

COMMENTARY

Register-based studies on cannabis-based medicines and medical cannabis need reliable diagnoses and cannabis treatment details

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This journal recently published a paper by Hjorthøj et al. (2021) entitled "Cannabis-based medicines and medical cannabis for patients with neuropathic pain and other pain disorders: Nationwide register-based pharmacoepidemiological comparison with propensity score matched controls". The urgent need to accrue evidence for effect of cannabis-based medicines or medical cannabis (CBM/MC) in pain management is hindered by lack of high-quality randomized controlled trials (RCTs), leading to divergent conclusions of systematic reviews and differing recommendations by national guidelines and position papers (Fisher et al., 2021; Petzke et al., 2021).

Well-designed register-based studies provide an alternate method to examine efficacy and safety of CBM/MC in a real-world setting, can complement results of RCTs and support guideline recommendations. Databases that are linked to national registries, as used by the Danish researchers, have the advantage of including populations unselectively, analysing sociodemographic information, and providing details of prescribed medications and healthcare utilization. The trade-off may be less accuracy in specific diagnosis, less information about disease severity and importantly absence of information on individual treatment response.

Hjorthøj and colleagues used the National Danish Prescription Registry to identify all individuals who redeemed at least one prescription of CBM/MC between 1

January 2018 and 31 October 2019 for a pain-related indication. Two groups were identified: one group comprised 1817 subjects with neuropathic pain (based on having redeemed a prescription on which the indication was labeled as "neuropathic pain") and the second group "other or unspecified pain disorders" was comprised of 924 subjects. Many prescriptions only contained the word "pain" or similar in the field regarding indications. These prescriptions were referred into the group "other or unspecified pain disorders". Each case was matched 1:1 using propensity score matching to a control subject redeeming a prescription other than CBM/MC for the same indication. Other databases were accessed to enable study of multiple outcomes such as analgesic and overall medicine consumption, primary and secondary healthcare utilization, weeks unemployed, signals of potential harms (medical encounters due to other diseases) and death rates.

A major limitation of this study is the reliability of diagnoses which limits any robust conclusion on the effectiveness of CBM/MC for selective sub-groups of chronic pain patients. Unfortunately, International Classification of Diseases (ICD) codes were not available in the databases used. Furthermore, pain disorders included in the "non-neuropathic pain group" are not further specified, and may have included some with neuropathic pain as some in this group had redeemed prescriptions for gabapentin,

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a treatment generally used in treatment of neuropathic pain. Therefore, the results of statistical comparisons of the neuropathic and non-neuropathic group should be interpreted with caution. Furthermore, the multiple comparisons of various cannabinoid prescriptions in both groups provide a heterogeneous picture of efficacy and safety, with an increased probability of type one error.

A striking finding of this study is that CBM/MC were not associated with a reduction of medications in general, and opioids in particular. Even sleep medication use was increased for the neuropathic group receiving CBM/MC. Reasons for this finding can only be speculative. CBM/MC may have been prescribed for those with greater symptom severity and less responsive to medications. Prescriber characteristics may have influenced continued medication use, too.

The results of the study are in contradiction to the ones of an Israeli multi-centre, prospective cohort study in which neuropathic pain predicted treatment failure (Aviram et al., 2021). In view of the methodological flaws inherent of this registry study and the divergent findings relative to the study of Aviram and coworkers (Aviram et al., 2021), the conclusion of Hjorthøj et al. that CBM/MC are possibly efficacious for neuropathic pain, but not other pain disorders, cannot be endorsed without further evidence from samples with more reliable diagnoses.

Details about CBM/MC would be helpful for the clinician, including daily average dose, switching from one product to another, simultaneous use of different products and reasons for discontinuation. Dosages of prescribed CBM/MC are not given by the authors. There is also no information on past or current recreational cannabis use, with some studies reporting an association of recreational cannabis use with MC use.

This study does provide reassuring information on safety of CBM/ MC particularly concerning major adverse psychiatric events. Cannabis use disorder was only reported for a single subject receiving CBM/MC, but interestingly for three control subjects not receiving CBM/MC. The encouraging findings on safety in this current study are in line with those of an Israeli multi-centre, questionnaire-based prospective cohort study (Aviram et al., 2021).

In conclusion, we urge that register-based studies should provide reliable data that should include the ICD code of the pain disorder, the descriptor of chronic pain (nociceptive, neuropathic, nociplastic and mixed) and the prescribed doses of CBM/MC. Pending further clarification, clinicians will be tasked with making individual decisions about use of CBM/MC, even in the context of differing recommendations by various associations and expert guideline panels.

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CONFLICTS OF INTEREST

Winfried Häuser has received reimbursement for travelling and accommodation by Bioevents, a congress organizer, for co-organizing a congress on controversies on CBM in 2018 and 2019. He was the head of an EFIC task force of a position paper on cannabis-based medicines and MC for pain management and member of a task force of a position paper on the same topic by the German Pain Society. Mary-Ann Fitzcharles is a core member of Science Advisory Committee on Health Products containing Cannabis of Health Canada, international advisory member of the Australian Center for Cannabinoid Clinical and Research Excellence and first author of a position paper of the Canadian Rheumatology Association on MC use for persons with rheumatic diseases. She has received reimbursement for travelling and accommodation by Bioevents, a congress organizer, for giving lectures at a congress on controversies on cannabis-based medicines in 2018 and 2019.

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