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EDITORIAL

Parasitic pharmacology: A plausible mechanism of action for cannabidiol

Doctors treating patients with epilepsy are increasingly confronted with a request for "cannabis-oil" instead of well-studied and registered anti-epileptic drugs (AEDs). While the possible anti-epileptic potential of cannabidoids has been known for decades, beginning with the first reports of beneficial effects of cannabidiol (CBD) in animal models of epilepsy 40 years ago, patients with epilepsy asking to be treated with CBD is a development stemming from more recent years. CBD appears to be the most important non-intoxicating constituent of cannabis and is sold without prescription as an oil solution in many jurisdictions at concentrations ranging typically from 1% to 5%. There is an array of targets at which CBD has been demonstrated to interact that may underlie its anti-epileptic activity in seizure models, including inhibition of voltage-gated sodium channels, transient receptor potential (TRP) channels, calcium channels, glycine receptors, and G-protein-coupled receptor-55 (GPR55) that may also underlie its ability to control neuroexcitability.[1-5] Furthermore, CBD has been demonstrated to interact with 5HT1A receptor controlled pathways in brain,[6] an activity that has been linked with certain types of epileptic activity.[7]

Evidence for the efficacy of CBD in humans was primarily based on case reports, or open-label[1] and uncontrolled studies, and therefore, the scientific quality of the data for CBD in the treatment of seizures was considered weak. However, recently, two randomised placebo-controlled and appropriately powered studies were performed with CBD in patients with Lennox–Gastaut syndrome (LGS) and severe myoclonic epilepsy of infancy, also known as Dravet syndrome (DS).[8,9] Both of these randomised placebo-controlled trials (RCTs), published in the *New England Journal of Medicine* (NEJM), met their primary endpoint of comparative CBD efficacy, and in June 2018, this led to the FDA approval of Epidiolex (CBD) for the treatment of seizures associated with these rare and severely disabling epilepsy syndromes. Specifically, these studies showed that in patients with LGS, 20 mg/kg/day CBD was able to induce a median percent reduction in drop-seizure frequency of 41.9% as compared to 17.2% in the placebo group, and in paediatric patients with DS, treatment with CBD 20 mg/kg/day led to a reduction in drop seizure frequency of 6.5% compared to 0.9% in the placebo group.[8,9]

Devinsky et al, the same authors as the NEJM published studies pivotal to the CBD listing, earlier published the results of an open-label intervention trial in patients with treatment-resistant epilepsy on stable doses of antiepileptic drugs, also in the NEJM.[10] This open label study showed a reduction in monthly motor seizures of 36.5% after treatment with 2 to 5 to a maximum of 50 mg/kg/day of CBD.[10] However, this publication provoked some critical responses,[11] related to the suggested interaction between CBD and clobazam, an AED often used by paediatric patients with severe epilepsy syndromes, and likely responsible for the observed reduction in motor seizures in the open-label trial. It is known that CBD has an inhibitory effect on CYP450 iso-enzymes CYP3A4 and CYP2C19, which are also involved in the metabolisation of clobazam. In previous studies, CBD doses of 20 mg/kg/day had shown to increase the exposure of the active metabolite of clobazam (*N*-desmethylclobazam) with on average fivefold, but with a range (90% CI) of twofold to sevenfold in children with refractory epilepsy despite clobazam dose reductions[12] and with threefold in adults with epilepsy (NCT02565108).[13] Data from both the Devinsky open-label and the randomised controlled trials in LGS and DS patients show that, respectively, 52%, 49%, and 66% of the patients taking CBD during the studies were taking clobazam as a concomitant antiepileptic drug. This fact urged Tang et al to express their concern in a Letter to NEJM, referring to the known drug-drug interaction between clobazam and cannabidiol,[14] supported by the aforementioned increase of the active metabolite of clobazam in children with refractory epilepsy[12] and to the acknowledged effect of clobazam on seizure frequency.[15] In response, Devinsky el al stated that "subgroup analyses" would not be appropriate in view of the small sample size of the RCT in DS (n = 120), referring to a publication on statistics in medicine published in NEJM and to an FDA guideline.[16,17] This is unusual considering a PK substudy to investigate this specific fact was detailed in the clinicaltrials.gov registration of this study, and an author of the Devinsky group was the senior author of the 2015 manuscript detailing this very interaction.[12]

Further evidence that a drug-drug interaction may have been responsible for the reduction in seizure frequency was also pointed

out to the NEJM based on other analyses. The side effect profile of cannabidiol in the RCT with CBD in LGS showed that serious adverse events (SAEs) occurred in 16% of CBD patients vs 5% of placebo patients.[8] This pattern of (S)AEs was remarkably similar to the side effect profile of clobazam, leading to the hypothesis that there must have been an important increase in clobazam and *N*-desmethylclobazam concentrations, which could have led to both the increase in side effects due to clobazam, and the observed decrease in drop seizures among the patients on clobazam. After being approached, NEJM replied in a response to the submitting team of clinical pharmacologists that the point of a possible drug-drug interaction had already been made by others, referring to the letter by Tang et al, and that they were not interested in publishing the manuscript. Ultimately, this observation was made public in the form of an article published in Clinical Pharmacokinetics in 2018[18] as it was considered that this was a significant issue for clinicians, medicine regulators, and payers to be aware of.

The authors of the NEJM papers did acknowledge the possibility of a drug-drug interaction between CBD and clobazam based on the results of the registration trials,[11] but argued that data showing a correlation between *N*-desmethylclobazam metabolite and CBD concentrations related to safety or efficacy outcomes were lacking. Surprisingly, GW Research Ltd and Devinsky et al were also involved in the initiation of a trial about possible drug-drug interactions between CBD and clobazam (NCT02565108),[13] that was noted in their study protocol, completed in 2016 but which is not in the public domain.

Following the ongoing concerns raised about a drug-drug interaction between CBD and clobazam and Devinsky's various rebuttals, we still see an important issue that is undervalued. Based on nonclinical studies, there is biological plausibility suggesting that CBD could have anti-epileptic effects.[1,2,4,5,7,19-22] However, we hypothesise that the reported effect of CBD on drop-seizure frequency in the open-label trial and the RCTs of Devinsky et al[8-10] could also be attributed solely to the drug-drug interaction with clobazam. To evaluate this hypothesis, we conducted clinical trial simulations with emphasis on the pivotal trial in LGS. In the paper published on page x in the current issue of *BJCP*, the results of this study are presented. Through clinical trial simulations, for which we used the Devinsky et al NEJM 2018 paper and data available in the public domain, we demonstrate that the reduction in seizure frequency observed in the CBD groups can be entirely explained by a drug-drug interaction with clobazam. We believe this has important implications for the use of CBD as an anti-epileptic drug, for the credibility of the NEJM papers and by extension the FDA registration of Epidiolex. The lack of publication of the pharmacokinetic data, which was part of the original trial, in NEJM and the apparent dismissal of the strength of the concern by international pharmacologists writing directly to the NEJM are also of significant concern.

We believe that one of the most important aspects of scientific research is the need for objectivity and self-critical investigation. And while cannabis itself and derived cannabinoids have received a large amount of media attention,[23,24] it is of utmost importance to be guided by appropriate rigorous data from unbiased trials instead of the public opinion. As to the reasons why the NEJM decided to not even consider publication of both the manuscript on the side effect profile of CBD that resembles that of clobazam and of our clinical trial simulations we can only guess, but this may be related to a diminished interest or understanding in pharmacology that can also be observed globally.[25] As clinical pharmacologists, we observe that this decreasing interest leads to less familiarity with basic pharmacological phenomena such as common CYP450 inhibition and drug-drug interactions and thereby to important medical errors. We should prevent that it also leads to registration of a drug that may actually not be better than grapefruit juice and significantly more expensive.

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COMPETING INTERESTS

There are no competing interests to declare.

Keywords

cannabinoids, drug interactions, epilepsy, modelling and simulation

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