Good morning, thank you very much. I’m happy that everybody is here this morning, hope that you enjoy the program. I’m going to start out this morning by focusing on devices, which is a very important area in psychiatric research as well as in neurology and other branches of medicine.

The history of interventions based on surgical procedures in psychiatry is quite checkered. In 1935 was one of the first planned experiments, this was conducted in Europe. Egas Moniz, a European neurologist had developed a notion about a way of treating psychiatric illness by selected cuts and ablation procedures in the frontal lobes of the brain and he collaborated with a neurosurgeon and they actually conducted a small study of 20 subjects. And these subjects had depression, anxiety disorder, schizophrenia or bipolar disorder, and actually published his experience with those 20 subjects in 1936.

In the U.S. Walter Freeman brought the same procedure to the United States and using much of the same surgical techniques worked with James Watts, a neurosurgeon. But his interest was in really developing something that could become office based. And that led to sort of a deterioration in the quality of rendering the procedures and it’s often referred to as his ice pick therapy because of the crudeness of the procedure and really the deterioration of neurosurgical techniques. But his interest was in broadening it to a wider scope of chronically ill patients with a variety of psychiatric illnesses. And that led to really a burgeoning of these procedures up until the mid-1950s, so about 20,000 individuals worldwide at some point had one of these procedures for severe chronic intractable
illnesses, and not necessarily related to schizophrenia, it often involved individuals with mental retardation, depressive illness and other ill defined groups of psychiatric patients.

In 1949 Moniz actually received the Nobel Prize for his earlier work. And the procedures that he had done and his selection of patients in many ways was much better than what Walter Freeman brought to the U.S. And unfortunately it was the work that Walter Freeman did that was one of the downfalls of surgical procedures so that the broad use of these interventions in any type of patient population, the type of procedure that was done there was a lot of ill effects from it. So it really suffered from a reputation standpoint in terms of how these patients were treated and what happened with them. But obviously in the mid-1950s pharmacotherapy was introduced, Chlorpromazine, Thorazine introduced in 1955 and then tricyclic antidepressants and monoaminoxidase inhibitor antidepressants in the late 1950s and those drugs ushered in really the era of modern psychopharmacology in the 1970s, 1980s and even until today.

The other problem with these types of procedures is it’s hard to do controlled studies, and it’s hard to do modulations or changes with treatments to obtain the best response. But these procedures still exist, they can certainly be done and there are certain institutions, Mass General and other places in this country and around the world that still in selected, carefully selected patient populations with either treatment resistant depression or treatment resistant obsessive compulsive disorder can still do these types of procedures when all other fail – therapies have failed. But really following on sort of the history of psychosurgery is the notion that devices could be used as a treatment for psychiatric
illness. And for a lot of individuals devices to treat a psychiatric or psychologic problem is kind of odd or foreign or unusual, so I’m going to talk this morning about a variety of approaches using different types of devices that are used to not create ablative lesions, permanent lesions in the brain but do serve to modulate the function of different brain regions in order to treat a variety of psychiatric illnesses.

So I refer to this as therapeutic brain stimulation but it really should be considered neuromodulation because with these types of stimulations you can actually excite brain tissue or you can inhibit brain tissue but it’s entirely intended to be reversible, potentially reversible and also modifiable. So that depending on what the device is and the type of stimulation that you are using is you can actually adjust it much like you would adjust the dose of a medication or change the focus of a psychotherapy. And these have actually been used in many respects to treat neurological disorders and in more recent years to treat depression and also refractory OCD. But they also have some potential utility in actually studying brain function because they don’t cause permanent lesions and you can use different types of stimulation to assess what regions of the brain have particular functions, either behavioral functions or motor functions.

Now one of the most common types of therapeutic brain stimulations is ECT. This has been in use for many, many years, it predated the era of modern psychopharmacology, it was actually developed during the same year that psychosurgery was conducted in the 1930s and became of greater use in the 1940s and since then. ECT is still considered the gold standard treatment for treatment resistant
depression so patients that have failed any type of therapy, medication, psychotherapy, ECT is still sort of the stand alone therapy in terms of what maybe potentially effective. It does suffer from its own bad reputation although with qualified hands the administration of ECT really is considered very safe and it can be very effective not only for treatment resistant depression but psychotic depression and certain patient populations where you may have particular concerns about the safety of medication. Women during pregnancy suffering from severe psychiatric disorders and also geriatric patients may greatly benefit from ECT and also have the benefit done safely. The most prominent adverse effect I think for most people who are familiar with it are the cognitive effects. And part of – some of the studies it will talk to today about using other devices are predicated based on using not dissimilar principles to ECT but to try and minimize some of the adverse effects of ECT.

Transcranial Magnetic Stimulation, TMS, is another type of device based therapy. This involves the use of a rapidly alternating magnetic current to induce a weak electric current in underlying brain tissue. So this does not involve a brain surgery but it does involve a stimulation by applying the TMS to different brain regions. And this is one type of device that has been used to study brain function but also have a lot of therapeutic and potential therapeutic applications in neurology and psychiatry. And psychiatry does have FDA approval of a particular device manufactured by Neurostar. The labeling for the device are for individuals with depression that have failed one antidepressant therapy, so the labeling is quite limited. But the existing literature published studies looking at its
utility in various forms of depression suggest that there may be some benefit although not a very strong benefit for patients with more extensive forms of treatment resistant depression.

Surprisingly the studies that have been done in anxiety disorders have not really shown a significant benefit, but it has been applied also in other neurological conditions and there are ongoing studies, for example auditory hallucinations in patients suffering from schizophrenia, pain conditions, tinnitus and other disabling neurological conditions.

Now an offshoot of TMS is something referred to as Magnetic Seizure Therapy, this, the intended purpose of Magnetic Seizure Therapy is to actually induce a seizure. So with TMS the usual stimulation does not induce a seizure, but with a high enough intensity the underlying brain tissue can be induced to propagate a seizure. And the therapy behind MST is to really limit the focal area of the seizure, at least the induction of the seizure. And the idea is eventually to replace or to supplement the use of ECT with a similar procedure with fewer adverse effects. There is very limited human experimentation though with MST so it is investigational. But the principle is to use a type of TMS but to induce a seizure, so it’s a mixture of TMS and what one intend to do with the use of ECT. And again the patient population of interest would be patients with refractory depression.

Another type of therapy is called Cranial Electrotherapy Stimulation, and this actually is an old treatment. The literature goes back many, many decades. The studies though are generally of poor quality but this is a device that actually was approved by the FDA in 1979 for anxiety, depression
and insomnia. But the approval of this device is based on old regulatory guidelines that were in place in the 1970s and it’s not clear to me today whether this type of a device based on the available studies would necessarily receive FDA approval. It is a low risk device and the administration of CES is quite safe, there are few if any side effects. And this involves the use of very low pulsed micro currents and typically the treatment would be administered by ear clips and the device would pass a very low essentially undetectable current through the brain, and probably the only thing that a patient might experience is a tingling where the point contact is with the electrodes. So this is a device that actually one could use, you could certainly find a practitioner or a manufacturer of the device, but my reading of the literature would suggest is that the studies that you know are suggesting some benefit for depressive disorders, anxiety disorders, etc really are not high quality studies. So you have a device that’s approved, a low risk but not necessarily effective for patients with more severe types of depression or anxiety disorders or patients with treatment resistant conditions.

Another type of stimulation is Transcranial Direct Current Stimulation and this is somewhat different than CES, this is also investigational. There is one pilot study that demonstrated some benefit in patients with treatment resistant depression, there was also more recently an unpublished clinical trial, a randomized sham controlled trial in 64 patients with treatment resistant depression suggesting benefit to this type of intervention. That study is recent and I’m not sure that it’s yet been published but it is in Prowse. And this is predicated based again on notions of inducing electric currents, the intent is not to cause a seizure as a part of its therapeutic benefit and the types of side effects that one
would experience with that qualitatively and quantitatively are different than what are experienced with ECT, in particular adverse cognitive effects.

And with this type of procedure it’s applied externally and you need two electrodes and typically one would be placed on the motor cortex near the crown and then a second electrode would be placed above the eye so the contralateral orbit, and this low level direct constant current is then passed from one electrode to the other and the therapeutic benefit in some ways based on the administration of that low level current. Some muscle contractions and perhaps some muscle pain are a potential side effect. It is possible that you could induce a seizure although with the currents that are used that would be considered unlikely.

Another type of procedure, this is actually related to ECT because the machine that’s used to induce the electric current is the same type of machine that’s used to administer electroconvulsive therapy. And the principle of it though is to focal, focalize the current to a particular brain region. And it does so by altering the current so that it goes in one direction and also the theory is that if you use a larger electrode and then a smaller electrode like a funnel the current will be funneled to a particular area of the brain. So this is an experimental procedure investigational, most of the work and there is some human experiments you know looking at how the electrodes are placed but no clinical studies. But the intent of this would be to use it as sort of a modified or alternative type of ECT, because with a high enough administered current and voltage you can actually induce a seizure so that there are two alternative forms, one that does not cause a seizure and the other than would be intended to
cause a seizure. But the point of this procedure is really to limit the current to a particular brain region and to avoid sort of the broad spread of the current that might be associated with adverse effects, especially the cognitive effects that you see with ECT. The work that’s been done with FEAST inducing seizures has actually only been done in animals studying this type of an effect, but the principle again is the same.

Now the frontal lobe of the brain is quite important and some of the procedures, TMS for example, are predicated based on understanding what happens in the frontal lobes in individuals with depression. The types of psychosurgical procedures that were developed in the 1930s were based on the notion that the fibers connecting the frontal lobes to the deeper structure of the brain in some way were functioning abnormally and by severing or cutting those fibers that you may induce an improvement in the underlying psychiatric symptoms, depression, anxiety. So there is some relationship between the older procedures and some of the newer surgical based procedures in what are done with things like TMS. Now TMS is focused on an area of the brain in the dorsolateral prefrontal cortex, and this area especially on the left side of the brain is relatively underactive and that part of the brain may be relevant for understanding mood symptoms as well as cognitive symptoms. So TMS is based on the notion that stimulating that particular region of the brain may lead to a clinical improvement. And so as I mentioned a device manufactured by Neurostar currently had FDA approval and is currently labeled to be available for patients with depression that have failed a single antidepressant therapy.
Curiously there are differences between the right and left dorsolateral prefrontal cortex. So the usual high intensity TMS stimulation is directed at the left region, a lower intensity stimulation of the right dorsolateral prefrontal cortex also has antidepressant effects as well, so there does seem to be a bilateral difference in that type of stimulation. So high frequency is effective on the left side, low frequency is effective on the right side although the device that’s approved in the labeling is indicated for application to the left DL PFC.

Now a modified type of TMS is investigational. This uses the same type of stimulation, rotating magnets, but the intensity of the magnetic stimulation is less than what is intended with TMS. It also is applied to both sides of the brain, so the brain region is different than TMS, standard TMS and also the intensity of the stimulation. And this is intended to change cortical frequencies and oscillatory frequencies and in particular the alpha band waves. So the type of treatment, and this is a schematic of how this type of TMS is administered, involves 3 magnets. One is placed on the crown of the skull, the other the middle of the forehead just above the eye and then the third one in between so it’s a midline application, so it causes TMS stimulation to both hemispheres, so it’s not directed at the left dorsolateral prefrontal cortex. And the intent of this lower level stimulation because it’s tied to the alpha frequency that’s measured for each individual patient is to try and tune those frequencies and to try and reset oscillatory frequencies throughout the brain through this type of stimulation.

So this is what the device actually looks like. A patient would lie on the table and their head fits neatly, so this is above the forehead and the other magnet is at the crown and then the middle one, so
it covers it neatly. And patients would lie there and have this treatment administered. At the beginning the device will actually measure a patient’s alpha wave, and then the TMS is programmed to the same frequency of that individual patient’s alpha frequency. And then they would sit in the device for 30 minutes and they have to be awake to maintain the alpha frequency but they have the stimulation. And the belief is that that type of stimulation over time has some type of an effect on oscillating frequencies throughout the brain that may be important for regulating or connecting disparate brain regions. And some of the work hasn’t been publicized or published, but it is based on notions about disconnected brain regions and the importance of different EEG wave forms in terms of how different regions are connected and making changes in terms of being on or being off. So the intent of synchronized TMS is very different than standard repetitive TMS in terms of its application and the intensity.

Now there is a published study, this was actually presented at a meeting as an abstract, a pilot study, it was sham controlled using STMS and subjects with major depression for 4 weeks. So half the subjects had the device activated, the other half the device was not activated. And it was conducted in a double blind and what the pilot study showed is that the act of treatment had an antidepressant effect in terms of response rates and remission rates compared to the sham treatment. So this took it from principle to an actual clinical population. And this has led to a larger collaborative study and we are participating in it in Pittsburgh. This is focusing on the use of STMS in patients with major depression, it’s a double blind placebo, or sham controlled study. And this is focused on patients
with a limited form of treatment resistant depression. So it’s using the same type of device with the same application but in a little bit different patient population.

So we’ve already enrolled one subject in Pittsburgh and the inclusion criteria for this study are adults suffering from major depression, no history of bipolar disorder, no history of psychosis. And patients cannot be considered chronically depressed, so their current episode duration has to be less than 2 years. And the population for this particular study was based on the current labeled population from the FDA approved TMS device, so patients that had failed one antidepressant therapy who were suffering from major depression are eligible for this particular project. So it’s a very narrow patient population, they are not treatment naïve and they also do not have extensive histories of having failed a variety of antidepressant therapies. But it’s similar to what is currently approved in the labeling for the TMS device on the market.

And patients that are eligible would discontinue their current antidepressant medication. At the beginning visit they would sit in the device and have their individual alpha frequency analyzed and then the device is programmed to match that. And because it’s a sham control one of the devices is active, the other device is not active and there is no way of distinguishing the two. When STMS is administered you don’t feel anything. In theory you can have headache, muscle contraction, but the intensity of the TMS stimulus is so low that you would rarely expect those types of effects. So the blinding for this is somewhat easier compared to other types of device interventions.
One of the other difficulties in doing this is TMS typically is administered 5 days a week over a period of weeks. So the current approved TMS device was based on studies where patients received the treatments 5 days a week for up to 6 weeks. Then they actually have to come to the clinic, so it’s very different than doing a drug study where somebody takes a medication at home or even very different than psychotherapy study where a patient might come in twice a week for a period of weeks. So this is sort of a labor intensive intervention for the approved treatment, but also for the study from the patient’s perspective. And then in this particular study patients who receive the active treatment and there is an optional open label phase where again the blind is not broken so we don’t know whether the subjects have had active STMS or not, but will receive active treatment over a period of time. And this is randomized, double blind placebo controlled.

Now I’m going to focus a little bit about devices that do involve neurosurgical procedures, but again these types of procedures are not intended to cause lesions or ablations in brain regions, so they do involve surgery often to implant electrodes or the pulse generators, the pacemakers to generate the type of stimulus that’s used. And the ones that we are familiar with are Vagus Nerve Stimulation, Cortical Brain Stimulation and Deep Brain Stimulation. VNS and DBS have certain FDA labeled indications, each of them has also been studied in depression. Cortical Brain Stimulation is considered investigational, it’s been studied in depression, I’ll present some of the results of the study that we participated in.
Vagus Nerve Stimulation may be something that you are all familiar with to some degree or another. This is FDA approved for treating refractory epilepsy, certain subtypes of epilepsy as well as treatment resistant depression. And this involves a procedure where the electrode is placed in the vagus nerve and the vagus nerve runs up through the neck, so it doesn’t involve a procedure to the brain itself. And the device, the pulse generator is connected to the vagus nerve. And the principle is that the propagation of the current causes a direct and indirect stimulation of various brain regions, so this is an antiseizure therapy, it doesn’t induce seizures. But the changes that often occur, chemical changes and probably regional changes in different parts of the brain that are relevant to mood regulation are altered, and so based on this chronic intermittent stimulation of the vagus nerve is that there are antidepressant benefits. So the device is FDA approved for treatment resistant depression.

There are a number of pilot studies that have been conducted and most of these have been published in a variety of conditions ranging from treatment resistant anxiety disorders to Alzheimer’s disease, a study done in Sweden because of the potential positive cognitive effects of stimulation of the vagus nerve. The most recent study though in depression is referred to as D21 and we participated in that in Pittsburgh.

This is a study looking at 3 different dose levels of vagus nerve stimulation in patients with treatment resistant depression. So this study was randomized and double blind and patients were randomized to 3 different stimulations, low, high and intermediate stimulation and these are the baseline
characteristics, which is really to illustrate how sick this patient population is. When you look at the percentage of patients that have received ECT in the past or in their current episode is very high, 50%, without an adequate response. In the past more than 90% of the patients had failed more than 6 different types of antidepressant therapies, and in the current episode down here about 80% of the patients had failed 6 or more antidepressant treatments in their current episode. And these patients in their current episode were depressed for an average of 9 years. So they were very chronically ill, severely ill and also very refractory to treatment. And so these were patients randomized to 3 different dose levels of VNS.

So the acute phase was through 22 weeks and there were different assessments that were done measuring improvement in depression symptoms. And what you see is that there is a numerical difference between high, middle and low doses but it wasn’t statistically significant. And the study enrolled more than 200 subjects, so there was a hint that higher stimulation doses were more effective but it really didn’t achieve statistical significance. And this was after 22 weeks. And these are the remission rates, again showing numerical differences favoring the higher stimulation but no statistically significant difference among the three different dose levels.

And this is then tracking patients over time using one of the depression measures. So after the acute phase patients continued for up to nearly a year’s time, and what this study also demonstrated is over time there really wasn’t very much of a difference in the three different dose levels. But what is known from prior VNS studies and what this study confirmed is that there seemed to be an
accumulating benefit over time. So that over time patients with chronic treatment resistant depression tended to get better.

And one of the things about treating treatment resistant depression with pharmacotherapy is that there is a high risk of relapsing. It’s not uncommon for patients with TRD to show some initial benefit to a new treatment but then that benefit peters out or dissipates over time. So the persistence of a benefit over time is really one of the difficulties in managing this type of patient population. So this was the analysis looking at the persistence, comparing what happened at 22 weeks versus 50 weeks. And what the analysis showed is that a significant proportion, the majority of the patients were able to maintain their 22 week benefit for up to a year’s time. and again this is I think very important in terms of thinking about what happens with these types of patients over time when they are treated with non-device based therapies. You might find something that works for a period of time but then lose the benefit and you have to go through these iterative cycles of trying different treatments or different treatment combinations. And there really again wasn’t much of a hint that there were different dose effects over time although there was a suggestion that the patients in the lowest stimulation dose were less likely to maintain their initial benefit from week 22 to week 50. So in the clinical use of VNS one might adjust the stimulation to higher and higher levels over time to try and either enhance the benefit or to maintain the benefit.

Now like all treatments there are adverse effects with VNS, but VNS has actually been used in many thousands of patients around the world for epilepsy and now depression, so there really is a lot of
human experience with VNS. And really for the most part it’s a very well tolerated treatment. There aren’t any measurably severe significant side effects, and over time even the side effects that do occur, the voice alteration, etc. tolerance can develop to that. So over time one can adjust the stimulation to higher and higher levels to try and gain a better response, but over time side effects typically do not multiply or increase in either their severity or their persistence.

Now Cortical Brain Stimulation is another type of stimulation. This involves a surgery and it involves placing electrodes on the surface of the brain, so there is one surgical incision to place the pulse generator in the chest and then a second one where the electrode array is placed on the surface of the brain. It’s investigational and it’s been looked at in stroke, tinnitus and also depression so the location of the electrode array will depend on the indication. And this is how it’s setup, the pulse generator and the electrode array. For depression where the electrodes are placed on the surface of the brain is the left dorsolateral prefrontal cortex, so the same region of the brain that is the target of interest with TMS. And the theory behind using a surgical intervention is to bring the stimulation in more direct contact with the brain because the administration of TMS has to go through the scalp and the skull and that’s resistance. And so by the time TMS reaches the brain the intensity may be either dissipated and weakened at that area or it may be spread through different areas of the brain. So the principle is really to apply the same stimulation but more directly to that brain region.

And the other problem with TMS is that it requires a constant application 5 days a week for 6 weeks during acute treatment, it’s hard to do maintenance treatment with something like that. So in theory
using a surgical intervention providing a similar type of stimulation to the brain can be done automatically through this battery generated pulse generator. So it was really designed to sort of replicate what TMS does but to make it more of a long term therapy but also for more, for a more varied treatment resistant patient population.

So this study was actually just published this month in the Journal Neurosurgery. This was a pilot feasibility study of 12 subjects and the patient population in terms of severity is similar to what we saw with VNS, so they are chronically depressed, an average of about 7 years, they’d failed a large number of antidepressant and psychotherapies all targeted at depression. So this population is a lot messier than the typical patient population that would be used for TMS.

And so in the first phase of the study patients were treated for 8 weeks and this was a sham controlled, so some of the patients had the device activated, the other half the device was not activated. After 8 weeks it was activated for all subjects and they went through another 8 weeks and then long term treatment. So these are percentage changes in depression. During the acute sham controlled phase there was no statistically significant difference between active treatment and sham treatment although there was a small numerical difference. But you have to keep in mind that this was a pilot study, it was not intended to show efficacy it was primarily focused on safety features. But also the sample size of 12 subjects would make it very, very difficult unless there was a very large magnitude difference in benefits. What we also found over time was that there were small
persistent changes over time, suggesting that this therapy could be beneficial for patients suffering from chronic treatment resistant depression.

And like Vagus Nerve Stimulation, Deep Brain Stimulation there is certain side effects, but the targeted area the risk of seizures is very unlikely because the stimulus that’s actually applied to the surface of the brain is fairly weak. You could turn up the juice enough and eventually you could induce a seizure but how the device is programmed is really limited to stimulating that cortical surface of the brain. Adverse effects in terms of changes in mood were not observed in the pilot study and also no adverse cognitive effects.

And then finally Deep Brain Stimulation, this one also involves implanted electrodes but rather than being placed on the surface of the brain are directed at various targets in deeper regions of the brain. But like VNS and Cortical Stimulation are driven by pulse generators, so an external stimulation to the brain. But this is focusing on brain regions. And this has actually been studied quite extensively. So again the pulse generator is because the stimulation is in both hemispheres of the brain rather than a particular single region, involves two electrodes.

And in order to direct the electrode to a particular target deep inside the brain one has to direct the electrode in 3-dimensions. So a stereotactic device is placed on the skull and a computer guided needle is inserted, so a burr hole is drilled in the skull creating a space and then based on the particular location that’s determined in 3-dimensions the electrode is then placed into the target of
interest. So for different indications it may be the motor nuclei of the brain for treating Parkinson’s
disease or tremors, for depression there are several areas of interest.

And then for the procedure once the electrodes are in place but before the pulse generator is planted
the patient wakes up and clinical assessments are done. So if one is treating somebody for
Parkinson’s disease one would do clinical assessments for tremors and other aspects to determine
whether the stimulation seems to have any type of acute affect. For depression we look for acute
mood changes. And the reason is really to make sure that an area that would be considered hot or
potentially beneficial has been identified but also to identify any particular acute adverse effects. So
if you turn the stimulation on and a person has a very unusual or noxious effect is that you learn that
based on doing a systematic assessment. So this is all done within the operating room. And once
that’s been determined then the pulse generators are implanted in the chest and they are connected to
the electrodes.

And this is showing what happens after the electrodes are implanted, so you can see the insertion, the
leads are tunneled under on top of the – under the scalp and on top of the skull and through the neck
and are connected to the pulse generators in the chest. And then the pulse generators can be
programmed and they can be adjusted over time. So again the intent of Deep Brain Stimulation is
not to cause a lesion but to cause some type of disruption in the functioning of a circuit or a brain
region. And because you can adjust the stimulation you can change the type of stimulation, so the
intent is not to be destructive but to cause some of a modulation, whether you are modulating the
tremors and other symptoms of Parkinson’s disease or to change the mood effects of a patient with depression or obsessive compulsive disorder.

And it is FDA approved for certain neurological conditions, it also has a humanitarian device exemption approval for clinical use in refractory obsessive compulsive disorder. It’s currently being studied or has been studied for treatment resistant depression. It also has potential applications and there are small studies in different types of conditions, Turret’s syndrome, tardive dyskinesia, other types of neurological conditions. And the reason the DBS can be used in such a wide variety of neurological and psychiatric conditions is based on the fact that you can target the electrodes to different underlying brain regions. So in contrast with TMS it’s based on the notion that the dorsolateral prefrontal cortex is under-functioning in some way, the same thing with Cortical Stimulation. In Vagus Nerve Stimulation a single procedure involving stimulation of a single nerve, but with DBS depending on what the clinical indication is the brain region if it’s been identified can be targeted. And as I mentioned at the beginning one can do controlled studies where the device is active or not active to determine whether it’s efficacious.

With lesion studies you create the lesion and that’s that, you really can’t do a control and it’s very difficult to make modulations or adjustments. So doing studies to identify the therapeutic benefits of lesion studies is very, very difficult and it’s difficult to interpret the outcome.
So two areas of interest in depression in particular, an area 25, CG25 and also the nucleus accumbens is in the region of the ventral capsule, ventral striatum. And these are two areas that there have been a number of studies conducted. The first was publicized in 2005, the group by Helen Mayberg and her colleagues initially in Canada and then in Atlanta was focusing on a very chronically and severely ill patient population with treatment resistant depression. Their initial publication in 2005 and then a follow-up 6 months in 2008, this involved 20 subjects that were implanted. And you can see the response rates and the remission rates after 6 months and after 12 months.

And then earlier this year a longer term follow-up 3 to 6 years was published in the American Journal of Psychiatry again showed a fairly significant persistent benefit in terms of response and remission rates, again keeping in mind that these are very ill patients in terms of their treatment history and nonresponse, chronicity and disability, so these types of response and remission rates are quite healthy for this patient population. For a non-chronic, non-treatment resistant depressed population a drug study showing these benefits you know would probably be not very remarkable, but for this type of patient population this is quite good.

The other area of interest is the nucleus accumbens, last year a study published, this was a European group, an open study in a similar patient population suggested benefits for patients with TRD. Similar response and remission rates after 12 months.
And then another pilot study was conducted by another group, a group that we’ve collaborated with, again similar brain region. This involved 15 subjects and over time there was a significant response and remission rate to the use of DBS targeted the nucleus accumbens. And that led to a larger study that we participated in Pittsburgh, it was designed as a feasibility study involving 30 subjects, double blind and sham controlled involving the same group at Cleveland but also some other centers. And these patients were very ill based on their treatment history, the severity of their depression and also the chronicity of their depression. So this study has been completed but I’m not able to report on the results yet because they haven’t been released. I was hoping that it would be available by the time of the conference. So this is the most recent DBS study for treatment resistant depression that’s been completed but the results are not yet publicly available.

And DBS also has potential side effects in terms of surgical risk, it does have more of a risk of internal bleeding in the deeper ranges of the brain is also seizures, but again like VNS there is a lot of human experience with DBS because it’s been used for a variety of neurological conditions and also some limited use in patients with refractory OCD. Because it does involve the implantation of these electrodes using an MRI scanner would be contraindicated, using therapeutic ultrasound is contraindicated as well. So you have to be careful about the use of certain diagnostic procedures with patients that have DBS implanted.

Then I’m going to finish by kind of putting these devices in perspective. One of the largest clinical studies in depression was STAR*D, and STAR*D involved patients with major depression that were
treated initially with a single medication and treatment failures then went through different levels of treatment. So to think about what happened in STAR*D these are the percentage of patients that showed a remission after their first treatment, and non-responders went to Level 2, these are their remission rates and then after Level 3 and after Level 4. According to current labeling patients that have failed Level 1 treatment would be eligible to receive TMS treatment, although clinically based on literature there is some suggestion that patients that had failed 2 or 3 treatments might benefit from TMS. But for this type of device it would be targeted for this range of the pharmacologic treatment resistant patient population.

Now Vagus Nerve Stimulation, according to the current labeling are patients that failed at least 4 different antidepressant therapies, and that might include ECT. So according to that labeling patients that would be eligible for VNS would be down here, having gone through a range of at least 4 therapies.

Now DBS is not approved for treatment resistant depression but if any of the studies are successful would be likely to be indicated for patients at that end of the spectrum as well, patients that have had extensive treatment failures and possibly including patients that have been treated with and have failed electroconvulsive therapy. Now DBS is indicated, has an indication for treatment resistant obsessive compulsive disorder, and that label mentions having failed at least 3 different SSRI antidepressant medications. So that would be patients treated 1, 2 and then 3 might be potentially eligible to receive DBS for OCD.
So this really I think puts it in perspective in terms of where a device might fit in based on the labeling, or the types of studies that are conducted. But for the more invasive procedures you are really dealing with patients that have failed a variety of medication therapies and combination therapies as well as psychotherapies. And then if you add ECT to the mix some patients may not like ECT, so for ECT intolerant patients there is also I think a potential role for some of these devices.

So just wanting to acknowledge the people that I work with, we’ve done device studies for about 10 years now and we’ve actually done 5 different device studies. Doing device studies is very, very difficult from a clinical standpoint and a regulatory standpoint, so it does involve a lot of man hours of work to be able to do the studies, to do the double blinding and the assessments and also all of the regulatory paperwork and also ethical reviews. So I want to acknowledge and thank all of the people that I work with who have been involved in different aspects of these studies. Thank you very much.