So a few interrogatory points here about epilepsy, the third most common neurological disorder, worldwide burden, similar with breast cancer in women and lung cancer in men. Risk of epilepsy up to age 20 is 1% and lifetime it's 3%. Now we are not talking about seizures, that's 10%. And 3 million people in the U.S. have active epilepsy.

Epilepsy treatment right now we have antiepileptic medications, seizure surgery, neurostimulation, dietary therapy immunomodulation. Now we are going to talk today mostly about neurostimulation. And first we have to try drugs. Whatever physician sees the patient first has this 51 chance that the drug will work if it's well tolerated. The second drug 7% response and then the third, fourth are polytherapies really are low response. 35% will have resistant epilepsy. They will not respond to the medications.

Now in 2010 they came with a definition, epilepsy n which seizures persist and seizure freedom is very unlikely to be attained with further manipulation of antiepileptic drug therapy. What you have to do is two tolerated and appropriately chosen antiepileptic medications. If you fail the first two your chances are really low. The patient should be referred early for surgery. Now I'm not talking about neurostimulation, I'm talking about executive surgery because this remains the only cure.

So today we are going to talk about neurostimulation. Now what do we know about focal seizures? And when I talk about neurostimulation we are mostly going to talk about focal epilepsies and not the generalized epilepsies. Even untreated seizures are brief, self limited events. Seizures are characterized by transient increased network synchrony. Seizures from a single focus in a given

patient have similar dynamics, particularly at seizure onset. The seizure usually starts at the same spot in the same frequency band. Seizure termination can be abrupt and synchronous over a broad region. Most seizure terminations are abrupt, but we do see in our patients that sometimes the seizure spreads and then you continue the seizure on the other side but that's not the rule. Seizure termination may not require inhibition, we just need to desynchronize the network. Termination of seizures may represent the synchronization or diminished activity.

Now brain stimulation, there are two types from my point of view as an epilepsy doctor: chronic stimulation which may disrupt reduced baseline network synchronization and acute stimulation which may disrupt abnormal activity during seizures altering seizure dynamics and reducing seizure duration. Inhibition may not be necessary for seizure termination and we only need a small current. Now we are not defibrillating the brain, we are not applying large currents. And when we talk about synchrony yes we do need synchrony in the brain otherwise you are in a coma or you are dead, but we are talking about seizures having I shouldn't say but it's almost like a hyper synchrony.

Neurostimulation to treat epilepsy. Avoid additional toxic cognitive, any side effects from medications, and patients are typically unaware of intracranial stimulation. There were some early unsuccessful trials of neurostimulation and that was in 1978 and 1992 they tried cerebellar stimulation which kind of was the wrong way to go because they are firing continuously. And then they tried a centromedian thalamic stimulation. Those were not successful for epilepsy.

Now in 2004 what we have FDA approved as devices, we have the VNS and it has been approved from the '90s, we'll go back to that and we have enough experience with VNS. It's constant intermittent stimulation and then placement is external, it's on the left side in the chest. Also we have more recently in 2013 the RNS, the responsive neurostimulation approved which we are considering a closed loop will detect your seizure and stimulus is delivered in response to seizure activity. The stimulator is intra - it's not intracranial, it's like really in the bone and then the electrodes are intracranial. Devices awaiting FDA approval, we have anterior thalamic stimulator which is a constant intermittent stimulation, almost like the VHS. We have intracranial probes but for this DBS, our DBS for epilepsy it's also an external device in the chest.

And devices undergoing trials we have trigeminal nerve stimulation which is constant intermittent stimulation and placement of stimulation is extracranial. In fact you have this band which patients are wearing it on the forehead and you have to keep it like 12 hours every night. These hours not so good for now. And then transcranial magnetic stimulation which is also discrete treatment periods, extracranial stimulation. I'm not going to talk about them.

Back to the types of brain stimulation. Chronic stimulation, the open loop, like the VNS like the DBS you have - not continuous but regular periodic stimulation independent of seizure occurrence, like the VNS used you stimulate, you are off, you stimulate, you are off. We have option for patient activation at seizures with a magnet for the VNS. And then you have the closed loop which is the responsive stimulator designed to stimulate brain at seizure onset. The goal is to terminate seizure or

significantly reduce seizure duration. We can hopefully top a seizure at the electrographic or aura phase. It does require sophisticated seizure detection algorithms.

VNS, the one that has been in use for a long time, so this is the one that's implanted, this is the magnet. This is our device. Right now it looks more like a laptop, they changed it. This is the wand that's connected to your device. This is not the wireless device. And then the patient in the chest on the left side has this little device implanted. There is kind of going into a wire and we'll show it soon what it does. And just loops around the vagal nerve, and it is on the left because of the less side effects, cardiac side effects.

VNS mechanism of action, it's unknown. Antiseizure and antiepileptic properties in animal models they did the studies in cats may be mediated by enhanced noradrenergic activity, locus ceruleus, and some think can be neuromodulator and might alter plasticity.

A VNS therapy, this is 3 years and we are talking about the patients that responded and we had a 42% of patients that were responders, that means they achieved more than 50% seizure reduction. Data, longer data at 12 years show that the patients - the reduction numbers were higher and higher in time. They went into the high 40s for the number of patients responding and for each individual patient that responded they got better and better seizure reduction, so more than the 50%. Based on the studies FDA approval was in 1997 and 1994 for Europe and was indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients over 12 years of age. It was initially for partial onset seizures but now we know we use it in generalized epilepsies as well. The

evidence based guideline that came in 2013. VNS is associated with a 50% seizure reduction in 55% of the patients. So 55% of the patients had 50% seizure reduction.

We know the safety profile, we had it for a while. We did not see any increase in SUDEP. In animal studies. In animal studies it was okay to use with no harm to the fetus and no problems in infertility, and then I have some patients that are pregnant and they didn't - I have some patients that already delivered, we have not seen any problems with the VNS in the mother or in the fetus.

So this is what we have, this is our baseline, this is what we have for epilepsy, this is what we had for a long time. But right now they came up with you know the RNS, and we'll talk about it. But quickly just one page about this trigeminal stimulation. So earlier studies reported responder rate of 40%, so 40% of patients had more than 50% reduction. But then when they did a recent double blinded controlled studies they only had 50 patients, they looked in this drug resistant epilepsies and there was no significant difference between the responder rate in treatment group versus the active control group. The device does not have approval here in the U.S. but has been approved in Europe and Canada.

Now the intracranial stimulation. So the intracranial stimulation we have two devices. One is our DBS that's not approved and one is the RNS that is approved. I'll touch base on both of them.

Patients with medical intractable focal epilepsy and seizures that significantly affects quality of life you are not going to put this in any patient that's controlled with medications even in polypharmacy.

Patients that are not good surgical candidates if you can do resection that remains the only cure. Patients who have failed seizure surgery you can try the device.

The first one that's not FDA approved is the stimulation of the anterior nucleus of the thalamus. And I'm sure there was a lot of DBS being presented but the device is external, you have two leads going in. After the implantation they see this decrease in seizure frequency in active and in controls in the first month. Now when you go down that's good, that's a seizure reduction. The control actually started picking up by 3 months and the only one that continued having seizure reduction was the active stimulation.

Now there were 110 patients in the SANTE trial, the stimulation of the anterior nucleus, and they seen at the 3 months blinded period they seen a 38 reduction compared to the 14.5 on placebo. Now by the end of the couple of years they only had 87 patients in the study. And out of these 87 patients they seen that the patients that responded slowly increased. There were some patients that were seizure free in the study, 6 patients. But again the median, so 56% of the patients had over 50% reduction of seizures.

Now in the DBS study it worked better for the temporal lobe, and everything we have actually worked better for the temporal lobe. Our surgeries work better too, and did not work as good in frontal parietal and occipital epilepsies. Treatment work after surgery or after vagal nerve stimulator, they might have had a VNS for years. Higher incidence of spontaneous reported depression and memory problems and anxiety in the active group, but that was not confirmed by

objective testing. So this is what we had and it was not approved. Now for the numbers so at the end of the 2 years we had 56 responder rate with a over 50% reduction in seizures. I'm not so sure how much difference was with the VNS even if we were intracranially on the device. But it is possible that in time we are going to see better reduction. That was just at 2 years what I presented, while for the VNS we already have like 12 year studies.

So now this is the one we are very excited about the responsive stimulator, the closed loop. And why we are excited is because this is a smart device. It's continuously monitoring brain electrical activity, it has 1 to 2 electrodes. Now this 1 to 2 electrodes you can place them in a single region, both of them, you can cover like more superficial if you have like - yeah a more superficial seizure focus or seizure network, you can put one of the subdural or you can go with a deep like a depth electrode if it's like you know periventricular area or kind of a hippocampus or anything different than temporal lobe. So you are monitoring the device, it's acquiring the data and it's storing the data. Now the data storage is temporary.

In a phase II you are going to program the device to recognize seizures. You are going to see what the seizure signature is, you are going to program the device to recognize this. And when it recognizes to deliver a very small current. Your hope is to stop the seizures. So FDA approval, individual 18 years of age or older with partial onset seizures, what we call focal seizures with alteration of awareness, diagnostic testing that localizes no more than two epileptogenic foci, you cannot have a multifocal patient here, a refractory to 2 or more antiepileptic medications. It's used in

conjunction with medications. Currently have frequent and disabling seizures either the motor partial, the complex partial, some secondary generalized seizures, not just auras.

How does it function all this? So you implanted the device in the skull, you are recording through those two other depths or subdurals. The patient almost every day, sometimes every 2 days will have to with this wand kind of wirelessly transfer the data and the data goes into the database. You can access the database by yourself if you have time or whenever you are sitting with the patient in the clinic. You have to be able to read electronic cartography, you have to be able to read - to identify seizures intracranially. And after probably one month in which you are just acquiring the data you see how many seizures onset you are recognizing you are going to start programming.

So you've identified big spikes happening, you identified this kind of frequency building up sometimes and then you have to - you detect, you will deliver, you will deliver - I mean not you, the device will deliver a little buzz. Probably you have to adjust at each visit, you are not done. So you are going to see that in some seizures, that you are stimulated too late, that you recognize the seizure set 3 seconds and maybe if you are delivering at 2, at 1 second and every - or maybe you missed some seizures, maybe in the first month only one of the clusters was or firing and the second one was not. So you are going to - in time you are going to learn what seizures you missed, you are going to learn that maybe you missed them because you haven't seen them before or because you stimulated too late and the seizure continued. And you are going to improve.

So in the studies they had 230 studies, 230 patients. They seem the same as we see in the DBS, we seem to see improvement in the seizure reduction before you even started stimulating, but then once you turned on stimulation the seizure reduction continued while the other ones that were not stimulated kind of almost returned to their baseline.

Two-year responder rate for over 50% seizure reduction was 55%, somewhere over there. And you can see how the device, not the device but the patients are actually slowly in time getting better. There were some side effects, some of them related to the implantation site, they seen some deaths, most of them were not related to the device. We do have SUDEP epilepsy and the rates of SUDEP were not larger than in our chronic intractable epilepsy population.

The side effects we see no side effects on cognition, no adverse effects on mood, patient was unaware of therapy. It takes months to be properly adjusted both seizure detection and programming, Optimal stimulation parameters are unknown and we are still working through this. Intracranial surgery is mainly for implantation and the battery change was a problem. Initially they were expecting 5 to 7 years on the batter life, but then they seen that in 2 years your battery was running out. So they were wondering why. And under detection they seen it was expected to be you know whatever 10, 20 seizures and patients can have it a day, some patients you know are per months, but then they were seeing 500 detections and they were seeing 500, and the detections were not false detections. So they were seeing detection of abnormal epileptiform kind of electrical activity. And that's why the battery was running so fast. Now there is another question, is it possible that not only you have the closed loop so you've seen the seizure onset, you've recognized it and the

device already buzzed that seizure and stopped the seizure but on top of that with the 500 seizures, seizure activity today you have also a chronic stimulation going on almost like in the other VNS and the DBS for epilepsy.

So who should get RNS? Disabling drug resistant focal onset epilepsies, we are not talking about patients that have generalized epilepsies. We are not talking about (inaudible) patients that are multifocal. Not good candidates for execute surgery, remember that remains the only cure for epilepsy. One or two seizure foci, not multifocal. Relative localization of seizure onset zone and intracranial monitoring is not required. We really don't know how close we need to be to the seizure focus, we don't know. We think that the closest we are the faster we are going to be seeing the seizure. We are not going to see a seizure spread in the network, we are actually going to see the real seizure onset so we should be as close as possible because that will allow us to identify the seizure and deliver the current much faster. But we don't know how close we need to be. You should be somewhere in the network for sure.

Very good candidates are the bitemporal epilepsies. We've been frustrated for years because we couldn't offer them anything. You have seizures coming bilateral hippocampus and this is a device that we expect that will work really nicely on our seizure focus in our eloquent cortex, so you were intracranial, you identified the seizure onset, you are really happy, the single seizure onset, it's a really small area, it's really good for eviction but you can't because you are in the motor area, you are in the language area, you really can't take that out. So this will be something also to be strongly considered.

Now as a conclusion, we had pivotal trials with responder rate 38% during blinded phase and rising over 50% in open label period. Just as a reminder, we don't know the stimulation parameters and we don't know how close to the seizure focus stimulation needs to be. And not knowing this we still got over 50% responders. The better we are going to become I expect the numbers are going to improve. And as I said with typically tuned detection algorithms RNS delivers therapy more than 500 times a day. And that's a lot of -