

## Commentary

# Cannabis for Chronic Pain: We Simply Don't Know

State policy and public opinion regarding the therapeutic role of cannabis for chronic pain, which is the most commonly reported indication, has rapidly outpaced the evidence. To further complicate matters, scientific groups have differentially characterized the same body of evidence about the therapeutic benefits for chronic pain from substantially supportive to largely insufficient [1–3].

To understand these different interpretations, the devil really is in the details. First, it is important to distinguish neuropathic from nociceptive pain. The latter has largely been unstudied, but the two have been conflated in a summary of findings from two widely publicized reports [1,2]. Second, the dosages and formulations of cannabis have varied across studies and do not closely approximate what is typically available to and used by consumers. Finally, the trial duration is important to consider because chronic pain is likely to require prolonged treatment. Among the studies that reported therapeutic benefit in neuropathic pain, most had very short follow-up, on the order of hours to days [2].

The burden of proof required to clearly demonstrate long-term benefit depends, in part, on the potential for harm. If the likelihood for harm was low, then it might be more reasonable to extrapolate short-term data or data from other populations. Frequent cannabis use, however, is associated with significant and underappreciated concerns, chief among them mental health and addiction risks [2]. There is a growing body of evidence consistently supporting a link between frequent cannabis use and the development of psychotic symptoms [2], a risk that may be magnified in vulnerable groups including adolescents and young adults. Over the last several years, emerging data have underscored the seriousness and frequency of cannabis use disorder. More than one in three adults reporting past-year use met criteria for cannabis use disorder in a nationwide study, and nearly half of those had moderate- or high-severity disease [4].

Moreover, there are safe and effective nonpharmacologic treatments available for chronic pain, including movement therapies and psychological interventions [5]. It is challenging, however, to realize the benefits of movement therapies in real-life practice on a widespread basis because lack of access and treatment burden can be major barriers to ongoing patient engagement. In light of these barriers, it is

tempting to reach for any nonopioid pharmacologic alternative, such as cannabis.

The burgeoning interest in cannabis as a treatment for chronic pain is also fueled by concerns about our current, and devastating, illicit opioid epidemic. Policy makers, clinicians, and the public are understandably exploring every avenue to reduce adverse opioid events, including addiction and overdose. Cannabis has often been invoked as a safer alternative and potential partial solution to the opioid epidemic. High-profile retrospective ecologic studies have suggested that states that have legalized cannabis have lower opioid overdose-related deaths [6]. These analyses, however, are complicated by many potential confounders. Some cross-sectional studies, on the other hand, suggest that cannabis may be associated with increased rates of opioid aberrant behaviors, increased substance use, and poor mental health and pain outcomes [7].

At least one state has proposed legislation to allow medical marijuana to be used as an alternate to opioids [8], but we should proceed cautiously. The practical implementation of this policy would require careful titration off opioids while simultaneously introducing marijuana. This would be especially complex among those who have been on high doses for a long duration. In addition, there is currently no standardized mechanism to prescribe an exact amount of cannabis. Rather, clinicians have to rely on patient report for cannabis dosage and route of administration, and there is a high degree of variability in dispensaries, in terms of what is commercially available in dispensaries. For some, using medical marijuana as an alternative to opioids may present yet another barrier to engaging in more active, effective, and safer forms of chronic pain management.

Though it is an imperfect comparison, we should draw some lessons from the opioid story. Although cannabis does not cause overdose deaths, there are significant potential harms, and we do not yet know their societal impact. We also do not know how cannabis affects the experience and long-term outcomes of chronic pain. It took many years to understand the seemingly paradoxical phenomenon of opioid-induced hyperalgesia, for instance. We should recognize that people were not skeptical enough about opioids, and we should not make the same mistake now.

## Nugent and Kansagara

By the same token, skepticism about the potential benefits of cannabis and concern over harms has all too often manifested as a demonization of cannabis and those who use it. It is very difficult to discuss cannabis use in the United States without invoking its tumultuous legal, political, and social history. Skepticism should not be ideological: It should be entirely rooted in clinical considerations, and it should be in service of inspiring more research urgently. Given other contemporary struggles in our society including the opioid crisis, the medicinal potential of cannabis is alluring and its harms may seem trivial. Nevertheless, we need to ask the question: Is cannabis a safe and effective long-term treatment for chronic pain? We simply do not know the answer.

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SHANNON M. NUGENT, PhD, AND DEVAN KANSAGARA, MD,  
MCR  
*Oregon Health & Science University, Portland, Oregon,  
USA*

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