CORRESPONDENCE

Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

by Prof. Dr. med. Winfried Häuser, Prof. Mary-Ann Fitzcharles, MRCP (UK), FRCP (C), Prof. Dr. med. Lukas Radbruch, and Prof. Dr. med. Frank Petzke in issue 38/2017

Considerable Heterogeneity

Cannabinoids are an extremely varied group of substances with different methods of application, and they show large inter-individual differences in effectiveness and tolerability. The result is considerable clinical heterogeneity.

Widely defined inclusion criteria increase the clinical heterogeneity between the studies. Neuropathic pain is diverse anyway, but the argument of unsatisfactorily diagnosed neuropathic pain was used in order not to include one of the largest studies of cannabinoids in multiple sclerosis (1).

The I^2 statistic was used to test for heterogeneity of the randomized controlled trials (RCTs). In small numbers of RCTs, this statistic is subject to systematic biases; it is not precise, and it requires reporting the I^2 confidence interval (2). In such a situation, only individual (raw) data should be used, instead of aggregated data, and definitive conclusions should be avoided.

“Do not do a meta-analysis”—this is what the Cochrane Collaboration’s handbook cited by Häuser et al. (3) recommends as a possible way of dealing with heterogeneity, which is the case here to a relevant degree.

The report by the National Academies of Sciences has reached a different conclusion: “There is substantial evidence that cannabis is an effective treatment for chronic pain in adults” (4).

Cannabinoids have been found to facilitate reductions in the use of opioids and reduce chronic stress reactions and emotional learning—important components in chronic pain. We recommend stratification approaches in this direction.

The cannabis dilemma lies in the fact that after decades of defaming cannabis as merely an intoxicating agent—coupled with restrictions—the scientific, clinical, and economic development of cannabinoid research has been hampered and continues to be.

Evidence-based medicine (EBM) has three components: external evidence, the physician’s experience, and the patient’s experience. In order to reach a clinical decision in the individual case, all three sources are relevant. Systematic reviews and meta-analyses are part of the external evidence and are therefore not to be considered identical to EBM. DOI: 10.3238/arztebl.2018.0143a

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Conflict of interest statement

Prof. Karst has received consultancy fees from Hanover Social Welfare Court in connection to the subject matter. He has received travel expenses from Bionorica ethics and the Sertürmer Gesellschaft, and speaker honoraria from Bionorica ethics and Grünenthal.
Prof. Passie declares that no conflict of interest exists.

In Reply:

Karst and Passie highlight several problems in the discussion of the benefits of cannabis-based medications in pain medicine.

Most randomized controlled trials (RCTs) that have been conducted of oral sprays containing tetrahydrocannabinol (THC)/cannabidiol (CBD) were funded by the manufacturer of the preparation. As only one study of medical cannabis was included, however, a systematic review did not show any relevant differences of the different cannabis-based medications regarding their efficacy and tolerability in neuropathic pain (1). In order to base the discussion of the importance of medical cannabis on more solid data, publicly funded studies are required that compare the efficacy and tolerability of a) proprietary medicinal product containing defined doses of THC and/or CBD, b) types of cannabis flowers selected according to the physician’s experience, and c) established therapeutic approaches.

We agree that combining all chronic pain syndromes in systematic reviews of RCTs is problematic. For this

reason, we differentiated—as far as was possible—in our review article by individual categories of pain syndromes.

Review articles have reached different conclusions about the quality of the evidence and benefits of cannabis-based medications. The stricter the inclusion criteria and the required quality of the evidence, and the more systematic the literature search, the more sobering the results (3). The US National Academies of Sciences, Engineering, and Medicine did not follow established standards in defining the evidence. The authors therefore qualify the conclusion as follows: “This hierarchy of evidence does not imply the magnitude of the observed effect or the importance of the health effect from an individual or population standpoint.” For a presentation that is of high methodological quality we refer readers to a recently published overview that was funded by the German Federal Ministry of Health (4). DOI: 10.3238/arztebl.2018.0143b

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The author declares that no conflict of interest exists.

Erratum

In the article entitled “Indications for the Surgical Management of Benign Goiter in Adults” by Detlef K Bartsch et al. in issue 1–2/2018, the unit of measurement of the calcitonin concentration was incorrect on two places. On page 4 as well as in *Box 1*, pg/L and pmol/L are incorrect—it should have been **pg/mL**. On page 4 the corrected sentence should therefore read: “Basal calcitonin levels of **>26 pg/mL** in women and **>60 pg/mL** in men are indicative of MTC with a probability of >95%.”

Box 1 should read: “Indications for surgery in patients with goiter with or without nodules include: Reasonable suspicion of malignancy, especially with [...] —basal calcitonin serum level increase **>26 pg/mL** in women and **>60 pg/mL** in men (warning: assay-dependent).”

MWR