Interview with Dr. Snead

UTMJ Interview Team (Happy Inibhunu and Annie Yu)

Dr. O. Carter Snead III

Dr. O. Carter Snead III, M.D., FRCP(C) is the Co-Lead of Project ECHO Ontario: Epilepsy Across the Lifespan, a Clinician Scientist in the Division of Neurology at the Centre for Brain & Mental Health and a Senior Scientist in the Neuroscience & Mental Health Program at the Research Institute of the Hospital for Sick Children, a Professor of Pediatrics, Medicine (Neurology), & Pharmacology with the Faculty of Medicine at University of Toronto, and a Member of the Institute of Medical Sciences within the School of Graduate Studies at the University of Toronto.

Prior to his relocation to Toronto in 1996, Dr. Snead was head of the Division of Neurology at Children's Hospital Los Angeles and Vice Chair of the Department of Neurology and Professor of Paediatrics, Pharmacology, and Neurology at the University of Southern California School of Medicine.

In Toronto, at the Hospital of Sick Children, Dr. Snead's work in clinical and basic research in childhood epilepsy led to invasive brain monitoring for children who are candidates for epilepsy surgery and the ground-breaking study of magnetoencephalography as a non-invasive diagnostic tool to select children for epilepsy surgery. Currently, his research is centered on developments in the field of drug resistant epilepsy and the role of THC/CBD oil.

UTMJ: Can you tell us more about the current research process on cannabis?

CS: Research in cannabis has been geared towards a wide array of clinical applications. With regards to the research process, there is substantial anecdotal evidence, but we need more rigorous evidence to approve a drug for use in the world of evidence-based medicine. This means Level I or Level II evidence, which represents randomized double-blinded clinical trials. Such a study requires both a control group and a treatment group. Sometimes, it could be a crossover trial, in which people are on placebo for a while and then they switch over to the active drug, and vice versa. Other times, patients are either on the placebo or the drug treatment all the way through.

The FDA, the Food and Drug Administration in the United States, requires two randomized double-blind controlled trials for statistical proof of efficacy. However, there can be a large difference between statistical proof of efficacy and clinical efficacy. For example, with epilepsy, you can have a pediatric patient who has 100 seizures a week, whom you give drug X. With the administration of the drug, you ask the question: does drug X have anticonvulsive properties as effective as anticonvulsive drug Y? After going through the process previously discussed, there might be a statistical reduction in seizures in the children treated with Drug X. For example, patients on Drug X might go from a mean of 100 seizures a week to 80 seizures a week. So, Drug X reduces the seizures statistically, but practically speaking in terms of quality of life and clinical efficacy, both from the perspective of the clinician caring for the trail and from the patient's family's perspective, Drug X is not very effective since the child continues to have 80 seizures per week.

With that background, the least compelling evidence is Level IV, which includes case reports or retrospective studies. Until recently, all of the clinical reports of efficacy for cannabis or its active anticonvulsant cannabinoid compound, cannabidiol [CBD] fell into this category. Now there is good Class 1 & 2 evidence for the clinical efficacy of CBD in epilepsy, but the evidence for other uses of cannabis such as for pain, gastrointestinal problems, anxiety, and depression remains predominantly Class IV evidence.

UTMJ: How about the preclinical research on cannabis?

CS: In preclinical studies, researchers create an animal model of a disease where drug X is applied to see its effects. From these studies, if it is deemed that the drug is effective in animals, the next step is to take it into clinical trials. Phase I clinical trial asks the question of whether the drug is safe by looking for toxicity and determining the pharmacokinetics of the drug, how it behaves, its concentrations, and the dynamics of the movement of concentrations of drug from the blood to the brain. Phase II clinical trials are open trials in patients while Phase III trials are double-blinded. While there was a lot of preclinical stuff in CBD and marijuana in animals, the results were conflicting. The problem is that when we talk about marijuana, it's not just a wild marijuana plant that people smoke for a high; it has at least 26 different cannabinoids in it. The most active ones are thought to be tetrahydrocannabinol (THC) and CBD. Also, there

are organic compounds, like terpenes, which may or may not have a beneficial effect. In terms of clinical efficacy in epilepsy the animal data suggest that CBD has anticonvulsant properties, but the evidence for THC in this regard is contradictory.

UTMJ: Based on these various studies, is there convincing evidence that cannabis is effective for any disease?

CS: The literature is replete with studies in which cannabis, cannabidiol, and THC have been used for anxiety, depression, pain, and epilepsy. However, beyond epilepsy there is very little, except anecdotal, evidence that cannabis works for anything. There are a lot of people who use it for all kinds of ailments, and they think it works. In terms of epilepsy, prior to 2013, cannabis wasn't used at all on children, for obvious reasons. However, many [adult] patients with epilepsy do smoke marijuana.

UTMJ: So how did cannabis research first start in the field of epilepsy?

CS: In 2013, there was a show on CNN about a child with Dravet syndrome, a genetic and severe type of epilepsy, who had a miraculous response to treatment with a marijuana oil extract which contained CBD. This syndrome was named after Charlotte Dravet, a French pediatric neurologist, who in 1986 describes a specific group of patients who had epilepsy. These patients seemed normal when they were born and did well in their first year of life, but suddenly started having seizures later on. Their seizures were often associated with a fever, were quite prolonged, and often involved one side of the body more than the other. Over time, these seizures became drug refractory and became a terrible part of their lives. Further, these children showed regression in their development, so they lost their ability to walk normally and their language was delayed. In the early 2000's, the genetic mutation for this disorder was discovered, which turned out to be SCN1A, a subunit of a sodium channel. There are various types of mutations of this gene, likely linked with the various severities of the disease.

Along the way, people discovered serendipitously these cocktails of drugs that were more or less effective for this disorder, but the seizures associated with Dravet remained very difficult to control. In 2013, Sanjay Gupta, a neurosurgeon at Emory and a CNN correspondent, did a show on this little girl called Charlotte in Colorado. Charlotte had a particularly severe form of Dravet syndrome, where she had 50 seizures a day.

Her grandfather was quite a vigorous advocate on her behalf. He took it upon himself to go to the literature because she had failed every legal anticonvulsant medication. He looked into the preclinical literature, for which I previously alluded to, plus the anecdotal clinical literature, and thought it would be worth a try to give her marijuana. However, he understood that you cannot give marijuana with regular levels of THC to a three-year-old child. Somehow, he discovered the Stanley Brothers who grew not only regular marijuana, but also made hybrid marijuana plants, so they could alter the levels of THC. They worked in Oregon where medical marijuana was legal. The grandfather asked them to make a hybrid plant that had increased levels of CBD and decreased levels of THC, which the brothers agreed to try to do. They called it Charlotte's Web. After Charlotte's Web was given to Charlotte, she had a miraculous reduction in her seizures. She became almost seizure-free and still is to this day. After CNN's report on her, there was an explosion of interest amongst the general public. Keep in mind that epilepsy is the second most common neurological disease anywhere, the first being headaches, and it is the most common and serious chronic neurological disease so there are lots and lots of people out there, both adults and children, who suffer from this disorder.

UTMJ: And did more patients begin using Charlotte's Web?

CS: Patients with drug resistant epilepsy, that is with seizures that don't respond to treatment with two or more anticonvulsant drugs represent 1/3 of all patients with epilepsy and are desperate to find anything that could help control their seizures. After the public learned about Charlotte's Web, there was this enormous pressure brought to bear on the medical community for the compound to be available in the United States. As well, we in Canada too were deluged with requests from patients for Charlotte's Web oil.

We couldn't get it from the States because at that time medical marijuana was not legal; however, our patients where ingenious. We had a few patients who just moved to Colorado so they could get it. There were other patients who went there, got it, and smuggled it back. Some even tried to extract the oil themselves and measure the CBD. In an extreme case, there was one little girl who was nine months old and had horrible epilepsy. She was having many seizures every day and her father was determined to get Charlotte's Web, was successful, and she became seizure free.

UTMJ: You mentioned that the drug, despite popular demand, can't be obtained in Canada. What are the legal restrictions on the clinical use of cannabis?

CS: As I said earlier, drugs must have two studies showing its efficacy and one study showing its safety. Following the enormous interest in CBD oil that was generated by the CNN show a drug company in the U.K. created a pure CBD compound called Epidiolex, and there was a multinational group that organized rigorous clinical

trials of Epidiolex in patients with epilepsy, with an aim towards FDA approval. The first study showed safety and ultimately two or three additional studies were published that showed efficacy. Hence, Epidiolex was approved last year in the United States, but is not available in Canada.

Then, in 2015, the Supreme Court lifted restrictions on the medical usage of marijuana's derivatives. Prior to this ruling, patients could only have a limited amount of dried marijuana and they could only smoke it. The Supreme Court had decided that this restriction did not keep up with the evidence, so there was no longer restriction on medical marijuana in any formulation. This ruling led to an explosion of an industry in Canada which is now further supported with the legalization of marijuana in Canada; there are now 65 to 70 producers that make CBD-THC products with varying ratios of CBD to THC. You can now obtain formulations all the way from 50 to 1 (50 parts of CBD to one-part THC) to 1 to 1. Importantly, our group believes that there is a therapeutic advantage with THC. in other words, the combination of THC and CBD is probably better than CBD alone. The issue is what is the optimal ratio, since we are limited in children by how much THC we can give them.

As we sit here, CBD is used widely and legally in both Canada and the United States. The Stanley Brothers have a website called Realm of Caring, which I refer my patients to in order to get Charlotte's Web. The product is delivered across the border after the Supreme Court's decision. I had several my patients write letters to Health Canada, emphasizing that they had benefited from Charlotte's Web.

UTMJ: What do you think lies in the future of cannabis research?

CS: Once a drug becomes legal and widely used, it is very hard to study it in a rigorous way. If drug X is proven to be effective and available for treatment of a type of seizures you cannot ethically do a clinical trial of drug X and assign patients to a placebo. Besides, patients will use drug X anyway if they can get it. So, the question of what is the best CBD to THC ratio may be insoluble in terms of generating any robust evidence. It is important to understand that cannabis is not a magic bullet. This is a new anticonvulsant drug with proven efficacy in certain types of epilepsy in adults and children. Our policy now is that if the child fails two or three drugs and the family asks me about CBD, we are willing to give it a try. Currently, the biggest problem is that the drugs are extremely expensive, and they are not covered by any healthcare plan. The families tell me it's like making another mortgage payment every month.

UTMJ: How effective is cannabis in drug-resistant epilepsy?

CS: As I started to say, cannabis is not a magic bullet; it works well about a third of the time. Potential side effects are a psychotic reaction, possibly due to the THC, or even worsening of the seizures. Because of these side effects, physicians have to be very careful. That is why only experienced professionals manage these patients.

Additionally, it is a hassle to obtain the drug. It is not like a prescription drug where you write a prescription and then the patient goes to the drugstore to get it. What happens is the family decides they want to use CBD, and in conjunction with their doctor, they pick out which CBD/THC formulation they want. The family then needs to notify the maker of the product and then the maker of the product contacts the physician to confirm. Then they send the product to the family. The physician and the family work out the dose.

UTMJ: Why is Epidiolex not available in Canada, as it is in the United States?

CS: Epidiolex is not available at all in Canada. The unavailability of this new anticonvulsant compound with proven efficacy in Canada represents a generic problem for new drugs in Canada, at least for epilepsy, in my experience. In the States, before the drug company funds a large study, they do a marketing survey to see how many potential patients there are and what the sales are going to be. If the marketing data supports the financial investment and promises profits, the drug company will go through the expensive process of getting approval from FDA and then marketing the product. Following FDA approval and marketing of the drug in the U.S., the drug company next needs to decide about whether to bring that drug to Canada.

The decision is based on what kind of regulatory hoops they must jump through, how much it is going to cost, and what the market in Canada is like. There is a process in Canada called the Special Access Program to get drugs that are not available in Canada, but, it still takes a long time and is not always successful. The bottom line is that currently there is no pressure on the makers of Epidiolex or Health Canada to approve this drug, particularly in light of the availability of such a plethora of THC/CBD containing compounds in Canada

UTMJ: Do you find that there is significant pushback or restrictions from the medical field or any other groups against cannabis research?

CS: There was some initial pushback, with two to three years of working on an agreement in the epileptic community, on how to move forward with the development of cannabis usage in epileptic pediatric patients. However,

I think what has really helped here is there is clear evidence now that cannabis works. The evidence has been published in very high impact journals, such as the New England Journal of Medicine and The Lancet Neurology. Nonetheless, there are side effects, primarily gastrointestinal ones, and many drug-drug interactions between CBD/THC and those drugs commonly used for treatment of seizures in Dravet Syndrome and other types of epilepsy. However, all that said I think more and more epileptologists are using these CBD/THC formulations more and more in patients with drug resistant epilepsy.

The Canadian Pediatric Society came out with a position statement a year or two ago which discouraged any usage of CBD in Pediatric patients. This was a bit premature since carefully controlled clinical trials looking at the anticonvulsant effects of CBD in children with epilepsy already were underway. Now there is little question that CBD works as anticonvulsant drug in children with epilepsy, in particular, those with Dravet Syndrome.

UTMJ: Do you have any advice for aspiring physician-scientists like yourself who are interested in new, controversial research topics?

CS: The main thing is to find a good mentor because these days it is extremely hard to be a clinician-scientist. Your clinician colleagues think that when you are in a laboratory, you are not seeing patients, so you are not doing anything useful. Meanwhile, research colleagues think you are a dabbler because you are not doing research fulltime.

But there is obviously a tremendous amount of exciting intellectual benefits, such as understanding the pathophysiology of whatever disease you are interested in and bringing that understanding to the bedside. It makes you a better teacher because you are able to explain basic mechanisms of disease better if you are investigating these mechanisms yourself.

Lastly, I think if you are interested in being a clinician-scientist, you need to stage your training. The most important aspect of your training is your clinical training. In your clinical training, you obtain a deep understanding of medicine and what you might be interested in. Once you have gained that understanding and identified an area of interest about which you are passionate, then focus on that. The first thing I would advise is to get as well-trained clinically as you possibly can and focus on the research aspect of your career following the acquisition of your clinical skills.