10-001

An Assessment of Acute Pharmacodynamic Drug-Drug Interactions (PD DDIs) Between Cannabidiol (CBD) and Cenobamate (CNB) in a Mouse Model of Generalized Tonic Seizures

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Objective

- To assess the potential PD interactions between CBD and CNB in the mouse MES model using an isobolographic analysis

Conclusions

- Single administration of CBD or CNB exerted independent dose- and brain exposure–dependent anticonvulsive effects in the mouse MES model of acute generalized seizure
- An isobolographic analysis of concomitant administration of CBD and CNB using overall brain exposures (parent molecule and the active metabolite for CBD) revealed synergistic antiseizure effects at all 3 CBD and CNB ratios studied
- There were no statistically significant changes on overall CBD + 7-OH-CBD and CNB brain C_{max} (all changes were <2-fold) during concomitant administration versus single ASM. No significant effects were observed on motor coordination at all ratios tested
- This study reveals a PD synergistic DDI between CBD and CNB at all 3 ratios tested based on the normalized isobologram, CI, and ERI values in a mouse MES model, providing scientific rationale for exploring this interaction in clinical studies

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References: **1.** Patra PH, et al. *Epilepsia* 2019;60:303–314. **2.** Rosenberg EC, et al. *Epilepsy Behav* 2017;70:319–327. **3.** US Food and Drug Administration. Epidiolex® Prescribing Information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210365s023lbl.pdf. (Accessed 25 September 2025.) **4.** Morrison G, et al. *Clin Pharmacol Drug Dev* 2019;8(8):1009–1031. **5.** Rana RR, et al. *Exp Neurol* 2023;360:114286. **6.** Leo A, et al. *Eur J Pharmacol* 2024;962:176222. **7.** Deiana S, et al. *Psychopharmacology* 2012;219:859–873. **8.** Luszczki JJ, et al. *Epilepsy Res* 2010;90:186–198. **9.** Andres-Mach M, et al. *Pharmacology* 2014;93(3–4):172–177. **10.** Chou TC, et al. *Pharmacol Rev* 2006;58(3):621–681. **11.** Gray RA, Whalley BJ. *Epileptic Disord* 2020;22(suppl 1):S10–S15. **12.** Specchio N, et al. *Int J Mol Sci* 2021;22:9339. **13.** Sharma R, et al. *Eur J Pharm* 2020;879:173117.

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Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

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Introduction

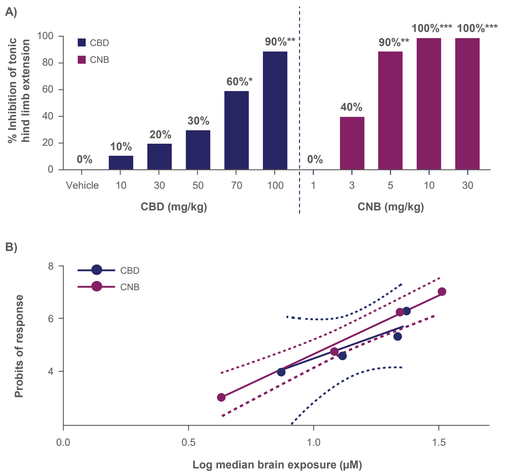
- Plant-derived, highly purified cannabidiol (CBD; Epidiolex®) is anticonvulsive, as shown in preclinical models of seizure and epilepsy,[1,2] and is approved for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex[3]
- The concomitant use of antiseizure medications (ASMs) is common in the management of epilepsy, especially refractory epilepsies[4]
- An isobolographic analysis in the mouse maximal electroshock seizures (MES) model of generalized seizures revealed a synergistic pharmacodynamic drug-drug interaction (PD DDI) between CBD and clobazam, and showed that the active metabolite of CBD, 7-hydroxy-cannabidiol (7-OH-CBD), was 5-fold more potent than the parent molecule[5]
- Cenobamate (CNB) has been shown to improve the suppression of generalized seizures in combination with other ASMs in the DBA/2 mouse model of generalized audiogenic seizures[6]

Methods

- Male C57BL/6J mice (7–8 weeks old; Charles River Laboratories, UK) were subjected to MES to evaluate the anticonvulsive properties of CBD (10–100 mg/kg intraperitoneal [IP]; Epidiolex® active pharmaceutical ingredient, Jazz Pharmaceuticals Research Ltd., UK) and CNB (1–30 mg/kg IP; synthesized on behalf of Jazz Pharmaceuticals Research Ltd., UK) independently and then in combination
- Mice were treated with CBD at 60 minutes[7] (n=10) or CNB at 30 minutes (n=10) before the MES test. Terminal brain and plasma samples were collected immediately after the MES test for bioanalysis at the expected time of maximum concentration (C_{max})
- Based on effective brain exposures that produced 50% anticonvulsive effects (b-EE_{50}) for each ASM alone as determined by inhibition of tonic hind limb extension, mice were then treated with 3 fixed ratios of CBD and CNB (1:3, 1:1, and 3:1) calculated using Loewe's equation[8] that yield a theoretical additive effect (b-EE_{50+ADD})
- The isobolographic method[8–10] for DDI analysis was used to assess potential PD DDIs including synergism, additivity, or antagonism between CBD and CNB using CalcuSyn[10] v.2.11 (Biosoft, Cambridge, UK)
  - This approach was justified because CBD and CNB do not selectively compete for the same molecular targets (CBD: GPR55, TRPV1, ENT1[11]; CNB: preferential inhibition of persistent sodium channels and gamma-aminobutyric acid type A receptor–positive allosteric modulator at a non-benzodiazepine site[12,13])
  - Assessment for any DDIs employed overall exposures in the brain (the site of action), considering parent plus active metabolite (namely, 7-OH-CBD[5]) exposures (normalized to parent potency)
- Rotarod evaluation was conducted on all CBD and CNB ratios to evaluate potential adverse effects on motor coordination
- These studies were conducted with the active pharmaceutical ingredient of Epidiolex® and results do not apply to other CBD-containing products

Results

Figure 1. CBD and CNB demonstrated (A) dose-dependent and (B) brain exposure–dependent efficacy in the mouse MES model

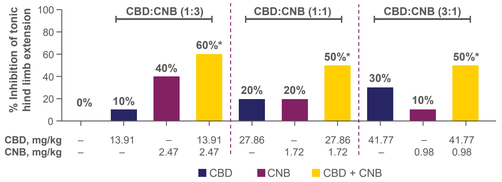


ASM administered	Goodness of fit, R^2 values	Derived b-EE_{50} (μM)
CBD	0.77	14.89
CNB	0.99	12.30

*P<0.05, **P <0.001, and ***P<0.0001 denote significant inhibition of tonic hind limb extension with CBD or CNB dose groups versus vehicle group (Fisher's exact test).
ASM, antiseizure medication; b-EE_{50}, effective brain exposure that produces 50% anticonvulsive effects; CBD, cannabidiol; CNB, cenobamate; MES, maximal electroshock seizures.

- CBD and CNB, when administered alone, exerted dose-dependent efficacy (**Figure 1A**)
- CBD and CNB, when administered alone, exerted independent and brain exposure–based efficacy with b-EE_{50} values of 14.89 μM and 12.30 μM, respectively (**Figure 1B**)
- Overall effect was derived for CBD + 7-OH-CBD after normalization of metabolite to parent potency,[5] before conducting the isobolographic analysis for DDIs

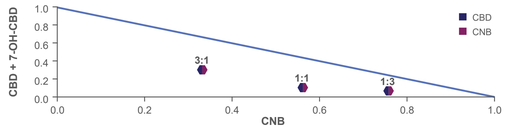
Figure 2. CBD and CNB (1:3, 1:1, and 3:1) exerted significant inhibition of tonic hind limb extension



*P<0.05 denotes significant inhibition of tonic hind limb extension with CBD or CNB dose groups versus vehicle group (Fisher's exact test).
CBD, cannabidiol; CNB, cenobamate.

- All assessed CBD and CNB combinations exerted significant inhibition of tonic hind limb extension versus vehicle (**Figure 2**)

Figure 3. Isobolographic analyses of CBD and CNB overall brain exposures reveal a synergistic DDI

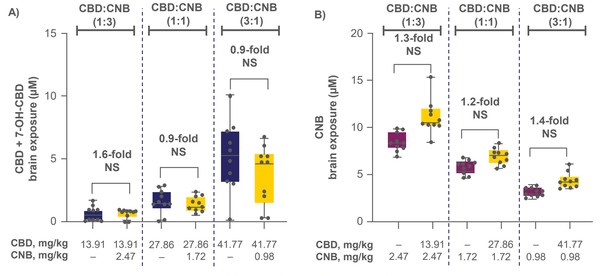


CBD:CNB (b-EE_{50+ADD}) ratio	Combination index	Combination index description	Exposure reduction index	
			CBD + 7-OH-CBD	CNB
1:3	0.795	Moderate synergism	26.04-fold	1.32-fold
1:1	0.638	Synergism	12.63-fold	1.79-fold
3:1	0.615	Synergism	3.53-fold	3.02-fold

7-OH-CBD, 7-hydroxy-cannabidiol; b-EE_{50+ADD}, theoretical additive effect on b-EE_{50}; b-EE_{50}, effective brain exposure that produces 50% anticonvulsive effects. CBD, cannabidiol; CNB, cenobamate; DDI, drug-drug interaction.

- Isobolographic analysis for DDIs using overall brain exposures against efficacy revealed synergy at all CBD:CNB ratios tested (**Figure 3**)
  - All combination data points lie under the theoretical line of additivity (blue) in the normalized isobologram and each combination index (CI) value was indicative of synergy (CI <1)
- Coadministration of CBD and CNB resulted in a 1.32- to 26.04-fold reduction in overall brain exposures versus single administration, depicting synergy by the exposure reduction index (ERI; ERI >1)

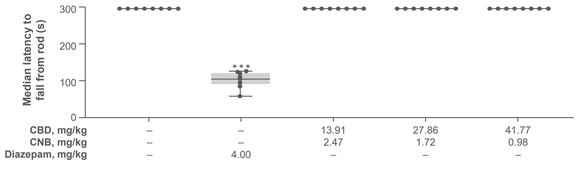
Figure 4. Synergistic PD DDI was revealed in the absence of any significant brain C_{max} changes during CBD:CNB coadministration versus single ASM



Note: Data (n=10) presented as box (median/IQR) and whisker (minimum and maximum) plots.
7-OH-CBD, 7-hydroxy-cannabidiol; ASM, antiseizure medication; CBD, cannabidiol; C_{max}, maximum concentration; CNB, cenobamate; DDI, drug-drug interaction; NS, not significant as determined by Kruskal-Wallis and Dunn's comparison tests; PD, pharmacodynamic.

- No statistically significant change was observed on overall CBD + 7-OH-CBD and CNB brain exposures at all CBD:CNB b-EE_{50+ADD} ratios when compared against single ASM administration. Furthermore, all changes were <2-fold (**Figure 4**)

Figure 5. Synergistic PD DDI was observed in the absence of any significant changes in motor coordination on the accelerating rotarod during CBD:CNB coadministration



Note: Data (n=8) presented as box (median/IQR) and whisker (minimum and maximum) plots.
***P<0.0001 denotes significant median latency to fall from rod(s) with diazepam versus vehicle group as determined by Kruskal-Wallis test with Dunn's multiple comparison.
CBD, cannabidiol; CNB, cenobamate; DDI, drug-drug interaction; PD, pharmacodynamic.

- No motor impairment effects observed upon CBD:CNB coadministration using the same combination doses used in the mouse MES compared to vehicle-treated mice (n=8) (**Figure 5**)
  - Bioanalysis was conducted on combination doses to confirm ASMs were present in the brain and plasma (data not shown)