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July 6, 2016

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Gerd W. Clabaugh, Director
Iowa Department of Public Health
Lucas Office Building
Des Moines IA 50319

Re: Report FY 2016 - Clinical Trials of Cannabidiol

Dear Members of the Iowa General Assembly and Director Clabaugh:

Pursuant to 2014 Iowa Acts, Chapter 1125 (SF 2360), enclosed is the report on Clinical Trials of Cannabidiol.

If there are any questions concerning this report, please do not hesitate to contact us.

Sincerely,

Robert Donley

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Enclosure
cc: Robin Madison, LSA
Legislative Liaisons
Legislative Log

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June 29th, 2016
University of Iowa

Jennifer Vermeer
Assistant Vice-President for Health Policy and Population Health

Re: **2016 Report to the Department of Public Health and the Iowa General Assembly**

2014 Systematic Review

A thorough systematic review of the medical literature was published in 2014 by the Cochrane Collaboration to evaluate the scientific evidence for Cannabinoids used to treat epilepsy.[1] They identified four randomized controlled studies that had used cannabinoids to treat epilepsy and these four studies had a total of 48 patients.[2-5] The systematic review stated that "No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients generally for short periods of time, and so the safety of long term cannabidiol treatment cannot be reliably assessed." There were 15 patients in the Cunha study from 1980 and they had received 200 to 300 mg of cannabidiol daily or a placebo.[3] The patients tolerated the medication for up to 4.5 months without toxicity, and 4 of the 8 who received the drug had a good response in decreasing seizures, 3 had some response and one had no improvement in seizure activity. The study by Ames in 1985 had 12 patients who received 200 to 300 mg of cannabinol daily or placebo.[2] After 4 weeks of treatment there was no difference in seizure frequency between the placebo and the treatment group. Mechoulam in 1978 had 9 patients randomized to placebo or cannabidiol.[4] Two of the four patients with cannabidiol showed some improvement in seizure control, but none of the placebo group had improvement. The fourth trial was unpublished data from 1990 by Trembly.[5] The unpublished abstract indicated that in their 12 patients no statistics had been done, but there was some improvement. One of the authors in a text book referred to this same study and said that 10 of the 12 subjects had no improvement in seizure character or frequency. Based on these four studies the authors said no reliable conclusions can be made regarding the efficacy of cannabidiol in epilepsy.

Recent Publications and additions since the last review submitted July 2015:

No new randomized controlled clinical trials have been published since the Cochrane review that mentions the trials – published in 2014, however, the following information is now available :

- GW Pharmaceuticals has done a press release about its results on Epidiolex for both Dravet syndrome and Lennox Gastaut syndrome: The details of these are to be published in a peer reviewed journal but in short the press release indicated:
  - The study for Dravet syndrome is a Phase 3 randomized study with 120 patients divided into

two arms, Epidiolex (CBD) 20mg/kg/day (n=61) and placebo (n=59). Epidiolex or placebo was added to current anti-epileptic drug (AED) treatment regimens. On average, patients were taking approximately 3 AEDs, having previously tried and failed an average of more than 4 other AEDs. The average age of trial participants was 10 years and 30 percent of patients were less than 6 years of age. The median baseline (before the study started) convulsive seizure frequency per month was 13. Study results showed that Epidiolex produced a median reduction in convulsive seizure frequency of 39% (from 13 down to 8 seizures per month) compared with 13% for placebo (from 13 down to 11 per month) assessed over the entire treatment period (which included the initial dose escalation period). Epidiolex was generally well tolerated and the most common adverse effects were consistent with previous data disclosures from the expanded access program.

  - For the Lennox Gastaut study per the press release: The study randomized 171 patients, with 86 in the 20 mg/kg CBD treatment group and 85 in the placebo group. The primary efficacy endpoint (benefit) of the study was the comparison between the reduction in monthly drop seizures across the entire treatment period, including the initial dose escalation. In the CBD group, the median drop seizure frequency reduction was 44%, compared with 22% in the placebo group (p=0.0135). A series of secondary endpoints also reinforced the overall effectiveness observed with CBD. From the safety point of view, CBD was reasonably well tolerated, with no unexpected new adverse events emerging.

- An open label study (where subjects knew what treatment they were receiving – which can sometimes bias the results) was published by Devinsky and coworkes in Lancet in 2016 (March). Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis, and 137 (64%) patients were included in the efficacy analysis. In the safety group, 33 (20%) patients had Dravet syndrome and 31 (19%) patients had Lennox-Gastaut syndrome. The remaining patients had intractable epilepsies of different causes and type. Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death-a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). The median monthly frequency of motor seizures was 30.0 (IQR 11.0-96.0) at baseline and 15.8 (5.6-57.6) over the 12 week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR 0-64.7).

- Similar results were published by Dr Devinsky in another journal, the New England Journal of Medicine in January 2016 from this same open label data.

- In August 2015, The Massachusetts general group presented their open label data using Epidiolex on 25 patients suggesting an interaction between Clobazam and Epidiolex causing increased side effects of sedation from Clobazam

These data would suggest that there might be a modest reduction in the frequency of seizures when CBD oil is used in the purified form that was available in these trials. However, there are still 11 ongoing trials that will provide additional valuable information and these trials are listed below. The CBD does often have adverse effects with Devinsky indicating that about 80% of the subjects receiving CBD had an adverse effect from the medication, although only 30% of them were serious adverse events.

Clinical Studies Currently Being Conducted

Study List: The following 11 studies are currently recruiting patients for epilepsy, several studies from last year's list have been completed and are in the process of being published and they are detailed above.

Study 1:

- Title: The Use of Medicinal Cannabinoids as Adjunctive Treatment for Medically Refractory Epilepsy
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy, Unspecified, Refractory (Medically)
- Interventions: Drug: Medical Cannabis
- URL: https://ClinicalTrials.gov/show/NCT02523183

Study 2:

- Title: Epidiolex and Drug Resistant Epilepsy in Children
- Recruitment No Results Available
- Conditions: Epilepsy
- Interventions: Drug: Cannabidiol (Epidiolex)
- URL: https://ClinicalTrials.gov/show/NCT02397863

Study 3:

- Title: Cannabidiol (CBD) and Pediatric Epilepsy
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Cannabidiol | Tetrahydrocannabinol
- URL: https://ClinicalTrials.gov/show/NCT02447198

Study 4:

- Title: Genetic Analysis Between Charlotte's Web Responders Versus Non- Responders in a Dravet Population
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Dravet Syndrome
- Interventions:
- URL: https://ClinicalTrials.gov/show/NCT02229032

Study 5:

- Title: An Open-label Extension Trial to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and Cannabidiol in Patients With Epilepsy
- Recruitment: Not yet recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02607904

Study 6:

- Title: A Randomized Controlled Trial to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and Cannabidiol in Patients With Epilepsy

- Recruitment: Not yet recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: GWP42003-P|Drug: Placebo
- URL: https://ClinicalTrials.gov/show/NCT02607891

Study 7:

- Title: A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy|Dravet Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo Control
- URL: https://ClinicalTrials.gov/show/NCT02224703

Study 8:

- Title: A Randomized Controlled Trial to Investigate Possible Drug-drug Interactions Between Clobazam and Cannabidiol
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: Placebo|Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02565108

Study 9:

- Title: A Study of GWP42006 in People With Focal Seizures - Part B
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy|Focal Seizures
- Interventions: Drug: GWP42006|Drug: Placebo Control
- URL: https://ClinicalTrials.gov/show/NCT02365610

Study 10:

- Title: An Open-label Extension Trial to Investigate Possible Drug-drug Interactions Between Clobazam and Cannabidiol
- Recruitment: Not yet recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02564952

Study 11:

- Title: A Randomized Controlled Trial of Cannabidiol (GWP42003-P, CBD) for Seizures in Tuberous Sclerosis Complex.
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Tuberous Sclerosis Complex|Seizures
- Interventions: Drug: GWP42003-P|Drug: Placebo
- URL: https://ClinicalTrials.gov/show/NCT02544763

References

1. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2014;3:CD009270.
2. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. S Afr Med J. 1986;69(1):14.
3. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980;21(3):175-85.
4. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften. 1978;65(4):174-9.
5. Trembly B, Sherman M. Double-blind clnicial study of cannabidiol as a secondary anticonvulsant. Marijuana '90 International Conference on Cannabis and Cannabinoids; July 8-11, 1990; Kolympari, Crete: International Association for Cannibinoid Medicens; 1990. p. 5.
6. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy & Behavior. 2015;45(0):49-52.
7. Hussain SA, Zhou R, Jacobson C, Weng J, Cheng E, Lay J, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox–Gastaut syndrome. Epilepsy & Behavior. 2015;47(0):138-41.
8. Mathern GW, Beninsig L, Nehlig A. Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: Result of Epilepsia's survey. Epilepsia. 2015;56(1):1-6.
9. Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia. 2014;55(6):783-6.
10. Phelps N. Dronabinol for emotion-induced reflex epilepsy. Journal of Pharmacy Practice. 2013;26(3):343-4.
11. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy & Behavior. 2013;29(3):574-7.
12. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Twelfth Eilat Conference (EILAT XII). Epilepsy Research. 2015;111(0):85-141.
13. Cilio MR, Thiele EA, Devinsky O. The case for assessing cannabidiol in epilepsy. Epilepsia. 2014;55(6):787-90.
14. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802.
15. Fernandez-Ruiz J, Sagredo O, Pazos MR, Garcia C, Pertwee R, Mechoulam R, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? Br J Clin Pharmacol. 2013;75(2):323-33.
16. Hadland SE, Knight JR, Harris SK. Medical Marijuana: Review of the Science and Implications for Developmental-Behavioral Pediatric Practice. Journal of Developmental & Behavioral Pediatrics. 2015;36(2):115-23.
17. Jones N, Hill A, Hill T, Peres I, Hadid R, Wright S, et al. Assessment of the Anticonvulsant Effects and Tolerability Profile of Cannabidiol: GW Pharmaceuticals' Preclinical Program (I6-5A). Neurology. 2015;84(14 Supplement).
18. Jones NA, Glyn SE, Akiyama S, Hill TDM, Hill AJ, Weston SE, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. Seizure. 2012;21(5):344-52.
19. Knezevicch E, Wu Y. Marujuana for the treatment of seziure disorders. US Pharmacist. 2015;40(1):24-8.
20. Robson PJ. Therapeutic potential of cannabinoid medicines. Drug Test Anal. 2014;6(1-2):24-30.
21. Szaflarski JP, Martina Bebin E. Cannabis, cannabidiol, and epilepsy — From receptors to clinical response. Epilepsy & Behavior. 2014;41(0):277-82.
22. Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 2012;5(5):529-52.
23. Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, Miller I, Flamini R, Wilfong A, Filloux F, Wong M, Tilton N, Bruno P, Bluvstein J, Hedlund J, Kamens Ret al. Cannabidiol in

patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016 Mar;15(3):270-8. 24.
24. Friedman D, Devinsky O. Cannabinoids in the Treatment of Epilepsy. N Engl J Med. 2016 Jan 7;374(1):94-5.
25. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015 Aug;56(8):1246-51.

Sincerely,

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