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Editorial

Reduced efficacy and risk of seizure aggravation when cannabidiol is used without clobazam

Benzodiazepines have broad efficacy as antiseizure agents, and are universally recognized as the treatments of choice for the termination of ongoing seizures and acute repetitive seizures (seizure clusters) [1]. Conventional 1,4-benzodiazepines, such as clonazepam, lorazepam, and diazepam, are not generally useful for the chronic treatment of epilepsy because their efficacy wanes over time. Such tolerance may occur anytime after a few days following initiation of treatment but most commonly occurs within one to six months of continuous treatment [2]. The 1,5-benzodiazepine clobazam, like 1,4-benzodiazepines, is a positive allosteric modulator of synaptic $GABA_A$ receptors; no other functionally relevant molecular target is known. However, in contrast to 1,4-benzodiazepines, clobazam is widely used in the chronic treatment of focal and generalized seizures, and has application in the treatment of diverse epilepsy syndromes [3,4]. The drug is often a component of the regimen used to treat epileptic encephalopathies, including Dravet syndrome and Lennox–Gastaut syndrome [5–7].

Clobazam is extensively metabolized in the liver by CYP and non-CYP transformations [8]. It has up to 14 metabolites. However, the major metabolite is *N*-desmethylclobazam (norclobazam), which is produced largely by CYP3A4. Norclobazam is then mainly metabolized by CYP2C19 except in CYP2C19-poor metabolizers with a CYP2C19 inactive allele. With long-term administration, levels of norclobazam, which has a longer half-life than clobazam, are 8- to 20-times higher than those of the parent. Norclobazam is an active metabolite. Following acute administration in mice, norclobazam is an effective antiseizure agent, but is 2.4-fold less potent than clobazam [9]. In cellular neurophysiological studies, norclobazam is equipotent with clobazam as a positive modulator of $GABA_A$ receptors [10–12]. However, in studies in mammalian cells, norclobazam is modestly less efficacious at enhancing $GABA_A$ receptor responses [10,12]. Limited data suggest that CSF levels of norclobazam are about 80% that of clobazam [13]. The reduced efficacy as well as modestly reduced blood–brain barrier permeation may account for the reduced antiseizure activity of norclobazam. Nevertheless, because norclobazam plasma levels are so much higher at steady state, seizure protection during chronic therapy is mainly due to norclobazam.

The maximum potentiation of $GABA_A$ receptor ($\alpha3\beta3\gamma2L$) responses with norclobazam is roughly one-half that of clobazam or diazepam [10]. Because norclobazam has reduced efficacy as a positive allosteric modulator of $GABA_A$ receptors, it can be considered a partial agonist. There is evidence that partial agonists at the benzodiazepine site of $GABA_A$ receptors exhibit less propensity for the development of anticonvulsant tolerance than full agonists [14–16]. Therefore, a plausible hypothesis to explain the infrequent occurrence of tolerance with clobazam is the partial agonist activity of norclobazam [17]. It is worth mentioning that animal studies do show robust tolerance to clobazam itself. However, it is not apparent that norclobazam is the dominant antiseizure principal in these animal studies as appears to be the case with chronic clobazam therapy in humans. Interestingly, clonazepam, which is a highly potent 1,4-benzodiazepine, has partial efficacy similar to that of norclobazam [10]. There is evidence from studies in laboratory animals that clonazepam has low propensity for tolerance development [18–21]. Clonazepam is commonly used chronically to treat a wide range of focal and generalized seizure types [22]. As is the case with clobazam, tolerance to clonazepam may be infrequent [23], which could also be due to its partial agonist character.

Cannabidiol oral solution (Epidiolex) was recently approved in the United States for the treatment of seizures associated with Lennox–Gastaut syndrome or Dravet syndrome. The drug can influence both phase I and phase II biotransformations of concomitant medications through effects on cytochrome P450 (CYP) isozymes and uridine 5′-diphosphoglucuronosyltransferases. Importantly, because of its activity as an inhibitor of CYP2C19, cannabidiol causes a 2.5 to 3-fold increase in plasma concentrations of norclobazam [24,25] (Fig. 1). A critical concern addressed by the Food and Drug Administration (FDA) in its review of Epidiolex is whether the drug has antiseizure activity alone or whether its effects are entirely pharmacokinetic and due to the elevation in norclobazam levels. The concern became evident when in an open-label trial of cannabidiol, only 27% of patients not taking clobazam experienced a reduction in seizures whereas 51% of those who did take clobazam were responders [26]. Similarly, in a trial in tuberous sclerosis, 33% of patients not taking clobazam experienced a response in comparison with 58% of those taking concurrent clobazam [27]. There is extensive evidence in animal models that cannabidiol has antiseizure activity, although the doses required are high [28,29]. Moreover, results from open-label uncontrolled studies have been interpreted as indicating that cannabidiol does reduce seizure frequency even in the absence of clobazam [30]. To rigorously address the issue, prospective controlled trials are required.

The best information available at present comes from the results of three pivotal clinical trials of cannabidiol presented for FDA registration [31]. Subgroup analyses of the data from these trials demonstrate that cannabidiol is more effective in the presence of clobazam and raise the question of whether cannabidiol has been shown to be effective in the absence of clobazam. As shown in Fig. 2, in all three pivotal studies, two in Lennox–Gastaut syndrome and one in Dravet syndrome, in subjects in whom clobazam was part of the baseline medications, when cannabidiol 20 mg/kg was added, there was a significant median reduction in seizure frequency that exceeded the placebo response. By contrast, when cannabidiol 20 mg/kg was added to a baseline regimen

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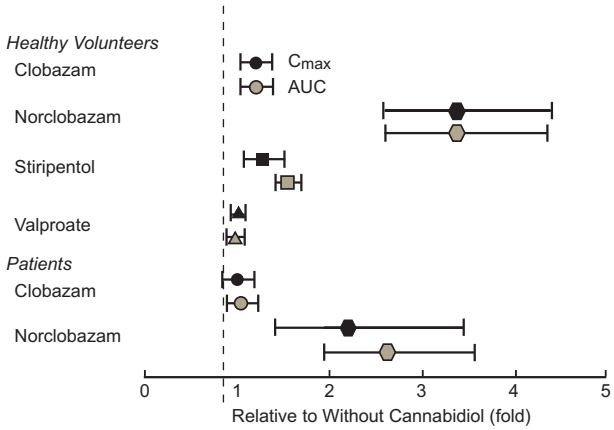

Fig. 1. Geometric mean ratios (relative to without cannabidiol) and 90% confidence intervals in healthy volunteers and patients for impact of cannabidiol on pharmacokinetic parameters of baseline medications and norclobazam after treatment with clobazam in healthy volunteers and patients. C_{max}, maximal concentration in plasma (black symbols); AUC, area under the concentration-time curve (gray symbols).
Adapted from Clinical Pharmacology and Biopharmaceutics Review(s), FDA Drug Approval Package: Epidiolex (Cannabidiol) [31].

that did not include clobazam, the placebo-subtracted median seizure reduction was less, and the 95% confidence interval encompasses 0. The only exception to this pattern is in the single cannabidiol 10 mg/kg group in Study 1414 of Lennox–Gastaut syndrome where the overall response was less than in the subjects treated with a 20 mg/kg cannabidiol dose and baseline clobazam status did not appear to be relevant. It is noteworthy that similar subgroup analyses examining other concomitant medications did not show a pattern comparable to that obtained with clobazam.

Taken together, the results of the two open-label studies [26,27] and the subgroup analysis of the pivotal trial data [31] suggest that concomitant clobazam may increase the efficacy of cannabidiol and raise the question of whether concomitant clobazam is necessary for the activity of cannabidiol. The FDA partially examined this question in a subgroup analysis of subjects taking clobazam and stiripentol in the pivotal Dravet syndrome trial (Study 1332B\). One possible explanation for the positive interaction between clobazam and cannabidiol is the increase in norclobazam caused by cannabidiol. Subjects in Study 1332B receiving stiripentol were presumed not to have had an increase in norclobazam when cannabidiol was added because stiripentol is also a CYP2C19 inhibitor and would be expected to maximally elevate norclobazam levels. In these subjects, there was an 80% reduction in seizures in subjects taking cannabidiol compared to 50% in placebo, leading to the FDA to conclude that elevation of norclobazam is not sufficient to account for the antiseizure activity of cannabidiol. However, this analysis does not exclude the possibility that there is a synergistic pharmacodynamic interaction between cannabidiol and clobazam.

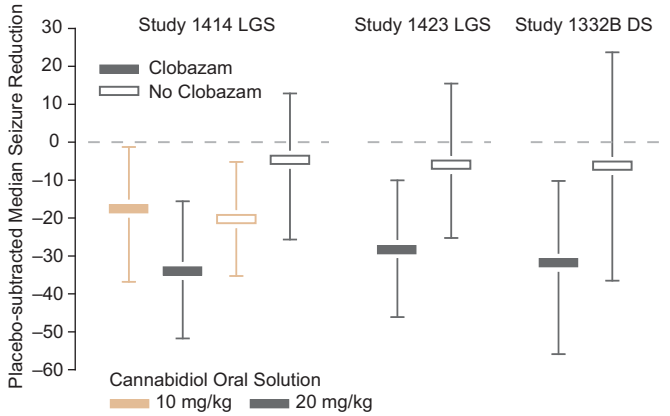

Fig. 2. Subgroup analyses in the three pivotal trials presented for registration of cannabidiol oral solution (Epidiolex) assessing cannabidiol responses in subjects who were and were not taking clobazam in their baseline medication regimen. Open (clobazam) and closed (no clobazam) rectangles indicate placebo-subtracted median difference values of percent reduction in seizure frequency. Error bars indicate 95% confidence intervals (CI) based on Hodges–Lehmann estimator. Study 1414 in Lennox–Gastaut syndrome (LGS) included placebo, and cannabidiol 10 mg/kg and 20 mg/kg dose groups. Study 1423 in LGS and Study 1332B in Dravet syndrome included placebo and cannabidiol 20 mg/kg dose groups. In all but one comparison, the magnitude of the effect was smaller in the no clobazam subgroup, and the 95% CI encompasses no seizure reduction (0%). The single exception is the 10 mg/kg cannabidiol dose group in Study 1414 where the magnitude of effect overall is less and there was no impact of clobazam. Subgroup analyses for the concomitant medications valproic acid, lamotrigine, levetiracetam, rufinamide, and stiripentol did not show such nearly consistent differences. Numerical values taken from Other Summary Review, FDA Drug Approval Package: Epidiolex (Cannabidiol) [31].

Somnolence, sedation, and lethargy are a common occurrence with cannabidiol. The rate of these adverse effects is considerably higher in patients on concomitant clobazam (44% in cannabidiol-treated patients taking clobazam compared with 13% in cannabidiol-treated patients not taking clobazam or valproic acid) [31]. Therefore, whether the interaction between cannabidiol and clobazam is pharmacokinetic or pharmacodynamic, it applies to adverse effects as well as efficacy.

While the predominant response to cannabidiol in clinical trials is a reduction in seizure frequency, some patients have experienced worsening, in a few cases dramatically so [32]. In an open-label trial, status epilepticus was reported as the most frequent treatment-emergent serious adverse event (6%) [26]. Many antiseizure drugs can cause an aggravation of epilepsy [33–35]. The aggravation can be manifest as an increase in the frequency or severity of existing seizures, the emergence of new seizure types, or the occurrence of status epilepticus. Seizure aggravation has been mainly attributed to an "inverse pharmacodynamic effect," in which specific effects of the drug on its antiseizure target lead to seizure worsening rather than improvement. The antiseizure target or targets of cannabidiol have not been identified so it is not possible to speculate on how it might cause an inverse pharmacodynamic effect. In symptomatic generalized epilepsies with multiple seizure types such as the Lennox–Gastaut syndrome, only certain seizure types may be aggravated. Seizure aggravation is believed to be a particular risk in children with refractory seizures in epileptic encephalopathies [35]. Therefore, it is concerning that there was evidence of excess seizure worsening in patients treated with cannabidiol who did not receive clobazam in the pivotal clinical trials [31]. As shown in Fig. 3, for patients taking concurrent clobazam (*left panel*), the number of patients exhibiting an increase in seizure frequency (intersection of curves with

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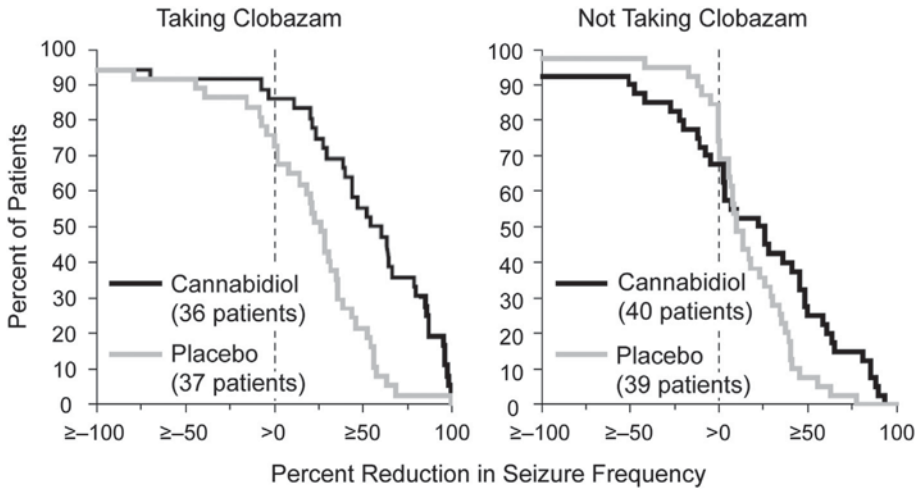

Fig. 3. Cumulative distributions for drop seizures during treatment period in Study 1414 (Lennox–Gastaut syndrome) for patients who were taking cannabidiol 20 mg/kg or placebo and were or were not taking clobazam concurrently (ITT Analysis Set).
Adapted from Combined Clinical and Statistical Review, FDA Drug Approval Package: Epidiolex (Cannabidiol) [31].

vertical dashed line) was reduced in the group receiving cannabidiol in comparison with the group receiving placebo, which is the expected favorable response to the drug. By contrast, for patients not taking clobazam (Fig. 3, *right panel*), the number of patients exhibiting an increase in seizure frequency was similar (~32%) in the two treatment groups. Moreover, the degree of worsening was greater in the cannabidiol group as is evident from the crossing of the cumulative distribution curves at about ≥8% seizure frequency reduction.

Increased drop seizures are concerning because these seizures subject patients to particularly high physical injury risk. Moreover, because uncontrolled or frequent seizures are a risk factor for sudden unexpected death in epilepsy (SUDEP) [36], the implications of seizure aggravation are especially ominous. Until further information is available, it would be prudent to limit the use of cannabidiol to adjunctive therapy in conjunction with clobazam.

Declaration of competing interest

Prior to the FDA approval of Epidiolex, the author participated in a compensated one-day advisory meeting for Greenwich Biosciences. There are no other relevant disclosures.

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