Medical Cannabis and Pain Management: How Might the Role of Cannabis Be Defined in Pain Medicine?

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Does cannabis represent society's next major misstep in its unending quest to relieve suffering from persistent pain? Perhaps. But instead, imagine if science could harness medical cannabis, with its myriad of biologically active compounds, to produce chemotypes tailored to the physical and mental presentation of each pain patient. By doing so, could this "simple" plant embody the leading edge of precision pain medicine to produce maximal benefit with minimal risk? This notion may be hard to conceptualize at present, although many clinicians might have thought it equally unimaginable, if asked a decade ago, to ever envisage a peer-reviewed editorial such as this one discussing the medicinal merits of cannabis. To be clear, the journey over the next decade or more to exploit the impact of medicinal cannabis as an analgesic will be challenging. Its success, or failure, will be determined by the willingness to reconsider several currently well-established tenets of pain and cannabis. These shifts in perspective include acknowledging the significance of, initially phenotypic and ultimately genotypic, interindividual variability within pain; recognizing that our understanding of cannabis and the endocannabinoid system is still in its infancy; and utilizing methodologies beyond traditional scientific inquiry to elucidate the putative benefits and risks of cannabis. In short, it will take a readiness to rethink, reexplore, and reconsider existing concepts in pain medicine with an open mind.

Status quo

With every passing day, the din surrounding the inappropriateness of cannabinoids in pain medicine grows quieter. While it would be remarkable to attribute this acquiescence to a growing body of robust supporting evidence, the reality is that the number and quality of clinical cannabinoid trials in pain medicine remain muted. Moreover, a significant portion of existing trials involve synthetic single-molecule cannabinoids rather than medical cannabis. A recent cursory PubMed literature search in May 2017 revealed approximately 12 randomized control trials published over the past 5 years contributing new evidence to this field. Over the same time span, the search identified an incredible 11 systematic reviews published in English all appraising similar sets or subsets of clinical trials on cannabinoids and pain. In short, the current clinical debate continues to be driven, in large part, by variable analyses and perspectives of the same extant clinical trials.

Despite these limitations, systematic reviews in acute pain are unequivocal in pointing out the lack

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of effectiveness of cannabinoids (*1*). In contrast, and maybe unsurprisingly, the reviews in chronic pain, mostly neuropathic, have all arrived at similar conclusions, that cannabinoids and medical cannabis provide small analgesic benefit, with a need for more high-quality trials with greater emphasis on concentration, dosing frequency, and delivery route (*2*). The latest systematic review does not depart from this mantra (*3*). Epidemiological studies also seem to be split, both supporting and refuting the benefits of cannabis to reinforce various positions. Earlier, well-publicized reviews summarized the findings of large cohorts clearly pointing to the potential negative effects looming ahead (*4*). The latest studies in this arena, however, intimate that recent trends in the use of cannabis may be associated with a decreased incidence of opioid mortality (*5*). Studies such as these have emboldened those in favor of prescribing cannabis as a means to promote harm reduction in pain management (*6*). Unfortunately, there appears to be no clear end in sight to this debate, at least as far as evidence is concerned. The time has come to stop reassessing the same set of trials, expecting this time that the evidence will be sufficient. Instead, greater efforts are required to answer more germane questions, such as what kind of quality original evidence could support the understanding of medical cannabis in pain and how will it best be captured?

Rethinking clinical pain trials

Basic science has contributed significantly to our understanding of the various mechanisms and pathways that propagate pain. These pathophysiological postulates subsequently framed our top-down hierarchies for determining the presumed causes of pain and were responsible for steering therapeutic algorithms. But should we take for granted that a model accounting for disease is also primarily responsible for the cause of pain? This type of reasoning, often illustrated in pain research, consists of choosing patients with specific disease entities (e.g., diabetic neuropathy or osteoarthritis) to represent the epitome of neuropathic or inflammatory archetypes, respectively. However, this categorization of disease and basis for pain may prove to be short-sighted. New tools and methods employed in pain research have triggered scientists to question old doctrines. For instance, osteoarthritis, a widely held exemplar of inflammatory pain (i.e., nociceptive pathology), appears to comprise a subset of patients who exhibit neuropathic qualities (*7*), whereas patients with complex regional pain syndrome (CRPS), a well-established neuropathic condition, may present with subtypes that display significant inflammatory characteristics (*8*).

The sole reliance on high-level diagnostic categorization to represent pain prototypes may, at least in part, be responsible for the documented limited success rates of pain treatments (*9*). Today, most clinical trials utilize single point estimates to assess therapeutic effectiveness. This method, often inappropriately and maybe deliberately, colors more significant positive and negative findings resulting from interindividual variability. The pain literature, in *post hoc* analysis, has confirmed this wide variability in treatment effect with analgesics and placebo responses and may imply that subsets of pain patients have more in common across disease categories rather than within (*10*). As the various facets of cannabis are explored clinically, it would be prudent to consider not only disease patterns but also document the many subsets of pain phenotypes (e.g., disturbed sleep, sensory loss vs sensory gain, anxiety, depression etc.) characteristic of pain patient cohorts. What is becoming abundantly clear is that our failure in pain medicine may be in relying too much on the averages and not enough on the outliers. Patient uniqueness counts.

Exploring cannabis not just cannabinoids

In 1964, Mechoulam discovered the most prolific phytocannabinoid, Δ^9-tetrahydrocannabinol

(THC), which has become almost synonymous in the nomenclature with the plant itself (*11*). Two decades later, researchers identified the cannabinoid receptors (CB1 and CB2) and the endogenous cannabinoid (anandamide) (*12*, *13*). The endocannabinoid system (ECS), as we refer to it now, is a novel neurotransmitter pathway, with ubiquitous reach involving peripheral and central pain pathways, mood, and sleep. With regards to the plant itself, scientists have identified over 100 phytocannabinoids and in excess of 200 terpenes and additional flavonoids (deriving plant pigment). Although grounded in simplicity, it may be presumptuous to assume that the major clinical effects of cannabis are derived solely from THC and cannabidiol (CBD). What becomes lost in the rhetoric is the importance of associated compounds found in the whole plant; in particular, the putative analgesic effects of terpenes and flavonoids have already been well described (*14*, *15*). Although the biological activity of many of these still needs to be explored, preliminary work suggests that some may operate synergistically to produce an "entourage effect" (*16*). This interaction, resulting from the interplay between each of these biological moieties, may be responsible for outcomes not posited by molecules in isolation. In this regard, future work will necessitate inviting colleagues from the fields of botanical sciences and laboratory medicine to facilitate the identification of specific cannabis chemotypes, beyond THC and CBD, most suitable for pain patients. We don't know what we don't know.

Pioneering precision pain medicine

Big Data has many definitions. One proposed version is the ability to store and analyze either large or complex sets of data (*17*). Many industries have adopted this methodology with innovative machine-learning analysis techniques to identify patterns in near real-time, allowing an organization or system to quickly adapt to changes. In contrast to scientific inquiry, this newer methodology offers insights into complex data that may be too challenging to investigate through traditional statistical means. One of the main benefits of Big Data is its ability to create an observational database that develops clinical questions and, importantly to pain medicine, leads to better patient selection and generalizability (*18*). By using more robust analytical techniques, the feasibility of drawing upon unique patterns between the myriad of cannabis chemotypes and the numerous phenotypical presentations of pain patients becomes achievable. Realizing these capabilities will allow pain medicine to provide a highly focused assessment of cannabis, one that ideally matches the right panel of molecules to a patient's profile to optimize benefit while reducing risk. One size does not fit all.

Conclusions

Society's storied history with pain is well documented (*19*). We are now set to begin a new chapter with yet another grand experiment in pain medicine. And, not surprisingly, the direction and magnitude of the ultimate outcomes remain unknown. At this juncture, it is easy to be swayed in either direction with scant clinical research pointing to marginal analgesic effects in isolated pain conditions and mounting epidemiological evidence suggesting benefits in harm reduction. On the other hand, the opioid crisis is a reminder of what happens when a pharmacological experiment goes awry.

What is unquestionable at this stage is that patients are demanding change in the current paradigm of pharmacological pain management. While not a panacea, cannabis stands ready at the vanguard of precision pain medicine. As in many other industries, the public now has access to the tools, both political and technological, to move ahead. Disappointed patients, frustrated clinicians, and eager scientists have been empowered to seek a new solution to an old problem. The real debate is whether there is enthusiasm to meaningfully participate to

create a pioneering role for cannabis by embracing interindividual variability, shunning reductionism, and employing bold new methodological tools that depart from traditional scientific inquiry. Is there an alternative? Absolutely; remain on the sidelines and let patients find their own path.

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