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COMMENTARY

Medicinal cannabis for chronic pain: The bermuda triangle of low-quality studies, countless meta-analyses and conflicting recommendations

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The combination of the ongoing opioid crisis, inappropriateness of long-term use of NSAIDs, limited efficacy and tolerability of existing analgesics and the fact that no new analgesics (except for anti-migraine medications) were launched during the past two decades, has considerably depleted the arsenal of chronic pain pharmacotherapy. No wonder therefore, that the old-new player, medicinal cannabis (MC), has erupted onto the pain field. Indeed, MC, which consists of herbal cannabis (HC), in either inflorescence or oil extract forms, and cannabis-based medicinal products (CBMP), is being increasingly used in chronic pain management. As a result of public pressure by media, patient advocacies and political lobbyists, MC has bypassed established routes of regulatory approval in many countries. In addition, many unregulated cannabis-based products lacking robust efficacy and safety data, especially cannabidiol (CBD) containing preparations, are readily available in some countries.

Basic research has promoted considerable understanding of underlying mechanisms and sites of action of MC in nociceptive systems. Similarly, substantial evidence from preclinical studies in animal models of pain (nociception) support the notion than MC holds promise as effective analgesics in chronic pain (Häuser et al., 2018). However, translation of these observations into solid clinical evidence for the efficacy of MC in chronic pain—based on high quality randomized controlled trials (RCTs)—remains elusive. Altogether, around 60 RCTs were published so far, varying considerably in population sizes and characteristics (e.g. chronic vs. neuropathic or cancer pain), the administered MC (ranging from herbal cannabis to synthetic Δ9-trans-tetrahydrocannabinol (THC)), dosages and ratios of the main components THC and CBD, route of administration, duration of treatment (hours to months) and primary outcome measures, thus yielding equivocal results. Attempting to consolidate the results, systematic reviews and meta-analyses (SRMAs) began to emerge. Between 2010 and summer 2019, 57 such articles were published but confusingly, provided a wide scale of conclusions ranging from clear evidence for efficacy to the exact opposite. In a recent high-quality SMRA, only 36 of the RCTs met inclusion criteria, due to significant methodological faults, and those too had high and/or uncertain risk of bias (Fisher et al., 2021). As a result, the International Association for the Study of Pain (IASP) released a position statement in March 2021 declaring that

due to a lack of evidence from high quality research, it does not endorse the general use of cannabinoids to treat pain. Yet, IASP also stated it does not wish to dismiss the lived experiences of people with pain who have found benefit from their use (IASP, 2021). In contrast, based on only slightly different exclusion and inclusion criteria, another recent high-quality SRMA of 32 trials concluded that there was moderate to high certainty evidence that non-inhaled MC produced a small to very small improvement in pain relief (0.50 cm in a 0–10 cm VAS), physical functioning, and sleep quality among patients with chronic pain (Wang et al., 2021). Hence, even when done properly, the quality of the more or less same available trials can be assessed and weighted in different ways.

Prescribing MC for patients with chronic pain is a matter of significant magnitude for caregivers and patients on a daily basis. Clinicians around the globe often note relief of pain and accompanying symptoms (i.e. depression, anxiety, sleep disturbances) in patients with chronic non-cancer pain who did not respond to established non-pharmacological and pharmacological therapies. Some non-randomized prospective cohort studies have documented such effects (Aviram et al., 2021). MC has also benefited patients with rare painful diseases for which there will never be a RCT possible.

So what can help lost practitioners find their way out of this Bermuda Triangle? IASP advocates primarily for well-designed and appropriately powered future RCTs but in the meanwhile holds a RCTs-based 'non-endorsing' position. While RCTs typically provide the 'state of the art' evidence for efficacy of specific interventions, the question is will further RCTs and subsequent SRMAs provide a solution in the case of MC? The complex HC structure with hundreds of constituents, some of which with potential biological activity (e.g. CBC, CBG, CBN, THCA, THCV and others), and the possible synergistic interactions between then set significant barriers that impede the ability to conduct traditional pharmaceutical RCTs (which are typically based on precise dosing of a single molecule). Funding large RCTs also seems to be an ongoing challenge as indicated by the lack of adequately powered studies published during the past five years. Furthermore, even if the needle in a haystack is found and a certain constitutes combination does show efficacy, the results will likely be diluted and lost in subsequent SRMAs. Are there alternatives? GRADE (Grading of Recommendations Assessment, Development and Evaluation) allows to include in guidelines observational studies and to increase the level of quality of evidence in case of consistent and large effects. As mentioned earlier, some observational studies have already been published. Additionally, MC-registries for chronic pain patients have been established in the meanwhile in Italy, Germany and possibly in other countries as well.

Based on these principles, and in contrast to IASP statement, the position paper of the European Pain Federation has recommended to consider MC as a third line therapy for chronic neuropathic pain syndromes, whereas for all other chronic pain conditions, the use of MC should be regarded as an individual therapeutic trial if all established treatments have failed and after careful analyses and multidisciplinary assessment (Häuser et al., 2018). We advocate that future practical recommendations on potential indications, contraindications, and assessment of harms of MC should not only be based of RCTs, but also on large, national, or even international, carefully followed and well documented, large-scale prospective cohorts of patients, preferably in the form of interdisciplinary evidence- and consensus-based guidelines and include patient representatives.

Nonetheless, we wish to highlight the enormous need for rigorous MC-related research and for proper funding of MC studies.

CONFLICTS OF INTEREST

Elon Eisenberg received consulting fees, speaking fees, and/or honoraria from Rafa Laboratories, Syqe medical, Medison, Teva, Pfizer. Bart Morlion is past president of the European Pain Federation EFIC and was member of the EFIC task force which published a position paper on cannabis-based medicines and medical cannabis for pain management. Over the last 5 years he received fees for service for speaker's and/or consultancy activities from Grünenthal, Lilly, Mundipharma, Pfizer, Krka, Ache, Sandoz, Shionogi, TEVA, GSK, Kyowa-Kirin, Boston Scientific, Reckitt & Benckiser. Silviu Brill is Honorary Secretary of European Pain Federation EFIC and was member of the EFIC task force, which published a position paper on cannabis-based medicines and medical cannabis for pain management. He received reimbursement for travelling and accommodation by Bioevents, a congress organiser, for co-organising a congress on controversies on cannabis-based medicines in 2018 and 2019. He received consulting and speaking fees from Rafa Laboratories, Pfizer, TEVA and Dexcell. Winfried Häuser has received reimbursement for travelling and accommodation by Bioevents, a congress organiser, for co-organising a congress on controversies on cannabis-based medicines in 2018 and 2019. He was the head of an EFIC task force of a position paper on cannabis-based medicines and medical cannabis for pain management and member of a task force of a position paper on the same topic by the German Pain Society.

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