These are my disclosures.

As Dr. Richardson mentioned we do have experience with a variety of neurostimulation therapies for depression. The question that comes up though is why do we even need brain stimulation for depression? Dr. Hudak mentioned that OCD is in about 2% of the population depression, the prevalence at least lifetime prevalence is probably 10 times that. But it's only a very small percentage of patients with depression that would be considered chronic and treatment resistant. There are now 27 drugs that are marketed in the U.S. that are considered antidepressants, there is also a range of other psychotropic medications including some that would be considered medical medications and not psychiatric per se that are used as either alternatives or in combination for treating depression.

This is a representative study STAR D, the largest study ever conducted in depression. What I want to illustrate is the fact that each time a person is treated and does not respond to treatment the next treatment is less likely to be successful. And generally the cutoff is about 4 treatment failures where we really begin to look at a group of individuals that are chronically depressed and then classify them as treatment resistant. So this is a much smaller percentage of individuals suffering from significant clinical depression.

And the group of individuals that would have failed at least 4 different types of treatments, either mono therapies or combination therapies including psychotherapies are the types of patients that would be treated with a variety of brain stimulation therapies. ECT is most commonly done for

treatment resistant depression, it has long historical use. Surprisingly there are really no controlled studies but there is really no reason to think that it's not successful in treatment depression. But there is now a number of invasive and non-invasive brain stimulation approaches. ECT would be considered FDA approved because of the devices that are used. TMS is now available and is marketed for treating a limited form of treatment resistant depression. Vagus nerve stimulation is also FDA approved. That was originally done using an invasive approach that can now be applied noninvasively although that has not been as well studied in treating depression. And then the invasive approaches: cortical stimulation which we did a small pilot study here and also deep brain stimulation. I'm going to focus on DBS.

And this is a review of DBS for depression at least around 2012 when I looked at in detail at the studies. And these were all open label studies and there were at least 3 main targets that were included, the subgenual cingulate cortex, the ventral capsule, ventral striatum which is the same site that Dr. Hudak talked about for treating OCD and also the nucleus accumbens. And some of these are U.S. based trials, others have been done in Europe and also Canada. The number of subjects in these studies is actually very small so a total of 84 subjects that were treated and followed for up to 6 years. These were all open label so it did not involve sham control or double blind. And the response rates as you can see were fairly impressive, 29 to 90%, and also the remission rates, 33 to 58%. And keeping in mind these are not patients that would have been eligible for FDA trials for a new investigational drug. This is a patient population that would have been at the far end of the scale, so these are chronically depressed, they've failed multiple therapies, they are considered dirty in terms of clinical trial material. So these are very sick patients.

And similar to the experience in movement disorders the safety profile of DBS for depression is fairly similar, there is no real difference in terms of adverse effects, surgical effects, long term complications or cognitive effects. We are dealing with a depressed population so either suicide attempts or completed suicide would not be unexpected, and in these studies it's not at all clear that DBS itself was a precipitating or triggering factor for suicide.

Now the particular target that I'm going to focus on is the ventral capsule, ventral striatum and this is the target location. This was one of the studies that was done as a pilot that I had showed you earlier, a collaborative study focused on patients with chronic treatment resistant depression. The reason that this study was done was the observation in the OCD trial that those patients with their stimulation their mood and anxiety symptoms got better so that led to an interest in studying DBS for this particular site but focusing on patients not with OCD but were suffering from major depression. And as you can see that these subjects who were severely ill at baseline were depressed for a long time and they had failed about 12 different types of antidepressant therapies or combination therapies during their course of their illness showed fairly significant degrees of improvement over a period of time.

And this particular study then led to the first randomized sham controlled trial of DBS for treatment resistant depression. We participated in this study, the other sites are as listed. This study has not yet been published although it's now being reviewed for possible publication. I'm going to go through the results of this study. So again this is a randomized study, double blind, sham controlled,

so all of these subjects had non-psychotic, non-bipolar depression. We had specific inclusion, exclusion criteria in terms of their treatment resistance. They had to be chronically ill, all of then had to have received a course of psychotherapy. We didn't necessarily specify that they had to receive ECT but all but one of the subjects in the study had received ECT in the past.

So these subjects were screened and they had to maintain the same medications at the same doses during the screening period up to the time of implant. And then there was the 4 weeks postsurgery for stabilization and then subjects at that point in time were randomized. All of them had the implant but they were randomized to a sham control which is they went through the same programming procedure but did not receive active stimulation or the group that was actively stimulated. And the procedures for maintaining the double blind involved a programmer who would do assessments of side effects but had nothing to do with any of the clinical ratings. And then the clinical raters were blind to the treatment assignment.

And then patients were treated under those conditions for 4 months, 16 weeks, so that's a longer trial than would be considered typical for treating major depression. And part of the difficulty in doing a study like this is how long ethically can you maintain a sham controlled condition, especially since it involves an invasive surgical procedure. And at the end of the 16 weeks of the double blind phase all of the subjects were treated openly with active DBS and they went through an additional year of continuation treatment and then have been followed up long term. So we currently have 3 subjects that are still receiving DBS during long term stimulation.

And this shows the study flow. So 46 subjects were screened and 30 were randomized into the double blind phase. And all 30 of the subjects completed the double blind phase but one of the subjects became disinhibited and their stimulation was turned off so they were not counted in terms of an efficacy assessment but they were maintained for safety assessments. And then all of the 29 subjects went through an additional year of continuation treatment and thereafter 3 subjects had discontinued not for safety reasons but for lack of efficacy.

And here are some of the characteristics of the patients at baseline. Somewhat unusual for a depression trial is a preponderance of male subjects. Most clinical trials in depression about 2/3 of the subjects are females and depression is more common in women than men; this is a point that I'll go back to a little bit later. But the average age of this group was similar to most clinical trials, more severely ill than most clinical trials in depression and also the duration of their illness, more than a decade in their current major depressive episode.

And this is some of the treatment characteristics, all but one had received ECT, some of the subjects had received vagus nerve stimulation or TMS. Three of these subjects had received an investigational type of cortical stimulation which was one of the pilot studies that we did here and two of our subjects actually had received cortical stimulation, another invasive procedure, and that was explanted and they were eligible for the DBS trial. And this demonstrates the number of trials and the current episode and lifetime of these subjects. So again they were depressed for an average of 11 years and had received a large number of mono therapies and combination therapies as well as

psychotherapy without an adequate response to their treatment making them eligible for this trial. And here is the primary end point.

And the trial had failed, it did not show a significant benefit during the double blind phase for DBS versus the control. There is a numerical difference favoring the active treatment but it was not statistically significant. And the percentage change in the MADRS score at the end of 16 weeks was not significantly different either. And this shows graphically during the course of the 16 weeks how the two, the active treatment group and the control group, fared.

And this also shows the individual subjects. So 3 of the subjects in the active group were considered responders which is a 50% or greater response, or decrease in the MADRS score from baseline to endpoint and 2 of the control subjects. What you see is kind of a curious spread of the control subjects during the course of 16 weeks. With the active treatment there is kind of clustering that they didn't really show much of a change at all, and that was a curious finding given the fact that by the end of the treatment period there was no average difference in outcome between the two groups.

And this is long term follow-up and it's focusing on the percent change in the MADRS. So baseline, the end of blinded phase, and then at that point in time all of the subjects received active open label DBS. Now during this phase their programming can change and their medications could change, so you really can't draw any conclusion in terms of absolute effectiveness of DBS simply because it was uncontrolled. But we did find that there is a change over time suggesting long term benefit in the subjects that were receiving active DBS. And again keeping in mind that they were chronically

depressed and had failed a variety of antidepressant therapies including ECT. So these changes, about a 40% drop in the MADRS score over a period of 2 years for this type of patient population is actually significant and clinically meaningful as well.

And this again is showing graphically by subject how they fared. Here is the double blind phase and then year 1 and year 2. The dark circles are patients that would be considered remission where they actually had very low level depression symptoms and that's ideal. And so patients in remission are a subgroup of individuals that are responders. So again you do see a trend downward is that there is a spread of individuals over time most of whom show no significant change, but there is a group of individuals that again having been depressed for an average of 11 years and have failed a lot of therapies is meaningful for them in terms of the drop in their depression scores.

Safety, this is during the blinded phase. In general the type of surgical side effects, adverse effects that you see in the movement disorders literature is really no different for depression and the same thing for OCD. What was curious was some of the acute effects that occurred only in the active group, hypomania, mania, the mention of the superman syndrome probably is a mood elevation. One subject became disinhibited, very impulsive and this individual had the DBS not explanted but the device was deactivated. And again this suggests that there was something that was happening in the brain even though at the time the data were collected that they were blinded to the treatment group but did suggest that there was a small clinical signal.

And then looking at safety during all of the phases of the trial, again the types of problems and adverse effects really are not significantly different for patients in this depression study compared to the movement disorder literature and the OCD trials.

So to summarize the pilot study seemed to suggest that focusing on the ventral capsule, ventral striatum may be a beneficial antidepressant therapy. Controlled study which is the first one that's been conducted for depression, treatment resistant depression did not support that although there was some hint for long term benefits. And this is one of the difficulties in doing device studies in chronic psychiatric illness is being able to do a controlled study for a longer period of time in an ethical fashion. And although we've emphasized, Dr. Hudak emphasized for OCD, the chronicity and the treatment resistance, the same thing for depression one cannot necessarily exclude the possibility of a placebo effect. Placebo effects occur in the movement disorders literature. So this is one of the difficulties is being able to find a study in terms of demonstrating benefit beyond a double versus showing something that involves an invasive procedure over a period of time.

It is possible that simply the VC/VS is not an effective target for DBS for depression based on this study but the long term data would suggest that it probably should not be something to give up on. It's also possible that the treatment effects couldn't be detected. This was a 30 subject study so it was not highly powered, and the study was actually designed initially to be the introduction feasibility study of a larger pivotal study involving a larger number of subjects. But at the end of this phase in breaking the blind and really not finding any significant benefit the decision was not to move further to enrolling further subjects.

The other possibility is an alternative study design. Again if you think about doing an implant and being able to determine under a sham controlled condition how do you actually design the study, so in this particular study patients had the implant and then at the beginning were randomized to active treatment or sham. An alternative would be to use DBS actively in all individuals for a defined period of time, 4 months or 6 months, and then to plan a randomized double blind discontinuation of active stimulation. And that's something that has been considered in other particular studies as being used as an alternative study design, again focusing on a determination is the device effective under a sham controlled condition.

And just to put this in perspective, this is the study that I just talked about, this is the Pilot Study in the same target. The MADRS group focusing on the said subgenual cingulate cortex has gotten a lot of PR and press and they have an ongoing study, a double blind sham controlled study but no definitive results have been presented. But their outcomes are the ones that have been publicized and then VNS and TMS is to look at some of the characteristics. For example the average number of failed trials for our trial was much higher than what was seen in the VNS studies and the TMS studies for treatment resistant depression.

I had mentioned earlier the proportion of patients in the study that were males is actually greater than would be typical in most clinical trials but also with the exception of TMS for the other device studies. And we don't really understand whether there may be gender differences in terms of treatment effectiveness. There is some evidence from the pharmacologic literature in depression, so

this I think may be an issue to look at in additional studies. The other factor too is the length of depression was considerably longer in the other device studies. So even though this is a treatment resistant patient population the clinical characteristics were not exactly the same. So putting it into context the results from this particular double blind study with what's been done in the literature I think is important.

DBS is still going on despite the negative results from this trial, there are other targets to consider, and if you look at clinicaltrials.gov there are a number of open label studies and also sham controlled studies that are either still actively recruiting individuals with treatment resistant depression or ongoing in terms of assessment but have not yet published their outcome findings. And one of these trials is focused on bipolar depression because most of these other studies have been with unipolar or non-bipolar, nonpsychotic depression. Thank you very much.