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

Re: Report FY 2015 - 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 25, 2015

Dr. Charuta Joshi, MBBS,
Professor in Pediatric Neurology
and
Jennifer Vermeer
Assistant Vice-President for Health Policy and Population Health

Re: 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 The fourth trial was unpublished data from 1990 by Trembly.[5] The unpublished abstract indicated that in their 12 patients no statistics had been done, but there was some improvement.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

No new randomized controlled clinical trials have been published since 2013 when the above systematic review was completed. Press and colleagues[6] did conduct a retrospective chart review of children and adolescents who were given oral cannabis extracts in a Colorado tertiary epilepsy center. The review identified 75 individuals that had received the medication and 57% reported an improvement in seizure control and 33% had a greater than 50% reduction in seizure activity. It was interesting that the responder rate was 47% if the family moved to Colorado to receive the medication, but the responder rate was only 22% for those that already lived in Colorado. The type of epilepsy affected the responder rate, 23% for those with Dravet syndrome, 0% for those with Doose, and 89% for those with Lennox-Gastaut Syndrome; all 3 are special types of intractable epilepsy. Additional benefits included improved behavior/alertness (33%), improved language (10%) and improved motor skills (10%). Adverse events occurred in 44% of

patients including increased seizures (13%) and somnolence/fatigue (12%). The authors indicated there were some challenges with the retrospective review and there were possible confounding factors (conditions that can alter the interpretation of the results) so they urged further controlled blinded studies are still needed.

Hussain and coworkers[7] chose to do an online survey to identify information from parents of children with epilepsy associated with infantile spasms, Lennox-Gastault syndrome or Dravet Syndrome and who had received cannabinoid products. There were 117 survey respondents that met the qualifications. The vast majority of respondents reported using cannabidiol enriched oil-based extracts that were typically administered 2 to 3 times per day. Results indicated that five patients had an increase in seizure frequency, 11 reported no change and 100 had a decrease in seizure frequency with 16 (14%) stating they were seizure free. The authors concluded that the study suggested a possible role for cannabidiol in the treatment of these disorders, but due to potential confounding associated with the survey study design it did not provide compelling evidence for efficacy or safety.

Mathern and colleagues[8] who are editors with the journal *Epilepsia* conducted an online survey in 2014 seeking opinions about the use of medical marijuana and specifically cannabidiol for the treatment of epilepsy. The survey had eight questions, four that asked if there was sufficient evidence on both the safety and efficacy of medical marijuana and if they would recommend that cannabidiol should be made readily available and if they would recommend it to treat a patient with intractable epilepsy. The other four questions focused on the demographics and occupation of the respondent. There were 776 people who completed the survey. Patients from North America made up 58% of the respondents and 22% were specialists in epilepsy or general neurologists from Europe or North America. A minority of these medical specialists said there was sufficient safety data (34%) and efficacy data (28%) and only 48% would advise using medical marijuana in severe epilepsy. In contrast, nearly all patients said there was sufficient safety data (96%) and efficacy data (95%) and 98% would recommend the treatment. General physicians, basic researchers, nurses and allied health professionals were somewhere in between with sufficient safety data (70%), efficacy date (71%) and 83% would recommend treatment. About 78% of all respondents said that medical marijuana should be made available.

There have been additional case reports published that advocate the use of cannabidiol.[9-11] About 18 of these 21 cases have shown some benefit. There have been numerous reviews that discuss the role of cannabidiol in the treatment of epilepsy, but none have presented any new evidence.[12-22]

Clinical Studies Currently Being Conducted

The encouraging news is that there are 14 randomized controlled studies that are listed on the ClinicalTrials.gov website that report studies that are currently being done looking at cannabidiol use in patients with epilepsy:

Study 1:

- Title: Cannabidiol (CBD) to 25 Patients (Aged 2 Years - 19 Years) With Drug Resistant Epilepsy
- Sponsor: University of Utah
- Recruitment: Recruiting
- Conditions: Epilepsy
- Interventions: Drug: Cannabidiol
- URL: http://ClinicalTrials.gov/show/NCT02286986

Study 2:

- Title: A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome
- Sponsor: GW Research Ltd
- Recruitment: Recruiting

- Conditions: Epilepsy|Dravet Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo Control
- URL: http://ClinicalTrials.gov/show/NCT02224703

Study 3:

- Title: Antiepileptic Efficacy Study of GWP42003-P in Children and Young Adults With Dravet Syndrome
- Sponsor: GW Research Ltd
- Recruitment: Recruiting
- Conditions: Epilepsy|Dravet Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo control
- URL: http://ClinicalTrials.gov/show/NCT02091375

Study 4:

- Title: A Dose-ranging Pharmacokinetics and Safety Study of GWP42003-P in Children With Dravet Syndrome
- Sponsor: GW Research Ltd
- Recruitment: Active, not recruiting
- Conditions: Epilepsy|Dravet Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo control
- URL: http://ClinicalTrials.gov/show/NCT02091206

Study 5:

- Title: Treatment of Drug Resistant Epilepsy
- Sponsor: University of Florida
- Collaborator: James and Esther King Biomedical Research Program
- Recruitment: Available
- Conditions: Epilepsy
- Interventions: Drug: Epidiolex®|Other: Blood Test
- URL: http://ClinicalTrials.gov/show/NCT02461706

Study 6:

- Title: Cannabidiol (CBD) and Pediatric Epilepsy
- Sponsor: University of Colorado, Denver
- Recruitment: Not yet recruiting
- Conditions: Epilepsy
- Interventions: Cannabidiol |Tetrahydrocannabinol
- URL: http://ClinicalTrials.gov/show/NCT02447198

Study 7:

- Title: Cannabidiol Oral Solution in Pediatric Subjects With Treatment- Resistant Seizure Disorders
- Sponsor: INSYS Therapeutics Inc
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Seizures
- URL: http://ClinicalTrials.gov/show/NCT02324673

Study 8:

- Title: Cannabidiol Oral Solution as an Adjunctive Treatment for Treatment-resistant Seizure Disorder
- Sponsor: INSYS Therapeutics Inc
- Recruitment: Not yet recruiting
- Conditions: Seizures
- Interventions: Drug: Cannabidiol Oral Solution
- URL: http://ClinicalTrials.gov/show/NCT02318602

Study 9:

- Title: Epidiolex and Drug Resistant Epilepsy in Children
- Sponsor: Georgia Regents University
- Collaborator: State of Georgia
- Recruitment: Available

- Conditions: Epilepsy
- Interventions: Drug: Cannabidiol (Epidiolex)
- URL: http://ClinicalTrials.gov/show/NCT02397863

Study 10:

- Title: A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults
- Sponsor: GW Research Ltd
- Recruitment: Recruiting
- Conditions: Epilepsy|Lennox-Gastaut Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo control
- URL: http://ClinicalTrials.gov/show/NCT02224560

Study 11:

- Title: A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults
- Sponsor: GW Research Ltd
- Recruitment: Recruiting
- Conditions: Epilepsy|Lennox-Gastaut Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo Control
- URL: http://ClinicalTrials.gov/show/NCT02224690

Study 12:

- Title: An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet or Lennox-Gastaut Syndromes
- Sponsor: GW Research Ltd
- Recruitment: Not yet recruiting
- Conditions: Epilepsy|Dravet Syndrome|Lennox-Gastaut Syndrome
- Interventions: Drug: GWP42003-P
- URL: http://ClinicalTrials.gov/show/NCT02224573

Study 13:

- Title: Cannabidiol Oral Solution as an Adjunctive Therapy for Treatment of Subjects With Inadequately Controlled Dravet Syndrome
- Sponsor: INSYS Therapeutics Inc
- Recruitment: Not yet recruiting
- Conditions: Dravet Syndrome
- Interventions: Drug: Cannabidiol Oral Solution|Drug: Placebo Solution
- URL: http://ClinicalTrials.gov/show/NCT02318563

Study 14:

- Title: Cannabidiol Expanded Access Study in Medically Refractory Sturge-Weber Syndrome
- Sponsor: Anne Coni, MD
- Collaborators: GW Pharmaceuticals Ltd and Faneca 66 Foundation
- Recruitment: Recruiting
- Conditions: Sturge-Weber Syndrome
- Interventions: Drug: Cannabidiol
- URL: http://ClinicalTrials.gov/show/NCT02332655

Sincerely,

Ronald A. Herman

Ron Herman

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.