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CONSENSUS

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Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control

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Abstract

Aims: Opioid misuse and overuse have contributed to a widespread overdose crisis and many patients and physicians are considering medical cannabis to support opioid tapering and chronic pain control. Using a five-step modified Delphi process, we aimed to develop consensus-based recommendations on: 1) when and how to safely initiate and titrate cannabinoids in the presence of opioids, 2) when and how to safely taper opioids in the presence of cannabinoids and 3) how to monitor patients and evaluate outcomes when treating with opioids and cannabinoids.

Results: In patients with chronic pain taking opioids not reaching treatment goals, there was consensus that cannabinoids may be considered for patients experiencing or displaying opioid-related complications, despite psychological or physical interventions. There was consensus observed to initiate with a cannabidiol (CBD)-predominant oral extract in the daytime and consider adding tetrahydrocannabinol (THC). When adding THC, start with 0.5-3 mg, and increase by 1-2 mg once or twice weekly up to 30-40 mg/day. Initiate opioid tapering when the patient reports a minor/major improvement in function, seeks less as-needed medication to control pain and/or the cannabis dose has been optimised. The opioid tapering schedule may be 5%–10% of the morphine equivalent dose (MED) every 1 to 4 weeks. Clinical success could be defined by an improvement in function/quality of life, a ≥30% reduction in pain intensity, a ≥25% reduction in opioid dose, a reduction in opioid dose to <90 mg MED and/or reduction in opioid-related adverse events.

Conclusions: This five-stage modified Delphi process led to the development of consensus-based recommendations surrounding the safe introduction and titration of cannabinoids in concert with tapering opioids.

1 | INTRODUCTION

Opioids are commonly prescribed for chronic pain management and although data support their role for managing acute and cancer-related pain, the evidence to support use in chronic pain is not robust.[1-4] Prescription opioid misuse has contributed to a widespread opioid overdose crisis resulting in the deaths of hundreds of thousands of individuals worldwide.[5,6]

Medical cannabis containing different concentrations of cannabinoids—such as Δ^7-tetrahydrocannabinol (THC) and cannabidiol (CBD)—is increasingly being used for the management of chronic pain.[8] Cannabinoids have a lower risk for dependence compared with opioids and the predicted median lethal dose for THC is >1000 fold higher than the effective dose.[7,9,10] Previous studies have found that cannabinoids can improve pain-related outcomes, quality of life and, importantly, have an opioid-sparing effect.[8,11-18] In addition, it has been reported that patients commonly use medical cannabis as a substitute for opioid medication.[19-24] However, the effectiveness of cannabis substitution for opioids is not universally observed.[25,26]

Although these findings are noteworthy, the majority of clinical studies investigating cannabis and cannabinoids as substitutes or adjuncts to opioids are cross-sectional or small sample-size randomised controlled trials. This lack of high-quality evidence makes providing classical evidence-based recommendations inaccessible.

What's known

Patients taking opioids, and the physicians prescribing them, are leveraging medical cannabis to support opioid tapering. However, there is limited clinical guidance on how to safely titrate cannabinoids in the presence of opioids for the treatment of chronic pain.

What's new

Using a modified Delphi process to find expert consensus-based recommendations, this article provides a practical guidance algorithm on how to safely and effectively titrate cannabinoids and taper opioids in patients with chronic pain.

Despite the paucity of clinical trial evidence, physicians and patients are using cannabis to support opioid tapering. In many countries, patients with chronic pain have access to cannabis, and patients have reported self-administering cannabis to reduce their opioid dose in the absence of clinical guidance.[21,27,28]

Although cannabis has a lower risk of dependence compared with opioids, it is not an inert therapy.[29-32] At high doses, CBD-related side effects can include fatigue, diarrhoea and changes in appetite and

weight.[33] THC-related side effects can include sedation, syncope, tachycardia, risk of cannabis-use disorder, psychosis and anxiety.[34,35] With patients having access to prescribed cannabinoids and self-treating with cannabis to reduce their opioid dose, clinical guidance on safe cannabinoid initiation and titration is urgently required. Randomised placebo-controlled clinical trials examining how to co-manage cannabinoids and opioids are unlikely to be provided in the near future. Hence, there is an immediate unmet need for guidance on this topic.[36]

To provide guidance to healthcare professionals on how to safely manage opioids and cannabinoids in patients with chronic pain, we employed a modified Delphi process to develop a consensus-based guidance algorithm. The modified Delphi process has been used extensively in healthcare settings to provide consensus-based recommendations surrounding important clinical questions.[37] A previous Delphi study related to opioids and cannabis was undertaken between 2015 and 2016 and aimed to develop consensus guidelines for responding to patients on long-term opioids using cannabis; however, the experts disagreed on many of the proposed topics.[38]

The purpose of the present initiative was to develop consensus-based recommendations on 1) when and how to safely initiate and titrate cannabinoids in the presence of opioids, 2) when and how to safely taper opioids in the presence of cannabinoids and 3) how to monitor patients and evaluate clinical outcomes when treating with opioids and cannabinoids.

2 | METHODS

2.1 | The modified delphi process

A modified Delphi process was used to develop this consensus guidance document and associated algorithm.[39-41] The methods used for this report have been previously published in abstract form.[42] The participants were recruited based on extensive clinical experience with prescribing and managing patients on medical cannabis and/or extensive research expertise with cannabis. The consensus process incorporated a five-step modified Delphi method similar to previous reports[43-45] and took place between July 2019 and November 2019 (Figure 1 and Table 1). In step one, a core scientific committee of cannabinoid subject matter experts from the United States and Canada (n = 9) identified key areas of focus. From these areas of focus, an initial draft of consensus questions was developed, and these questions were incorporated into four domains:

1. When to consider introducing cannabinoids in patients with chronic pain taking opioids
2. How to introduce cannabinoids in patients with chronic pain taking opioids
3. When and how to taper opioids in patients with chronic pain taking cannabinoids
4. Evaluating clinical outcomes and guiding patient monitoring and safety

In step two, the core scientific committee reviewed the initial draft of questions and provided comments. Following the inclusion of the suggested changes to the consensus questions, a teleconference was conducted to gain verbal approval from the scientific committee to send out the questions for review by the rest of the consensus summit participants (n = 13).

In step three, the consensus summit participants were provided a reference package and sent the consensus questions for their review and associated comments. Twelve of the 13 participants provided their comments and suggestions.

Following the inclusion of these updates into the consensus questions, step four was initiated and all summit invitees, which included the core scientific committee and the participants,

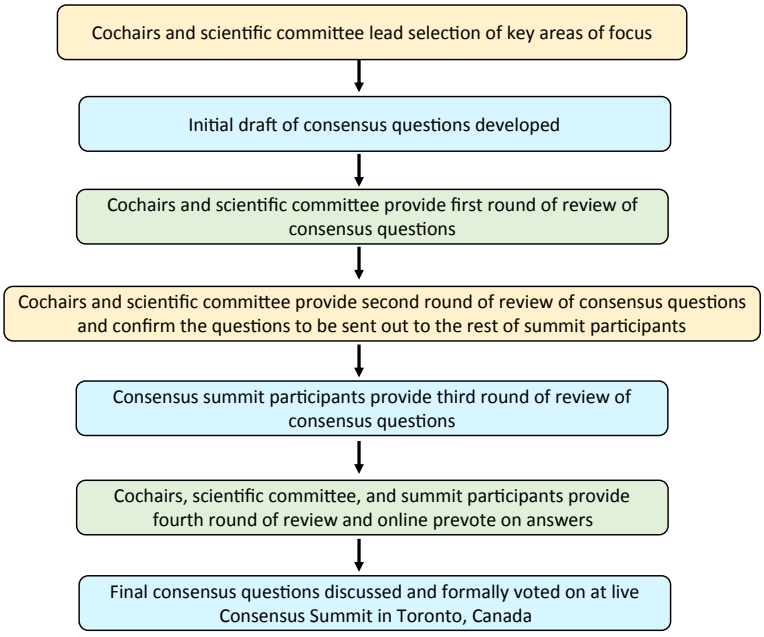

FIGURE 1 Flow of modified Delphi process

TABLE 1 Participation during the modified Delphi process

Modified Delphi process development	Consensus question development	Consensus voting	Manuscript development
AS, BKS, CO	AS, BKS, MJM, ZDC, HC, BLF, JP, KR, DS, RS, MO, SAA, CC, PD, KE, AD, DF, AB, VN, ZW, AB, DEM, CO	AS, MJM, BLF, KR, DS, RS, MO, SAA, CC, PD, KE, AD, DF, AB, VN, ZW, AB, DEM, CO	AS, BKS, MJM, ZDC, HC, BLF, JP, KR, DS, RS, MO, SAA, CC, PD, KE, AD, DF, AB, VN, ZW, AB, DEM, CO

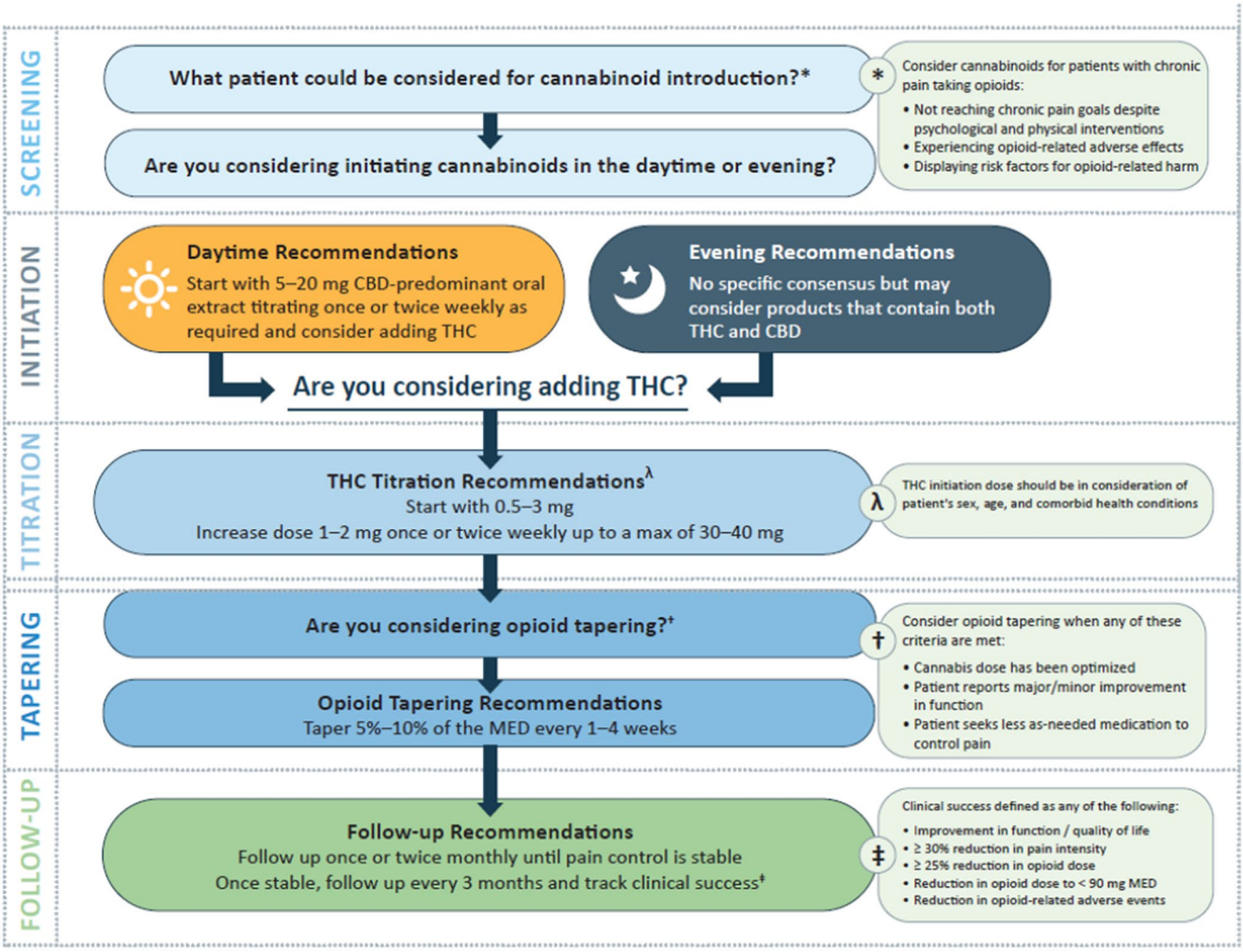

FIGURE 2 Consensus-based algorithm for titrating cannabinoids and tapering opioids in patients with chronic pain

reviewed the consensus questions and prevoted using an online software. Sixteen of the 22 summit invitees provided a prevote. These prevote results were then used at the live event to focus the discussion on topics where a lack of consensus was apparent. In step five, a formal voting session took place at an in-person meeting in Toronto, Canada: The Opioids and Cannabinoids Consensus Summit. The voting was public but anonymous using live polling software (Slido, www.slido.com). Nineteen participants took part in the live voting session; however, the opportunity to abstain from answering questions was available.

For consensus to be declared, a predetermined threshold of ≥75% of the voters had to agree on a specific answer, or ≥75% of the voters had to strongly agree or agree (or strongly disagree or disagree) on an answer. This consensus threshold is similar to previous studies using a modified Delphi method.[43,46] At the in-person event, revisions to the questions and associated answers, and revotes, were permitted. The voters were instructed that the patient they were considering was a patient with chronic pain taking opioids who was not currently using cannabis, recreationally or medically, to treat their chronic pain. The voters were instructed that the term *cannabinoids* refers to the

most studied of the cannabinoids, that is, THC and CBD. The voters were instructed to assume that there were no patient access or financial limitations to consider when choosing a given answer.

3 | RESULTS

The results described below highlight what we believe are the key consensus findings. The full complement of questions and answers are available in the Supplementary Tables. A treatment guidance algorithm for healthcare professionals was developed based on the answers where consensus was reached (Figure 2).

3.1 | Domain 1: When to consider introducing cannabinoids in patients with chronic pain taking opioids

The first domain asked questions about patient factors that may influence the suitability of a patient for treatment with cannabinoids. The key consensus findings are:

1. If a patient has a history of psychosis, is pregnant or breastfeeding or has had an adverse reaction to cannabinoids, cannabinoids should be avoided. Although, when considering a patient with a history of psychosis, THC appears to be the more significant causal agent and CBD may in fact reduce psychosis.[47,48] Physicians may consider medical cannabis in a patient: taking opioids at any morphine equivalent dose (MED), not reaching chronic pain goals, experiencing opioid-related adverse effects and/or displaying risk factors for opioid-related harm. It is important to note that this consensus initiative does not aim to suggest that all patients taking opioids should reduce their opioids. In a recent commentary, the Centre for Disease Control guidelines for opioid tapering were clarified to highlight that clinicians should avoid increasing the opioid dosage to ≥90 MED, but not necessarily discontinue opioids in patients on a high dose.[49] Dialogue and shared decision-making with the patient and carefully evaluating the benefits and risks associated with tapering and discontinuation of opioids are strongly encouraged. In addition, before the introduction of any additional pharmaceutical intervention, evidence-based psychological and physical therapy interventions to reduce opioid use should be attempted and maximised.[50,51]
2. There was consensus that no age restrictions were recommended for CBD or THC use. With respect to CBD, the group quickly reached consensus as high doses of CBD have been shown to be safe in children, albeit in a patient population dissimilar to typical patients with chronic pain.[52,53] Conversely, there was debate surrounding the minimum age recommendation for THC. When using THC, careful consideration in the younger population should be made as the nervous system is not fully developed until 25 years of age.[54] However, the consensus summit participants debated that if a young patient is already on opioids, it did not seem rational to withhold cannabinoid therapy until they turn a specific age. Similarly, although there was no maximum age agreed to, careful consideration must be given when considering cannabinoids to the elderly people, while also recognising that the elderly people are particularly susceptible to the adverse effects of opioids.

3.2 | Domain 2: How to introduce cannabinoids in patients with chronic pain taking opioids

The second domain asked questions regarding how to administer, initiate, titrate and dose cannabinoids in the presence of opioids. The key consensus findings are:

1. There was consensus that the preferred format of administering cannabinoids was the oral route, using oil extracts or capsules. Sublingual tinctures may also be considered. There was consensus strongly recommending against smoking cannabis. Caution should be exercised in jurisdictions where regulated and standardised medical cannabis products are unavailable.
2. In the daytime, it was agreed that a patient should initiate with CBD oral dosing at a range of 5-20 mg. For THC, there was consensus that the initial THC dose range should be 0.5-3 mg and then titrated up by 1-2 mg every 1 or 2 weeks to reach chronic pain goals.

This initiation and titration protocol deserves further discussion. CBD was recommended as the initiating cannabinoid for daytime dosing partly because there is limited sedation or intoxication associated with CBD. [55] In addition, CBD unaccompanied by THC has been observed to support opioid tapering and reduce cue-induced cravings for opioids.[56,57] Published CBD doses range from tens of mg to thousands of mg yet from a practical standpoint, the cost of CBD may become a limitation at high doses. As such, there was no consensus on how high up the CBD dose should be titrated. It is important to note that the available evidence for CBD alone to improve chronic pain control is weak.[58-61] Preliminary studies examining topical application of CBD have observed that this route may be efficacious for treating pain, although further research is required.[62,63]

In contrast to CBD, the available evidence for THC to improve chronic pain control is relatively strong.[8,64] During the consensus summit, it was noted that some patients can reach pain control goals with CBD alone, but it was quickly pointed out that many CBD preparations, both medical and recreational, contain a small percentage of THC and thus it could be the low concentration of THC providing the pain relief associated with CBD, especially at high CBD doses. Healthcare professionals may consider adding THC soon after CBD initiation if the patient is not reaching their chronic pain control goals.

The initiating dose range of 0.5-3 mg THC was chosen based on clinical observations that patients typically begin to experience

psychoactive effects at 2-2.5 mg of THC, which is similar to the reported effective dose of dronabinol, a synthetic isomer of THC,[65] and many patients would prefer to avoid the psychoactive effect. In addition, there is individual variability regarding the response to THC, and taking a 'start low and go slow' approach is recommended.

There are reported sex differences in the response to THC.[66-68] For example, a recent placebo-controlled study observed that women experience similar psychoactive effects at a lower THC dose in comparison to men,[69] and previous observational studies observed that women accelerate to complicated cannabis use faster than men.[70,71] As such, sex, age and comorbid health conditions have been specifically highlighted in Figure 2 as factors to consider when initiating THC.

Our consensus findings on how to initiate and titrate cannabinoids in the presence of opioids are similar to a previously published editorial on cannabinoid dosing for chronic pain management.[72] A caveat to the 'start low and go slow' approach may be considered with a patient at high risk for opioid-related harm. The need to rapidly increase cannabinoids may be apparent as the opioid taper may need to be more aggressive. Therefore, under certain circumstances, it may be appropriate to start low but go fast with cannabinoid introduction and titration. Patient-specific factors, such as response and access to close monitoring, may allow for a more aggressive cannabinoid titration and be a valuable strategy in a patient where the opioid risks are high.

1. For night-time use, there was no consensus on the CBD or THC dose, or the THC:CBD distribution ratio, although there was discussion around the potential importance of THC for sleep quality, which may support chronic pain relief.[73]
2. For breakthrough pain, vaporisation of dried cannabis flower was recommended. It is important to note that vaporising dried flower differs from vaping through an electronic cigarette device. Vaporisation of dried flower is ideally accomplished with approved medical devices, although many different types of vaporisers of differing quality could be used.[74] In contrast, vaping cannabis using electronic cigarette devices may expose the patient to unsafe additives and increase the risk of a novel lung disease, EVALI (e-cigarette or vaping product use-associated lung injury).[75,76] Until such a time that electronic cigarette devices are proven safe, inhalation of medical cannabis for breakthrough pain should be undertaken exclusively with medically approved vaporisers using dried cannabis flowers.

3.3 | Domain 3: When and how to taper opioids in patients with chronic pain taking cannabinoids

The third domain discussed questions around when and how to taper opioids in patients being administered opioids and cannabinoids. The key consensus findings are:

1. Depending on the patient, begin the opioid taper when any of the following criteria are met: the patient has an improvement in pain/function, the cannabinoid dose has been optimised or the patient begins to seek less 'as needed' medication. Importantly, it was recommended to not begin tapering opioids at cannabinoid initiation or a specific cannabinoid dose.
2. When initiating the opioid taper, a gradual opioid dose reduction of 5%-10% of the MED every 1 to 4 weeks was agreed upon. The timeline for the frequency of dose reduction is broad to allow for patient tailoring, and is similar to previously published opioid tapering recommendations.[1,3] More recently, the US Department of Health & Human Services have published opioid-tapering guidelines.[77,78] These guidelines do not provide specific MED targets and encourage a highly individualised opioid tapering approach and collaborative shared decision-making with the patient. Indeed, there may be patients who could benefit from a 20% to 50% rapid taper after titrating to an effective cannabinoid dose, depending on their objectives and needs.

3.4 | Domain 4: Evaluating clinical outcomes and guiding patient monitoring and safety

The fourth domain examined questions around monitoring, safety and efficacy measures in patients with chronic pain taking opioids and cannabinoids. The key consensus findings for this domain are:

1. During the early phase of opioids and cannabinoids co-administration, it was recommended to follow-up with patients once or twice monthly until the patient is stable. Once the healthcare professional and the patient are comfortable, it was agreed that follow-up could occur every 3 months. It was also agreed that the monitoring of these patients could be led by healthcare professionals other than the treating physician, and that these follow-ups could be done via phone call or home visit depending on what works best for the healthcare professional and patient. At this point, even though a patient may be stable with respect to their chronic pain control, variations in dosing and administration of medical cannabis may be required for optimal pain control.
2. When considering the safety of a patient taking both opioids and cannabinoids, healthcare professionals should screen for opioid withdrawal, illicit opioid use, cannabinoid-related adverse effects, use of other illicit substances and symptoms of psychosis. Cannabinoid titration should be halted: when the patient's goals are met; when cannabinoid treatment reaches an efficacy plateau (ie, no change in pain relief after a dose increase); or if the patient experiences a cannabinoid-related adverse event. If the patient experiences a cannabinoid-related adverse event, it is recommended to reduce the dose of the associated cannabinoid. If a patient experiences opioid withdrawal symptoms, it was agreed that the healthcare professional should consider slowing or pausing the patient's opioid taper.
3. When considering treatment success, no consensus was found on the need to use a validated questionnaire to establish efficacy.

However, there was consensus on initiating and documenting discussions with the patient around the degree of pain relief, sleep quality and everyday functionality throughout treatment. In concert with this, it was agreed that clinical success when titrating cannabinoids and tapering opioids is most clearly defined by an improvement in patient function.

4 | DISCUSSION

Globally, cannabis is being used to support a reduction or cessation of opioid use for pain. This utilisation of cannabis is occurring despite a lack of placebo-controlled, randomised clinical trials and highlights a practical unmet need for expert guidance on the safe co-management of cannabinoids and opioids. The aim of the present project was to develop consensus-based recommendations on how to safely and effectively manage cannabinoid initiation and titration with opioid tapering. The primary consensus findings are provided as an algorithm (Figure 2) to be applied in clinical practice by the healthcare team.

An important stipulation when considering these consensus-based recommendations is that a patient's personal considerations should always be taken into account, and that the treating physician's clinical rationale and individual assessment of the patient are paramount. Many of the consensus recommendations are presented as ranges to allow the healthcare professional to tailor the cannabinoid and opioid management strategy on an individual basis. Additionally, it is important to maximise psychological and physical therapy treatment interventions before initiation of cannabinoids or any additional pharmaceutical therapy.

A limitation of the consensus-based recommendations provided herein is that they are based primarily on expert opinion developed through a modified Delphi process, and not placebo-controlled, randomised clinical trials. However, as there is a lack of high-quality literature investigating opioids and medical cannabis, the authors of this document leveraged their real-world experience across tens of thousands of patient interactions to support the development of this guidance algorithm with a focus on safety. As new evidence becomes available related to the use of cannabinoids and opioids in patients with chronic pain, the recommendations made within this document will be updated and refined.

We also note that the education of healthcare professionals surrounding the safe and effective use of medical cannabis is lacking.[79,80] We hope that the introduction of this algorithm will initiate more extensive conversations about key educational needs surrounding the safe and effective use of medical cannabis, which may include focused dialogue on the divergent, but perhaps complementary, physiological effects of CBD and THC that lead to the support of opioid tapering and improved pain control. We would recommend learning modules on chronic pain treatment with medical cannabis be completed before prescribing.

The unmet need for expert guidance on co-managing cannabinoids and opioids prompted the development of this consensus-based document. Additionally, in the midst of an opioid crisis, the validation of strategies to reduce exposure to opioids is of interest for public health policy. We employed a modified Delphi process to add robustness to our scientific process as these expert consensus-based recommendations are derived primarily from real-world clinical experience in lieu of placebo-controlled, randomised clinical trials. This modified Delphi process led to the development of a series of consensus-based recommendations surrounding the introduction and titration of cannabinoids in concert with the tapering of opioids. These recommendations should be evaluated prospectively to examine if target reductions in opioids may be met. Future rigorous experimental studies in this area will be integral in helping shape formal guidelines.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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