potentially be treated with either cannabis alone or in combination with a lower dose of opioids. From a pharmacological perspective, cannabinoids are considerably safer than opioids and have broad applicability in palliative care. Had cannabis not been removed from our pharmacopeia 7 decades ago and remained available to treat chronic pain, potentially thousands of lives that have been lost to opioid toxicity could have been prevented. As our population ages and palliative medicine continues to grow as a specialty, the argument for cannabis to be reclassified by the DEA as a scheduled III or higher becomes increasingly important.

As palliative medicine practitioners, our specialty should embrace the scientific process, which continues to document the therapeutic effects of cannabis. As is often the case in hospice, we must be willing to advocate for our patients who want to legitimately access a medicine that could potentially be very beneficial for them and is safer than other options such as opioids. The medicinal cannabis user should not be considered a criminal in any state and the DEA and our legal system should be using science and logic as the basis of policy making rather than political or societal bias.

Declaration of Conflicting Interests

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