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Presenting the outputs of the IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia

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This special issue of *PAIN*® consists of a series of linked articles that represent a rigorous and extensive appraisal of the basic and clinical science evidence pertaining to the potential analgesic effects and safety of cannabis and cannabinoids. It represents the collated outputs, gathered over a two and a half year effort, of the IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia (IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia membership, list available at: https://www.iasp-pain.org/About/Content.aspx?ItemNumber=7917. We were tasked with conducting a robust and comprehensive interrogation of the preclinical and clinical evidence for analgesic benefit and also for harm. Emphasis was placed on mitigating against the impact of bias by systemically identifying and appraising the available evidence and using the highest quality evidence available. The Task Force then used this knowledge to inform IASP's position statement that is published concurrently with this edition of *PAIN*.[7] The key message conveyed by the position statement is that although there are substantial preclinical data supporting the hypothesis of cannabinoid analgesia, current uncertainties in the clinical evidence base led the Task Force to conclude that we could not support the general use of cannabis nor cannabinoids and related medicines for analgesic use at this point in time.

The Task Force organised their evidence appraisal into 4 workpackages:

Workpackage 1 was chaired by David Finn and was tasked with reporting on the current state of knowledge of the basic science and clinical pharmacology of this complex and diverse range of bioactive compounds. The main output compromises an extensive narrative review of the field.[1] The efficacy section of this narrative was, uniquely, informed by a systematic review and meta-analysis of the published evidence derived from animal models, led by Nadia Soliman.[11,12] To cope with the large volume of information in this literature, the systematic review used innovative crowd science and machine learning methods to assist with screening of articles for inclusion and with data extraction. The overall conclusion of this workpackage is that a substantial literature supports the concept of cannabinoid-mediated analgesia. However, the considerable challenges inherent in translating such data into safe and effective medicines are recognised, as are uncertainties in ascertaining the impact of bias on such findings.

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Workpackage 2 was led by Christopher Eccleston and comprises assessments of the evidence from clinical trials that investigated human analgesic efficacy. In a first step, Andrew Moore et al. systematically reviewed the existing evidence syntheses in the area.[2,9] They identified and included 57 systematic reviews of such trials, most published since 2010. They concluded that these existing reviews were of insufficient quality for the purpose of informing the position statement. Therefore, a new and robust systematic review of randomised controlled trials was led by Emma Fisher.[2,3] Thirty-six trials met their inclusion criteria, of which 22 examined cannabis-based medicines. The review revealed that most studies were associated with either an unclear or a high risk of bias, and consequently, the outcomes of those trials were rated as low-quality or very low-quality evidence. The overall conclusion was that the available clinical evidence neither supports nor refutes claims of analgesic efficacy or safety (within the limitations of the clinical trial evidence) for cannabinoids, cannabis, or cannabis-based medicines.

Ian Gilron led workpackage 3 that was tasked with appraising the relevant evidence of harm associated with the use of cannabis and cannabinoids. Analgesic clinical trials are generally of insufficient duration and not powered to sufficiently detect many adverse effects. Therefore, Mohammed Mohiuddin et al. conducted an overview of systematic reviews that investigated risks of harm with cannabinoids, cannabis, and cannabis-based medicines.[4,8] They identified 79 such reviews, which covered 2200 individual reports describing diverse harms data from a range of primary study formats that explored the question of harms in a variety of settings. Overall, there was a general exposure dependent association of general harm associated with cannabinoid use (risk ratios [1.86-2.18], although no significant association was found with rates of serious adverse events or death. However, there does seem to be exposure-related increased risk of psychosis, motor vehicle accident, and respiratory disease. In addition, low birth weight is associated with in utero cannabis exposure. A particularly concerning and important harm is the risk of psychosis and other psychiatric adverse effects associated with cannabis use. Marta Di Forti et al. give an expert summary of the current state of this area.[10] They discuss acute psychiatric effects as well as the emerging area of cannabis use disorder but focus mainly on a comprehensive summary of convergent lines of evidence confirming the association of heavy cannabis use and psychosis. The implications of further elucidating this risk in the context of therapeutic use of cannabis are self-evident. The authors also emphasise the importance of risk factor identification in therapeutic settings. Zinboonyahgoon et al.[13] report on Thailand's experiences during the recent introduction of cannabis-based medicine to the country; this experience is informative for all, but particularly for low-income and middle-income countries. Importantly, monitoring during this introduction suggests that it was initially associated with adverse events and an

increase in referrals to the national drug toxicology service. They highlight the importance of public and professional education, quality control of marketed products, and long-term monitoring of efficacy, safety, and socioeconomic impacts when cannabis-based medicines are introduced.

The final workpackage was led Simon Haroutounian and produced 2 articles: First, they discussed the broad and complex societal and policy implications of cannabis and cannabis-based medicines in the context of analgesic usage.[6] There is a focus on the importance of robust regulatory processes governing the cultivation, manufacture, licencing, and marketing of such substances. They also consider the inherent dangers when the conventional protections afforded by professional medical oversight of medication use are effectively bypassed in jurisdictions where the recreational use of cannabis is permitted. The impact of cannabinoids on the ability to conduct critical activities that require full cognitive function, such as motor vehicle driving and flying, is discussed, and protection measures required for vulnerable populations are considered. The second article draws together the knowledge gaps identified by the other workpackages and collates them into a research agenda.[5] They identified what the Task Force considers to be the most important and pressing basic science, clinical, and epidemiological research priorities in the field. We hope this will be an important signposting publication for researchers, funders, patients, and policymakers.

Finally, we thank all Task Force members who so freely contributed to the considerable workload and consensus building of the Task Force. Equally, we thank all those other colleagues who contributed their expertise and who are listed as authors on the various publications.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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