

Patient-Centered Outcomes Research in Dravet Syndrome

Day
of Dravet Summary and White Paper
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Raising hope & changing lives through research

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Introduction

Dravet syndrome is a lifelong catastrophic form of epilepsy that begins in the first year of life. First described by Charlotte Dravet in 1978, it is characterized by frequent, often prolonged generalized tonic clonic or hemiclonic seizures, myoclonic seizures, various other seizure types, speech impairment, developmental delay, gait abnormalities, dysautonomia, and specific seizure triggers including fever or illness, temperature changes, lights, patterns, emotion, and excitement (Dravet 1978; Wirrell et al. 2017). At least 90% of patients with Dravet syndrome have a mutation in their *SCN1A* gene, which codes for a sodium channel protein that acts as a voltage gated pore situated on the membrane of nerve and cardiac cells, allowing sodium ions into and out of cells to propagate action potential and nerve cell firing (Djémié et al. 2016). Most mutations are de novo, or new to the child and uninherited from a parent, although some may be inherited from a parent with a history of seizures or no symptoms at all. Dravet syndrome carries an unexpectedly high mortality rate of 15-20% by adulthood, most often due to Sudden Unexpected Death in Epilepsy (SUDEP) or complications from prolonged seizures (Cooper et al. 2016).

Since its inception in 2009, the Dravet Syndrome Foundation (DSF)'s mission has been to aggressively raise funds for research and education surrounding Dravet syndrome. Because of this focus, DSF's medical and scientific community are paving the way in understanding the basic mechanisms and clinical presentation of Dravet syndrome. However, as results of this research began to translate to potential treatments, DSF realized the community of caregivers was not as prepared for research as their professional counterparts, and sought to bridge the gap between the speed of research and the need for meaningful patient input. In 2016, DSF received a Patient Centered Outcomes Research Institute (PCORI) Pipeline to Proposal (P2P) grant to help prepare the "stakeholders" (parents, clinicians, researchers, and industry) for research.

One of the P2P project's activities - a caregiver engagement workshop that took place at each of our five regional Day of Dravet workshops in the fall of 2017 - involved a brief introduction to Patient-Centered Outcomes Research (PCOR) and Comparative Effectiveness Research (CER) and then a structured discussion among caregivers about what their priorities might be for future projects. Despite the extensive dialogue that took place within the age-stratified caregiver groups in each session, it quickly became clear that caregivers needed much more in-depth information about the research process and their role in it than we were able to give in our brief presentation. Caregivers were unclear about what could be studied, how studies could be designed, and what comparative effectiveness meant. In order to conduct CER, one must identify two or more treatments that are already proven effective and design research that will compare the proven effectiveness in a given population. Somewhat fortuitously, as the project unfolded, it became increasingly clear that CER would not be appropriate for most of the top research priorities in Dravet syndrome because there are no treatments or methods already proven effective in these categories. The task for DSF broadened from establishing CER priorities for research to engaging the community in general research design, implementation, and dissemination.

The Project

In 2018, DSF was awarded a Eugene Washington Engagement Award for a 2-year project to expand engagement in the community. The project contained various components, which have been described previously (see links in References) but the largest undertaking involved gathering caregivers and allowing them to discuss their research needs while introducing them to the concepts in patient centered outcomes research. Through this two year grant, we have held ten one-day Day of Dravet workshops in 10 different regions of the country. In 2018, the focus of the PCORI portion of the workshop was “Defining Outcomes in Dravet Syndrome,” while in 2019 the focus returned to establishing research priorities and brainstorming possible solutions.

The Workshops: Design

In the fall of 2018, 20-40 caregivers attended each of five regional workshops in Chicago (IL), Boston (MA), Seattle (WA), Ft. Worth (TX), and Atlanta (GA) for a total of 167 caregiver participants. The workshops began with a brief presentation on the top research priority areas established by the community leading up to the workshops (Sleep, Behavior, Cognition, Seizures/Status Epilepticus, SUDEP, and Gastrointestinal/Nutrition) and description of what appropriate outcomes are (namely: well-defined, measurable, and capable of determining the success or failure of an intervention). After grouping the caregivers at round tables based on the age of their patient, we asked each table to choose a topic from the list of priority research areas and to come up with some possible outcomes that were meaningful to them and could be used in a study on that topic. A spokesperson for the table reported back to the entire room after 20 minutes of discussion. We then asked the groups to list barriers that would prevent them from participating in a study on that topic, and each group reported back to the entire room after another 20 minutes of discussion.

In 2019, the five regional workshops were held in Los Angeles (CA), Richmond (VA), Hackensack (NJ), Ann Arbor (MI), and Houston (TX) and attracted 20-30 families each for a total 101 families. DSF took extreme care to host these workshops in places where there had not been DSF events or opportunities for caregivers to learn about patient centered outcomes research before, thus the caregivers in attendance were quite new to the idea of PCOR. As such, we started from the beginning with this group, describing PCOR and the work done so far, and then asking the broad question, “If you could ‘fix’ one thing about Dravet, what would it be?” followed by, “What would that ‘fix’ look like?” As in 2018, each group took 20-30 minutes for discussion of each question and then reported back to the entire room.

Results

BEHAVIOR

Most caregiver groups, regardless of the age of the patient, chose to discuss behavior. However, the content of the discussions varied widely among age groups. In the younger patients, caregivers discussed interventional strategies and Applied Behavioral Analysis (ABA, a technique used with Autism diagnoses), noting that many of their children required an Autism diagnosis before insurance would pay for ABA. Some parents found ABA techniques to be helpful while others did not. There was consensus

among the parents of 0-4 year olds that it was difficult to keep up with the constant motion, hyperactivity, lack of safety awareness, inability to control urges, and outbursts/tantrums in their children. Caregivers of younger children aged 0-4 years reported their issues with behavior might be based on frustration about their inability to communicate with the parent and suggested focusing on expressive language tools and measuring their use against behavioral outbursts.

Behavior discussions in groups with older patients centered more on repetitive behaviors, lack of interest in non-preferred activities, and refusals, which can be difficult to deal with or move on from when patients weigh >100 pounds and cannot be picked up. Most caregivers agreed that location and environment are key, both in triggering unwanted behaviors and in preventing unwanted behaviors. Interestingly, lack of routine was frequently mentioned as a trigger for behavioral issues in the caregivers whose children are 5-10 years old, perhaps because these patients often spend their days in school, where routines are emphasized. Self-injurious and aggressive behaviors appear to be a problem in the older (>5 yrs) age groups. In patients age 16+, caregivers relayed their difficulty with obtaining mental health services for behaviors that were so aggressive or injurious that they put their family at risk.

Caregivers in all age groups indicated they do not feel professionals understand the behaviors related to Dravet syndrome. They explained that, while the behaviors sound similar to those seen in Autism and Obsessive Compulsive Disorder (OCD), the strategies used in ABA and OCD often do not work in patients with DS. They discussed how memory impairment from frequent seizures presents a significant challenge to ABA, which depends on repetition, and lack of cognitive reasoning skills present a challenge to OCD therapies that require reasoning techniques, both challenges that professionals with training in behaviors sometimes forget.

Possible outcomes suggested by parents included: Fewer outbursts; fewer episodes of hitting or kicking; decreased frequency of self-injurious behavior; and ability to re-direct behavior >80% of the time.

Caregivers listed time as the most common potential barrier to participation in a research study on behavior. They explained that intensive therapies requiring an hour or more of active treatment per day, frequent travel to therapy centers, or extensive training time for behavior mitigation would prevent them from participating. Other common barriers included significant cost of the therapy, childcare for siblings, non Dravet specific studies, and hesitation to add behavior medications to an already heavy load of anti-seizure medications.

COGNITION

Often discussed as a corollary to behavior, cognition was chosen as a stand-alone topic among many caregiver groups. Caregivers of younger patients age 0-4 tended to discuss regression in conjunction with our apart from seizures, language delay, concern about development and the practice of aggressive therapies to prevent decline, while caregivers of older patients age 6+ tended to focus on measuring cognition over a longer range of time.

Parents expressed frustration at the lack of evidence that aggressive speech, physical, and occupational therapy or educational support results in better cognitive outcome. Given the multiple challenges in raising patients with Dravet syndrome, parents are eager to focus their efforts on the areas proven to be

most beneficial. Lack of consistent measurement and controlled studies complicates this risk-benefit analysis. Compounding this frustration is the fact that very few patients with Dravet syndrome are on monotherapy for their seizures, and caregivers feel medications affect cognition significantly enough to make any study quite complicated.

At the same time, caregivers were hesitant to commit to long-term studies that would require extensive cognition tests, such as neuropsychological exams which can take 4-8 hours per test. They were also not interested in studies on cognition that would require them to travel long distances, pay for any therapies that are not covered by their insurance, or take many hours per week to implement. Parents suggested a simple yearly measurement scale to estimate approximate cognitive age vs. chronological age as a way to describe and track cognition in the population. Other suggestions included toilet mishap monitoring or simple repeated tests that could be reported by parents.

SEIZURES/STATUS EPILEPTICUS

Seizures and status epilepticus (seizures lasting > 5 minutes) was the next most commonly chosen topic to discuss. Caregivers discussed the relationships among medication changes, medication side effects, dietary therapies, alternative or homeopathic therapies, vagal nerve stimulation (VNS), the evolution of Dravet syndrome, and their effects on seizures. Caregivers were especially interested in controlled studies that would tease out these interactions but recognized the difficulty involved in designing these types of studies. The importance of consistent seizure description and measuring was discussed, with parents noting that even their own tracking, either with pen and paper or with seizure-tracking applications, proved inconsistent as the patient aged and seizures evolved. What they tracked from age 0-3 was often quite different from what they track in adolescent or adult patients. Parents expressed an interest in pooling their children's data to identify trends in seizures, side effects, etc., but also realized parent-reported data could be difficult to interpret accurately.

Many parents wanted more research on seizures and their physical impact on brain development and cognition. Discussions about seizure frequency as a function of treatment vs. disease progression emerged most often in the 4-12 year old groups, and adolescent age groups suggested a national standard of care so it does not vary so widely state to state in the US.

Caregivers of adult patients age 18+ expressed frustration that seizure control does not seem to be a priority for their providers. Some stated physicians believe seizure frequency has decreased and they are often excluded from clinical trials. At the same time, several also expressed fear of relinquishing control of their patient's medical treatment as would be required in a clinical trial, citing burnout from years of trial and error. One caregiver described it as "Blazing new trails fatigue." Others felt behavior and comorbidities were their top concerns and clinical trials for anti-seizure medications would not address these issues.

Status epilepticus was chosen more frequently among caregivers of young patients (0-4 yrs) than older patients, perhaps reflecting the fact that status seizures, although present in all age groups, are more frequent in younger patients.

SUDEP (Sudden Unexplained Death in Epilepsy)

Parents across age groups and regions are concerned about SUDEP and use a variety of methods to monitor for seizures overnight including co-sleeping, audio and video monitors, movement monitors, and pulse oximeters. However, only some of these methods truly monitor for SUDEP, namely pulse oximeters that alarm when oxygen saturation or heart rate falls below a set level, which would occur in SUDEP, and movement monitors, which can be set to alarm in the complete absence of movement including cessation of respiration. Regular audio and video monitors, often recommended by physicians to alert caregivers to seizures, do not actually monitor for a life-threatening silent event such as SUDEP.

Caregivers who used or wanted to use pulse oximeters expressed frustration that medical professionals are often unwilling to prescribe them, citing lost sleep due to false alarms and lack of medical necessity as reasons. Caregivers felt this was a barrier to them accessing the monitors and noted they are the first thing attached to a patient when they are admitted to a hospital for any reason for the express purpose of notifying someone if the patient suffers a life threatening event, even without a diagnosis that would indicate such an event is likely. Parents unanimously agreed it should be their decision whether any lost sleep due to false alarms outweighed the possible benefit and believe the medical necessity is proven by universal hospital use of the machines, coupled with the high mortality rate in Dravet syndrome. If it is necessary when the patient is in the hospital, even for routine procedures, it is certainly necessary when the patient is at home and at a 15-20% risk of sudden death.

Groups who chose SUDEP as a discussion topic all wanted more research on the issue. Most were willing to sign up for a prospective research study that would track monitoring methods and the rate of SUDEP that occurs in the population with each. Caregivers whose physicians refused to prescribe pulse oximeters were especially interested in potential studies that would include access to the machines.

SLEEP

The topic “Sleep” was interpreted differently by different groups. Some focused on the patient’s sleep and how to reduce midnight awakenings and nocturnal seizures, while others focused on the caregiver’s sleep.

The groups concerned about patient sleep tended to be caregivers of 4-6 year olds, the age at which neurotypical children tend to outgrow mid-night awakenings and need for nighttime interventions. It also coincides with the increase in nocturnal seizures seen in patients with Dravet syndrome between 4-11 years of age (median 6.5 yrs) (Losito 2017). A few parents were concerned about sleep apnea.

Regarding caregiver sleep, there was consensus that parents need to feel the patient is safely monitored in order for them to sleep soundly and these groups advocated for nighttime movement or pulse oximetry monitoring.

Barriers to participating in studies regarding sleep included an unwillingness to commit to a particular intervention because parents are “just getting by” in whatever manner they can, and are already exhausted. Other barriers included sacrificing perceived patient safety for the sake of the study, which may be asked if any type of monitoring or co-sleeping is discontinued or changed during a study.

MISC

Transition came up somewhat frequently in the 11+ age groups. Caregivers expressed concern over what will happen/has happened to their patient after aging out of the public education system and what will happen when they are no longer able to care for the patient. Lack of guides, resources, and frustration that the process and resources differ widely by state were concerns raised by parents. Transition of medical care was also discussed among older patient groups and parents were frustrated with the low number of adult neurologists experienced in Dravet syndrome.

Families across the U.S. are having difficulty finding respite care. Reasons range from low reimbursement rate or low pay rate for respite through Medicaid funds and difficulty of finding qualified people to the need for skilled care or persons authorized to administer medication. Respite outside of the home is particularly difficult to find in the U.S. Families discussed the unique entanglement of life-threatening medical complexity and developmental delay that is not often found in other patients in group homes or respite facilities. Nurses are able to manage life-threatening illnesses in care facilities, and group homes are able to manage developmental delays, but it is difficult to find a facility (respite or long-term) that can handle both. In the case of adults away from their legal guardians, patients need their anti-seizure medications but if they refuse, the nurses are not required to administer them, leaving the patients in life-threatening danger of seizures which has resulted in death in at least one Dravet patient.

CLINICAL TRIAL OR STUDY PARTICIPATION

Most caregivers were eager to participate in studies on their chosen topic. Barriers to participation included concern about placebo arms, concern in enrolling patients whose communications abilities are so low that they can't easily express feelings, including side effects, time commitment, financial constraints such as travel or time off from work, and frustration over the rigidity requested in changing existing treatments as needed for the health of the patient.

Caregivers noted they are more likely to participate in a study when they hear other parents talking about the study and/or their experiences. Studies with limited communication, non-disclosure agreements, and other types of perceived secrecy made parents skeptical and less likely to enroll.

WHAT IS THE ONE THING YOU WISH YOU COULD "FIX?"

While the 2017 and 2018 workshops focused on single characteristics or comorbidities of Dravet syndrome, the 2019 workshops asked caregivers to discuss the main issue they would like to see fixed in Dravet syndrome. Overwhelmingly, caregivers wanted to fix the underlying problems caused by *SCN1A* mutations. They believe fixing the mutation or augmenting production of healthy sodium channels to make up for the haploinsufficiency caused by the mutation will, in turn, ameliorate many of the characteristics and comorbidities discussed in the previous years' workshops. Whether it was gene therapy or upregulation of healthy *SCN1A*, they believed this was the pathway to substantive progress in treating Dravet syndrome.

The second question, “What would a ‘fix’ look like?” spurred conversations about what could help caregivers *now*. Parents of patients age 0-10 years wanted counseling (not just for the patient but for the entire family), a guide to resources and funding available to help them, and assistance with advocacy and insurance appeals. They suggested Family Navigators at children’s hospitals who are knowledgeable about local resources, multidisciplinary clinics, whole syndrome care, and education pamphlets specific to our population. Caregivers of all ages stated the level of assistance in school was insufficient. Some advocated for more nursing, 1:1 nursing, and increased time with aides, while others advocated for better training for the existing assistants. Caregivers of younger patients age 0-10 years were more likely to request increased nursing, while caregivers of older patients 11+ were more likely to request increased aides or training for aides, perhaps aligning with the decrease in frequency of status epilepticus observed in older patients with Dravet syndrome (Chiron 2018).

Parents believe diagnosis should come with more information from their medical provider. Upon diagnosis, caregivers want to receive immediate access to public insurance (Medicaid), counseling, automatically-approved therapies, counseling, and other resources. They were frustrated by the “wait and see what becomes necessary” approach from their providers, wishing instead to be allowed to address issues before they become substantial problems for their families.

The caregivers of adult patients were more likely to list “none” under possible fixes. They expressed a feeling of burnout, of having tried many of the solutions suggested by parents of younger patients with little to no success. They were also skeptical that a gene therapy or upregulation technique would cause significant improvement in their patients, aside from seizure reduction, believing instead that years of relentless seizures and development under the dysfunctional neuronal network has caused too much damage to be reversed by what may be disease-modifying treatments for younger patients.

Discussion: Where do we go from here?

It is clear that Dravet syndrome entails much more than seizures and its effects spread to the entire family. It also became increasingly apparent that the caregivers have more questions than the professionals can answer, creating the perfect environment for patient-centered outcomes research. Some research that wasn’t possible 5 years ago because of the rarity of Dravet (such as research about night time monitors or other interventions for SUDEP) are possible today with the right coordination given the rapidly expanding caregiver community. Caregivers’ other questions focus more on the practical/clinical aspects of Dravet syndrome than on the basic science aspect, which is currently being addressed through development of disease-modifying treatments. Which begs the question: If caregivers have practical concerns, and the patient numbers would support a clinical study, why are these studies not being performed, and what can we do as a community to address that?

One possibility is that the caregivers’ concerns tend to lie in the most difficult to measure areas such as behavior and cognition. During the 2018 workshops, which asked caregivers to identify possible outcomes and measurement methods, the conversations digressed and very few actual outcomes were generated. It has been the same in other patient-centered outcomes research projects in which DSF has participated: In fact, the working stakeholder group spun off from a foundation-laying project nearly 5 years ago has been trying to develop and adapt appropriate mobility and cognition questionnaires that are sensitive enough to differentiate between the varying levels of ability in the Dravet community and

robust enough to capture their profound differences from their healthy peers. How do you measure cognition that is usually quite delayed from the standardized assessments given to developmentally typical children and validate it among a small group of patients? Parents offered ideas about how to measure changes in their own child's behavior or cognition (# of toileting accidents per day, # of outbursts per day, etc.), but using the same measure across a heterogeneous population with very different behavioral challenges would be difficult.

This leads to a second barrier: Clinician time and resources. Studies on behavior in Dravet syndrome are not only difficult to implement, they're difficult to develop. Clinicians don't have the luxury of starting with a set of behavioral strategies that can be implemented to determine which works best in Dravet syndrome. Patients with Dravet syndrome are often diagnosed with Autism, but usually it is an atypical form of autism due to scattered anomalies like their *increased* socialization and affection (Villas 2017). The time it takes to develop outcome measures along with variables to study such as strategies can be daunting to researchers.

Another possibility is that we have failed to engage an important stakeholder: Psychologists and developmental or behavioral therapy researchers. When we identified the stakeholders for the Engagement Award, we focused on clinicians, researchers, caregivers, industry representatives, and insurance representatives, but we did not actively recruit psychological science partners. Although there are hundreds of behavioral therapists engaged with our patients, none is playing a research role, and the active therapists are not necessarily focused on publishing research studies. The autism community has set an example for us to follow, utilizing research teams at academic institutions to evaluate behavioral strategies such as game-based treatment (Lalonde 2020). Dravet syndrome is rare and thus not often a focus of academic psychological science research. As a community, we need to be more aware of this gap and recruit these stakeholders, perhaps beginning with the 2021 DSF Family and Professional Conference.

Another possibility is the absence of any long-term cognition monitoring studies in Dravet syndrome. The academic world is focused on publication, which favors short term studies, 1-2 years in length, with results published within 3 years. This can be incredibly valuable, but does not give the community a sense of a child's developmental course or a natural progression of the disease. Snapshots of age groups can give a false sense of understanding of the natural history because the medications and treatments available to treat the seizures associated with Dravet syndrome today are far better than they were 10 years ago, and they continue to improve. Status epilepticus is much better managed at home with today's rescue medications than it was 10 or 20 years ago, and Dravet syndrome is diagnosed earlier, leading to decreased use of contraindicated medications that exacerbate seizures in the early formative years. To understand how our patients change over time, we need true longitudinal studies and committed researchers, using the same standardized measures over the course of 10-20 years. This requires the right team, the right outcomes, the right measures, the right patients, and substantial funding that does not yield results quickly.

And lastly, the rarity of the disease presents obvious challenges. Although diagnosis is becoming more frequent and is estimated to affect 1:15,700 infants, even the largest centers still only see 90-120 patients, often from a surrounding area including several nearby states, requiring travel for study participation. Patient-centered outcomes research will need to utilize coordination between multiple study centers across the U.S.

Clearly, the Dravet syndrome community has our work cut out for us in addressing caregiver priorities for research. We need to expand our professional community, continue to engage patients and communicate the challenges associated with non-seizure related research, identify and modify assessment tools that will enable us to accurately characterize the diverse population, identify funding mechanisms to support studies with delayed publication opportunities, and continue to follow up with clinicians and patients to ensure promising studies are carried out and not lost in the brainstorming phase. We have come a long way since the realization that reducing seizures does not necessarily result in a dramatically improved quality of life for our patients, and now is the time to act on that realization.

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Links to previous project descriptions:

<https://www.dravetfoundation.org/scc-lay-summary/>

<https://www.dravetfoundation.org/wp-content/uploads/2018/08/PCORI-Conference-2018.pdf>

<https://drive.google.com/file/d/10ng6NqHkK9kBcEujmhXGeXJ6gVH4ohFx/view>

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