



AMERICAN
EPILEPSY
SOCIETY

www.AESnet.org

135 SOUTH LASALLE STREET, SUITE 2850
CHICAGO, IL 60603

OFFICE 312.883.3800

FAX 312.896.5784

EMAIL info@aesnet.org

Supplemental Appendix B. *Literature Search Results Illustrating a Range of Potential Cannabis-Drug Interactions*

American Epilepsy Society (AES)

**Written Comments to Norman E. "Ned" Sharpless, MD
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration (FDA)
Department of Health and Human Services (HHS)**

on Docket ID# FDA-2019-N-1482

***Scientific Data and Information about
Products Containing Cannabis or Cannabis-Derived Compounds;
Public Hearing; Request for Comments***

Submitted on: July 16, 2019

Appendix B. Literature Search Results Illustrating a Range of Potential Cannabis-Drug Interactions.

1. Patsalos P, Gidal B, Szaflarski J, Vanlandingham K, Critchley D, Morrison G. Drug-drug interaction (DDI) studies with coadministration of cannabidiol (CBD) and Clobazam (CLB), Valproate (VPA), Stiripentol (STP) or Midazolam (MDZ) in healthy volunteers (HVTs) and adults with epilepsy. *Developmental Medicine and Child Neurology*. 2019;61 (Supplement 1):14. <http://dx.doi.org/10.1111/dmcn.14119>
2. Opitz BJ, Ostroff ML, Whitman AC. The Potential Clinical Implications and Importance of Drug Interactions Between Anticancer Agents and Cannabidiol in Patients With Cancer. *Journal of pharmacy practice*. 2019;897190019828920. 10.1177/0897190019828920
3. Morrison G, Crockett J, Blakey G, Sommerville K. A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects. *Clinical pharmacology in drug development*. 2019. 10.1002/cpdd.665
4. Miziak B, Walczak A, Szponar J, Pluta R, Czuczwar SJ. Drug-drug interactions between antiepileptics and cannabinoids. *Expert opinion on drug metabolism & toxicology*. 2019;15(5):407-415. 10.1080/17425255.2019.1605355
5. Leino AD, Emoto C, Fukuda T, Privitera M, Vinks AA, Alloway RR. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2019. 10.1111/ajt.15398
6. Foster BC, Abramovici H, Harris CS. Cannabis and Cannabinoids: Kinetics and Interactions. *The American journal of medicine*. 2019. 10.1016/j.amjmed.2019.05.017
7. Damkier P, Lassen D, Christensen MMH, Madsen KG, Hellfritzsich M, Pottegard A. Interaction between warfarin and cannabis. *Basic & clinical pharmacology & toxicology*. 2019;124(1):28-31. 10.1111/bcpt.13152
8. Cox EJ, Maharao N, Patilea-Vrana G, et al. A marijuana-drug interaction primer: Precipitants, pharmacology, and pharmacokinetics. *Pharmacology & therapeutics*. 2019;06. <http://dx.doi.org/10.1016/j.pharmthera.2019.05.001>
9. Cossu AE, Latham LB, Hardacker DM, Jea AH. Pharmacologic chaos: severe hypotension from interactions of anesthetics, marijuana, amphetamines, and paroxetine. *Journal of clinical anesthesia*. 2019;55:17. 10.1016/j.jclinane.2018.12.040.
10. Rong C, Carmona NE, Lee YL, et al. Drug-drug interactions as a result of co-administering Delta(9)-THC and CBD with other psychotropic agents. *Expert opinion on drug safety*. 2018;17(1):51-54. 10.1080/14740338.2017.1397128
11. Petri H. The interaction potential of cannabinoids. [German]. *Krankenhauspharmazie*. 2018;39(9):397-401.

12. Leino A, Emoto C, Fukuda T, Privitera M, Vinks A, Alloway R. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus: A case report. *American Journal of Transplantation*. 2018;18 (Supplement 4):744-745. <http://dx.doi.org/10.1111/ajt.14918>
13. Knappertz V, Sommerville K, Crockett J, Blakey GE, Morrison G. Bidirectional drug-drug interaction with coadministration of cannabidiol and clobazam in a phase 1 healthy volunteer trial. *Epilepsia*. 2018;59 (Supplement 3):S11. <http://dx.doi.org/10.1111/epi.14612>
14. Grayson L, Vines B, Nichol K, Szaflarski JP. An interaction between warfarin and cannabidiol, a case report. *Epilepsy & behavior case reports*. 2018;9:10-11. 10.1016/j.ebcr.2017.10.001 .
15. Gaston T, Cutter G, Liu Y, Perry L, Bebin E, Szaflarski J. Effect of pharmaceutical formulation of purified cannabidiol (CBD) on seizure frequency and severity is independent of drug-drug interactions with other anti-epileptic drugs (AEDS). *Neurology Conference: 70th Annual Meeting of the American Academy of Neurology, AAN*. 2018;90(15 Supplement 1).
16. Bouquie R, Deslandes G, Mazare H, et al. Cannabis and anticancer drugs: societal usage and expected pharmacological interactions - a review. *Fundamental & clinical pharmacology*. 2018;32(5):462-484. 10.1111/fcp.12373
17. Blakey G, Sommerville K, Crockett J, Morrison G. Bidirectional drug-drug interactions with coadministration of cannabidiol and stiripentol or valproate in a phase 1 healthy volunteer trial. *Epilepsia*. 2018;59 (Supplement 3):S74-S75. <http://dx.doi.org/10.1111/epi.14612>
18. Ben-Menachem E, Gunning B, Arenas Cabrera CM, et al. A phase 2 trial to explore the potential for a pharmacokinetic drug-drug interaction with valproate when in combination with cannabidiol in adult epilepsy patients. *Epilepsia*. 2018;59 (Supplement 3):S51. <http://dx.doi.org/10.1111/epi.14612>
19. Alsherbiny MA, Li CG. Medicinal Cannabis-Potential Drug Interactions. *Medicines (Basel, Switzerland)*. 2018;6(1). 10.3390/medicines6010003
20. Neuman MG, Cohen LB. Medical cannabinoids-alcoholmisuse-herbal medication interactions. *Alcoholism: Clinical and Experimental Research*. 2017;41 (Supplement 1):125A. <http://dx.doi.org/10.1111/acer.13391>
21. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia*. 2017;58(9):1586-1592. 10.1111/epi.13852
22. Be aware that the use of tobacco, cannabinoids and smoking cessation may result in pharmacokinetic interactions with other drugs. *Drugs and Therapy Perspectives*. 2017;33(7):339-344. <http://dx.doi.org/10.1007/s40267-017-0410-1>
23. Geoffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015;56(8):1246-1251. 10.1111/epi.13060
24. Ranganathan M, Skosnik P, Hugueneel B, Williams A, Sewell RA, D'Souza D C. The interactions of cannabidiol and delta-9-tetrahydrocannabinol in humans. *Biological psychiatry*. 2014;1):266S. <http://dx.doi.org/10.1016/j.biopsych.2014.03.015>

25. Horn JR, Hansten PD. Drug interactions with Marijuana. *Pharmacy Times*. 2014;80(12).
26. Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. *European journal of clinical pharmacology*. 2013;69(4):825-834. 10.1007/s00228-012-1393-4
27. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience*. 2013;248:637-654. 10.1016/j.neuroscience.2013.04.034
28. Schulz S. MDMA & cannabis: a mini-review of cognitive, behavioral, and neurobiological effects of co-consumption. *Current drug abuse reviews*. 2011;4(2):81-86.
29. Anonymous. Drug interactions with cannabis. *Prescrire international*. 2011;20(115):100.
30. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clinical pharmacology and therapeutics*. 2011;90(6):844-851. 10.1038/clpt.2011.188
31. Drug interactions with cannabis. *Prescrire international*. 2011;20(115):100.
32. Spano MS, Fadda P, Fratta W, Fattore L. Cannabinoid-opioid interactions in drug discrimination and self-administration: Effect of maternal, postnatal, adolescent and adult exposure to the drugs. *Current drug targets*. 2010;11(4):450-461. <http://dx.doi.org/10.2174/138945010790980295>
33. Yamreudeewong W, Wong HK, Brausch LM, Pulley KR. Probable interaction between warfarin and marijuana smoking. *Annals of Pharmacotherapy*. 2009;43(7-8):1347-1353. <http://dx.doi.org/10.1345/aph.1M064>
34. Parrott AC, Milani RM, Gouzoulis-Mayfrank E, Daumann J. Cannabis and Ecstasy/MDMA (3,4-methylenedioxymethamphetamine): an analysis of their neuropsychobiological interactions in recreational users. *Journal of neural transmission (Vienna, Austria : 1996)*. 2007;114(8):959-968. 10.1007/s00702-007-0715-7
35. Patel S, Cravatt BF, Hillard CJ. Synergistic interactions between cannabinoids and environmental stress in the activation of the central amygdala. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2005;30(3):497-507. 10.1038/sj.npp.1300535
36. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life sciences*. 2004;74(11):1317-1324.
37. Haney M, Bisaga A, Foltin RW. Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology*. 2003;166(1):77-85. 10.1007/s00213-002-1279-8
38. Bielenberg J. Cannabis. 1. Effects of cannabinoids on the central nervous system. 2. Interactions with drugs. [German]. *Arztezeitschrift fur Naturheilverfahren und Regulationsmedizin*. 2003;44(12):907-912.

39. Welch SP, Eads M. Synergistic interactions of endogenous opioids and cannabinoid systems. *Brain research*. 1999;848(1-2):183-190. 10.1016/s0006-8993(99)01908-3
40. Manzanares J, Corchero J, Romero J, Fernandez-Ruiz JJ, Ramos JA, Fuentes JA. Pharmacological and biochemical interactions between opioids and cannabinoids. *Trends in pharmacological sciences*. 1999;20(7):287-294.
41. Stoll AL, Cole JO, Lukas SE. A case of mania as a result of fluoxetine-marijuana interaction. *The Journal of clinical psychiatry*. 1991;52(6):280-281.
42. Foltin RW, Fischman MW, Pedroso JJ, Pearson GD. Marijuana and cocaine interactions in humans: cardiovascular consequences. *Pharmacology, biochemistry, and behavior*. 1987;28(4):459-464.
43. Vieweg WV, Hillard JR. Adverse interactions of cannabis with psychotropic medicines. *Psychiatric medicine*. 1986;4(1):69-77.
44. Hollister LE. Interactions of cannabis with other drugs in man. NIDA research monograph. 1986;68:110-116.
45. Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *The American journal of psychiatry*. 1983;140(2):243-244. 10.1176/ajp.140.2.243
46. Hatoum NS, Davis WM, Elsohly MA, Turner CE. Cannabichromene and delta 9-tetrahydrocannabinol: interactions relative to lethality, hypothermia and hexobarbital hypnosis. *General pharmacology*. 1981;12(5):357-362.
47. Benowitz NL, Nguyen TL, Jones RT, Hering RI, Bachman J. Metabolic and psychophysiologic studies of cannabidiol-hexobarbital interaction. *Clinical pharmacology and therapeutics*. 1980;28(1):115-120. 10.1038/clpt.1980.139
48. Consroe P, Carlini EA, Zwicker AP, Lacerda LA. Interaction of cannabidiol and alcohol in humans. *Psychopharmacology*. 1979;66(1):45-50.
49. Singh PP, Das PK. Studies on the interactions of copper and cannabis. *Psychopharmacology*. 1978;56(3):309-316.
50. Singh PP, Bhattacharya SK, Das PK. Interaction of cannabis, reserpine & chlorpromazine on body temperature & mechanism of hyperthermic response to cannabis in tolerant albino rats. *Indian journal of experimental biology*. 1978;16(3):326-329.
51. Segal M, Edelstein EL, Lerer B. Interaction between delta-6-tetrahydrocannabinol (delta-6-THC) and lithium at the blood brain barrier in rats. *Experientia*. 1978;34(5):629.
52. Munson AE, Sanders VM, Bradley SG, Loveless SE, Harris LS. Lethal interaction of bacterial lipopolysaccharide and naturally occurring cannabinoids. *Journal of the Reticuloendothelial Society*. 1978;24(6):647-655.
53. Kaymakcalan S. Pharmacological similarities and interactions between cannabis and opioids. *Advances in the biosciences*. 1978;22-23:591-604.