Patterns of "Hemp Extract" Usage by Utah Patients with Intractable Epilepsy: Results of the Utah Hemp Extract Application Review and Survey

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Abstract:

OBJECTIVE: To better understand patterns of use, access limitations, and effects of hemp extract on Utah patients with intractable epilepsy to improve patient care and inform policymakers.

BACKGROUND: Since the 2014 enactment of Utah House Bill 105, allowing use of hemp extract for intractable epilepsy, many families turned to non-pharmaceutical cannabis products made by marijuana/hemp growers and producers with minimal standardization or usage guidelines (termed *vernacular* products). In conjunction with the Utah Department of Health registry, the University of Utah division of pediatric neurology was awarded the task of studying the effects of hemp extract usage and attempting to better understand the experience of these patients.

METHODS: Three overlapping datasets were employed through retrospective, observational or survey designs. The "total dataset" provides a complete count of original hemp extract applications and renewals since HB 105 (n=262). "Application review dataset" assessed basic usage patterns, effect on seizures, and other benefits or side effects (n=140). More detailed data was collected from a subset of patients who replied to a voluntary 12 item usage survey (n=46), named "survey dataset".

RESULTS: A total of 262 Utah patients have obtained hemp extract registration cards since July 1, 2014, and 124 remain active as of April 30, 2018. Most cited reasons for not renewing were lack of benefit, cost, or access challenges. Not all patients commented on or responded to every item of interest, thus limiting results. For the "application review dataset," median patient age was 17 years with an even male/female split. Of the 63 applications reporting seizure effects, 45 (71%) endorsed improved seizure burden, including complete seizure control in one child. In the "survey dataset" of 38 patients who provided enough data to analyze, 17 (85%) of the 20 pediatric patients and 10 (56%) of the 18 adult participants reported improved seizure control. A minority of patients (18% of reporters in the "application review dataset", and 22% of reporters in the "survey dataset") described adverse effects including diarrhea, fatigue, or increased seizures, which were often transient. Other benefits beyond seizure control such as improved sleep, alertness, and mood were endorsed by many (48% of reporters in the "application review dataset", and 66% of reporters in the "survey dataset"). In the "application review dataset" only 17% (22/133 of applicants who had started using hemp extract) could report an actual product concentration versus 56% (23/41 respondents had started using hemp extract) in the "survey dataset." Most frequent dosing was twice daily, average usage duration was 14 months, and average cost was $177/month (range $40-500).

CONCLUSIONS: The majority of Utah patients with intractable epilepsy using hemp extract reported improved seizure control with few, generally transient, side effects. Many endorsed more sustained benefits beyond seizure control. Results are limited by unconfirmed hemp product contents, as well as responder and self-reporting bias, but can help inform patient care, future research, and legislation regarding use of hemp extract for epilepsy, namely the need for standardized hemp products

Introduction and Objectives:

In early 2014 the Utah State Legislature, at the urging of constituents, enacted HB 105 which allows parents and guardians of children and adults with severe intractable epilepsy to legally possess and administer "hemp extract" to their child in the hopes of improving their child's seizure control and quality of life. In so doing, the legislature was responding to the plea from families of children with severe intractable epilepsy who wished to provide their children with access to cannabidiol (CBD)-rich extract of cannabis that had been widely reported in social media to be miraculously effective in the improvement of a few widely publicized cases of intractable childhood epilepsy.[1-3] However, the fact was then and remains now that there is limited scientific information regarding the efficacy and risks of "medical marijuana" in the treatment of children with epilepsy.[4-8]

HB 105 required that the Utah Department of Health (UDOH) maintain a database of the registrants and it authorized the department to share records with a higher education institution for the purpose of studying hemp extract. In 2016, Utah lawmakers approved HB 58, which required that UDOH issue a request for proposals (RFP) from higher education institutions to conduct a study of hemp extract. The RFP was awarded to the University of Utah.

This mandate to study the benefits and effects of "hemp extract" in Utah provides a unique but significantly challenging opportunity. By ascertaining this cohort, we may be better able to assess patterns of use and measure the potential benefits and adverse effects of hemp extract use for the treatment of intractable epilepsy in Utah. However, the information to be gained is significantly hampered by the inherent limitations of research based on surveys and questionnaires generated primarily by self-report.[9]

Background:

The increase in popular interest about medical marijuana and cannabidiol, in particular as it relates to the treatment of epilepsy, began in 2011. On June 4, 2011, the parents of Jayden David, a child with severe intractable epilepsy due to a relatively rare genetic condition known as Dravet syndrome, gave him his first dose of a reportedly "CBD rich Marijuana extract."[1] His parents reported that "(The) first day I gave him medical marijuana, thank God. (It was) the first day he went seizure free in his life."[1] This extraordinary outcome was rapidly disseminated by social media. Not long afterwards, in 2013, the nearly miraculous experience of a child from Colorado, Charlotte Figi, was widely publicized on YouTube, and other social media platforms.[2,3] This child also suffered from very severe uncontrolled epileptic seizures caused by Dravet syndrome. According to her parents, Charlotte had responded to a form of medical marijuana consisting of an extract high in CBD and low in tetrahydrocannabinol (THC). By their reports, Charlotte had gone from a severely encephalopathic state associated with nearly continuous seizure activity to a happy, engaged little girl who could participate in age appropriate activities. In addition, her parents reported that in contrast to standard pharmaceutical anti-epileptic medications, which in their estimation caused severe side effects, the cannabis extract actually resulted in a variety of beneficial effects such as improved behavior, alertness, mood and in a reduction in autistic behaviors.[2,3]

Fueled by the efficiency of modern social media, the public response to these anecdotal experiences was both dramatic and rapid. The high visibility of this child and a few others then culminated in a CNN Special which aired in August 2013. In this program, reportedly entitled "Why I Changed my Mind on Weed " [https://www.cnn.com/2013/08/08/health/gupta-changed-mind-marijuana/index.html],[2] Dr. Sanjay Gupta appeared to publicly endorse the use of medical marijuana for children with intractable epilepsy. This particular incident then provided what could be perceived of as an official stamp of approval from the medical establishment and more widely opened the door for discussion.

Understandably, many parents of children with intractable epilepsy throughout the US were interested in obtaining CBD-rich medical marijuana products for their own children. However, this was complicated by the regulations regarding cannabis products in the United States. According to the Controlled Substance Act of 1970, all cannabis products fall under Schedule I such that possession and use is in fact illegal in the United States.[10] However, individual states have enacted state-specific legislations liberalizing or legalizing the production and/or use of cannabis products within the confines of the state. As a consequence, , specific regulation regarding the use of cannabis ("medical marijuana") products for the treatment of various medical ailments varies widely from state to state[10-16] , resulting in considerable confusion regarding the enforcement of discrepant regulations within a given jurisdiction.

Before 2014, any use of cannabis products in Utah for any reason was illegal by State and Federal law.[10] This led various advocacy groups to petition the legislature to legalize access to high-CBD, low-THC cannabis products for families of children with intractable epilepsy. Specifically, a collective of patients with epilepsy and parents of children with intractable epilepsy formed a group called "HOPE 4 CHILDREN with Epilepsy." They partnered with a marijuana growing company from Colorado, known then as the Stanley Brothers, to petition the Utah Legislature to pass a provision allowing Utah patients with epilepsy to gain legal access to CBD rich "hemp oil." This bid ultimately led to the passage and implementation of HB 105 as noted above.

Since the implementation of HB 105 in July 2014, a total of 262 patients had obtained hemp extract registration cards as of April 30, 2018. The initial application fee for the card is $200 and the renewal fee is $50. Cards expire after one year unless renewed. As of April 30, 2018, there were 124 patients with active hemp extract registration cards in Utah. To date, relatively little information is available regarding the experience of these patients

Despite the popularity and public enthusiasm about cannabis extracts for the treatment of children with epilepsy, there is limited scientific data that actually supports such an approach.[17-20] Prior to the last two years, only four small clinical trials with ample limitations pertaining to cannabis use in epilepsy had been published.[20-22] These early results were difficult to assess, applied to only a small number of patients, and were therefore of marginal scientific merit.[20] Additionally, the products and doses varied widely and were minimally standardized.[23,24] Meanwhile, reports from patients using CBD-predominant products in California suggested that a number of patients responded well with surprising reductions in seizure frequency and improvements in self-reported quality of life.[25] These contrasting reports added to the confusion surrounding the use of medical marijuana for epilepsy.

While the above referenced anecdotal reports suggested possible benefits of CBD in the treatment of epilepsy, scientific reports from states and countries in which marijuana is either liberalized (for medical use) or legalized (for medical and recreational use) indicate that access to cannabis products can have substantial negative consequences, both in terms of personal side effects as well as potential adverse societal effects.[26-32] For example, legalization in Colorado has been accompanied by alarming increases in admissions of children to emergency departments and intensive care units for acute THC intoxication.[27,30-32] Similarly, concerning reports from the Netherlands and other countries have documented the increased risk of psychosis and mental health concerns among adolescent cannabis users.[33-38] Usage of medical marijuana in MS has been consistently associated with a variety of cumulative neuropsychological problems and with broad ranging neurological adverse effects further confirmed by functional MRI.[39-41] Thus, while data supporting the use of vernacular medical marijuana for epilepsy is quite limited, scientific information demonstrating widespread adverse effects of

various marijuana products at the personal and societal levels is more compelling, particularly when it comes to impact on children and adolescents.[16,42-46]

Finally, these issues are even further complicated by the fact that "medical marijuana" is not "one thing."[5,15,17,44,47,48] The marijuana plant, *Cannabis sativa*, contains over 60 chemically related but distinct compounds known as cannabinoids.[14,49-53] The most prevalent of these in "recreational" marijuana products is the psychoactive chemical delta-9-tetrahydrocannabinol (THC).[14,54] However, varietals have been developed and refined that have high levels of another phytochemical, cannabidiol (CBD) and low levels of THC.[51,53,55,56] CBD, in contrast to THC, has no psychoactive properties and therefore likely has no abuse potential.[7] Besides these two, the marijuana plant also contains various concentrations of numerous other cannabinoids, many of which may have particular biological effects/properties in their own right.[50,53,55] Thus, any given product made by non-pharmaceutically regulated marijuana growers and producers (***vernacular*** products) could contain a complicated mixture of these various phytochemicals.[24,48,52,57,58] There are innumerable preparations, various ways of ingesting the products, quality control is extremely variable and consumers have limited ability to verify the relative purity, quality, reliability and safety of any one product.[23,24,52,57,58] In addition, medical marijuana treatments are not covered by insurance, can be very costly, and physicians are either reluctant or unable to provide guidance about their use.[17,44,47] Add to this the possibility of adverse effects, drug interactions, and the risk of discontinuing or not attempting scientifically proven effective treatments and the possible risks of medical marijuana usage become quite significant.[5,17,42,44,46,47]

Therefore, it is incumbent on the medical and public health community to better understand the potential risks and benefits inherent in the use of vernacular medical marijuana products for the treatment of epilepsy.[16,17,44,46,47,59] The implementation of HB 105 in Utah provides an opportunity to learn from such a societal experience. This executive summary documents the information gained from analysis of the information that exists regarding the experience of families of children and patients with intractable epilepsy who opted to obtain a Hemp Extract Registration Card through the Utah Department of Health.

Combining our clinical experiences with all of the risks, hopes, and complexities surrounding medical marijuana as outlined above, we aim to address the following hypotheses in this study on the use of hemp extract in Utah patients with intractable epilepsy:

1. Benefits from use of hemp extract are variable and unpredictable.
2. The majority of patients do not experience >90% seizure control
3. The majority of families who have started treatment with hemp extract will discontinue its use within one year.

4. The majority of patients will NOT be able to define "dose" of cannabidiol being administered to their family member in terms of milligrams (mg) of CBD per day or equivalent.
5 Discontinuation of treatment is most often due to lack of efficacy or cost considerations, rather than due to adverse effects.
6. Serious adverse effects are absent or very rare.
7. Rates of adverse effects overall are low and adverse effects are well tolerated and not a reason for medication discontinuation.
8. The majority of families report other perceived benefits separate from seizure control.

We hope that this analysis will allow for more informed patient care and decision making with respect to future legislation addressing medical marijuana usage and availability in the State of Utah.

Design/Methods:

Three overlapping datasets were employed for this study.

1. "**Total dataset":** This includes information from all patients obtaining a hemp extract registration card from the Utah Department of Health from July 2014 through April 2018. This group represents the scope of the total cohort. A retrospective, observational count of the total number of original applications and renewal applications was collected. Number of patients (n) in this cohort was 262.

2. **"Application review dataset"**: This subset of the "total dataset" consists of data from patients obtaining a hemp extract registration card from the Utah State Department of Health from July 2014 to May 2017. The details of their original application and renewal application, as outlined below, were analyzed after retrospective, observational review. Number of patients (n) in this cohort was 140.

   The following data was available for all of these registrants:
   a) Original patient/family application form (Appendix 1).
   b) Original Neurologist Certification Form (Appendix 1).

   For those patients renewing their registration card (required annually):
   a) Renewal application form (Appendix 2).
   b) Renewal Neurologist Certification Form (Appendix 2).

   Information requested in the above (see Appendix 1, 2 for details) includes:

   i) Information about the patient such as date of onset of epilepsy, type of seizures, frequency and previous treatments utilized (information requested from the certifying neurologists).
   ii) Information about products used: Name (s) of product(s) used, amounts ("doses") used.
   iii) Information regarding reported perceived clinical response to treatment with "hemp extract." Families are also queried by the Utah Department of Health about effect on seizures, occurrence and nature of adverse effects, and occurrence or not of any other perceived benefits.

3. **"Survey dataset"**: This second subset of the "total dataset" consists of data collected via survey from patients obtaining a hemp extract registration card from the Utah State Department of Health from July 2014 to October 2016. These patients were offered the opportunity to complete a mailed, non-validated 12 item questionnaire/survey (Appendix 3) asking more detail regarding their experience with hemp extract. This was in an effort to obtain more detailed information than afforded by the above mentioned documents obtained automatically with registration or renewal. Number of patients (n) in this cohort was 46.

IRB oversight and approval: Approval from the IRB at the University of Utah was sought for this project. The mandate to the Utah Department of Health (UDOH) from the Utah Legislature specifies that the effect of hemp extract be studied. This requires that the UDOH obtain information from families who have elected to obtain a hemp extract registration card. (See http://health.utah.gov/hempregistry/index.html for other details). This information was and continues to be collected by the UDOH independently from any specific IRB approval and was in effect required by state law.

In addition, as mentioned above, the large majority of the patients who are receiving a hemp extract product via this program are patients cared for by members of the Division of Pediatric Neurology at the University of Utah. This is because the majority of these patients are children, and the large majority of children with intractable epilepsy in Utah are cared for by our group. Therefore, for a large subset of these patients, the university's medical records necessarily contain information regarding the effects of hemp extract in these children and young adults. This information has been and continues to be collected in a non-standardized fashion by our neurology providers in the course of the standard and usual care of our patients.

We proposed to the IRB at the University of Utah that this existing information regarding hemp extract use for all patients who have received a hemp extract registration card from the UDOH would be reviewed and collated. In addition, we proposed we would review survey data (also existing data obtained from the UDOH) and existing data from our own medical records (not from other neurologists/physicians unless part of our own medical records). Because the data will be either de-identified when it is provided to us (the data provided for us from the UDOH) or will be gleaned from our own existing medical records, we sought a waiver of informed consent from our IRB, which was granted. The University of Utah IRB permitted the study to proceed as described with the stipulations defined above. It continues to provide human subjects research oversight on this project.

With the de-identified data from the UDOH, we will analyze patterns of use, costs, and will attempt when possible to correlate the responses described with hemp extract doses assessed as amount of CBD administered per day (in mg/kg/day). Descriptive statistics are used to describe the patterns of hemp extract use and corresponding clinical responses identified accordingly. Specifically, self-reported responses with respect to seizure occurrence, rate and nature of adverse effects and of any other reported benefits will also be analyzed using descriptive statistics. Other data points of interest will be reported using similar statistics.

Results:

Total dataset:

Since the implementation of HB 105 in July 2014, as of April 30, 2018, a total of 262 patients have obtained hemp extract registration cards (Table 1). Cards are active for one year and expire if not renewed. Of the 262 registrants, a total of 202 had held their registrations for at least one year as of April 30, 2018, and were eligible for renewal. Only 91 (45%) of these 202 renewed at least once. Of the 91 who renewed once, 62 were eligible for renewal a second time. Of the 62 eligible for renewal a second time, 38 (61%) renewed. Of the 38 eligible for renewal a third time, 11 (28%) renewed. A total of 124 cards are currently active in the state of Utah, either as originally issued cards in their first year or renewed cards.

Table 1.

Year	Number of Original Applications
2014	47
2015	80
2016	50
2017	66
2018 (as of 4/30/ 2018)	19
Total (n)	262

Application review dataset:

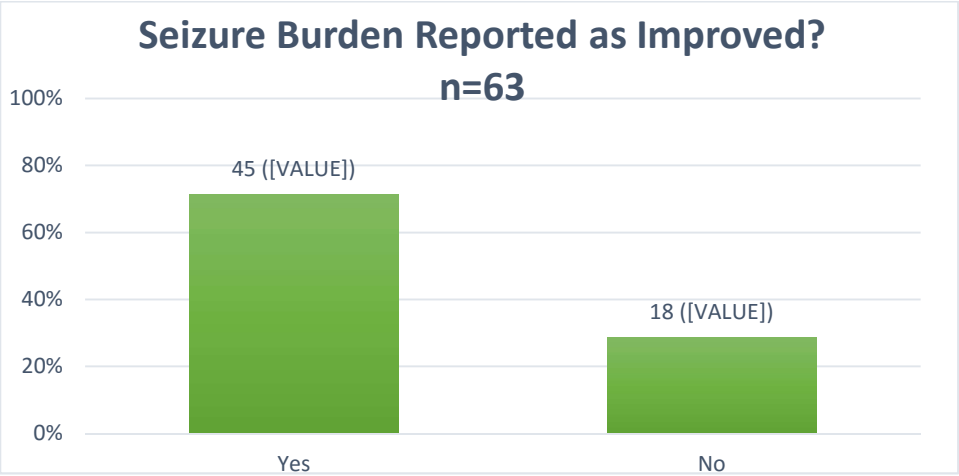
Applications of 140 patients registering between July 2014 and May 2017 were reviewed and included in the application review dataset analysis. Seven of these patients had not yet started hemp extract at time of review (Jan 1, 2018) and were excluded from analyses pertaining to seizure effect, side effects, and other benefits, but were included in demographic evaluations if available. As this was a retrospective, observational review we could not control for the fact that some applications were incomplete and missing details of interest to our investigation. This explains why most of the various data points have differing number of responders used as the denominator in the percentage calculation.

Age and gender were not reported on 20 of the 140 applications reviewed. Of the 120 with data on these points, the average patient age was 20 years (SD 15) and median age was 17 years (range 1-74 years) at time of analysis (1/1/2018). This breaks down to 65 children under 18 years of age and 55 adults. Gender was evenly distributed with 60 (50%) males and 60 (50%) females (n=120).

Within this subset only 31 (27%) of the 116 patients eligible to renew their registrations at least once did so. This is a lower number compared to that reported in total dataset for at least one hemp extract card renewal. Some of these patients could have renewed after the time of our application analysis and their renewal would therefore not be counted in this dataset. Only 10 of the 116 patient applications who were eligible to renew at least once indicated one or more reasons for not renewing their hemp extract registration card. All 10 cited lack of benefit, two also cited unspecified adverse effects, and one also cited cost as reasons for not renewing.

Only 63 (47%) of the 133 applications of patients who had started using hemp extract reported anything about impact on seizures. Of these 63 applications, 45 (71%) endorsed improved seizure burden, including complete seizure control in one pediatric patient (Figure 1). Fourteen renewal applications estimated seizure counts before and after taking hemp extract. The estimated seizure reduction ranged from 8-100%, with the majority reporting 60-85% reduction. These patients also described seizure type, and 7 (50%) of these 14 participants reported convulsive seizures as their primary seizure type.

Figure 1.



Sixty-one (45%) of the 133 applicants who had started using hemp extract reported any information about side effects or other benefits beyond seizure control while using hemp extract. Eleven (18%) of these 61 applications described one or more adverse effects, while 50 (82%) reported no adverse effect. See Table 2 for breakdown of reported adverse effects. A number of adverse effects were described as mild or transient after dose changes and some patients reported more than one side effect. This break down was similar between the adult and pediatric populations.

Table 2.

Reported Adverse Effects? (n=61)	Total #	% of 61
Yes	11	18%
Diarrhea	3	5%
Change in Appetite	1	2%
Disrupted Sleep	1	2%
Fatigue	3	5%
Increased seizures	4	7%
Mouth swelling/Bleeding	1	2%
Balance Problems	1	2%
No	50	82%

Twenty-nine (48%) of the above described 61 patients who reported anything on side effects also endorsed other benefits separate from or in addition to impact on seizure burden. Most common reported benefits related to improved sleep, increased alertness, or better mood. A few adult participants reported reduced anxiety and an ability to reduce other seizure medications as a result of hemp extract; these benefits were not described in the younger cohort. Increased sociability and improvements in speech and language skills were described specifically within the pediatric population.

Finally, only 22 (17%) of the 133 patients who had started taking hemp extract reported an actual product concentration on their original or renewal application.

Survey dataset:

At the end of April 2017, 140 patients who had received a hemp extract registration card between July 1, 2014 and October 31, 2016 (and hence had been able to legally obtain and administer/use a hemp extract product for epilepsy for at least 6 months) were sent a survey as noted in the Designs and Methods section above. Technically, 168 patients had applied during this time frame, but 28 of the 168 patients with hemp cards issued before October 31, 2016 were initially missed and therefore only 140 surveys were mailed out. Of the 140 mailed surveys, 46 (33%) were completed and returned for our review.

Forty-one (89%) of these 46 respondents had started taking hemp extract and provided additional information. Age and gender were not available for three (7%) of the 41 respondents taking hemp extract and therefore only data from 38 patients were analyzed when comparing pediatric and adult data.

In this subset of 38 patients, 17 (85%) of the 20 pediatric patients and 10 (56%) of the 18 adult participants reported improvement in seizure burden (frequency and/or severity). Additional information regarding reported seizure effects are detailed in Figures 2 and 3.

Figure 2.

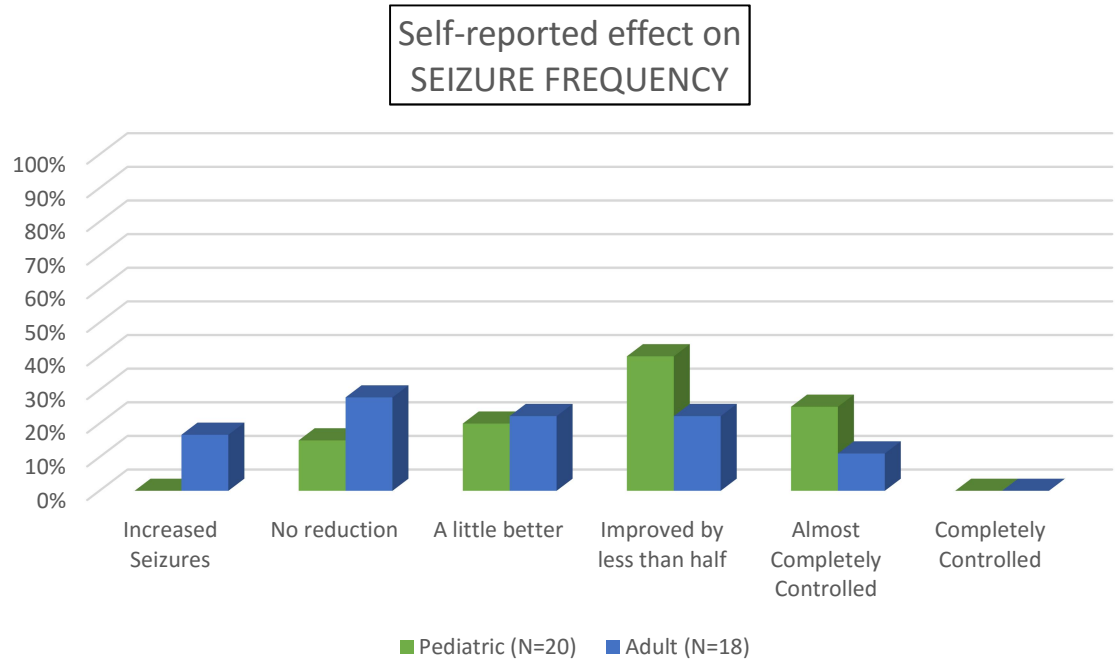
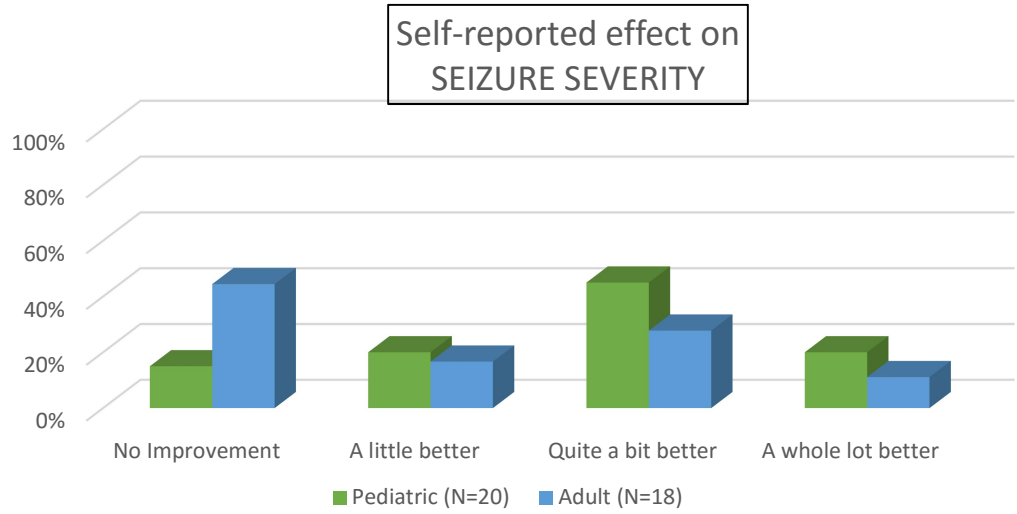


Figure 3.



Nine (22%) of the 41 survey respondents endorsed one or more adverse effects while taking hemp extract (Table 3). Meanwhile, 27 (66%) of the 41 survey respondents reported one or more beneficial effects while taking hemp extract (Table 4).

Table 3.

Adverse Effects Reported	Number (% of 41 respondents)
Any other adverse effect?	9 (22%)
Tired	3 (7%)
Diarrhea	3 (7%)
Decreased Appetite	2 (5%)
Increased Appetite	1 (2%)
Coordination Problems	1 (2%)
Moody	1 (2%)
Vomiting	0 (0%)

Table 4.

Beneficial Effects Reported	Number (% of 41 respondents)
Any other beneficial effect?	27 (66%)
Improved Sleep	16 (39%)
More Alert	14 (34%)
Happier	11 (27%)
Improved Speech	7 (17%)
More Social	6 (15%)

Thirteen (32%) of the 41 survey respondents using hemp extract reported that they had renewed their card at least once. The 28 (68%) of the 41 survey respondents who did not renew their card cited lack of efficacy, high cost, or difficulties with obtaining or administering the hemp extract product.

Regarding patterns of use, 33 (80%) of these 41 users reported knowing product concentration, but only 23 (56%) could provide an actual mg/mL concentration. Notably, this is a much higher percentage of patients able to report an actual concentration compared to the 17% of the application review dataset. The most prevalent product used was one produced by the Stanley brothers in Colorado, called "Charlotte's Web" (32 (78%) of the 41 respondents using hemp extract). Most common dosing was twice daily (20 (54%) of the 37 respondents who answered this question). Average usage duration was 14 months (range 1-36m) and average cost was $177 per month (range $40-500/month).

Key Findings/Discussion:

Acknowledging all of the limitations inherent in a study based on retrospective, observational, self-report[9] from patients and caregivers using a variety of disparate preparations at often unspecified doses, a number of key points can be gathered from this study.

First of all, many individuals paid a considerable amount of money out of pocket for access to a substance with limited scientific or medical support, but strong societal endorsement. This is an important factor, as it testifies to the power of community opinion and grassroots movement, in contrast to the public's relative skepticism and suspicion directed toward establishment medicine and the pharmaceutical industry.[3,60-62]

Secondly, the available data is sufficient to either support and/or prove our eight hypotheses. Specifically, the data indicates or suggests that:
1) Benefits from use of "hemp extract" were variable and unpredictable;
2) The majority of patients did not experience >90% seizure control;
3) The majority of families who started treatment with "hemp extract" discontinued its use within one year (*or at least choose not to renew their hemp extract registration*);
4) The majority of the "application review dataset" patients were not able to define the "dose" of cannabidiol administered to their family member in terms of milligram (mg) of CBD per day. However, just over half (54%) of the survey respondents were able to provide a concentration or daily mg dose.
5) Discontinuation of treatment was most often due to lack of efficacy or cost considerations rather than due to adverse effects;
6) No serious adverse effects were reported;
7) Rates of adverse effects overall were low and adverse effects did not appear to be a major reason for medication discontinuation;
8) Many patients or families (48% of the "application review" cohort and 66% of the survey respondents) reported other benefits beyond or in addition to seizure control.

We hypothesized that after a year most eligible patients/families would choose not to renew their registration cards. In fact, as shown in the "Total dataset", of the registrants eligible to do so at least once, only 45% actually renewed their registrations. Presumably a decision not to renew represented a perception that renewal was not worth the cost or effort. In other words, for a substantial fraction of patients, the benefits of the product did not outweigh the drawbacks. However, this insufficient degree of benefit could represent a combination of factors including lack of efficacy, adverse effects, difficulty obtaining the products, cost, hassle involved and finally difficulty identifying optimal product and "dosing." Each of the latter challenges was identified by more than one family, and clearly these represented significant obstacles for some. In addition, based

on our clinical experience with many of these patients, we believe that confusion regarding regulations may well have contributed to a decision not to renew. Specifically, the growing access to the same or alternate hemp extract products via purchase on the web or in retail shops may have led some patients/families to obtain these products without choosing to renew their registration cards.

On the other hand, the fact that a small but significant subset of patients/families chose to expend additional cost and effort to renew registration at least once and some twice and three times, presupposes that these individuals were convinced of the benefit of treatment with "hemp extract." While data from this type of study does not prove efficacy, it suggests that hemp extract (or some forms of it) may be beneficial to some patients and/or may provide benefits beyond seizure control. This warrants serious consideration and further study.

The data clearly shows that adverse effects were infrequent, transient, or, in most cases, absent. Few or no patients/families discontinued treatment exclusively due to adverse effects. In the more detailed survey dataset, only two families reported "concerning" or "serious" adverse effects, namely mouth sores and increased seizures. However, neither of these qualify as "Severe adverse effects" or "SAEs" by FDA criteria for clinical trials. Finally, since our pediatric neurology practice cares for about 67% of these patients, and we track serious complications and severe adverse outcomes as part of our division's "Morbidity and Mortality" review process, we know that none of our patients experienced a "hemp extract"-related serious adverse event.

Surprisingly, even though CBD is known to interfere with the biodegradation of other drugs undergoing metabolism through the CYP2C19 pathway (notably desmethyl-clobazam)[63-66] , we are not aware of any of our patients developing evidence of toxicity from clobazam, and no adjustments in antiepileptic drug doses were necessitated strictly on account of the co-administration of "hemp-extract" products. It is, however, very likely that the actual doses of CBD (in mg/kg/day) were comparatively lower for these individuals using hemp extract when compared to doses utilized in published clinical trials using pharmaceutical grade CBD (up to 50 mg/kg/day).[67-69]

As mentioned, the "application review" data does demonstrate that most families could not provide an actual dose of "hemp extract" in terms of mg/kg/day of CBD (or equivalent), however just over half (54%) of the survey respondents could. One could speculate that this is due to bias in that those who responded to the survey are more invested in the product or process, and have greater product knowledge. Still, many families would indicate they were giving a certain number "of drops" or an amount "equal to about a grain of rice" or similarly vague or poorly quantifiable volumes or measurements. Some families would even vary the amount administered depending on the child's condition that day or week. Some families identified difficulty selecting a "dosage" or a product as reason for discontinuing, and many families used more than

one product over time in the hopes of achieving better seizure control. All these challenges stem directly from the fact that vernacular medical marijuana products are not standardized and constitute a wide array of products with widely differing constituents.[23,24,52,57]

In this respect the specific experience of these families and patients represents a microcosm of the broader scope of "medical marijuana" in which any standardization of dosing in studies of "vernacular" marijuana products becomes nearly impossible (see below).[44,47,70-72]

Psychological reasons for turning to non-standard therapies (Complementary/ Alternative Medicine or "CAM", including medical marijuana) are complex and can include a quest for additional therapeutic options, the hope for a cure, a belief in "natural" and "holistic" therapies, concerns regarding the adverse effects of conventional products, or even a suspicion of government and the pharmaceutical and medical establishments.[73-75] CAM usage in pediatrics is common and correlates with chronicity of illness and the failure of conventional therapies.[73-75] Thus, there is a correlation between lack of success or efficacy of more standard medical therapies and the tendency to seek benefit from CAM. This has been demonstrated in a number of pediatric conditions including Tourette syndrome and epilepsy.[76,77]

In addition, studies suggest that in alarming or discouraging medical circumstances, patients often turn to anecdote to inform their medical decision making.[78,79] For example, in a well cited study of men with prostate cancer, patient treatment preferences, particularly with respect to prostatectomy or not, were influenced more so by anecdotes based on the experiences of others with cancer, than on formal medical evidence.[80] With the advent of social media it is now even more feasible for a single or a few apparently exceptional anecdotal experience(s) to have widespread national and even international impact.[5] This appears to be what happened with "medical marijuana" and specifically CBD when it comes to intractable epilepsy and particularly Dravet syndrome.[2-4,25] This social media-driven enthusiasm for an unproven, anecdotal treatment prompted specific legislation in multiple states, often named after or fueled by the particular experience of a specific child, and reportedly caused a large number of families to uproot their lives and relocate to Colorado in order to access this treatment for their children.[81] In fact, in their studies, pediatric neurologists in Colorado found that the main predictor of perceived success of medical marijuana treatment was the very fact of moving to Colorado[81], presumably pointing to the power of suggestion and of the placebo effect.

Overall, Utah's experience with "hemp extract" for epilepsy as reported here is similar to that reported from other regions both in the US and without. Specifically, our

colleagues in Colorado have carefully studied the experience of their patients with vernacular medical marijuana products[81-83] and have also reported that the percentage of patients reporting improvement of seizure control is modest. Specifically, 49% of the Colorado cohort reported at least some benefit though only 24% were deemed to be "responders" (i.e., experienced a >50% reduction in seizure burden).[83] Colorado patients also reported "nonseizure benefits" in a substantial percentage of cases.[83] Finally, 71% of the Colorado cohort discontinued the use of hemp extract products during a comparable 1.5 year period.[83] The experience reported initially from California was much more positive[25], but this analysis was based on a self-selected, small group of patients. The experience from, Alabama[84], other locations in the United States[82] , Canada[85]and Israel[86] is more closely comparable to that reported from Colorado and our own.

With respect to adverse effects, it appears that all of the above mentioned reports as well as published open label and controlled trials using pure cannabidiol[67-69] concur that adverse events are modest and are generally well tolerated. While our data suggests that adverse effects rarely result in discontinuation of treatment, Treat and colleagues[83] found that the presence of adverse events was significantly associated with faster discontinuation of oral cannabis extracts. They report the most common adverse effects as worsening of seizures (8%), somnolence (sleepiness; 6%), and gastrointestinal symptoms (5%).[83] The rate of adverse effects reported in clinical studies (open label and controlled) of pharmaceutical grade cannabidiol[67-69] has been higher, though again very few serious adverse effects have been noted. In the latter studies[67-69], the most common adverse effects include (more or less in order of frequency) diarrhea, vomiting, fatigue, pyrexia (fever), somnolence, and abnormal results on liver-function tests. In these more carefully conducted controlled trials withdrawal from at least one of the studies was more common in the cannabidiol than in the placebo group.

Finally, it is appropriate to point out that one of the major limitations of this study is in fact one of the major limitations/challenges of studying "medical marijuana" in general. It becomes increasingly obvious that "medical marijuana" is "not one thing"[5,44,70-72] despite the fact that when discussed by proponents its benefits are touted without consideration of this critical fact. Not only are the means of delivery variable (including smoking, vaping, oral, mucosal etc…) but the range of marketed products is enormous.[48,49,55] The marijuana plant contains more than 60 distinct phytochemicals many of which are bioactive in their own right and likely have diverse biological actions.[15,18,50,55] Different varietals (cultivars) are specifically cultivated for specific phytochemical content.[52,57] The relative proportion of THC and CBD is the most obvious distinction but it is possible if not likely that the relative content of other components such as cannabivarin or tetrahydrocannabivarin may affect bioactivity.[5,53,56] Proponents of the concept of the "entourage" effect argue that the ultimate beneficial effect is modulated by the complex chemical milieu of the natural product such that the effects of one varietal prepared in a given manner could differ substantially if not

dramatically from another.[53,87] There is of course no standardization of vernacular products and no existing uniform means of confirming phytochemical content or purity.[23,24,48,57] State regulations vary with respect to the degree to which these products must be subjected to confirmatory analyses.[10,23] Furthermore, as clearly demonstrated in the Utah data as well as that from other states, there is no uniformity of "dosing" and families and patients are utilizing widely differing amounts of CBD.[4,5,25,82,84-86,88-90]

Very little is known with respect to the actual content of vernacular preparations and of the reliability of measurements of content provided by the manufacturers.[24,57] These are often now reported as some amount of "hemp extract" per serving size. For example, one of the most popular products among our patients is reported to have 43 mg of hemp extract per serving, and a serving is defined as 0.5 ml. Very few studies exist which independently and objectively analyze the cannabinoid content of vernacular preparations.[57,58] Those doing so report variability of up to 20% and some cases in which actual content differed dramatically from labeling.[57] In addition, there is the interesting consideration that National Institute on Drug Abuse (NIDA)-based marijuana strains available for research on "medical marijuana" differ greatly from existing varietals currently in usage in multiple states.[58] Specifically, the NIDA-available strains contain relatively lower THC and CBD concentrations than most products being used for "medical marijuana" purposes in Colorado, California and Washington.[58]

Consequently, it is very difficult for physicians encouraged to practice evidence-based medicine to find sufficiently well-conducted research to support the use of "medical marijuana" products for the treatment of any clinical condition. While there is scientific support for the use of synthetic THC for the treatment of AIDS-related and cancer-chemotherapy related anorexia,[18,49,55,91] and for the use of a 50-50 mixture of THC and CBD for the treatment of MS-related spasms (not approved in the US)[19], there is very little quality evidence supporting any other use of "medical marijuana" products.[18,20,49,91] Since the interest in CBD for epilepsy developed there have been a number of scientific studies (controlled, as well as open label) investigating the effect of pharmaceutically manufactured, pure cannabidiol products (Epidiolex) in epilepsy and the outcomes of these studies have been published.[67-69] These studies clearly demonstrate the clinical efficacy of pure CBD in a dose of 25 to 50 mg/kg/day for epilepsy in Dravet syndrome and Lennox-Gastaut syndrome and suggest efficacy and certainly the lack of serious adverse effects in a number of other childhood epilepsies.[67-69] However, it is critical to recognize, for the reasons outlined above, that the results of these more carefully scientifically conducted studies, cannot be extrapolated to the use of diverse, vernacular "medical marijuana" products in which cannabinoid content is uncertain and widely variable and in which the purity of the products is simply not formally and consistently monitored.

Conclusions:

Information collected from the Utah experience with hemp extract for epilepsy indicates that many patients or caregivers reported improvement in seizure burden (frequency and severity) while using "hemp extract." However, many did not renew their hemp extract registration cards and presumably discontinued use of hemp extract. Overall, most patients appeared to tolerate these vernacular "hemp extract" products well, as few reported adverse effects and many reported additional benefits during use. Side effects were often described as mild or transiently associated with dose changes, while benefits beyond seizure control were reported as more sustained effects.

However, problems inherent in the use of an uncontrolled, unregulated product subsumed under the rubric of "medical marijuana" are apparent. In our larger "application review" dataset, less than a quarter of those using "hemp extract" could report an actual dosage, though many used the product for >1 year despite an average cost of $177 per month in addition to annual hemp registration card costs.

Results of this data are limited by the risk of self-reported response bias. Since the process instituted in Utah allows for significant variability in the detail reported by neurologists completing the "Neurologist Certification Forms" and subsequent forms, the resultant data is of extremely variable quality. Outcomes are also subject to the problems previously discussed that apply to all unregulated medical marijuana products. These products can contain a variety of potentially bioactive, synergistic or antagonistic components and, consequently, can variably influence any resultant bioeffects.

Future directions for this project could include analysis of clinical and demographic details of respondents to better investigate such biases. We would also like to better investigate the contents of various vernacular hemp extract products and correlate to perceived clinical effects. Even with the stated limitations, these retrospective, observational, and self-reported results can help inform and guide providers, patients, families, and policymakers about the use of hemp extract in Utah patients with intractable epilepsy and other diverse medical conditions.

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Utah Department of Health
Office of Vital Records and Statistics

Application for Hemp Extract Registration Card

Applicant Information

Full Legal Name: _____
First Middle Last

Mailing Address: _____
Street/PO Box City State/Zip

Telephone Number: _____ **Date of Birth:** _____

Gender: ☐ Male ☐ Female **Email Address:** _____

Parent/Guardian 1 Information

☐ **Parent responsible for minor's medical care** ☐ **Legal guardian responsible for patient's medical care**

Full Legal Name: _____
First Middle Last

Mailing Address: _____
Street/PO Box City State/Zip

Telephone Number: _____ **Date of Birth:** _____

Email Address: _____

Parent/Guardian 2 Information

☐ **Parent responsible for minor's medical care** ☐ **Legal guardian responsible for patient's medical care**

Full Legal Name: _____
First Middle Last

Mailing Address: _____
Street/PO Box City State/Zip

Telephone Number: _____ **Date of Birth:** _____

Email Address: _____

I understand that information and documentation submitted with this application may be released to a higher education institution for the purpose of studying hemp extract. I certify that to the best of my knowledge, the information in this application and all supporting documents is true and correct.

_____ _____
Print Name of Applicant or Legal Representative Date

_____
Signature of Applicant or Legal Representative

Hemp Extract Registry
288 North 1460 West ◦ PO Box 141012 ◦ Salt Lake City, UT 84114-1012
Email: hempregistry@utah.gov
Phone: (801) 538-6264 Fax: (801) 536-0954

Neurologist Certification Form

This form is to be completed by a board certified neurologist. This is not a prescription. The neurologist may prepare and sign this form or a statement with the required elements on the neurologist's letterhead. The neurologist may provide a completed form or statement directly to the patient.

Patient Full Name: _____
First Middle Initial Last

Date of Birth: _____ **Today's Date:** _____

Does this patient exhibit symptoms or signs indicative of intractable epilepsy? ☐ **Yes** ☐ **No**

This patient may benefit from the use of hemp extract. ☐ **Yes** ☐ **No**

Neurologist Name: _____

DOPL Number and Expiration Date: _____

American Board of Psychiatry and Neurology certified? ☐ **Yes** ☐ **No**

Board Certification Number (Optional): _____

This written certification is consistent with my evaluation and observation of the patient (e.g., Evaluation Record). ☐ **Yes** ☐ **No**

Neurologist Signature: _____

Phone Number: _____ **Email Address:** _____

Complete Mailing Address: _____

Patient Evaluation Record Form

This form is to be completed by a board certified neurologist. The neurologist may prepare and sign either this form or a statement with the required elements on the neurologist's letterhead.
The neurologist must provide a completed form or statement to the Department of Health.

Patient Full Name: _____
First Middle Initial Last

Date of Birth: _____ **Today's Date:** _____

Date of Last Office/Clinical Visit: _____

Has this patient received a diagnosis of epilepsy? ☐ **Yes** ☐ **No**

Does the patient exhibit symptoms or signs indicative of intractable epilepsy? ☐ **Yes** ☐ **No**

Neurologist Name: _____

DOPL License Number and Expiration Date: _____

Neurologist Signature: _____

Patient Medical History

Utah Admin. Code R436-55-5 (3) recommends that neurologists provide UDOH the information requested in this section. The information may be released to a higher education institution for the purpose of studying hemp extract.

Date of Onset of Epilepsy: _____

Seizure Type and Average Frequency (per month):

Type 1 and Frequency: _____

Type 2 and Frequency: _____

Type 3 and Frequency: _____

Antiepileptic Medications	Dose/Frequency	Reported Side Effects	Currently Used? (Y/N)

Vagal Nerve Stimulator? _____

Ketogenic Diet? _____

Other Modalities (Describe): _____

_____

Application Checklist and Instructions

This checklist is for your convenience. You do not need to include it with your application.

NOTE: Incomplete applications will be denied.

To apply for a Hemp Extract Registration Card, you must complete the application packet as described below. You must be over the age of 18 and suffer from intractable epilepsy or be a parent or legal guardian of a patient who is under the age of 18 and suffers from intractable epilepsy. You must be a Utah resident. If you make a mistake, please complete a new form.

All applicants are required to submit the following items to complete the application:

- ☐ An application form completed and signed by you.
- ☐ A copy of your Utah ID and proof of residence.
- ☐ A Neurologist's Certification Form statement signed by your or your minor child's neurologist.
- ☐ A completed Patient Evaluation Record Form.
- ☐ Payment of $200. Payment includes cash, check, money order, or credit/debit card. Please do not pay with cash if mailing the application. Checks and money orders need to be made payable to "Utah Office of Vital Records and Statistics."

1. If the patient is under the age of 18, the parent or legal guardian of the patient must complete the application. The parent or legal guardian must attest that s/he is responsible for the patient's medical care.

2. If you are the legal guardian of the patient, you will need to provide a certified copy of the court order.

3. You must be a Utah resident to obtain a Hemp Extract Registration Card. You must provide proof of your identity and residency.

4. Submit the application in person or by mail to the Office of Vital Records and Statistics. A Hemp Extract Registration Card cannot be mailed to an out-of-state address.

Mail to:
Office of Vital Records and Statistics
Attn: Hemp Extract Registry
PO Box 141012
Salt Lake City, UT 84114-1012

In Person:
Office of Vital Records and Statistics
Cannon Health Building
288 N 1460 W
Salt Lake City, UT 84114-1012

If you have questions, please contact us via email address, hempregistry@utah.gov, or at (801) 538-6264.

Proof of Identity and Utah Residency

Please do not send original documents. Send a clear, readable copy

Primary Documents		Secondary Documents
<u>One (1) of the following:</u> -Utah Driver's License -Utah ID -Temporary Utah Driver's License -Temporary Utah ID -US Passport or Passport Card -US Military ID -Tribal ID -Out of State ID or Driver's License	**AND**	**<u>One (1) proof of residency</u>** -Proof of Utah employment (paycheck stub/W-2/certified Utah tax return) -Copy of a utility bill, rental agreement, property tax assessment. -Copy of an entire government issued benefit letter (PERA, SSI, Disability, etc.)

- If you cannot provide one (1) primary document and one (1) secondary document, please contact the Registry at (801) 538-6264 to discuss other options.
- All documents must be valid when received at the Registry.
- Damaged, expired, or tampered IDs are not valid.
- The address on the ID does not have to match the mailing address on the application.
- All IDs must be verifiable and have specific issue and expiration dates.
- At least one (1) document must show the patient's date of birth.
- Passports must include full photo page and the signed signature page. Passport cards must include copy of front and back.
- Proof of residency materials must be dated with 60 days of date the Registry receives them, unless otherwise noted.
- As proof of Utah employment, the W-2 or certified Utah tax return must be for the most recent tax year and have a Utah mailing address.
- Bills from telephone, electricity, water, gas, trash, cable or internet providers are considered valid and verifiable utility bills. Bills must include the organization name, logo, and contact information.
- All government benefit letters must include the issuing agency's logo and contact information, the patient's name and address, and an account or case number. Examples of acceptable benefit letters include PERA, Medicaid/Medicare, SNAP/Food Stamps, TANF and Social Security.

Utah Department of Health
Office of Vital Records and Statistics

Renewal Application for Hemp Extract Registration Card

Applicant Information

Full Legal Name: _____
First Middle Last

Mailing Address: _____
Street/PO Box City State/Zip

Telephone Number: _____ **Date of Birth:** _____

Gender: ☐ Male ☐ Female **Email Address:** _____

Parent/Guardian 1 Information

☐ **Parent responsible for minor's medical care** ☐ **Legal guardian responsible for patient's medical care**

Full Legal Name: _____
First Middle Last

Mailing Address: _____
Street/PO Box City State/Zip

Telephone Number: _____ **Date of Birth:** _____

Email Address: _____

Parent/Guardian 2 Information

☐ **Parent responsible for minor's medical care** ☐ **Legal guardian responsible for patient's medical care**

Full Legal Name: _____
First Middle Last

Mailing Address: _____
Street/PO Box City State/Zip

Telephone Number: _____ **Date of Birth:** _____

Email Address: _____

I understand that information and documentation submitted with this application may be released to a higher education institution for the purpose of studying hemp extract. I certify that to the best of my knowledge, the information in this application and all supporting documents is true and correct.

_____ _____
Print Name of Applicant or Legal Representative Date

_____
Signature of Applicant or Legal Representative

Renewal Neurologist Certification Form

This form is to be completed by a board certified neurologist. This is not a prescription. The neurologist may prepare and sign this form or a statement with the required elements on the neurologist's letterhead. The neurologist may provide a completed form or statement directly to the patient.

Patient Full Name: _____
First Middle Initial Last

Date of Birth: _____ **Today's Date:** _____

Does this patient exhibit symptoms or signs indicative of intractable epilepsy? ☐ **Yes** ☐ **No**

This patient may benefit from the use of hemp extract. ☐ **Yes** ☐ **No**

Neurologist Name: _____

DOPL Number and Expiration Date: _____

American Board of Psychiatry and Neurology certified? ☐ **Yes** ☐ **No**

Board Certification Number (Optional): _____

This written certification is consistent with my evaluation and observation of the patient (e.g., Evaluation Record). ☐ **Yes** ☐ **No**

Neurologist Signature: _____

Phone Number: _____ **Email Address:** _____

Complete Mailing Address: _____

Renewal Patient Evaluation Record Form

This form is to be completed by a board certified neurologist. The neurologist may prepare and sign either this form or a statement with the required elements on the neurologist's letterhead.
The neurologist must provide a completed form or statement to UDOH.

Patient Full Name: _____
First Middle Initial Last

Today's Date: _____ **Date of Last Office/Clinical Visit:** _____

Neurologist Name: _____

DOPL License Number and Expiration Date: _____

Neurologist Signature: _____

Describe hemp extract's effect on seizure control: _____

_____

_____

_____

_____

_____

_____

List any adverse effects or other effects that may be attributed to use of hemp extract: _____

_____

_____

_____

_____

_____

_____

Hemp Extract Registry
288 North 1460 West ◦ PO Box 141012 ◦ Salt Lake City, UT 84114-1012
Email: hempregistry@utah.gov
Phone: (801) 538-6264 Fax: (801) 536-0954

Patient Medical History

Utah Admin. Code R436-55-5 (3) recommends that neurologists provide UDOH the information requested in this section. The information may be released to a higher education institution for the purpose of studying hemp extract.

Date of Onset of Epilepsy: _____

Seizure Type and Average Frequency (per month):

Type 1 and Frequency: _____

Type 2 and Frequency: _____

Type 3 and Frequency: _____

Antiepileptic Medications	Dose/Frequency	Reported Side Effects	Currently Used? (Y/N)

Vagal Nerve Stimulator? _____

Ketogenic Diet? _____

Other Modalities (Describe): _____

_____

Frequency of Seizures Before Hemp Extract Use: _____ **After:** _____

Hemp Extract Supplier and Product Description: _____

_____

Hemp Extract Dosage: _____

Hemp Extract Use Frequency: _____

Hemp Extract Use Duration: _____

Renewal Application Checklist and Instructions

This checklist is for your convenience. You do not need to include it with your application.
NOTE: Incomplete applications will be denied.

Applicants are required to submit the following items to complete the application:

- ☐ A renewal application form completed and signed by you.
- ☐ A copy of your Utah ID and proof of residence if there have been any changes within the past year.
- ☐ A Renewal Neurologist's Certification Form statement signed by your or your minor child's neurologist.
- ☐ A completed Renewal Patient Evaluation Record Form.
- ☐ Payment of $50. Payment includes cash, check, money order, or credit/debit card.
- ☐ Do not pay with cash if mailing the application. Make checks and money orders payable to "Utah Office of Vital Records and Statistics."

1. If the patient is under the age of 18, the parent or legal guardian of the patient must complete the application. The parent or legal guardian must attest that s/he is responsible for the patient's medical care.

2. If you are the legal guardian of the patient and there is not a copy of the court order authorizing guardianship on file in this office, you will need to provide a copy of the court order.

3. You must be a Utah resident to renew your Hemp Extract Registration Card. You must provide proof of your identity and residency.

4. Submit the application in person or by mail to the Office of Vital Records and Statistics. A Hemp Extract Registration Card cannot be mailed to an out-of-state address.

Mailing Address:
Office of Vital Records and Statistics
Attn: Hemp Extract Registry
PO Box 141012
Salt Lake City, UT 84114-1012

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Office of Vital Records and Statistics
Cannon Health Building
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- If you cannot provide one (1) primary document and one (1) secondary document, please contact the Registry at (801) 538-6264 to discuss other options.
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HEMP EXTRACT
Registration Card
QUESTIONNAIRE

Applicant Name _____

Date of Birth _____

Who is completing this questionnaire?

☐ Applicant ☐ Parent/Guardian

☐ Other *(specify relationship)* : _____

Name *(if not applicant)* _____

Q1 Have you actually started treatment with hemp extract for yourself, your child, or a family member?

- ☐ Yes
- ☐ No

✪ If you answered **YES**, what product(s) have you used?
Please provide details about the products you have used below (you may need to look at the label or internet information provided about the products).

a) Name of Product(s), Manufacturer(s):

✪ If you answered **NO**, why not?
Check all that apply.

- ☐ Too Expensive
- ☐ Could not figure out what product to buy
- ☐ Could not figure out where/how to get the product
- ☐ Could not figure out the dose
- ☐ Other (explain below):

Q2 Do you know the concentration of the product(s) you have used?
Concentration will appear as a number of milligrams or grams of cannabidiol, cannabinoids, or cannabis product per volume of the solution.
(Ex: 50 mg CBD/milliliter, 40 mg cannabinoids/milliliter)

- ☐ Yes
- ☐ No

✪ If you answered **YES**, please specify the **CONCENTRATION** of the product(s) below:

Q3 What is the maximum amount (dose) of the product(s) you have ever administered?

a) Name of Product:

Maximum amount given at a time:

How often per day?

b) Name of Product:

Maximum amount given at a time:

How often per day?

Q4 What is the maximum amount of time (in months) you have continuously given a hemp extract product to yourself, your child, or a family member?

✪ If you have decided to continue an amount that is **LESS** than the maximum amount you ever gave yourself, your child, or a family member, what is the amount that you decided to give?

Q5 Do you plan to continue the hemp extract?

- ☐ Yes
- ☐ No

Q6 Has the hemp extract been helpful?

- ☐ Yes
- ☐ No

✪ If you answered **YES**, has it reduced the frequency of the seizures (how often the seizures happen)?

- ☐ Yes
- ☐ No

FLIP OVER PAGE

✪ If you answered **YES** to the previous question, by how much did it reduce **HOW OFTEN** the seizures happen?
Choose the answer that bests describes the situation for you, your child, or the family member.

- ☐ A little better
- ☐ Less than ½ as many seizures as before
- ☐ Almost completely controlled
- ☐ Seizures are completely gone

Q7 If the hemp extract has reduced the **SEVERITY** of the seizures (how bad they are), how much better are they?
Choose the answer that best describes the situation for you, your child, or the family member.

- ☐ A little better
- ☐ Quite a bit better
- ☐ A whole lot better

Q8 Has the hemp extract caused any side effects?

- ☐ Yes
- ☐ No

✪ If you answered **YES**, check all that apply.

- ☐ Tiredness
- ☐ Increased Appetite
- ☐ Decreased Appetite
- ☐ Diarrhea
- ☐ Vomiting
- ☐ Irritability/Moodiness
- ☐ Balance or Coordination Problems
- ☐ Increased Seizures
- ☐ Other (explain below):

✪ Has the hemp extract caused any **SEVERE** or **SERIOUS** side effects?

- ☐ Yes
- ☐ No

✪ If you answered YES, what **SERIOUS** or **SEVERE** side effects occurred?

Q9 Has the hemp extract been helpful in any other way than helping with seizures?

- ☐ Yes
- ☐ No

✪ If you answered **YES**, please check all that apply:

- ☐ More Alert
- ☐ More Happy
- ☐ Sleeps Better
- ☐ More Social
- ☐ Speech/Language Improvement
- ☐ Other (explain below):

Q10 Are you planning to continue the hemp extract?

- ☐ Yes
- ☐ No

✪ If you answered **NO**, why not?
Check all that apply.

- ☐ Too Expensive
- ☐ Did not work
- ☐ Too difficult to get
- ☐ Other (explain below):

Q11 How much do you pay for the hemp extract on average per month?

THE NEXT QUESTION IS ONLY FOR FAMILIES WHO HAVE HAD THE REGISTRATION CARD FOR MORE THAN A YEAR:

Q12 *If you have had the Hemp Extract Registration Card for more than a year, Utah law requires that you renew the card.*
Have you renewed?

- ☐ Yes
- ☐ No

✪ If you answered **NO**, why?
Check all that apply.

- ☐ We no longer plan to administer hemp extract
- ☐ We did not realize that we needed to renew
- ☐ We have tried to renew, but it is confusing how to do that
- ☐ It is too expensive
- ☐ It is too difficult
- ☐ Other (explain below):

Thank you very much for completing this questionnaire and returning it to us. We are hopeful this will help us to better understand which patients may benefit from treatment with "hemp extract".