International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia

research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management

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IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management

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Abstract:

The President of the International Association for the Study of Pain (IASP) established a Taskforce on Cannabis and Cannabinoid Analgesia, to systematically examine the evidence on (i) analgesic pharmacology of cannabinoids and preclinical evidence on their efficacy in animal models of injury-related or pathological persistent pain, (ii) the clinical efficacy of cannabis, cannabinoids and cannabis-based medicines (CBM) for pain, (iii) harms related to long-term use

of cannabinoids, as well as (iv) societal issues and policy implications related to the use of these compounds for pain management. Here, we summarize key knowledge gaps identified in the Taskforce outputs and propose a research agenda for generating high-quality evidence on the topic.

The systematic assessment of preclinical and clinical literature identified gaps in rigor of study design and reporting across the translational spectrum. We provide recommendations to improve the quality, rigor, transparency, and reproducibility of preclinical and clinical research on cannabis and cannabinoids for pain, as well as for the conduct of systematic reviews on the topic. Gaps related to comprehensive understanding of the endocannabinoid system and cannabinoid pharmacology, including pharmacokinetics and drug formulation aspects, are discussed. We outline key areas where high quality clinical trials with cannabinoids are needed. Important remaining questions about long-term and short-term safety of cannabis and cannabinoids are emphasized. Finally, regulatory, societal and policy challenges associated with medicinal and non-medicinal use of cannabis are highlighted, with recommendations for improving patient safety and reducing societal harms in the context of pain management.

Keywords: cannabis; cannabinoids, endocannabinoids, research agenda; IASP; pain; chronic: pain; pain research; Clinical Trials; Systematic review

1. Introduction

The isolation of pharmacologically active cannabinoids, especially Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) from the cannabis plant, and the subsequent discovery of the endogenous cannabinoid (endocannabinoid) signalling system, has sparked interest in how the

endocannabinoid system regulates somatosensation, pain, mood, appetite, and other homeostatic functions.[23,32] Drug discovery has focused on modulation of the endocannabinoid system to treat disorders in which dysfunctional endocannabinoid signalling may play a role.[29,60]

Given the current limited success with pharmacological therapies for chronic pain,[8,9,15,19] and substantial safety concerns with the chronic use of medications such as opioids, it is not surprizing that the past two decades have witnessed a consistently increasing number of preclinical and clinical scientific papers examining the potential of cannabis, cannabinoids, and cannabis-based medicines (CBM) in alleviating pain or altering pain-associated behaviours.[53,54] Considering the complex pharmacology of cannabis and cannabinoids, the heterogeneity of the preclinical and clinical evidence, and heightened public interest, the President of the International Association for the Study of Pain (IASP) established a task force on Cannabis and Cannabinoid Analgesia.[3] Its mandate is to systematically examine and summarize the evidence on (i) analgesic pharmacology of cannabinoids and preclinical evidence for their antinociceptive efficacy in animal models of injury related or pathological persistent pain, (ii) the clinical efficacy of cannabis, cannabinoids and CBM for pain, (iii) harms related to long-term use of cannabinoids, as well as (iv) societal issues and policy implications related to the use of cannabinoids, cannabis and CBM for pain management. This review summarizes key knowledge gaps identified in the task force outputs and proposes a research agenda for generating high-quality evidence on cannabis, cannabinoids and CBM for managing pain.

2. Preclinical pharmacology in animal models of injury-related or pathological persistent pain[a]

[a] The term 'animal model of pain' is not a universally agreed descriptor, but given that it is common usage we will use it herein as shorthand. It is also worth noting that there is a distinction between 'model' which reflects the underlying disease or injury and the pain-associated outcome measures used in evaluating such models.

Animal models help understand the molecular, cellular and neurochemical mechanisms of endocannabinoid signalling, thus elucidating the role of this endogenous lipid signalling system in nociceptive processing, and facilitating the investigation of potential analgesic properties of compounds that act on different targets within this system.[30,41,57] A systematic review and meta-analysis quantitatively analysed 374 studies that met inclusion criteria for antinociceptive effects of cannabis-based medicines, cannabinoids and endocannabinoid system modulators in rodent models of pathological or injury-related persistent pain.[a,52] The systematic review revealed an overall unclear risk of bias, and low prevalence of reporting methodological quality criteria, common of preclinical literature.[12,17] These criteria included blinded assessment of outcome, randomization, predetermined animal exclusion criteria and exclusions, allocation concealment, and sample size calculations. The effect size associated with the antinociceptive effects of all drugs studied in all models, calculated as Hedge's G standardized mean differences (SMD), averaged at 1.32 [95 % CI 1.23 – 1.41]. Variables such as rodent species (mice vs. rats), strain, and sex, model type (e.g., nerve injury vs. inflammation vs. diabetes), pharmacological class of the tested compound, the type of pain-associated outcome measure (e.g., evoked limb withdrawal vs. complex behavioral models, particularly in rats) accounted for a significant proportion of heterogeneity in the results. Selective CB_1, CB_2 and non-selective cannabinoid receptor agonists and palmitoylethanolamide demonstrated antinociceptive efficacy in a broad range of inflammatory and neuropathic pain models. Fatty acid amide hydrolase (FAAH) inhibitors, monoacylglycerol lipase (MGL) inhibitors and CBD demonstrated consistent antinociceptive efficacy in neuropathic pain models but yielded mixed results in inflammatory pain models. Overall, the results of the meta-analysis indicate that evidence from laboratory experiments supports the hypothesis of cannabinoid-induced analgesia. Concerns have been raised about how

well animal models reflect the clinical conditions they are modelling. The common use of reflex withdrawal responses in preclinical studies may be appropriate for some but not other injury-related or pathological persistent pain models. As the preclinical meta-analysis highlights, important goals within preclinical pain research in general, and not solely cannabinoid research, remain the development and validation of improved animal models with high contruct and predictive validity to address more ethologically-driven behaviors, as well as transparent study design and reporting.[38,43,46,47]

Our understanding of the pharmacology, biochemistry and neurobiology of cannabinoids and the endocannabinoid system has evolved significantly over the past 30 years. A wide variety of cannabinoids and endocannabinoid system modulators have been tested for antinociceptive effects in animal models, but most have not yet been tested in human pain patients, where testing has concentrated mainly on plant-derived materials and synthetic analogues of Δ^9-THC. The narrative review of the pharmacology of cannabinoids and endocannabinoid system modulators,[38] together with a systematic review focusing on the preclinical efficacy of these compounds,[51] identified several knowledge gaps, related both to cannabinoid pharmacology specifically, and to methodological issues in preclinical pain models more generally. These key gaps, summarized as the main basic and translational research priorities, are outlined in Table 1.

3. Clinical trials of analgesic efficacy

A systematic review of the literature on the analgesic efficacy of cannabis, cannabinoids, and CBM in pain was conducted, and included studies on people with acute or chronic pain, excluding experimental pain, receiving cannabinoid products of any type, natural or synthetic, and delivered by any route.[21] The systematic review only considered randomized controlled trials

(RCTs); such trials were included if they compared a cannabinoid, endocannabinoid system modulator, CBM or cannabis with any placebo or active comparator. RCTs retaining <30 participants per trial arm were excluded from the meta-analysis because smaller studies of low quality or with publication bias magnify effect sizes in meta-analyses.[14] The primary outcome was the proportion of patients with pain reduction ≥30% or ≥50%. Secondary outcomes included changes in pain intensity with a validated pain scale, disability and physical functioning, emotional functioning, and adverse events, amongst others.

The review found 36 trials qualifying for inclusion (representing a total of 7217 participants). Most studies focused on cancer pain, acute pain, multiple sclerosis pain, and neuropathic pain, with only a few studies on musculoskeletal pain and abdominal pain. Of these, 8 studies tested individual cannabinoids or endocannabinoid system modulators, 6 tested cannabis, and 22 tested CBMs. Review authors rated all trials as having either an unclear or high risk of bias. Using the GRADE criteria, all outcomes were judged as low or very low-quality evidence for all types of cannabis, cannabinoids, and CBM studied to-date, regardless of the type of pain.

To improve confidence around the estimate of effects in systematic reviews, high quality RCTs are required. General recommendations for study design, conduct, and reporting, are outlined in Appendix 1 (available as supplemental digital content at http://links.lww.com/PAIN/B330); recommendations specific to studying cannabis, cannabinoids, and CBM, summarized as research priorities, are outlined in Table 2.

Cannabinoid RCTs should pay special attention to drug-drug interactions, especially concerning drugs in widespread clinical use. Wash-out periods, especially important in crossover trials, and adjunctive administration with other analgesics, could affect baseline measures of pain, and

therefore require rigorous controls and interpretation. Prominent central nervous system side effects of cannabinoids (euphoria, sedation, distorted reality, etc.) increase the risk of bias and may necessitate the use of non-analgesic placebos with similar side effects. End-of-treatment blinding questionnaires may help identify active placebos that mimic the key distinguishing adverse effects of cannabinoids, and will help tease out analgesic effects.[10] Multiple imputation methods should be compared and reported with a stated rationale for each.[5,35] Full data supporting published results analyses should be shared to increase transparency and allow replication.

Additional research agenda items related to clinical trials were identified from the review of the literature on cannabinoid pharmacology.[18] These pertain mainly to gaps associated with cannabinoid pharmacokinetics, pharmacodynamics, drug-drug and drug-disease interactions, variability in response based on demographics, genotype, and other factors, as well as optimization of cannabinoid combinations (e.g. THC and CBD) to obtain favorable risk to benefit profile (Table 2). A rigorous approach to determine which patient factors increase the likelihood of response to a particular cannabinoid in a particular condition would be critical to developing personalized treatment approaches. The importance of involving patient partners in clinical trial design and execution, as well as result interpretation and dissemination is increasingly recognized in different therapeutic areas.[44,50] While currently available data are scarce, investigating and optimizing patient engagement processes to improve patient-centered outcomes would be an important area for future pain research on cannabis and cannabinoids.

4. Systematic reviews of harms related to cannabis, cannabinoids, and CBM

An overview of systematic reviews on harms of cannabis and cannabinoids in chronic pain and other conditions was conducted.[33] Methodological quality was assessed using AMSTAR-2 (Assessing the methodological quality of systematic reviews tool version 2) and accordance with the PRISMA harms checklist.[49,59] The 79 included reviews investigated psychiatric and psychosocial harms, cognitive/behavioral harms, motor vehicle accidents, cardiovascular, respiratory, cancer-related, pregnancy concerns, and general harms. A total of 72 reviews addressed cannabis (smoked, vaporized or ingested), and 7 reviews addressed individual cannabinoids; therefore, most of the safety data refers to cannabis use, rather than single cannabinoid compounds. Highlighting the lack of specific harms data in pain studies, almost all reviews assessed the safety of cannabis in mixed populations, outside of a pain management setting specifically, with one systematic review summarizing only pain-related data from 31 studies.[56] Overall, 76 of 79 included reviews received a 'critically low' score; and 3 received a 'low' AMSTAR-2 score. Per PRISMA, reviews consistently failed to register their protocols, outline risk of bias assessment methods, and present results on risk of bias.

The overview findings included a variable association between self-reported cannabis exposure and psychosis, motor vehicle accidents, and respiratory problems. While adverse events were noted to be higher in nabiximols and THC treatment groups compared to control, individual RCTs did not report harm and/or adverse events consistently, possibly underestimating the adverse effects. A more systematic approach to reporting adverse effects in all pain RCTs is needed to measure the full spectrum of harm,[11,16] although this issue is not specific to cannabinoids, and is rather common in the pain field.

Better adherence to current guidelines on clinical trials harms assessment and reporting is needed, including descriptions of validated methods to assess harms, with explicit reporting of serious adverse events, and quantitative reporting of adverse event frequencies.[34] Both trial investigators and journal editors should be championing this change. Population research methods using "real world data" are urgently needed for tracking harms and benefits from the highly prevalent use of non-prescribed cannabis for pain management. It would be important to compare these outcomes to high-quality data from patients who are treated with prescribed medicinal cannabis under expert medical supervision. Epidemiological studies of cannabinoid harms must attempt to accurately correlate measures of dose. There is also critical lack of reliable data on cannabinoid doses, blood concentration levels, and duration of exposure and their relation to the degree of harm.

While regulatory agencies approach therapeutics development by including toxicology screening (e.g. multiples species, organ systems, teratogenicity, carcinogenicity etc.), most plant-based cannabis products reach consumers without rigorous testing processes or regulatory oversight. A rigorous approach is needed to determine which factors confer susceptibility vs resilience to adverse effects from cannabinoids.

The development and implementation of administrative database linkage studies with careful documentation of prescribing, use, patient-reported outcomes, and "hard" outcomes like hospitalization, emergency department visits and mortality, is an elusive but particularly promising future direction given how poorly the use of cannabinoid products for pain is regulated.

Careful fundamental research is required to understand the dose relationship and the mechanisms contributing to harms reported in large scale studies,[6] including psychiatric disorders, cognitive

effects, cardiovascular and pulmonary toxicities, as well as effects in vulnerable populations such as children, adolescents, pregnant women, and older adults. The investigation of harms should be conducted in a translational manner, to correlate clinically observed harms with preclinical results, which could help future screening of compounds with potentially problematic adverse effect profile(s). Given the complex interplay between harms and benefits of cannabinoids to the individual and to society as a whole, multidisciplinary consensus initiatives that employ multicriteria decision analyses – as has been previously done in related settings[40] – may provide a framework to contextualize harms of cannabinoids in light of their potential benefits and other broader considerations. Recommendations specific to studying, assessing, and reporting harms of cannabis, cannabinoids, and CBM, summarized as research priorities, are outlined in Table 3.

Systematic reviews of cannabinoids for pain

An overview review was conducted to assess the quality, scope and results of the many existing systematic reviews of cannabis, cannabinoids, and CBM efficacy for pain relief.[36] The review included self-defined systematic reviews, included people of any age with any form of acute or chronic pain (except experimental pain), any type of natural or synthetic cannabinoid product, any route of administration, and any comparison intervention for the purpose of pain reduction. The primary outcome of interest was analgesic efficacy. Methodologic quality was assessed using AMSTAR-2 and techniques important for bias reduction in pain studies.

A total of 103 papers were identified and 54 were included, with 15 distinct pain conditions. Confidence in the results using AMSTAR-2 definitions was generally poor: critically low (39 reviews), low (8), moderate (5), high (2). Fewer than 10% of reviews used criteria important for assessing pain. Effect estimates were highly variable, with extreme examples of data pooling.

Overall, it was determined that current reviews were lacking in quality and could not provide a basis for decision-making.

Table 4 summarizes recommended research priorities. Pre-planned systematic reviews of high quality RCTs provide the greatest value to people with pain, their clinicians, and policy-makers. Future systematic reviews should be conducted when considerable new evidence is accumulated, they need to meet the Cochrane definition of a systematic review, and provide at least moderate confidence in the results using the generic AMSTAR-2 system.[37]

5. Societal issues and policy implications of the widespread use of cannabinoids for pain.

The IASP task force was asked to identify how local, regional, and national regulatory and legislative approaches can affect the use of medicinal cannabis in people with pain.[18,26] Many countries appear to be legalizing or decriminalizing cannabis use.[58] Cannabis market economics, supply and demand, illegal market size, governmental taxation, and advertising revenue affect local availability and can have a significant effect on public health. Legal frameworks vary widely, shaping a complex relationship between cannabis-based products, chronic pain patients, and potential prescribers.

The regulatory landscape has not expanded at the same rate as the interest in the development of cannabis products, and research regulations related to controlled substances add limitations on conducting large-scale multicenter clinical trials. Regulators also remain ill-equipped to handle the influx of new, often mislabeled, products of inconsistent quality and purity, containing variable amounts of CBD and THC.[4] Chemical and microbial contaminants pose health risks, particularly in immunocompromised patients.[48] Globally, high-THC cannabis crops, which may

be inappropriate for those using cannabis for pain relief, are often favored by growers for the large market of non-prescribed use. In fact, a recent systematic review and meta-aanylsis identified that from year 1970 to 2017, THC concentrations in herbal samples increased by 0.29% per year, while no significant change was observed in CBD concentration in herbal cannabis.[7,22] There is a concern that legalization of cannabis for non-medicinal use will lead to medicinal users bypassing medical advice on dosing, resulting in adverse outcomes.[55]

Coherent policies need to be adopted by government agencies. Strong consideration should be given to those programs that have been proven to mitigate tobacco- and alcohol-related harms.[25,42] Regulation of production, sales, and defining the allowable THC contents of any product may increase safety and limit undesirable outcomes.[31] Education programs to help mitigate the increased risk of dependence and harm in vulnerable populations will be important, coupled with restriction of advertising.[28] In addition, specific legislations for motor vehicle drivers, machine operators, and aviation pilots are required.[39] Strict reinforcement of evidence-based approaches for limiting driving under cannabinoid influence may help reduce the number of motor vehicle accidents and save lives.[27]

Importantly, people suffering from chronic pain continue to lack access to high quality interdisciplinary care, which may increase the risk of pursuing self-management with unregulated cannabis products.[13] Improving global access to proper chronic pain care can indirectly minimize harms related to unregulated cannabinoid use.

The use of cannabis products without strict regulation of manufacturing and supply, together with ready access to an already unregulated market results in major societal risks. While current data may be insufficient to make evidence-based conclusions on each of these matters, the rate of expansion of the cannabinoid markets is outpacing both the regulatory framework and the ability

of scientific community to generate high-quality data regarding the effectiveness and potential adverse effects of cannabinoids in medicinal use.[24]

As there is an ethical responsibility to provide high quality research in support of any marketing claims pertaining to benefits of cannabis, one approach to improve medicinal cannabis quality and patient safety is to encourage or oblige the cannabis industry to fund rigorous research – either directly or through taxation. Unfortunately, such approaches are not broadly implemented. Some jurisdictions where cannabis is legalized (for example, California and Washington state in the USA), allocate a small percentage (0.1-0.3%) of tax revenue to medicinal cannabis research.[45] In many other jurisdictions, however, no such allocation exists, although tax funds remain distributed for goals such as criminal justice reform programs and substance abuse programs.[1,2,58] This is a missed opportunity, as consistent and considerable support from the industry could be a major catalyzer to making important advances in cannabinoid research.

Given the paucity of high quality data on cannabis efficacy and safety, rapid implementation of top-down measures and safeguards is needed, as these have been associated with reduction of untoward effects and societal harm.[58] Key agenda items for future research are outlined in Table 5, but adherence to evidence-based recommendations as they emerge will be critical for balancing between harm reduction and access to therapeutically indicated medicinal cannabis under medical supervision.

6. Summary

The IASP task force has summarized the current evidence of the analgesic pharmacology of cannabinoids and preclinical evidence of the antinociceptive efficacy of cannabinoids, cannabis-based medicines, and endocannabinoid system modulators in animal models of injury-related or

pathological persistent pain; the clinical efficacy of cannabis, cannabinoids and CBM for chronic pain; harms related to long-term use of cannabinoids; as well as societal issues and policy implications related to the use of cannabinoids, cannabis and CBM for pain management.[20,21,26] Research agenda items are outlined, based on the current gaps identified in the preclinical and clinical literature.

Study quality, rigor, and transparency of reporting both benefits and harms need to be improved across the entire translational research spectrum. Advances are required in understanding of the neurobiology of cannabinoid-mediated regulation of pain, and in establishing clinically-relevant behavioural preclinical models with high translational value. Higher quality data are required to determine analgesic efficacy and safety of cannabis, cannabinoids and endocannabinoid system modulators from well-designed and appropriately powered primary RCTs as well as high quality population health studies. It is also important to understand the role of the individual compounds within a broader framework of effective pain management at a health system level. Major challenges exist in performing clinical research on therapeutics that are subjected to tight regulatory control, and significant reforms in cannabinoid research regulations may be required to facilitate the needed high-quality research. Overall, numerous knowledge gaps exist across preclinical, clinical and regulatory aspects of cannabinoid research. Collaborative, multidisciplinary, and rationalized research efforts across the translational spectrum to address the gaps identified by the task force can catalyse the development and delivery of safe and effective medicines to treat pain.

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Conflicts of Interest:

Dr. Haroutounian reports grants from Disarm Therapeutics, personal fees from Vertex Pharmaceuticals, Medoc Ltd, and Rafa Laboratories, outside the submitted work. Dr. Degenhardt reports grants from Indivior and Seqirus, outside the submitted work. Dr. Di Forti reports personal fees from Janssen and Lumbeck, outside the submitted work. Dr. Finn reports grants from Alkermes Inc and Science Foundation Ireland, grants from Shionogi Ltd., B. Braun Ltd. and Science Foundation Ireland, grants from Irish Research Council, CNPq Brazil, and EU INTERREG, outside the submitted work. Dr. Finnerup reports personal fees from Merck, Almirall, NeuroPN, Vertex, and Novartis Pharma, grants from IMI2 PainCare, outside the submitted work. Dr. Gilron reports non-financial support from Canopy Health, Toronto Poly Clinic, and Cann Trust, personal fees from Adynxx, Biogen, Eupraxia, and Novaremed, outside the submitted work. Dr. Hohmann reports grants from the National Institutes of Health (National Institute on Drug Abuse, National Cancer Institute, National Institute of Neurological Diseases and Stroke), Indiana Addiction Grand Challenge and is a co-inventor on a provisional patent related to CB2-opioid interactions. Dr. Kalso reports personal fees from Orion Pharma and Pfizer, outside the submitted work. Dr. Rice reports support from IASP, during the conduct of the study; personal fees from Imperial College Consultants (last 24 months this has included remunerated work for: Abide, Confo, Vertex, Pharmanovo, Lateral, Novartis, Mundipharma,

Orion, Shanghai SIMR Biotech, Asahi Kasei, Toray & Theranexis) , Dr Rice was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015 and from which milestone payment occurred until 2019. Dr. Rice has a patent WO 2005/079771 pending, and a patent WO 2013 /110945 pending. The remaining authors have no conflicts of interest to disclose.

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TABLE 1: **Research Priorities – Pre-clinical aspects of cannabinoid pharmacology and the endocannabinoid system**

• Further research to elucidate the neurobiology of endocannabinoid signaling in relation to pathological pain processing, and investigation of additional potential analgesic targets within, or interacting with, the endocannabinoid system.
• Nuanced understanding of cannabinoid receptor signaling and the role of allosteric modulation and biased agonism of the cannabinoid receptors.
• Better alignment between compounds tested in clinical trials with those tested preclinically, to allow improved understanding of translational (and back translational) pharmacology of targeting the endocannabinoid system for analgesia.
• Investigation of the pharmacology of cannabinoids beyond THC, including CBD and other phytocannabinoids.
• Detailed characterization of pharmacokinetic properties of cannabinoids, and determination of pharmacokinetic-pharmacodynamic (PK-PD) relationship between plasma concentrations, effect site concentrations, and antinociception in the context of specific preclinical models.
• Optimization of modes and formulations of drug delivery to achieve consistent drug exposure at the site of action.
• Further investigation of the analgesic potential of cannabinoid receptors and targets outside the CNS, to circumvent unwanted central side effects.
• Understanding the physiological interactions between the endogenous cannabinoid and opioid systems in pain modulation.
• Further research on the role of the endocannabinoid system and cannabinoids in modulating the affective-motivational and cognitive dimensions of pain processing and pain experience.
• Improved external validity of animal models and outcome measures used to determine antinociceptive effects (particularly long-term ones) of cannabinoids and endocannabinoid system modulators
• Improved rigor and transparency of design, conduct, analysis and reporting of preclinical studies.

TABLE 2: **Research Priorities - Primary clinical trials of cannabinoids for pain**

• Outcome measures in cannabinoid trials should include pain intensity, and in the context of chronic pain also the assessment of effects on sleep, quality of life, function, and the affective-motivational and cognitive dimensions of the pain experience, particularly those most important from the patient perspective.
• Dose and titration methods (if applicable) should be explicit; placebo and active comparators should be encouraged, as should studies examining cannabis, cannabinoids or CBM administered both as monotherapy and adjunctively with other pain medications.
• Analysis of patient demographic, phenotypic and genotyping characteristics pertinent to a possible personalized treatment response are desirable, and should be adequately powered.
• Investigation of relationships between cannabinoid plasma/target concentrations and pharmacodynamics effects, for both efficacy and toxicity endpoints.
• High quality trials studying cannabidiol (CBD) in specific pain conditions.
• High quality trials studying those cannabinoids, endocannabinoid system modulators and CBMs that show most promise in preclinical studies.
• Further conduct of experimental pain study designs with cannabinoids that would translate to meaningful clinically-relevant analgesia.
• Investigation of interactions between opioid-based and cannabinoid-based interventions on: 1) analgesic efficacy, 2) side effect profile – e.g. abuse liability, respiratory depression, 3) change in or inhibition of withdrawal symptoms during opioid tapering or abstinence.
• Determination of optimal therapeutic ratios of cannabinoids (e.g. THC:CBD) in particular pain conditions; e.g. strategies that attempt to separate analgesia from adverse effects.
• High-quality trials with inhaled/vaporized cannabinoids, with adequately powered sample size, sufficient duration, detailed pharmacokinetic analysis, and rigorous controls.
• High quality population health-based studies that yield useful 'real-world' data on the benefits and harms of cannabis, cannabinoids and CBM in large numbers of people with pain.
• Unified quantification of major/minor phytocannabinoid content for cannabis preparations evaluated in clinical trials.
• Determination of the effects of regulatory restrictions on cannabinoid clinical research.

TABLE 3: **Research Priorities - Harms assessment and reporting**

• An effort on identifying the following potential harms in the context of long-term use of cannabis, cannabinoids and CBM for chronic pain management: - Cognitive effects, with emphasis on different age groups - Neurodevelopmental effects pertaining to infants, children and adolescents including neuronal development, effects on learning, learning impediments and academic achievement - Mental health disorders, with emphasis on psychosis and depression - Neurological effects - Cannabis use disorders - Pulmonary effects - Effects in pregnancy and breastfeeding - Effects on driving and operating machinery - Cardiovascular effects - Carcinogenicity, with emphasis on genitourinary cancers.
• Investigating the role of a cannabinoid compound, dose, route, exposure (pharmacokinetics) and duration of use in specific short-term and long-term adverse effects.
• Investigating drug-drug interactions, particularly with drugs with narrow therapeutic windows (e.g., anticoagulants, immunosuppressants, opioids, intravenous general anesthetics).
• Understanding individual factors (e.g. demographic, psychological, genetic, comorbidity, concomitant medication use) that confer susceptibility vs resilience to adverse effects from cannabinoids.
• Compare harms related to the use of cannabis and synthetic cannabinoids for medical purposes under medical supervision to those associated with use in the absence of expert medical supervision.
• Population research methods to track self-prescribed cannabis use specific for pain management, and track both potential benefits and harms from that mode of use.
• Improve approaches to assess and report harms of cannabis, cannabinoids and CBM in pain RCTs with appropriate post exposure duration of follow up for long-term adverse events.

TABLE 4: **Research Priorities - Systematic reviews**

• Systematic reviews should meet the Cochrane definition of systematic reviews, and provide sufficient detail to be of moderate or high confidence according to AMSTAR-2.
• Should be pre-registered, outlining aims, primary and secondary outcomes, and data analysis strategy.
• Should use properly randomized, double blind trials in people with a defined pain condition and moderate or severe initial self-assessed pain.
• Should examine the potential of bias from small studies, imputation methods, and potential risk of publication bias.
• Should declare the perspective of the review in advance; choose efficacy or effectiveness outcomes relevant to that perspective.
• Should perform individual-level meta-analysis, where possible.

TABLE 5: **Research Priorities - Policy and societal issues**

• Establish standards and regulations for testing cultivation and manufacturing quality, efficacy, and safety of cannabis products (similar to biopharmaceutics standards) before prescribing / marketing.
• Research marketing and advertising of cannabis products. Investigate consequences (use, effects) of banning benefit claims unsupported by robust data. Disallow advertising to children and adolescents.
• Investigate approaches to establish robust guidance for driving under cannabinoid influence.
• Establish education programs for vulnerable populations; leverage patient partners to improve outreach.
• Engage with clinicians and patient partners to establish education programs for healthcare providers to provide reliable information to patients, including in developing countries and countries where English is not the primary language.
• Investigate broader societal harms (e.g., addiction, psychosis, cognitive effects) in the context of pain management.
• Investigate approaches to incentivize or oblige the cannabis industry to fund high-quality cannabis research to support claims of efficacy, and for improving product quality and patient safety, while minimizing and managing conflict of interest.