Cannabinoids dosing for osteoarthritis-authors' reply

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We thank Miles et al.[1] for taking an interest in our work and for their kind acknowledgement of our randomized controlled trial (RCT) on oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee.[2]

In their correspondence they have raised concerns about the tolerability (and maybe also the safety) of the fixed high dose of CBD (600 mg/d) utilized in our trial that we would like to address in more detail.

On the subject of the well-established general recommendation "start low, go slow" in chronic pain management, we consider it absolutely essential to clearly distinguish the non-hallucinogenic pure cannabis ingredient CBD from the classical psychotropic substance tetrahydrocannabinol (THC) and various other compounded cannabis extracts, which are correctly but indiscriminately categorized as "cannabinoids" or "cannabis-based medicines".[3] What is shared by the respective two substances is obviously their origin from cannabis, but not a common pharmacology. The conceptual confusion is partly due to the not science-based, legislative definition of illicit cannabis drugs as parts, constituents or products from cannabis plants. In fact, the two phytocannabinoids CBD and THC, though direct cannabis constituents, vary substantially in their distinct pharmacological mechanisms, targets and properties.[3–6]

As practising pain physicians, we fully agree with our Canadian colleagues and their cited recommendation "start low, go slow", when commencing therapy with THC or THC-containing preparations. THC can produce substantial, dose-dependent acute cognitive and psychomotor impairment, acute psychotic symptoms, altered perception, increased anxiety and cognitive deficits.[3–6] Vegetative adverse events such as tachycardia may also occur.[5] Because of these side effects, cautious and careful titration of THC and THC-containing preparations is mandatory, especially when applying the substance in vulnerable patients such as elderly and or multimorbid individuals. Often such THC side effects hinder therapeutically intended dose increments.

By contrast, CBD has been reported to be void of unwanted acute psychoactive and cardiovascular effects, or to potentially even reduce the psychiatric symptoms of THC described above.[5,6] Pure CBD was well tolerated in RCTs on childhood epilepsy in doses exceeding those applied in our trial (10–20 mg × kg^{-1} × d^{-1} vs. 4.6–10 mg × kg^{-1} × d^{-1}). Reported adverse events in these trials were mild to moderate and included elevated blood concentrations of liver enzymes, somnolence, decreased appetite, diarrhoea, and pyrexia.[7,8] Particularly no severe psychotropic adverse events were observed.

Also the World Health Organization identified pure CBD as generally well tolerated and with a good safety profile.[9] Consequently, in many countries, CBD products are freely available over the counter and marketed as food supplements or wellness products that are not subject to drug regulatory standards[10]; e.g., in the European Union, CBD is marketed as a "novel food". The major safety concern regarding such commercially available non-pharmaceutical grade CBD preparations remains impurities, the most common of which is THC.[10]

In our RCT, hemp-derived pharmaceutical grade pure CBD (purity >99.8%) was utilized. In order to generate convincing data on the possible analgesic potential of CBD, we deemed it necessary to apply high doses that come close to those used in the RCTs on epilepsy. Furthermore, in our trial CBD was gradually titrated to the definite maintenance dose of 600 mg/d in three 200 mg steps within a week, just to be on the safe side. At the end of the maintenance phase, CBD was tapered off again in three 200 mg steps over one week in view of possible–but very unlikely–withdrawal symptoms. Following this protocol with a pure CBD preparation (<0.2% impurities), the oral application of high CBD doses was well tolerated by all elderly patients.[2]

In our study, diarrhoea, elevations of serum liver aminotransferases and γ-glutamyltransferase (γ-GT), abdominal pain and fatigue were the most frequent adverse events.[2]

Importantly, all adverse events were mild to moderate in severity and fully reversible.[2] Serum liver aminotransferase and γ-glutamyltransferase (γ-GT) elevations, but no cardiovascular or psychiatric adverse events were predominantly seen in CBD-treated patients. Therefore, our primary general recommendation,

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when commencing oral, pharmaceutical grade CBD therapy is not "start low, go slow" (if in doubt about CBD tolerability in an individual patient, this is always possible), but to closely monitor liver parameters.

Contributors

SP, SS and HGK contributed to the drafting of the manuscript and literature search.

Declaration of interests

The authors declare no competing interests.

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