Research agenda for medical cannabis in palliative care

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There is a persistent disconnect between patients and clinicians on what role medicinal cannabis (MC) should play in palliative medicine.[1] Last century, the lack of options for symptom management in advanced cancer coupled with the HIV epidemic led to strong popular support for prescribing MC.[2] Though it was occasionally difficult to differentiate narrow efforts to permit medical use from a broader decriminalisation movement, much of the public effort was in good faith. Clinicians were less enthusiastic, pointing to evidence that other already legal agents were demonstrably superior for symptom management.[3] Even so, they recognised the legitimacy of the patient perspective and debated the issue vigorously.[4]

This century, both public enthusiasm and clinician hesitancy for the medical use of cannabinoids are still present although the context is advanced cancer, not AIDS. This article considers a framework for considering why patients are so optimistic about MC and yet clinicians are not. By considering the debate from both perspectives, a two-pronged research agenda—patient and clinician centred—naturally emerges.

THE CLINICIAN–PATIENT DIVIDE
The clinician–patient divide may in part be explained by the disruptive journey MC has taken into the clinical armamentarium. Most medications are conceived in the laboratory or discovered in nature without any strong prior expectations. As such, they are unencumbered by emotional baggage. In contrast, cannabis has been consumed for thousands of years across many cultures. Like any enduring cross-cultural phenomenon, individuals within the culture will have been exposed to it and have formed an opinion of it. Strong prior expectations of clinical utility—positive or negative—inevitably produce some degree of cognitive dissonance when these expectations are juxtaposed with the ambiguous literature.

The traditional research mechanism is functional when the public has no prior expectation. Clinicians are free to set the agenda and the public largely accept their conclusions. This fails in the setting of strong public expectations, particularly when research conclusions are contrary to those expectations. The public feel that even if the answers to research questions are correct, the power to pose questions lies only with researchers whose motivations are not aligned with their own. Fortunately, there is much common ground.

CLINICIANS, PATIENTS AND MC: WHAT QUESTIONS NEED ANSWERING?
Clinicians need and want to know how MC might help, what symptoms it may benefit, which patients are more likely to respond, which products (composition, dose and delivery mechanism) will work best for specific symptoms and how best to design trials to assess these claims. Patients demand recognition that not all MC products are alike, that feeling better (overall well-being) in the absence of specific symptom benefit is important and that their desire to use what is popularly understood to be a 'natural' low-toxicity treatment is respected.[5] Promising avenues towards answering these questions are considered below.

CLINICIANS, PATIENTS AND CANNABINOID TRIALS
From the clinician perspective, trials of MC for advanced cancer symptom management are generally small, underpowered and of low quality. The few larger studies that exist tend not to be randomised placebo-controlled trials (RCTs). Multiple systematic reviews have repeatedly failed to demonstrate meaningful clinical benefit and highlight weaknesses such

as heterogeneous trial designs and lack of standard outcome measures.[6] Similarly, cannabis contains over 60 different cannabinoids plus terpenoids and other potentially active compounds. There is no consistency in the 'medicinal products' being tested. This makes it difficult for clinicians to develop realistic expectations for MC efficacy in clinical practice.

From the patient perspective, seemingly arbitrary ratios of tetrahydrocannabinol (THC) and cannabidiol (CBD) are used in most studies rather than 'crude' cannabis. This leads to the lay perception that the so-called entourage effect is either not recognised or ignored.[7] Products that make patients feel better overall are dismissed by clinicians as they are lacking evidence of benefit for any particular symptom. It could be argued that traditional medical research fails to measure what is important to patients.

No particular trial design can address all of these concerns. Product registration is dependent on RCTs and should be prioritised over further low-quality studies. Moreover, future studies should perhaps consider overall quality of life and symptom burden as primary outcome measures rather than specific symptom endpoints as this may align better with how patients describe the benefit.[8]

Where specific symptoms are chosen as primary outcomes, research should focus on those that have been shown to hold promise in previous studies. In our experience, the effect of MC on anxiety, depression and sleep in patients with advanced cancer merits further investigation. Care should be taken to avoid errors in inference, especially when trying to determine the reason for differential responses to MC.[9] Qualitative research is especially valuable in adding 'richness' to RCTs and investigating the views of patients and care-givers towards cannabis use.

HOW MC MIGHT HELP: CANCER, INFLAMMATION AND TREATMENT RESPONSE

Advanced cancer is often accompanied by a systemic inflammatory response and some cancers cause more inflammation than others.[10] The degree of inflammation correlates with the severity of certain symptoms. One large cohort study suggested pain, anorexia, cognitive dysfunction, dyspnoea, fatigue, physical dysfunction and poor quality of life were associated with more pronounced inflammation.[11]

Some MC components have been shown to have anti-inflammatory effect in animal studies and therefore are potentially anti-inflammatory in humans. In a murine asthma model, intraperitoneal CBD administration attenuated inflammatory cytokine increase associated with aerosol challenge.[12] This result is echoed in many other studies.[13]

This anti-inflammatory property has sought to be exploited in non-oncological conditions for clinical benefit. Cannabidiol has been shown in prospective randomised controlled trials to improve quality of life in

Crohn's disease.[14] Interestingly, there was no reduction in standard measures of inflammation (C reactive protein (CRP)) compared with placebo. If the benefit is real, this suggests that either the anti-inflammatory effect is not being captured by CRP measurement or that the mechanism of benefit is independent of inflammation.

WHICH PATIENTS MIGHT RESPOND: PHARMACOGENOMICS OF MC

As with inflammation, genomic variation represents another promising avenue for predicting response to cannabinoids. There is evidence that CYP2C9 and CYP3A4 are primarily responsible for THC metabolism and both CYP2C19 and CYP3A4 are responsible for CBD metabolism.[15] Genetic variation in the expression of these enzymes might therefore be expected to alter the pharmacokinetics of cannabis in individuals. Genetic variation in opioid receptors (eg, OPRM1 polymorphism) may be associated with cannabinoid dependence.[16] Similarly, variation in cannabinoid receptors (CNR1) have inconsistently been associated with cannabinoid dependence.[17] In vitro ligand binding affinity, ligand-induced activity and constitutive activity are affected by CNR2 polymorphisms.[18] CBD-induced changes in multidrug resistance (MDR1) gene expression requires simultaneous activation of CB2 and TRPV1 receptors.[19] The clinical significance of these findings is unknown although they may underpin interpatient variability.

Polymorphisms in genes governing pharmacokinetics (CYP3A4, CYP2C19, CYP2C9) and pharmacodynamics (CNR1, CNR2, OPRM1, TRPV1) are prudent targets to identify predictors of cannabinoid responsiveness. The tumour genomic landscape itself may also influence symptom severity. An understanding of how patient and tumour genomics influence palliative symptoms may open the door to personalised medicine in palliative care.

THE FUTURE OF CLINICAL MC RESEARCH: AN AGENDA

Clinical MC research should pursue a focused agenda to avoid repetition of the same findings. In the short term, this agenda should include:

1. High-quality, adequately powered RCTs rather than observational uncontrolled studies.
2. Assessment of the effect of MC on total symptom burden rather than individual symptoms to better align with how patients describe MC benefit.[8]
3. Development of outcome measures that reflect the patient perceived benefit of MC, for example, overall well-being or 'happiness' scales.
4. Where individual symptom effects are assessed, priority should be given to those symptoms that are relatively underinvestigated and that pilot studies have shown may be improved by MC such as sleep, depression and anxiety.[20]
5. Qualitative research to understand the lived experience of patients and carers in order to harmonise the patient and clinician research agendas.

6. Targeted pathophysiology research (inflammation, patient and tumour genomics) as a bridge to personalised palliative treatment.

CONCLUSION

Clinician and patient research priorities for MC are not closely aligned. Patients find it puzzling when their use of MC is restricted due to a lack of evidence. They feel the experience of other patients improving while on cannabinoids is dismissed by clinicians on irrelevant, technical grounds. Clinicians struggle to convince patients that non-cannabinoid treatments for their symptoms have proven benefits. There is deep seated suspicion of doctors and big pharma modifying results to suit their purposes. Conversely, clinicians find it difficult to justify the expense in the absence of evidence showing benefit.

MC has shown only limited measurable benefit outside a few specific indications and yet patients continue to use it and believe strongly in the benefit. This should prompt a re-assessment of whether we are measuring the correct outcomes. Understanding how MC modifies the physiological state of advanced cancer may direct clinicians to better outcome measures.

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