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Quick Pulse

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VAGUS NERVE STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

Based on interviews with sources at 25 major medical centers and depression clinics, it appears that use of Cyberonics' Vagus Nerve Stimulator (VNS) in treatment-resistant depression is catching on very slowly. Psychiatrists are not referring many patients, surgeons have put in very few devices so far, and there are not significant numbers in the evaluation process. Furthermore, insurance coverage remains difficult and spotty.

VNS has been approved for treatment of epilepsy since 1997, and in July 2005 the FDA approved the device to treat severely depressed adults who have not responded to at least four different treatment regimens. VNS is a tiny, implantable device that automatically delivers mild electrical pulses for 30 seconds every five minutes to the vagus nerve, which carries information to parts of the brain that control mood and other functions.

Cyberonics claims that more than 2,000 psychiatrists and 250 surgeons have been trained on VNS, but it was difficult to find more than a handful of patients who have had the device implanted outside of clinical trials, and the numbers undergoing evaluation are not impressive. Several prominent medical centers are not using VNS for depression at all.

VNS for depression does have some strong advocates. Dr. Scott Aaronson, a psychiatrist at Sheppard Pratt Health System in Maryland, said, "The problem is how folks look at the (VNS depression trial) data. It was not the blow-your-socks-off kind of data, but it was very interesting data. There is a whole bunch more we want to learn about the device to figure out which patient population is most likely to respond and how best to adjust the device. It's actually not a tiny population (that could benefit)…Of the folks who have failed at least two adequate trials of antidepressant medications from two different classes – and that's different from what the FDA wants (which is four different trials) – but can include light therapy and psychotherapy, between 30%-50% meet the criteria for treatment-resistant depression (TRD)…Over 2% of the population may meet the criteria for TRD. This is a condition that is probably two to three times as prevalent as schizophrenia."

However, even some psychiatrists who were involved in the clinical trials of VNS for depression have mixed opinions about its efficacy, and many of their colleagues in the same practice or institution are not necessarily convinced either. A psychiatrist at a hospital that conducted VNS trials said, "My opinion is mixed. Some of the trials were done here, and the two primary clinical researchers split their opinions as to whether it was truly effective."

Most of the psychiatrists who were interviewed believe there may be value to VNS ***in the right patients***.

- *Dr. A. John Rush, a psychiatrist at University of Texas Southwestern Medical Center at Dallas:* "It is an effective and safe long-term treatment for patients with TRD…The results are impressive, given the treatment-resistant nature of these patients and the largely sustained benefits for those who do respond. Typically, in TRD, even if a response is achieved, it's often lost over time with medications."
- *Tennessee:* "I am of two opinions regarding VNS. If you look at the overall effect of VNS, it doesn't seem impressive on the surface. Responses (improvement rates) of ~45% and remission (wellness) rates of ~25% over 18 months are not terrific. However, given the realities of the patient population in treatment, it really is much better. That is, once people have failed four different modalities, the likelihood of responding or remitting to the next one is pretty small."
- *Dr. R. Bruce Lydiard, Director of Southeast Health Consultants in Charleston, SC:* "VNS is credible in terms of results, but I don't have any patients personally…I believe it will reach some patients unable to benefit from other available treatments."
- *Pennsylvania:* "We need another option. Looking at the patient population in the trials and the new modality, I believe this is a reasonable option for them."
- *Dr. Paul Mohl, psychiatrist, University of Texas Southwestern Medical Center:* "VNS appears to be effective in some highly treatment-resistant depressed patients."
- *Missouri:* "The data are pretty impressive. Seeing is believing. I was dubious when we first started researching it, but I am now a believer for a certain subset of individuals…Our trial had 10 subjects, and six responded. Four had home run responses, with complete remission sustained for more than three years, so we have been very pleased…This is a huge paradigm shift for psychiatrists. It is the first biologic, non-pharmacologic FDA-approved treatment since ECT (electroconvulsive therapy). This is quite big, and it takes sort of a different frame of mind, but I know that every psychiatrist with a practice has two to three or more patients with this type of depression, so the need exists."
- *Maryland:* "I don't think the study results adequately demonstrate the responses some people have had…The response rate is in the 50%-55% range, but there are even folks in that other 45% who are having some meaningful response that we may not be capturing. We can't predict who is going to fall into either group…There are a number of people who may only drop a point or two on the scales that we're using to judge what their moods are like, but their ability to function in life is significantly improved. We don't have the best tools to study this difficult population…We haven't teased apart who is likely to respond and who is not. And you may not see results for six months."
- *Dr. Darin Dougherty, Director of the VNS Service at Massachusetts General Hospital (MGH):* "VNS can take three, six, or 12 months to work. You need to continue doing the meds. VNS is an adjunct treatment, and it is twice as effective as usual medical therapy for TRD, but still only one in three patients will respond. But it beats what we have in our armamentarium now."

Much of the early demand for VNS appears to be coming from patients, not psychiatrists. Dr. Dougherty said, "Most of the patients we are screening are patients referring themselves. I don't think the ECT service gets a lot of self-referrals, but most of our patients so far have been self-referred." A New England doctor said, "There isn't such a thing as a last resort. There are at least 50 antidepressants, and you can also put patients on combination therapy. There is hardly anybody who has tried everything. Our first group for VNS are the sickest people with major depression who have not responded well to anything other than very frequent ECT treatments. Some are getting ECT once a week or every other week."

Psychiatrists who have accepted VNS for depression generally refer patients to a neurosurgeon for implantation of the device, though sometimes an ENT, a head and neck surgeon, or a general surgeon may do the procedure. Once the device is implanted, it generally is turned on a couple of weeks later by the psychiatrist, not the surgeon. At tertiary centers, a VNS-experienced psychiatrist may turn on the device. Dr. Dougherty explained, "We (psychiatrists at MGH) will do the programming after (the surgery), but there is also an option for the treating psychiatrist to do it. A lot of psychiatrists seem more comfortable with us doing that initially…The patient starts coming in two weeks after it is implanted for dose adjustments, starting with 0.25 milliamps (mAh) and going up in 0.25 mAh increments to a target dose of 1 mAh."

Surgeons who have been trained to implant VNS devices for depression agreed that the surgical protocol is exactly the same as for implanting the devices for epilepsy, but they are not getting many referrals for the procedure yet. Generally, only one psychiatrist at each facility is referring patients for VNS, and only one surgeon is implanting the devices.

- Dr. Bruce McIntosh, a general surgeon, is the only surgeon doing VNS implants at William Beaumont Hospital. He started implanting them about a month ago. He said, "The surgery itself is not really very hard. Anyone with a decent pair of hands can do this. This is not something every Joe Schmoe at every community hospital could do, but I certainly do a lot harder procedures…Primarily, one psychiatrist, who tends to be more cutting edge, is sending patients. He has sent a fair number, and they are in the midst of evaluation and clearance…They have not opened this (VNS) up here to every surgeon. They may if it becomes more mainstream. It is not that I like a monopoly, but they are not letting 20

surgeons each do two a year. As volume increases, they will bring more surgeons into the fold."

- Dr. Brian Kopell, a neurosurgeon, is the only person implanting VNS for depression at the Medical College of Wisconsin. He has put in a couple of devices. He said, "Right now, the referrals are all from one psychiatrist …We have a restorative neuroscience program with a multidisciplinary team that deals with refractory neuro and psych illness and chronic pain. We have a protocol where I work with the respective primary medical specialist. In psychiatry we have a single psychiatrist on neurostimulation for neuropsychiatric disease."
- Dr. Allen Maniker, a neurosurgeon at the University of Medicine and Dentistry of New Jersey/New Jersey Medical School (UMDNJ), is ready to do VNS for depression, but he hasn't had any referrals yet, and he hasn't done any so far. He said, "I am up and running to do it. Have I done one for depression yet? No. At this point in time, as the surgeon, I really depend on the referral of the psychiatrist. I think that, like any new medical device or treatment, it has to kind of disseminate through the medical community. If you look at physicians as a whole, they are a skeptical bunch, and the psychiatrists are examining the data for themselves and determining which patients they think are best for approval. My understanding is that there are several possibles in the pipeline, but they have not made it to me yet."
- Dr. Emad Eskandar, a neurosurgeon at Massachusetts General Hospital (MGH), implanted several VNS devices during the clinical trials, and he has about 10 patients lined up to get a device, but he hasn't implanted any since it was approved for depression. He said, "For the right patient, it is appropriate and relatively safe. The risk is pretty low. Probably the worst thing is if it doesn't work or the device gets infected or malfunctions and we have to take it out. But it is unlikely to cause major neurological problems."

Often, when a new treatment is approved by the FDA, there is an initial surge of use due to a bolus of patients on waiting lists who get the new device in the first few months. That does not appear to have been the case with VNS for depression.

Some prominent doctors and institutions have rejected the use of VNS for depression completely, at least for now. Seven of the 25 medical centers contacted are not implanting VNS for depression at this time, though several are either considering it or have already decided to start as appropriate patients present. A Rhode Island psychiatrist who decided not to use VNS therapy for TRD said his decision was based on the lack of data, "To date, only one placebo-controlled study, which was well-designed, has been conducted examining the efficacy of VNS therapy, and it had negative results…After the end of the 12-week study patients were continued on VNS for up to a year. The rate of improvement in this group was compared to the improvement rate in another group receiving routine clinical care. This is not good science…The evaluation of study patients may have been biased by knowing which treatment patients were receiving. The patients were not randomized to the treatment groups. Thus, there may have been important differences between the groups that were associated with differences in response rates. Consequently, valid conclusions cannot be drawn from such a poorly designed study…Because the results of the well-designed study were negative, we have decided not to offer VNS therapy at this time. If future, well-designed studies demonstrate that VNS therapy is effective, then we will revisit this decision."

Like this doctor, many psychiatrists are demanding more data before considering VNS for depression, even though data were published in fall 2005 in the ***Journal of Biological Psychiatry.*** One psychiatrist said, "We should wait to see the published data…(That) will tell us what factors predict response in which groups, but it would seem that the more treatment-resistant you are, the harder it is to get a good response." A California psychiatrist said, "The results of the published studies are provocative but not compelling." Dr. Matthew Berger at Moses Taylor Hospital in Scranton PA, who was not involved in the clinical trials of VNS but was an early adopter, said, "We are waiting for the peer review. The ***Journal of Biological Psychiatry*** is peer-reviewed, but psychiatrists are saying the data are still not compelling enough, and they want to see more results. But these patients are the worst of the worst, so you can't expect phenomenal results or an 80% response rate. What they are looking at is a 30%-40% response rate, and in this population, that is really good."

Major Medical Centers Not Currently Using VNS for Depression
Boston University
Cleveland Clinic
Duke University
Emory University
Rhode Island Hospital
San Francisco General Hospital
University of Houston

Asked why prominent sites like these aren't implanting VNS for depression, Dr. Aaronson suggested, "Unless someone in the center has a vested interest in this population, this isn't necessarily going to be a big profit category, especially for the department of psychiatry. And neurosurgeons aren't particularly going out after patients. So, unless there in a clinician who has an interest in the population or the device, you may not see a high level of interest."

On the Cyberonics' VNS website (**www.vnstherapy.com**) on January 5, 2006, there was a list of 42 sites which were described as "beginning to offer VNS Therapy to patients." Eleven sites from this list were contacted, and nine offered

estimates on procedure volume: A total of six devices have been implanted by these sites in the five months since VNS was approved for depression, and about 45 patients are in the pipeline (an average of 5 per site).

Cyberonics-Identified Sites Currently Offering Implantation of VNS for Depression

Facility	Implants post-approval outside of clinical trials	Patients in the pipeline
Hospital of the University of Pennsylvania	1	N/A
Massachusetts General Hospital	0	10
Medical College of Wisconsin	0	2
Medical University of South Carolina	2	2-3
NY Presbyterian Hospital/Columbia	N/A	N/A
Sheppard Pratt Health System, Maryland	1	5-6 pending insurance approval
St. Louis University Vagal Nerve Stimulation Clinic	0	Several *
Stanford	0	Several *
University of California, San Diego	0	2
UT Southwestern Medical Center, Dallas	N/A	N/A
University of Washington	2	10-15 awaiting insurance approval
TOTAL: 11 sites	**6 patients**	**~45 patients**

*** For purposes of the total, this is assumed to be ~5.**

Another seven sites were identified that are implanting VNS for depression. These sites estimated procedure volume as: A total of 4 patients already implanted post-approval, with about 42 in the pipeline (an average of 8 per site). Dr. Charles Conway, a psychiatrist at St. Louis University, explained, "In order to use this device, you need up-to-the-minute information on the previous treatments for depression. We had people on the waiting list a very, very long time. Once approval came, the primary sticking point became insurance approval."

Other Sites Currently Offering Implantation of VNS for Depression

Facility	Implants post-approval outside of clinical trials	Patients in the pipeline
Baylor College of Medicine	N/A	N/A
Mayo Clinic	N/A	N/A
Moses Taylor Hospital, Scranton PA	2	9 scheduled
UMDNJ/New Jersey Medical School	0	Several *
Vanderbilt University	N/A	"large" number **
William Beaumont Hospital	2	10-15
Yale	0	5
TOTAL: 7 sites	**4 patients**	**~42 patients**

*** For purposes of the total, this is assumed to be ~5.**
**** For purposes of the total, this is assumed to be ~10.**

Reimbursement for VNS may be more of an issue than Cyberonics has suggested. Cyberonics claims that at least 75 insurance carriers are reimbursing for VNS depression therapy, at least on a case-by-case basis, but most sources said insurance reimbursement continues to be a significant problem. Blue Cross does not appear to be covering it at all, and sources said they have had problems getting the other major private insurers – e.g., Cigna, Aetna, United Healthcare, etc. – to pay for it. Some sources said they have had patients turned down for VNS; others are encountering paperwork and delays. A psychiatrist explained, "Managed care companies carve out the mental health benefits and haven't made allowances to pay for this (VNS)…A lot of insurance companies pay a mental health management company a set sum of money to manage the mental health benefit, and I'm sure these companies aren't queuing up to pop for this…The argument is: Should it come out of the surgical benefit or the mental health benefit? I've seen that happen with other devices, and I'm sure it will take six months to sort out. I think it'll be a case-by-case issue for managed care companies."

Other comments on experiences with reimbursement included:

- *Dr. McIntosh, general surgeon:* "I need to make sure that we get paid. Many patients are going through the insurance process (now), and, since this is a fairly new procedure, it is a fairly onerous task that falls on my biller and scheduler and on Cyberonics…We have been turned down on reimbursement, but we are still working on those patients. It's kind of like bariatric patients. Insurance companies are kind of reluctant to put out for such an expensive procedure, but in the long-run, as these things become more mainstream, the process will become more streamlined and easier."
- *Dr. Kopell, neurosurgeon:* "We are getting approval from third party payors. They haven't turned down anyone yet."
- *Dr. Berger, psychiatrist:* "We've done two so far and have another nine on the drawing board, but the problem is insurance. I have a waiting list of 30-40 people who want the treatment, and I have 100 I could do. But the only insurance coverage at this point is Medicare. None of the private insurers in our area, including Blue Shield and Aetna, are covering it. We can't get pre-certification from Medicare. You have to do it, and then see if Medicare will pay. So far Medicare has paid for all implants in our area, but hospitals and doctors are nervous about putting out the money and not getting paid. Medicaid is not paying."
- *Dr. Conway, psychiatrist:* "Insurance is a big, big problem. We haven't done any yet, but we have several patients lined up…The primary sticking point at this juncture is insurance approval. We are running into some delays…They're familiar with VNS for epilepsy but not for depression. Right now, we have a number in the pending process, but no one has yet been approved at our site…We've submitted some patients to Medicare for pre-

certification, but we haven't heard back yet. It looks like we will get Medicaid coverage, but even that is not certain."

- *Tennessee psychiatrist:* "It's hit or miss. Some insurance companies reimburse right away. Others aren't yet, calling the treatment 'experimental.' I think what that really means is 'expensive,' in this case."
- *Dr. Robert Ostroff, a psychiatrist and director of the Electroconvulsive Therapy Center at Yale-New Haven (CT) Hospital:* "Reimbursement is definitely difficult… That is our biggest hang-up in getting started (with VNS) …That's why it is taking so long to get going. We have to walk each patient through (the process). Each time we applied, it's a new issue for the managed care company. It's going to be time intensive."
- *Dr. Ziad Nahas, psychiatrist, Medical University of South Carolina:* "Our first two cases were Medicare patients, and Medicare did not approve it. The patients were willing to take the risk of an appeal and take the financial responsibility. We had another couple of patients from North Carolina who are on Medicare and who said the same thing, and it is likely they will be scheduled soon – paying out of pocket and signing that they will take responsibility."
- *Dr. Dougherty:* "Reimbursement is the hold-up…Insurance companies don't want to pay thousands of dollars when they can pay for medications, but with each new (medication) trial, there are diminishing returns, a lower and lower chance the medications will work. On January 11, 2006, a hearing is scheduled where we will try to get Medicare to pay for VNS in Massachusetts."
- *Stanford University, California:* "We treated seven patients during the trials…but not any since it was approved. The primary obstacle is payment – it's not covered. But we do have several being evaluated, and we expect to be doing VNS."
- *Dr. Aaronson, psychiatrist:* "I think the insurers don't know how to deal with this yet. They're doing it generally on a case-by-case basis although some of the larger insurers have made a blanket decision that it's an experimental procedure and they're not going to approve anything. That's one of the reasons we've had fewer implantations in this neck of the woods. Blue Cross/Blue Shield of Maryland has been the most challenging…(In the case with one insurer) one patient got waived through, and when the company realized the VNS was for depression, they backpedaled and have been reasonably difficult to deal with."

Surgeons as well as most psychiatrists pointed out that only a select group of patients will benefit from VNS. Dr. McIntosh said, "Not everyone gets better with this. The long-term cure rate is 20%-30%, and significant improvement will be closer to 50%, but it takes time." Dr. Rush said, "VNS therapy is for patients with a chronic or recurrent course of illness who, therefore, need a long-term treatment and for whom medications and therapy have not been effective." Dr. Mohl said, "VNS is for patients who have failed both primary and secondary SSRIs with at least two additional trials of augmentation, especially with tricyclic antidepressants. They preferably haven't responded well to ECT, or it is contra-indicated." Dr. Berger said, "About 20%-30% of patients with depression or bipolar disorder are very refractory. In trials, patients had at least six to 13 failed courses of treatment, including medication management as well as up to and including ECT. These are patients who just weren't getting better. I have a large clinical practice, and we have done all the traditional things for these patients who, despite aggressive treatment, are just not getting better. We needed another option for them." Dr. Ostroff said, "The results are at best modest, but there are a few miraculous treatments…I don't think this is the all-new miracle cure."

Surgeons agreed that careful patient selection is critical and that the types of patients being referred for VNS are unlikely to change over the next six to 12 months. Dr. McIntosh said, "Patient selection is important. We don't want this as a front-line treatment. It is back-line salvage therapy for patients without a whole lot of other options." Dr. Kopell said, "People are, rightly, being very cautious rolling this out because it is a fragile patient population." Dr. Maniker said, "I won't implant (VNS in) an epilepsy patient until the patient is thoroughly evaluated by a neurologist who has gone through the appropriate steps and the patient is certified to be an appropriate patient. It's the same with psychiatrists. They need to present me with all the appropriate documentation that the patient meets all the institutional and departmental criteria." Dr. Eskandar said, "At MGH, we have had a long-standing interest in surgery for psychiatric disorders. We have a protocol for doing it, and a committee that reviews all cases. The committee includes psychiatrists, an ethicist, two neurologists, a neurosurgeon, and one or two lay people. We are using that same protocol with VNS for depression. I think that is good because it allows us to maintain a certain degree of oversight, and to be judicious in the application (of VNS), but it allows us to move forward easier than at other places without this situation pre-existing. You need a collaboration between psychiatrists and neurosurgeons which doesn't exist at many places…There is kind of a culture gap between the two disciplines, which has yet to be breached."

Some hospitals have added additional requirements over and above the four failed therapies the FDA mandates before neurosurgeons can implant VNS for depression. Dr. McIntosh said, "I've had to jump through an incredible number of hoops to get this approved (at Beaumont) to make sure the credentials committee was very comfortable that we are doing a reasonable operation, and a lot of that is educating people on the committees. I had to educate the credentials people about the whole pathophysiology of this process. And Beaumont has taken two extra steps beyond the normal. Beaumont requires us to go through a very strict referral process. We have to get a letter clearing the patients from a psychiatric

standpoint that they meet the criteria, that they have tried other medications without significant improvement. We also have to get a letter of clearance from the psychiatrist that the patient is competent, because many psychiatric patients may have an inability to make informed consent."

Psychiatrists also reported that the screening process for VNS is stringent.

- *Dr. Conway:* "We have several patients lined up pending insurance approval, but no one has been implanted because there is a whole elaborate screening process to see that we follow all the criteria…You have to be very meticulous about who gets it, and I am absolutely convinced that screening is going to be the key in terms of seeing a good response…We screen for people with relatively pure depression – depression that is not drug-related or a personality disorder. I'm not saying that each patient has to be absolutely pure, but, for example, I don't think a patient with a history of self-mutilation or destructive relationships would be a good candidate because a device won't repair those aspects of his or her personality, which I think probably contributed heavily to the depression. Patients with depression – predominantly bipolar – are probably good candidates."
- *Dr. Aaronson:* "This should not be a treatment for someone who is severely suicidal and shouldn't be for someone as a 'Last Chance Texaco' (a novel about troubled youth). If this doesn't work, that's going to provoke the suicidality. More important than screening to meet the criteria, you want to make sure the patient is emotionally prepared for something that is a significant medical intervention."
- *Tennessee psychiatrist:* "I follow the guidelines: (failure in) four good trials at the minimum."
- *Dr. David Dunner, Director of the Center for Anxiety and Depression at the University of Washington:* "This is for patients who have a current depression, are treatment-resistant, have failed or refuse ECT, and who have four or more documented antidepressant treatment failures. We also require a second opinion."
- *Dr. Nahas:* "The FDA criteria are more lenient than what we are going with. The FDA requires four failed trials, and you could count psychotherapy, an antidepressant, a mood stabilizer, and a benzodiazepine. We do the anti-depressant history based on class more than augmentation strategies. That makes more of an argument for getting cases approved (by insurers). We have about 30 people who have contacted our clinic with interest in being evaluated. The way I have elected to run the clinic is primarily as a tertiary referral for TRD, and if we happen to think VNS is indicated, then we discuss that as well. When patients contact us, we have somewhat of a lengthy pre-screening process in which my nurse talks to them on the phone, then we send them a substantial package to fill in on prior treatments, length of episodes, etc. They send the package back to us, and the nurse goes over the details and then calls them for a one-on-one interview. We then do an almost research-like clinical interview for diagnostic purposes. We fill out, based on the information provided, an antidepressant history, and we assess the treatment-resistance. Then I (or my colleague) sees the patient for an hour and a half. Then, we give our recommendation to the referring psychiatrist – whether there is pharmacotherapy that has not been tried or an experimental therapy that should be considered, ECT, and VNS. Because we are not just a VNS shop, we can only see two new patients a week."

Where will VNS fit in with ECT – before ECT, in combination with it, or in ECT failures? Dr. Dunner and Dr. Mohl both indicated that they believe VNS is for patients who failed ECT or in whom ECT is contraindicated. Dr. Dougherty said, "You can do ECT (in combination) with this device in. Some patients might be on maintenance ECT, which is helping some but not a lot. Or they may be having cognitive side effects. So, they will consider VNS to see if they can lengthen the time between treatments or not have to do maintenance at all in the future. ECT is very efficacious, but it is also associated with pretty severe cognitive side effects. ECT and VNS do not exclude one another." Dr. Eskandar, "I think it (VNS use) will be at about the same level as ECT. Some people may not want ECT and may opt for this, but the opposite may be true as well. Some will say they would rather try ECT first." Dr. Aaronson said, "We're tapping into the ECT population. One of the ideal populations may be the folks who have only responded to ECT and have had multiple trials of ECT. They may be a very ideal population. VNS may diminish their need for ECT."

The Cyberonics sales reps generally got pretty good marks from psychiatrists who have been visited by them, but not all sources have seen a sales rep yet. The sales reps appear to be helpful without being overly aggressive. A West Coast psychiatrist said, "The quality (of the sale reps) is high. They are very helpful." Another psychiatrist said, "They are good experts on the device and how to get insurance but less good experts on the depression data." A Midwest doctor said, "They are very helpful, but not any different than any other reps. They leave doctoring to the doctors and are not pushing devices." Another doctor said, "The reps typically are highly trained people, often pharmacists, and they usually are simply informative. They don't seem to be 'pushing' the treatment. Dealing with a device company has a different 'feel' than dealing with a pharmaceutical company…There is no real competition in the field, so there isn't any 'our drug is better than yours' going on." A fifth doctor said, "They are being very fair and honest, not saying it is a panacea – just another treatment option for refractory patients."

Psychiatrists and neurosurgeons agreed that it is too early to determine whether the clinical experience with VNS is comparable to that reported in the clinical trials. A California psychiatrist said, "I have an open mind, but it is a bit too early to tell if this will be a significant advance to therapeutics…I

have referred patients, but none of them has been implanted yet." Neurosurgeon Dr. Kopell said, "I think over the next two years we will have a better idea as more and more centers do this…The initial data on efficacy are fairly modest, but these are patients with very little recourse otherwise so even a modest amount of help is significant in their lives, but they need realistic expectations about the timeframe for efficacy which is usually a year plus – and the efficacy is modest. Managing expectations is important." Psychiatrist Dr. Dunner said, "The (pivotal) study showed a third not changing, a third with slight improvement, and a third with good improvement. Two local patients have been implanted within the last month, and it's too early to tell the results." A Tennessee doctor said, "I think the results so far have been generally good. The ones I have seen who have gotten it have responded, at least to some degree." Dr. Berger said, "It will be another nine to 12 months before I can determine clinical results. So far, from trials, the data are not great; a 30% response rate is not wonderful. But if you had terminal cancer and all the other options failed, that would be good. Some of the stigma around psychiatry plays a role. If this were cancer and you had a drug with 20% efficacy, they would say it's worth it. But it's different because these patients aren't actively dying, although, in some ways, they are." Dr. Eskandar, a neurosurgeon, said, "It is really early. The FDA approval just came. The wheels turn exceedingly slowly. It could be a year before it really takes off."

Most sources interviewed believe that VNS therapy will eventually find its niche. In a year or more from now, sources estimated that from 10 to 100 patients a year could get VNS at their facilities.

- *Dr. McIntosh, general surgeon:* "A hundred a year is not improbable in the future…Cyberonics quotes four million candidates, but I don't know if that is realistic, but the number of patients with refractory depression is much larger than the number with refractory seizure disorder."
- *Dr. Kopell, neurosurgeon:* "The outlook depends on the psychiatrist and when we see efficacy in the long-term."
- *Dr. Maniker, neurosurgeon:* "The issue is psychiatrists convincing themselves that this is a good and appropriate thing to do. Use also will depend on the public at large. Sometimes a new medical treatment comes on the market and catches the interest of the public at large, and then everyone is demanding it even if it is not appropriate for them. This has not reached that stage yet…The outlook depends on what the word in the psychiatric community is, whether psychiatrists convince themselves that they are seeing good improvements in patients. There is literature, but they want their own experience, and until that occurs, I have no way to predict (what usage will be)."
- *Dr. Eskandar, neurosurgeon:* "In a year, it is unlikely we'll do 100, but I could see us doing 10-20 a year…I think it will grow at a moderate rate. It will not explode …If people do a whole bunch and find it is helping, but it is not the be-all, end-all, that might change the rapidity with which it gets adopted." *Dr. Dougherty, psychiatrist at the same medical center:* "I think we could do 24 or so in 2006."
- *Dr. Conway, psychiatrist:* "There is a lot of patient interest here, and we are screening a lot of people…I would estimate that it is not unreasonable to implant 30-40 or more in a year. There are enough people with the type of depression for which this therapy is most promising to keep us busy for a couple of years."
- *Pennsylvania psychiatrist:* "Once the initial bolus of patients are put through, I envision, although I'm not completely sure, at least 100 a year."
- *Tennessee psychiatrist:* "Right now we have a fairly large backlog of people who were waiting for approval who have had many more treatment failures…In addition, the numbers may be deceptive. We know of patients who might not have met the response criteria who, nonetheless, have had significant improvement – for example, returning to work or having their constant suicidal thoughts go away."
- *Dr. Ostroff, psychiatrist:* "I think there is a limited use for this in a sick population. I run an ECT program, and I'll personally have more than five patients (a year for VNS). I see very sick people for various kinds of treatment-resistant depression. It's likely that I'd have more patients (than the average psychiatrist) because we see very sick people. But if you look at the research results, it's pretty modest…Realistically, we expect to do at least six that we screened and are now waiting to get the insurance approval."
- *Dr. Aaronson, psychiatrist:* "I'm assuming, as a major referral center, we will wind up having somewhere in the range of 50-100 patients in the next year…As with anything else, there are early adopters and late adopters. But when you have someone in your office with depression you haven't been able to make better after a lot of reasonable and thoughtful preventions, there are few folks who would say, 'This is more than I care to do.' Is this a more problematic intervention than ECT is?"

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