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COMMENTARIES

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Commentaries

April fool's commentary: In Praise of Placebos

I first learned that the FDA had approved the use of placebo for the treatment of "poorly defined, intermittent, focal, generalized and migratory pain syndrome" in *The Onion*, my main source of news concerning federal policies often "missed" by the Providence Journal and the New York Times.

One of the impressive things about placebo is that it's been tested in a large number of disorders over several decades. In fact, it's been tested for virtually everything, from cancer to multiple sclerosis, arthritis, hepatitis, depression, nail fungus, HIV, anemia, and pain, of course, and frequently at equal doses in the different disorders. It has demonstrated benefit in baldness, shingles, Alzheimer's disease, schizophrenia and both benign prostate hypertrophy and prostate cancer. It has been shown, believe it or not, to be equivalent to fetal cell implants inserted directly into the brain of people with Parkinson's disease. Who can say then that, "Placebo doesn't do anything?!" What other drug treats PMS, erectile dysfunction and asthma?

In fact, in a study of my own design, costing the NIH (Alternative Medicine Institute) over $10,000,000 (so you know it's got to be good), we determined that placebo was even better than Coenzyme Q10, assistant enzyme R11, super-reductase S12 or the **radical super scavenger (RSS)** GrrrrrDOG5 for slowing disease progression in the large **Neuro-Eponymic Retarding Disease Study (NERDS)**. In that study RSS GD5, used alone, or in combination with the other so-called "retarding agents" was less effective than placebo in slowing progression of a mix of subjects with Alzheimer's, Lou Gehrig's, Parkinson's, Creutzfeldt-Jakob, Steele-Richardson-Olszewski and Vogt-Harada-Koyonashi diseases. Interestingly, placebo was less, rather than more, effective than not enrolling in the trial, in the so-call "no intention to treat" arm of the study involving non-participating non-subjects. (For interested lawyers, a special HIPAA form, #XT743L177, 777,666,666.3, the so-called, "I don't understand" document, was obtained by all subjects, non-subjects, and others who lived in Rhode Island). The results of this study have, of course, been debated ad nauseum, both in these pages and in the pages of distinguished medical journals, about confounding of the "meaning" of Eponymic diseases by inclusion of the so-called "made up" or "spurious" diseases, with some people doubting the existence of Friedman disease types 1, 2, 3, or 7, and others suggesting that these were phenotypic variants of one eponymic disorder, rather than several different diseases.

Regardless of this distraction, the notion of placebo is still important, even in people who didn't receive it in the trial because they weren't subjects. Placebo has a property shared by very few drugs, which is that its side effect profile is not dose-related. You can't really overdose. Withdrawal syndromes are rare and few patients have allergic responses. The lack of a dose-related response means that manufacturers can market "regular strength," "extra strength" and "gargantuan strength" formulations without adding more drug. There is also a great cost savings in reduced quality control, in keeping with the latest federal mandates, "to let the market take care of itself" since the amount of placebo contained in any pill or capsule is immaterial. Placebo also works as well or better than many surgical procedures, and often at half the cost. Titration with placebo is extremely easy, and can be adjusted for each individual situation, without regard to complicated internet searches or text book reviews. No more embarrassing calls to the pharmacy, or the drug rep, asking how to start or stop a particular drug. Full strength can be given with the first dose, or, when a "strong" drug is given, a slow and complicated titration can be written out in advance, regardless of the disorder being treated.

The safety margin in placebo is as large as the therapeutic window. Dose administration is limited only by the imagination. Placebo can be given in pill, capsule, suppository (rectal or vaginal), topical, injectable or inhaled formulations. While it is true that different colors of placebo capsules have different benefits and side effects, this may be determined by individual patients who could choose which color and shape pill works best for them. Placebo benefits can be extended by simply changing pill shape, color or strength.

The FDA, in making up its mind, was finally persuaded by the tremendous savings that a marketed placebo would have, along with a helluva party thrown by certain disinterested lobbyists. Absolutely no money would be spent on research, so the entire budget for drug development could be applied to the marketing end, a true triumph of a market-driven medical economy. This means that the "sky's the limit on pricing," and more money would be available for influence peddling, where the "bang for the buck" is maximized, as everyone learns in pharmacology classes.

Marketing will be easy. By hiring one rep for each four doctors, the reps can be highly trained, to be experts on the benefits of placebo in particular organ systems: one rep for cardiorespiratory, another for renovascular, one for GI-endocrine, and a CNS rep for neuro and psych.

Even the most ardent placebo supporters agree however that placebos may cause adverse effects. These are deemed cases of "mind over matter" whereas placebo benefits are considered "the power of positive thinking." Placebos have been implicated in causing rashes, bronchoconstriction, angina, cancer, headache, dizziness, diplopia, diarrhea, constipation and, in 2005 alone, three cases of pregnancy. Of course, on the positive side, while not all adverse events resolved with drug withdrawal, most responded quite well to use of the "little purple pill," an hexagonal 5mm/edge purple coated pill containing 1 gm of inert ingredient #37.6 UPS. In those rare cases unresponsive to further placebo treatment, we note that causality is hard to prove in a court of law. Patients suffering placebo side effects (nocebo effect) would be hard pressed to win a case in court. "My hair fell out because of this placebo pill," will not be a convincing argument.

Placebo surgery doesn't require FDA approval unless a placebo biological or device is used. Until codes for billing are established, surgeons will need to continue billing placebo procedures using the established guidelines.

Joseph H. Friedman, MD

The bathhouses of Manhattan

"Cleanliness", said John Wesley, "is, indeed, next to godliness." In a perfect world, this precept would never be disputed. But in the world of New York's 19th Century tenement houses, densely populated with the poor, cleanliness was a fanciful idea since these apartments lacked basic bathing facilities; and further, there was neither time nor incentive to keep oneself clean. In 1880, a physician newly arrived from the South, tried to remedy this.

Simon Baruch, born in 1840, left his native Prussia at age 15 to voyage alone to these shores. He knew of an uncle, a storeowner in the town of Camden, South Carolina. And for the next few years young Simon learned English while working as his uncle's bookkeeper. By age 20 he was enrolled in the South Carolina Medical College; then transferring to the Medical College of Virginia where, in 1862, he was awarded the MD degree. Dr. Baruch joined the armies of the Confederacy, was senior surgeon to a South Carolina infantry division and was twice captured by the Union army. At the end of the Civil War, Baruch helped to establish his state's Medical Society and was appointed president of the State Medical Board of Health.

Baruch practiced medicine in South Carolina for the next 16 years but was increasingly dissatisfied with the indiscriminate use of unproven remedies which, as often as not, did more visible harm than good. His studies brought him to appreciate the healing philosophies of the Austrian physician, Vincent Priessnitz [1799-1852], who had established a successful therapeutic spa in the Silesian mountains. Preissnitz employed therapies largely confined to the use of water for frequent bathing and irrigating the gastrointestinal tract. His patients recuperated in a restful, tranquil environment, ate a prudent diet with neither alcohol nor tobacco, and were encouraged to exercise. He called his alternative form of medicine, hydrotherapy.

Simon Baruch found little in the realm of conventional therapies of the 1870s to meet his definition of appropriate medical care. With the exception of proven medications such as digitalis leaf, morphine and a few others, he was certain that the bulk of untested, unregulated chemicals and herbal extracts created more harm than benefit. His advocacy of minimal medication interventions came close to the views of Dr. William Osler and others who recommended doing nothing rather than doing harm, a phase of medical history sometimes called therapeutic nihilism.

South Carolina offered Baruch no further challenges and he elected to move his practice and family to New York City.

Baruch's defense of hydrotherapy found critics in New York; but there were many who flocked to his office for a treatment regime that avoided the standard drugs of the day, particularly the many mercurial and arsenical medications, the herbal decoctions, the mindless use of purgatives and opiates and the discredited blood-lettings. It would be decades before proven anti-syphilitic agents became available as well as newer drugs to combat heart failure and aid the kidneys in excreting burdensome fluids. Rational therapies for glandular diseases and diabetes would not emerge for another three or four decades.

Baruch now encountered something that he had not seen in South Carolina: masses of newly-arrived immigrants living in the increasingly congested, wretched tenements of the Lower East Side of Manhattan. Laws had not yet been enacted to standardize hygienic facilities in these crowded warrens. Apartments consisted of little more than airless bedrooms and perhaps a kitchen but no bathroom. The older tenements had outhouses while the newer ones provided a single indoor privy for each four apartments, with neither bathtub nor shower.

Fond mythologies have softened the image of tenement life in the New York City of 1880. The quaint tales of enterprising young people advancing from ownership of a push-cart to a clothing shop and finally to a massive department store have ignored the tragically high infant mortality rates, the life expectancies which rarely exceeded 49 years and the general lack of upward mobility for most immigrants.

Baruch witnessed how many of the newly arrived were left behind in the slow progress toward middle-class self-sufficiency. He noted the rampant enteric infections and tuberculosis within this embattled community, the utter absence of sanitary facilities and the general squalor. "The great unwashed" was a description born of stark reality. Baruch's social conscience led him to launch a campaign that would immortalize his name amongst the impoverished immigrants of lower Manhattan.

Using funds derived from his successful practice of medicine, Baruch proceeded to construct a series of public bathhouses throughout the neighborhood. These imposing buildings, a few still standing as a remembrance of what had once been, provided a place for the poor to bathe at frequent intervals. And these free facilities, conjoined with a community-based educational effort to inculcate the principles of rational personal hygiene amongst the newly arrived immigrants, measurably changed the morbidity and mortality rates. The health of the immigrant community improved, thanks also to socially-conscious community health organizations such as the Henry Street Settlement House.

Despite persuasive advocates such as Drs. Baruch and Kellogg [of breakfast cereal fame], hydrotherapy faded as a significant school of clinical therapy. The Baruch bathhouses, however, endured until the second decade of the 20th Century when the laws of New York City mandated private bathrooms in all apartment houses.

And Baruch, the secular apostle of cleanliness? He lived to see his children grow to maturity, including Bernard Baruch, financial advisor to six presidents of the United States.

Baruch's gift of public bathhouses seems modest by contemporary standards. But to a generation of unlettered, unwashed immigrants, it was a blessing which taught them the lessons of cleanliness, dignity and generosity. And when, some years ago, New York City built a shiny new junior high school on East 21st Street, they named it the Simon Baruch Middle School in remembrance of an immigrant physician of blessed memory.

Stanley M. Aronson, MD

Introduction: Neurostimulation

Kelvin L. Chou, MD

For a long time, the surgical treatment of neurological disorders like **Parkinson's disease (PD)** and epilepsy were limited to "otomies" or "ectomies", either creating a hole in the brain or taking out parts of the brain. While effective for a small subset of these patients, these procedures never took off, partly because they did not work for the vast majority of patients, and partly because of the irreversibility of the procedure. However, in the late 1980s, the development of neurostimulation (e.g. using electrical current to stimulate the brain) in the form of **deep brain stimulation (DBS)** for PD, and **vagal nerve stimulation (VNS)** for epilepsy, led to a resurgence of interest in surgical procedures for neurological disorders. Refinement of techniques for DBS led to FDA approval in the United States for tremor (1997), PD (2002), and dystonia (2002). VNS was approved in 1997 for the treatment of epilepsy.

Over the past decade and a half, as we learned more about the effects of electrical stimulation on the brain, the number of possible indications has expanded. DBS is now being explored in Tourette's and epilepsy patients, as well as psychiatric diseases such as depression and obsessive-compulsive disorder. VNS was just recently approved for depression. Investigators in Rhode Island are among the leaders in neurostimulation techniques such as DBS and VNS. In this special edition of *Medicine & Health/Rhode Island*, these leaders review the literature on DBS for PD and VNS for epilepsy (the conditions for which these neurostimulation techniques were first approved), and highlight their work in exploring and developing new indications for DBS and VNS. I hope you enjoy this issue and the information on these exciting treatments.

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Neurostimulation for Epilepsy

Andrew S. Blum, MD, PhD, and Babak Morvarid, MS, MD

Hauser and colleagues have estimated the lifetime prevalence of epilepsy to be 1-3% of the population at large.[1] Despite the impressive recent advances in **anti-epileptic drug (AED)** therapies, only ~70% of patients are seizure-free with AED therapy, alone or in combination,[2] with 30% or more remaining medically refractory. Refractory epilepsy poses significant psychosocial, financial, and physical burdens to patients and their families and a major societal burden in loss of time from work and school. Treatment options for refractory patients include resective brain surgery, the ketogenic diet (in children), experimental therapies, and **vagal nerve stimulation (VNS).**

When patients with partial epilepsy are found to be medically refractory, surgical resection of the seizure focus becomes a primary option.[3] However, not all patients are determined to be appropriate surgical candidates after pre-surgical evaluation, and a subset are reluctant to undergo brain surgery. In such patients, neurostimulation with VNS is a viable treatment option that should be considered.

History of Vagal Nerve Stimulation

Bailey and Bremer conducted pioneering studies concerning the physiologic effects of VNS in 1938.[4] Subsequent animal studies demonstrated desynchronization of EEG activity with vagal nerve stimulation,[5] and later demonstrated anticonvulsant properties.[6] In 1988, the first human patient was implanted with a VNS.[7] Subsequently, VNS has been substantially improved, extensively studied, and made routine. Pivotal multicenter studies in the 1990s led to the 1997 FDA approval of an implantable device made by Cyberonics, Inc. named the **NeuroCybernetic Prosthesis (NCP)** as an add-on treatment option for medically refractory partial epilepsy, in patients over 12 years of age. As of 2005, more than 25,000 patients worldwide have been implanted with the device for the treatment of epilepsy. This year, the FDA approved VNS for the treatment of medically refractory depression.

Mechanism of Action

The exact mechanism of action of VNS is unknown. VNS mainly excites afferent fibers that terminate in the **nucleus of the tractus solitarius (NTS)**.[8] The NTS, in turn, projects to the parabrachial nucleus, which has projections to various CNS targets that are known to play key roles in seizure onset and propagation. These include the hippocampus, amygdala, and hypothalamus.[8] As well, the NTS has important connections to the raphe nuclei and the locus ceruleus, both utilizing noradrenergic transmission and both with extensive cortical projections.[8] Depletion of CNS noradrenergic transmission in animal models attenuates the anticonvulsant effects of VNS.[9] Functional brain imaging studies such as **positron emission tomography (PET)** scanning suggest that widespread CNS circuits are impacted by VNS.[10]

"...The exact mechanism of action of VNS is unknown."

Clinical Trials: Efficacy

Two multi-center, double blind, randomized trials (EO3 & EO5) evaluated the efficacy of VNS in refractory partial epilepsy.[11, 12] All patients were implanted with the device, and then randomized to high-intensity or low-intensity treatment arms. The primary endpoint was change in seizure frequency after 12 weeks. The secondary endpoint was the percentage of patients who experienced a 50% reduction in seizure frequency, the "responder rate," a commonly used yardstick in epilepsy trials.

Both studies demonstrated statistically significant differences in efficacy between the high- and low-intensity treatment arms. In EO3 (114 patients) the mean reduction in seizure frequency was 24.5% for the high-intensity group vs. 6.1% for the low-intensity group. The responder rate for the high-intensity group was 31%.[11] In EO5 (196 patients) the high-intensity arm had a mean seizure reduction of 28% vs. 15% for the low-intensity arm.[12] Although the responder rate in EO5 was not statistically significant over the first three months of study, open label extension studies from the EO1-5 studies showed median seizure reduction rates of 44% and responder rates of 43% by two years.[13] This observed delay in achieving the full therapeutic effect of VNS has raised the notion that there may be beneficial long-term physiological CNS changes that accrue with this therapy.

Clinical Trials: Adverse Events

VNS adverse events can be grouped into those associated with implantation and those associated with subsequent everyday use. Important peri-operative side effects include infection, bleeding, vocal cord paralysis (due to injury to the left recurrent laryngeal nerve, a branch of the vagus), lower facial paralysis, pain, cough, nausea, and voice change.[11,12] Generally, peri-operative side effects resolved. Infrequently, postoperative infection required explantation.

The adverse event profile associated with everyday use was similar in the two pivotal studies. These involved hoarseness, throat pain, cough, dyspnea, paresthesia, and mild muscle pain.[11,12] Such side effects appeared to be related to intensity of VNS settings (dose) and were rated as mild to moderate. Most resolved after the first year of use in open label follow-up studies.[13]

Implantation and Programming

The NCP is comprised of a battery-powered generator with a connecting cable, terminating in helical contact electrodes. (Figure). The *left* vagus nerve is used for VNS to avoid cardiac dysrhythmia; fibers from the right vagal nerve innervate the sinoatrial node.

Implantation of the device is typically performed under general anesthesia and usually takes one to two hours, often as outpatient surgery. The electrodes are gently looped around the left vagus nerve, once it is exposed via an incision along the anterior border of the sternocleidomastoid. The generator is placed over the left chest, inside a subcutaneous pocket made along the pectoral fascia. The mean battery life of the current model NCP generator is 8-12 years. When the battery life wanes, the generator must be surgically replaced. Finally, the generator and the electrodes are connected via a subcutaneous tunnel between the two locations, before the leads are tested with appropriate monitoring.

Many centers wait 1-2 weeks before activating the device. Programming the generator is straightforward, using a hand-held, computer-driven wand to "instruct" the generator regarding stimulation parameters. With successive visits, the device settings are gradually ramped up to target stimulation goals. Using this graduated approach, one may minimize the side effects mentioned in the prior section. Some centers later adjust the timing of the stimuli. Default settings are 30 seconds on, 300 seconds off. However, the device may be cycled more frequently and this may prove beneficial in some cases. In addition to its "round-the-clock" pattern of stimulation, the device is programmed to deliver a pre-set pulse in response to activation with a magnet provided to patients. This mode of use may help attenuate threatened seizure activity in some instances.

Role of VNS

VNS therapy has been approved for add-on use in patients with refractory partial epilepsy, in those 12 years and older. It has mainly been used when epilepsy surgery is deemed unwise or unacceptable to the patient, or when AED-related complications become untenable. It goes without saying that epilepsy surgery in well-selected patients offers the greatest chance for seizure-freedom. But there is a still sizeable fraction of refractory patients for whom surgery is unlikely to be helpful (e.g. multifocal patients, non-lesional extra-temporal patients). VNS has also been studied in other populations (though not FDA approved for such); it has been extensively used off-label in children with refractory epilepsy[14] and in patients with refractory generalized epilepsy.[15] It appears to be particularly valuable to patients with drop attacks, as in Lennox-Gastaut syndrome.[16] Indeed, it has nearly replaced the corpus callosotomy for such patients, seeking respite from injurious drop attacks.

Its efficacy in pivotal studies appears to be comparable with that of many of the newer AEDs, though it has not been compared in a head-to-head fashion. For example, two newer generation AEDs, gabapentin and topiramate, demonstrated responder rates of 28.5% and 45.7%, respectively.[17] The safety and tolerability profiles of VNS are very good and, arguably superior to many available AEDs. It poses no drug interactions, does not contribute to dizziness or lethargy (usual AED CNS side effects), and carries no compliance burden. Important shortfalls of VNS include the requirement for surgery, lack of truly curative potential, and interference with the ability to obtain neck or body MRIs after implantation (fear of thermal injury to the vagal nerve). Prior cosmetic concerns have improved with strides in design.

Experience at Rhode Island Hospital

At the Rhode Island Hospital Comprehensive Epilepsy Program, we have implanted ~120 patients over the past 5 years with the VNS. Of these VNS recipients, approximately 50% are followed in our center. Neurologists within surrounding communities are following the other recipients. In our own experience, a high percentage of patients and their families are pleased with this mode of therapy. Improvement is frequently described to us, not only in reduced seizure tallies, but in other important ways. Many patients have decreased their AEDs post-VNS, leading to reduced side effect burden and greater compliance. Other patients have commented on shorter seizures and faster recoveries with shortened post-ictal phases. Some families can use the "magnet mode" to abort a threatened seizure or a seizure cluster. Many families comment on improved alertness with VNS. There appears to be a modest but significant mood benefit as well. For all these reasons, satisfaction rates with VNS appear high. It remains to be seen what fraction of VNS patients will elect to re-implant their generator upon the battery's end of service. We anticipate that this will be the majority of VNS recipients.

Future Directions

Deep brain stimulation has become nearly commonplace in the treatment of Parkinson's Disease. By contrast, direct CNS stimulation is still a subject of active investigation in epilepsy. Numerous CNS structures have been studied to date. Cerebellar stimulation was initially tried in epileptic patients with mixed results.[18] Subsequently, various cortical and subcortical loci have been pursued. Different groups are currently exploring diverse stimulation paradigms. For instance, Fisher and colleagues have been studying thalamic stimulation (anterior and centromedian nuclei).[19] A phase II trial of anterior thalamic stimulation for refractory epilepsy is underway. This approach, in theory, is not predicated upon knowledge of the seizure focus. It relies upon the widespread connections between thalamus and cortex to exert its effects. It is therefore a non-specific approach, much like VNS.

Other groups have targeted the

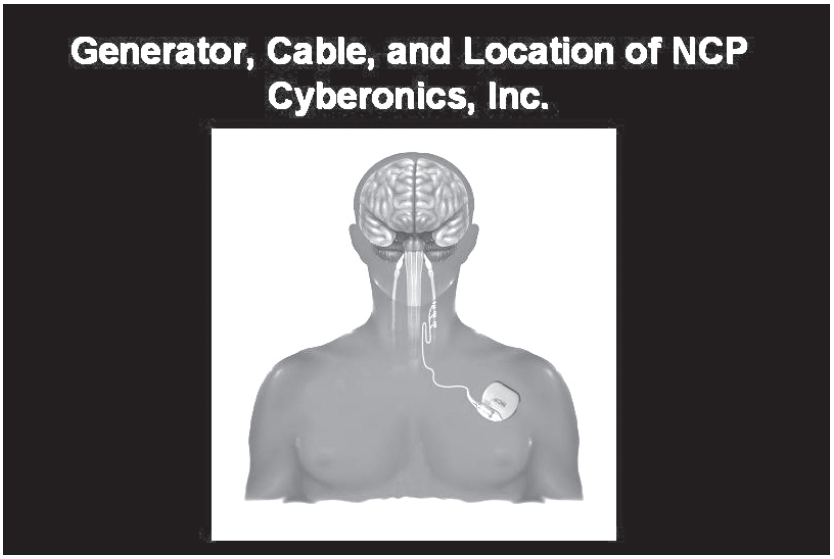
actual seizure focus. Both neocortical and limbic structures have been targeted in this paradigm. This requires detailed knowledge of the focus and relies upon indwelling subdural strips or grids to deliver stimuli to target structures. An underlying hope for this line of research is to ultimately devise a "closed loop" system in which the implanted grid contacts facilitate computerized detection of nascent or threatened seizure activity. This would trigger the delivery of electrical stimuli to a subset of the grid electrodes to abort or attenuate the threatened seizure. One prototype of this approach has been dubbed the **Responsive Neuro-stimulating (RNS)** device.[20] This elegant and "high-tech" approach has theoretical appeal but presumes pivotal advances in both seizure detection methodology and in neurostimulation to bring it to fruition.

Conclusion

VNS is the only FDA-approved form of neurostimulation for the treatment of epilepsy. Its specific indication is for medically refractory patients with partial epilepsy, age twelve and older. However, studies have also indicated efficacy in generalized seizure disorders and in children. Resective brain surgery still offers the greatest hope for seizure-freedom in refractory partial epilepsy but only a subset of patients are found to be good surgical candidates. For the remainder of refractory patients, VNS offers an important therapeutic alternative. It also offers the chance to reduce some of the burden of AED therapy for such patients, and appears to have salutary mood effects in some populations. It is recommended that patients with refractory epilepsy be considered for referral to comprehensive epilepsy programs to permit stratifying such patients for advanced treatment options, including VNS. Once implanted, the device is easily programmed, is generally very well tolerated by patients, and has an excellent safety profile. Finally, other forms of neurostimulation are being studied that offer great hope for future improvements in epilepsy treatment. We may look back one day and observe that VNS represents the start of an important paradigm shift in the treatment of epilepsy.

References

1. Hauser WA, Hesdorffer DC. *Epilepsy: frequency, causes, and consequences*. New York: Demos, 1990.
2. Cockerell OC, Johnson AL, et al. *Epilepsia* 1997; 38:31-46.
3. Wiebe S, Blume WT, et al, for the Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. *NEJM* 2001; 345:311-8.
4. Baily P, Bremer F. *J Neurophysiol* 1938; 1:405-12.
5. Chase MH, Nakamura Y, et al. *Brain Res* 1967; 5:236-49.
6. Zabara J. *Epilepsia* 1992; 33:1005-12.
7. Penry JK, Dean JS. *Epilepsia* 1990; 31 Suppl 2:S44-50.
8. Rutecki, P. *Epilepsia* 1990; 31 Suppl 2:S1-6.
9. Krahl SE, Clark KB, et al. *Epilepsia* 1998; 39:709-14.
10. Henry TR, Bakay RA, et al. *Epilepsia* 1998; 39:983-90.
11. The Vagus Nerve Stimulation Study Group. *Neurol* 1995; 45:224-30.
12. Handforth A, DeGiorgio CM, et al. *Neurol* 1998; 51:48-55.
13. Morris GL 3rd, Mueller WM. *Neurol* 1999; 53:1731-5.
14. Murphy JV. *J Pediatr* 1999; 134:563-6.
15. Labar D, Murphy J, Tecoma E. *Neurol* 1999; 52:1510-2.
16. Helmers SL Al-Jayyousi M, Madsen J. *Epilepsia* 1998; 39 Suppl 6: 169.
17. Marson AG, Kadir ZA, et al. *Epilepsia* 1997; 38:859-80.
18. Cooper IS, Amin I, et al. *Arch Neurol* 1976; 33:559-70.
19. Kerrigan JF, Litt B, et al. *Epilepsia* 2004; 45:346-54.
20. Kossoff EH, Ritzl EK, et al. *Epilepsia* 2004; 45:1560-7.



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Deep Brain Stimulation Surgery for Parkinson's Disease: The Role of Neuropsychological Assessment.

Melissa M. Amick, PhD, and Janet Grace, PhD

Deep brain stimulation (DBS) within the **globus pallidus internus (GPi)** or the **subthalamic nucleus (STN)** is an increasingly common treatment for **Parkinson's disease (PD).** PD patients who undergo this procedure demonstrate significant improvements in motor functioning and may have less need for anti-Parkinson's medications. From a neuropsychological standpoint, DBS is not commonly associated with dementia or severe psychiatric decline; however, modest changes in cognitive and affective functioning have occurred.

Before surgery, PD patients can have cognitive impairments in the areas of executive functions, complex attention, verbal fluency, and working memory.[1] Additionally, depression and anxiety disorders are prevalent in PD patients.[1] Those cognitive and emotional changes may be partly due to dysregulation of dopamine within the basal ganglia that disrupts multiple separate but parallel circuits involving the basal ganglia, thalamus, and different regions of the frontal lobes.[1] Consequently, surgery and stimulation affecting the basal ganglia would be expected to further disrupt cognition and affect. The importance of neuropsychological evaluation for DBS candidates is underscored by the inclusion of cognitive and behavioral assessment as part of the **Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD),** developed by a network of European medical centers that perform DBS.[2]

This manuscript will review the two main roles of neuropsychological evaluations in DBS: 1) the determination of a patient's suitability for surgery and 2) evaluation of the impact of deep brain stimulation upon neuropsychological and affective functioning by comparing assessments before and after surgery.

Exclusion Criteria for Neurosurgery

Neuropsychological assessment, as part of the DBS pre-surgical screening, has three main objectives 1) to determine whether the patient has a dementia, 2) to evaluate the patient for signs of cognitive impairment, which would suggest the presence of an additional neuropathology (e.g. Alzheimer's disease, progressive supranuclear palsy, or multiple systems atrophy), and 3) to assess for significant psychopathology including depression, psychosis, or other significant psychiatric issues. Several patient characteristics have been linked to poor DBS outcome including older age, advanced stage of Parkinson's disease, dementia, significant frontal lobe dysfunction, and severe anxiety or depression.[3]

"... At the present time, a disruption in verbal fluency is the only consistent cognitive decline associated with DBS."

Typically dementia is an exclusionary criterion for DBS because PD patients with dementia are at greater risk for cognitive decline following surgery.[4] Most centers exclude PD patients who meet DSM-IV criteria for dementia defined as, "*development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive impairments must be sufficiently severe to cause impairment in occupational and social functioning and represent a decline from a previously higher level of functioning.*"[5]

Accurate diagnosis of PD is also critical for DBS clearance. The presence of a second neuropathological process is exclusionary for DBS. The importance of neuropsychological evaluation is underscored by estimates that between 16.5% - 54% of PD patients meet criteria for dementia.[6] A diagnosis of PD with dementia can suggest the presence of an additional neuropathology. For example, in a sample of 100 patients clinically diagnosed with PD, at autopsy it was found that 76 patients fulfilled the pathological criteria for Parkinson's disease, whereas 24 patients were found to have been clinically misdiagnosed. Autopsy revealed that six patients had neuropathological findings consistent with progressive supranuclear palsy, six with Alzheimer's disease, five with multiple systems atrophy, three with vascular disease, two with postencephalitic parkinsonism, and one with no abnormal findings.[7] PD patients may have additional neurodegenerative processes, which might not be detected without neuropsychological evaluation.

Psychiatric symptoms frequently occur in patients with PD and have been linked with negative outcome following DBS surgery. Between 40-60% of PD patients are estimated to experience depression and over 22% of PD patients meet criteria for severe depression.[8] Depression can be associated with significant cognitive impairments in the areas of attention, memory, as well as executive functions. If mood is not properly assessed, neuropsychological testing of a severely depressed person might result in the exclusion of a patient who would otherwise be an appropriate surgical candidate. The presence of pre-surgical symptoms of depression also has been shown to interact with recovery following DBS surgery.[8] The presence of significant psychiatric symptoms might warrant

referral to a psychiatrist for further assessment before the patient is cleared for DBS surgery.

The main goal of neuropsychological assessment is to determine that the patient has PD uncomplicated by factors of dementia or depression. It has been documented that higher pre-morbid intellect, intact cognitive capacity as well as younger age at onset are associated with fewer cognitive changes following DBS surgery.[6]

Measuring the Outcome of DBS

Changes in cognition and mood caused by neurosurgery must be detected. Tests administered prior to surgery should be repeated following surgery. The number of publications on the cognitive and emotional outcomes of DBS is growing; however, reports vary across a number of factors including medication status at times of testing, sample sizes, and intervals between evaluations. The studies included in this brief review share the same relatively strict inclusion criteria: patients experienced substantial disability due to "off periods" or had medication-induced dyskinesias, had no dementia, no prior neurosurgery, no MRI evidence of other CNS disease, or no psychiatric complications. (Table 1)

Global Cognitive Functioning

Declines in global cognitive functioning and intellectual abilities are hallmarks of dementia. In general, studies of DBS of the STN or the GPi report no decline in global measures of cognitive functioning. [9,10,11] In the largest study of STN DBS, Funkiewiez and colleagues reported that total **Dementia Rating Scale (DRS)** scores tended to worsen following surgery: of 77 patients only 4 patient's DRS scores at a three-year follow-up assessment fell to less than 130/144 (the established cut-off for global cognitive impairment in DBS candidates[2]). In the four patients who declined post

Table 1: Summary of recent studies reporting the neuropsychological outcomes following DBS for PD.

Authors	Testing Interval	Meds. status	Location	Improvements	Declines
Alegret et al. (2001)	Baseline vs. 3 months PS	Off	STN (n=15)	Switching between conceptual sets (set shifting)	Verbal memory, inhibition of a dominant response, fluency, visuospatial functions
Ardouin et al. (1999)	Baseline vs. 3-6 months PS	Off	STN (n=49)	Set shifting	Fluency
			Gpi (n=13)	None	None
Dujardin et al. (2001)	Baseline vs. 3 months, & 12 months PS	On	STN (n=9)	3mo: Psychomotor speed and simple attention* 12 mo: RT	3mo: Verbal memory, categorical fluency* 12mo: Additional mild declines in executive functions
Funkiweicz et al. (2004)	Baseline vs. 1 year, & 3 years PS	Off	STN (n= 77)	None	Fluency, global cognition*, executive functions*
Perozzo et al. (2001)	Baseline vs. 6 months PS	On & Off	STN (n=20)	None	None
Pillon et al. (2000)	Baseline vs.On and Off PS	Off	STN (n=63)	Executive functions, RT, spatial and verbal* working memory	Categorical fluency (relative to baseline)
			Gpi (n=13)	None	None
Trepanier et al. (2000)	PS Baseline vs. 3-6 months PS	On	STN (n=9)	None	Set shifting, fluency, verbal & visual memory
			Gpi (n=4)	Attention*	Phonemic fluency, verbal memory
Saint-Cyr et al. (2000)	PS Baseline vs. 3-6 months, & 9-12 months	On	STN (n=11)	None	3-6mo: Speed of processing, RT, set shifting, fluency, verbal & visual memory. 9-12mo: Additional declines in working memory

PS = post surgery, **STN** = subthalamic nucleus, **Gpi**- Globus Pallidus, ***** = trend, **RT** = reaction tine

surgery, two had complications during surgery (intracerebral bleeding), while two showed a progressive decline in cognitive functioning unrelated to surgical complications. The findings suggest that significant global decline following DBS of the STN is rare (approximately 3% of patients).

Executive Functions

Many aspects of executive functions are disrupted in PD patients before surgery; e.g., difficulties on tasks of executive functions that require switching between conceptual sets (e.g. alternating between connecting numbers and letters in ascending order), inhibition of a dominant response (e.g. naming the ink color of a word rather than reading the word itself), and working memory (e.g. the ability to hold in mind and manipulate newly presented information without external cues, such as reciting numbers in a reverse order). Follow-up evaluation of executive functions has reported improvements, declines, and no change following surgery. When PD patients are evaluated off medications (both pre and post surgery), improvements in set shifting have been observed following DBS of the STN.[9,12] By contrast, when PD patients with DBS of the STN are tested in their optimal medication state declines in set shifting have been reported.[13,14] Inhibition of a dominant response has been found to decline following DBS of the STN, independent of medication status.[10,12] The effect of stimulation of the STN has been associated with improvements in aspects of executive functions.[11] Specifically, comparison of cognitive performance with stimulators switched on vs. off revealed improvements in set shifting, inhibition of a dominant response, spatial working memory and a tendency for improved verbal working memory.[11]

Executive functions are not significantly affected by DBS of the Gpi.[9,13,14] Non-significant changes in executive functioning of the GPi group may be due to small sample size (all studies n < 15), which can be associated with low statistical power to detect significant effects. It has been concluded that DBS of the GPi (relative to DBS of the STN) is associated with fewer cognitive changes but this may be due to the examination of small samples of GPi patients.

Language

Most aspects of language skills are not assessed in studies of DBS. Verbal fluency, (i.e. number of words generated in 60 seconds that are from a particular category or start with a certain letter) has been found to decline following DBS surgery, by all studies (see Table 1) (except Perozzo et al, 2001[15]). This impairment is unrelated to stimulation as Pillon and colleagues (2000) noted that declines in fluency remained, relative to baseline, even when the stimulators were turned off. Reduced verbal fluency should be expected following DBS and patients with poor verbal fluency should be counseled accordingly before surgery.

Learning and Memory

There are reports that memory is not affected by DBS of the STN or the Gpi.[8,4,9,15] and one report that stimulation, by itself, improves verbal memory performance.[11] However, learning of verbal material was observed to decline after DBS of the STN.[12] Furthermore, both STN and GPi patients have shown decreased verbal delayed recall.[13,14] Learning and delayed recall of visual material have been found to be impaired following DBS of the STN.[13,14] but visual memory was assessed in too few GPi patients to be conclusive.[14]

Visuospatial abilities

The prevalence of visuospatial impairment in PD patients is controversial;[16] and few DBS studies have assessed visuospatial skills. Constructional abilities (i.e. copy of a figure) appear to be unchanged in DBS of the STN[9,11] or the Gpi[9]. Alegret and colleagues, however, reported that DBS of the STN was associated with worsening visuospatial skills (i.e. difficulty matching lines presented at different angles). Future studies may want to focus on the impact of DBS upon visuospatial skills because behavioral and neuroimaging data suggest that visuospatial cognition is impaired in PD patients and this cognitive function might be vulnerable to decline following surgery involving the basal ganglia.

In sum, DBS appears to be a relatively safe intervention from a neuropsychological standpoint. In the largest study with the longest follow-up, Funkiewiez report that less than 4% of their patients developed dementia following this intervention.[4] While there may be subtle changes in cognitive functioning, results vary across studies and are not consistent with regard to medication status at the time of testing. Given the limited research conducted with patients with DBS of the GPi, future studies are recommended to evaluate the cognitive changes associated with this surgical site. Finally, there is much to be learned about the effects of stimulations upon cognition. To our knowledge, there has yet to be a study design which would disentangle the impact of medications vs. stimulation upon cognitive functions. This would require testing individuals under four different conditions (on medication & on stimulation, off medication & on stimulation, off medication & off stimulation, and on medication & off stimulation). Until these types of projects are undertaken, it will be difficult to conclude which aspects of cognition are truly altered following DBS.

Mood

In a review of the literature DBS was more likely to be associated with reductions rather than increases in symptoms of depression[17]. Only studies that measured depression symptoms with a reliable and valid clinical scale were reviewed. Between 16.7-76% of patients showed improved mood, whereas between 2.0-33.3% of patients showed decreased mood post surgery.[17] History of depression may be a risk factor for post-surgical depression as 3 out of 4 studies reviewed found a correlation between previous depression history and increased depression post DBS.[17]

In the domain of psychiatric functioning, several negative psychiatric outcomes have been documented following DBS of the STN. In the largest study to date, suicide attempts occurred in four of the 77 patients assessed, one patient died by suicide, and an additional patient developed severe depression that required hospitalization.[4] Dujardin and colleagues reported that four of the nine patients in their study experienced behavior changes, which were significantly concerning to family members/ caregivers.[10] In another study, six of 24 patients' mood declined to the moderate to severely depressed range and three were transiently suicidal soon after DBS of the STN.[18] Personal history and family history of depression and difference in motor improvements (i.e. UPDRS scores or reductions in medications) were not risk factors for developing depression after surgery but there were a higher proportion of women relative to men who became depressed.[18]

While DBS tends to improve rather than worsen mood, increased depression following the surgery can be a side-effect. Fortunately, in many cases, depression following DBS can be treated with an SSRI or an increase in dopaminergic medication.[4,18] These findings also suggest that PD patients with a history of severe depression should be counseled about the possibility of worsening of mood should they undergo surgery.

Symptoms of mania can be a side effect of DBS surgery. In a review of the effects of STN stimulation on mood states, symptoms of mania were observed at a frequency of 4.2-8.1%.[17] Three out of fifteen PD patients who underwent STN stimulation developed manic symptoms including elation, increased self esteem, over activity, logorrhea, flight of ideas, sexual indiscretions, and insomnia within 48 hours of the stimulator being turned on.[19] Before surgery none of these patients had a history of psychiatric disorders, impaired cognition, or mood fluctuations with dopaminergic drugs.[19]

In general, DBS is more typically associated with improvement rather than worsening of emotional functioning. Depression and the development of symptoms of mania are, however, serious but treatable side effects of DBS. It has been proposed that disrupted emotional functioning following surgery may be due to stimulation of the limbic fibers that travel from the STN, through the striatum, and project towards the prefrontal cortex, which are implicated in regulation of mood states.[20] Given that emotional functioning can decline post DBS, careful screening of psychiatric status and history prior to surgery and monitoring of affective functions following surgery is strongly recommended.

Summary

Neuropsychological assessment has two primary roles in the DBS process. First, assessment of cognitive and emotional functioning ensures that only appropriate candidates undergo this surgical procedure. Patients with dementia, cognitive performance suggestive of an additional neuropathological process, or significant psychiatric impairments should not undergo DBS. Second, neuropsychological assessment is essential to determine the cognitive and emotional outcomes following surgery. At the present time, a disruption in verbal fluency is the only consistent cognitive decline associated with DBS. While worsening of depression and the development of symptoms of mania are potential side effects from DBS, more studies find that DBS is associated with improvements in emotional functioning. Based on the growing understanding of the risk factors and potential side effects to DBS, neuropsychological assessment is necessary to ensure that patients selected to undergo this surgical intervention will likely have positive cognitive and emotional outcomes, in addition to the expected benefits in motor functioning.

References

1. Boller F, Grafman J. *Hand Book of Neuropsychology. Volume 6 Aging and Dementia* 2001; 311-72.
2. Defer GL, Widner H, et al. *Mov Disord* 1999; 14:572-84.
3. Fields JA, Troster AI. *Brain Cogn* 2000;42; 268-93.
4. Funkiewiez A, Ardouin C, et al. *J Neurol Neurosurg Psychiatry* 2004; 75:834-9.
5. *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition.* 1994; p. 134.
6. Saint-Cyr JA, Trepanier LL. *Mov Disord.* 2000; 15:771-83.
7. Hughes AJ, Ben-Shlomo Y, et al. *Neurol* 2001; 57:S34-8.
8. Pillon B. *Mov Disord.* 2002;17:S116-22.
9. Ardouin C, Pillon B, , et al. *Ann Neurol* 1999; 46:217-23.
10. Dujardin K, Defebvre L, et al. *J Neurol* 2001; 248:603-11.
11. Pillon B, Ardouin C, et al. *Neurol* 2000; 55:411-8.
12. Alegret M, Junque C, et al. *Arch Neurol* 2001; 58:1223-7.
13. Saint-Cyr JA, Trepanier LL, et al. *Brain* 2000; 123:2091-108.
14. Trepanier LL, Kumar R, et al. *Brain Cogn* 2000; 42:324-47.
15. Perozzo P, Rizzone M, et al. *J Neurol Sci.* 2001;192: 9-15.
16. Amick MM, Schendan, HA, Cronin-Golomb, A. *Neuropsychologia*; in press
17. Takeshita S, Kurisu K, et al. *Neurosurg Rev.* 2005;28:179-86
18. Berney A, Vingerhoets F, et al. *Neurol* 2002;59:1427-9.
19. Kulisevsky J, Berthier ML, et al. *Neurol* 2002;59:1421-4.
20. Chou KL, Friedman JH. *Handbook of Clinical Neurology. 3rd ed. Parkinson's Disease and Related Disorders.* in press.

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Surgical Aspects of Deep Brain Stimulation

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In 1817 James Parkinson described a condition in several patients who had tremors and gait abnormalities. At the time, little was known about movement disorders or about the brain's functions in general. It was not until the 1940s that the first attempts were made to try to treat movement disorders, especially Parkinson's disease (PD). Since an effective pharmacological treatment had not yet been discovered for PD, the first attempts of treatment were of surgical nature. With the introduction of stereotactic equipment in 1947 by Spiegel and Wycis, treatment became more precise and in the 1950s and 1960s, tens of thousands of patients with movement disorders were treated successfully (and unsuccessfully) with lesioning procedures such as thalamotomy and pallidotomy. With the introduction and widespread use of L-Dopa around 1965, however, surgery for Parkinson's disease and other movement disorders almost disappeared. Only when side effects from long-term use of L-Dopa medication were discovered did a resurgence of interest in neurosurgical treatment options ensue. Neurosurgeons had always used electrical stimulation during the course of lesioning surgery in order to guide the lesion placement and had found that stimulation using high- frequency electrical signals could abolish tremor. Since deep brain stimulation is a reversible and adjustable technique, it has become increasingly popular as opposed to the irreversible lesioning procedures. The introduction of deep brain stimulation electrodes makes it now possible to avoid lesioning procedures. The first successful DBS surgery attempts were reported in the 1970s but it took until 1987 until the first successful surgery with a fully implantable DBS system was reported in France by Benabid (1). Since then, about 50.000-100.000 DBS systems have been implanted worldwide.

"In properly selected patients, DBS is safe and effective."

Preoperative evaluation

DBS surgery today is not an experimental treatment for several conditions. It is approved for the treatment of essential tremor (FDA approval 1997), Parkinson's disease and parkinsonism (FDA approval 2002) and dystonia (FDA approval 2002). For these conditions, electrodes are placed in the area of the basal ganglia. The originally recommended target was the ventro-lateral nucleus of the thalamus, pars intermedius (VIM) and later the **globus pallidum internum (GPI)** and **subthalamic nucleus (STN)** were introduced as even better targets for some patients[2,4,7,8,10]

The best surgical outcome is expected in patients who meet all inclusion criteria. The most important factors for patient selection are acceptable patient age (typically 70 years or younger) and lack of significant medical problems such as uncontrolled diabetes or hypertension. For Parkinson's disease it is also important to document responsiveness to L-Dopa therapy. In our center, this is done by comparing the **Unified Parkinson's Disease Rating Scale (UPDRS)** scores in the ON and OFF phase as part of the prospective patient's preoperative full neurological evaluation. We also send these patients for psychiatric evaluation, as a small minority of PD patients can experience significant depression after surgery. One of the most important exclusion criteria for DBS surgery is the presence of dementia which has been associated not only with lack of responsiveness to DBS therapy but worsening of the patients' overall brain function after surgery. Therefore, all of our potential DBS candidates undergo a full preoperative neuropsychological assessment.

In addition, DBS surgery is under intense investigation regarding its potential role for epilepsy or psychiatric diseases such as severe **obsessive-compulsive disorder (OCD)** and severe treatment-refractory depression. Several case reports show promising results with placement of the electrodes into the basal part of the anterior internal capsule, certain thalamic nuclei, subthalamic nucleus or around the cingulate cortex.[3, 5, 9] At this stage this experimental treatment cannot be widely recommended to patients. It should be limited to dedicated research centers that have a history of collaboration between neurologists, psychiatrists, neurpsychologists and neurosurgeons.

Surgical Planning

Although the surgical procedure may differ slightly from center to center there are certain steps to every DBS surgery. The first step is the application of a stereotactic frame. This frame is a ring or rectangle, which is secured to the patient's head under local anesthesia. It allows the surgeon to identify any point inside the frame in the X, Y and Z direction in terms of Cartesian coordinates. Therefore, any point inside the patient's brain can also be identified and targeted using coordinates. These coordinates are obtained from the MRI scan that is performed as a next step in the procedure. Typically,the images produce a high contrast between gray and white matter. At our center, we rely on TIRM (turbo-inversion recovery) images in the axial and coronal planes with 2 mm thickness. In addition, a contrast-enhanced volumetric MP-rage study is obtained to outline vascular structures on the brain's surface. Once all MRI studies are completed the images are transferred

electronically to a stereotactic planning computer. On this workstation the images are reconstructed and aligned according to internal landmarks (AC - anterior commissure and PC - posterior commissure). The location of these landmarks in the brain is used as a reference to determine the location of the target area. The STN, for example, is typically located 11 mm lateral to midline, 8 mm anterior to PC and 4 mm inferior to the AC-PC plane. Although the STN can be visualized directly on MRI the coordinate system is used as a reference to verify the anatomical location. Other targets such as the VIM region are not directly seen on MRI and the anatomical location must therefore be determined using the internal landmark reference system alone. Once the target has been selected it is identified in terms of laterality (X-coordinate), anterior-posterior location (Y-coordinate) and superior-inferior location (Z-coordinate).

Surgery

After this planning procedure, the patient is brought to the surgical suite, where s/he is positioned on the operating table in the supine position. After shaving, prepping and draping, the patient receives anesthetic medication for sedation. Some of the surgical procedure is performed with the patient asleep in **monitored anesthesia care (MAC);** at other parts of the surgery the patient must be awake and able to cooperate. For the initial parts of surgery the patient is asleep. During this time, the coordinates are adjusted on the stereotactic frame system and the entry locations through the skull are determined. Local anesthetic is infiltrated and a 3 cm skin incision is made in the patient's forehead behind the hairline. Self-retaining retractors are applied and the skull is identified. Using a surgical drill, a burr-hole is placed at the appropriate location and the dura is exposed through the hole. The dura is opened in a cruciate fashion to expose the actual cerebral cortex covered with arachnoid and pia mater. A C-arm X-ray machine is positioned which allows us to visualize the electrode probe located inside the patient's skull.

For most DBS surgeries **micro-electrode recording (MER)** is performed as the next step. One to five microelectrodes record signals from the target area and surrounding structures. These electrodes allow for extracellular single-cell recording. Since most brain structures have unique cell assemblies with unique cell firing patterns it is possible to characterize brain structures by their electrical discharge signature. This method gives electro-physiological confirmation of the presumed location of the ideal target as determined by anatomical landmarks. Although MER is the most time-consuming part of DBS surgery, it is believed to be extremely useful in determining the ideal target location. Only in certain circumstances where a short surgery time is essential for patient safety is DBS surgery performed without MER.

Once the ideal target has been confirmed, the DBS electrode array is introduced. It is a shielded wire bundle with 4 exposed contacts at the tip. For the first time, the electrode array is activated in the operating room. For that, an external stimulator-box is temporarily connected to the electrode array and intraoperative stimulation is commenced. It is also the time when the beneficial effect of DBS surgery may become quite obvious. This is especially dramatic in patients who suffer from tremor where the tremor comes to a sudden arrest as soon as the electrode array is activated. When the temporary stimulator is turned off the tremor sometimes returns seconds later only to disappear again with the stimulator being turned back on. During this time the patient has to be awake and cooperative since stimulation-related side effects can be detected. It is then possible to change the final position of the electrode slightly to avoid or minimize these side effects.

Once the optimal location of the DBS electrode has been determined the electrode is fixated to the skull to prevent further dislodgement. The burr holes are then also covered mainly to give a pleasing cosmetic result. The last step for surgery is implantation of the implantable pulse generators which are basically the implantable battery units that also contain the electronics to provide chronic pulsed stimulation. These battery packs are placed subcutaneously in the sub-clavicular area or abdominal area. Many centers recommend having these stimulators implanted in a second surgical procedure 2-3 weeks after the electrode implantation. Since surgical planning, MER and electrode implantation can take 8 hours or more patients commonly agree with this two-stage approach.

Postoperative follow up

Most patients tolerate the often lengthy surgical procedure well despite being off their routine medications for almost the entire day. The majority of patients feel well enough to leave the hospital the day after surgery. Elderly patients may take extra days to recover but only rarely is inpatient rehabilitation necessary. Once the DBS system is implanted, patients follow up with their movement disorder neurologist, who then starts programming their DBS stimulators. The initial programming session in our center occurs at least two weeks after surgery. Multiple clinic visits are subsequently needed to optimize stimulator settings. This process can take several weeks or months since with every programming step and fine-tuning a change in medication may also be advisable. Patients are now given handheld programmers which allow them to interrogate the DBS system. Patients therefore are able to identify if the stimulator is turned on or off, they can turn the system on or off themselves if so desired.

Risks and Benefits

In addition to the routine surgical risks related to bleeding, anesthesia, and possible infection, DBS presents a small risk of neurological complications. There is approximately a 2-3% chance of brain hemorrhage that may be of no significance, or may cause paralysis, stroke, speech impairment or other major problems. This means that for every 100 patients who undergo surgery, two or three will experience a

permanent or severe complication. However, most patients will have no complications. Infection is a problem associated with any implantable device including DBS systems. While treatment of infection may require removal of the electrode, the infections themselves usually do not cause lasting damage. The electrode that is implanted in the brain and the electrical systems that provide stimulation is subject to failure as well.[6] However, they are generally well tolerated with no significant changes in brain tissue around the electrodes even decades after implantation.

Stimulation-related side effects are possible but can usually be minimized by changing the stimulation parameters of the DBS system (re-programming). Dependent on the location of the electrode stimulation may cause unwanted paresthesias in the face or hand (typically seen with the electrode in the VIM region), blurry vision or light flashes (with the electrode in the GPi region) or problems with eye coordination (location of electrode in the STN region). Also, if the electrode is close to but not in the ideal target location it may be impossible to evoke a beneficial response even with high energy output. An electrode misplacement of 2-3 mm in any direction can be enough to cause failure of DBS treatment.

Beneficial effects have been demonstrated to last for several years for patients with PD. Patients who initially responded well to medications, but over time have developed side effects, can experience between 60 to 80% improvement in such symptoms as tremor and slowness of movement. In addition, the majority of patients report significant improvement in their walking and balance. Similarly, patients with involuntary movements (dyskinesias) due to their medications, experience over 80 percent reduction in their involuntary movements. Most patients are able to reduce their medications by 50% or more following DBS of the STN.

Discussion and Summary

In properly selected patients, DBS is safe and effective. It has become standard of care for PD patients with refractory medication-induced motor problems and it is highly effective for patients suffering from essential tremor and dystonia. The promising results reported in the medical literature lead us to believe that DBS surgery will be offered in the near future to many more patients, including those suffering from epilepsy or certain psychiatric diseases.

References

1. Benabid AL, Pollak P, et al. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol* 1987; 50: 344-6.
2. Goetz CG, Poewe W, et al. Evidence-based medical review update. *Mov Disord* 2005, 20: 523-39.
3. Greenberg BD, Price LH, et al., Neurosurgery for intractable obsessive-compulsive disorder and depression. *Neurosurg Clin N Am* 2003; 14:199-212.
4. Lagrange E, Krack P, et al. Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurol* 2002 59:1976-8.
5. Mayberg HS, Lozano AM, et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651-60.
6. Oh MY, Abosch A, et al. Long-term hardware-related complications of deep brain stimulation. *Neurosurg* 2002 50:1268-74;
7. Rodriguez-Oroz MC, et al, Bilateral deep brain stimulation in Parkinson's disease. *Brain* 2005 (Epub ahead of print).
8. Vitek JL, Bakay RA, et al. Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. *Ann Neurol* 2003 53:558-69.
9. Vonck K, Boon P, et al., Neurostimulation for refractory epilepsy. *Acta Neurol Belg.* 2003 Dec;103:213-7.
10. Walter BL, Vitek JL, Surgical treatment for Parkinson's disease. *Lancet Neurol* 2004; 3: 719-28.

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Vagus Nerve Stimulation and Deep Brain Stimulation for Treatment Resistant Depression

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Although depression is most often treated with drug therapy alone, the published success rates of pharmacological interventions for major depression are inadequate. Approximately 50% of depressed patients do not respond to a trial of a particular antidepressant;[1] as many as 20% of patients do not respond to any antidepressant medication.[2] Even when medication is combined with psychotherapy, response rates range from about 45% to 90%.[3] The numbers describing those who progress from "response" (typically defined as a 50% decrease in symptoms as measured by a standard scale) to "remission" (defined as nearly complete absence of core depressive symptoms, and depression scale scores similar to those measured in nondepressed adults) are more discouraging.[4] Consequently, a substantial portion of patients with major depression remain inadequately treated, and some will go on to develop chronic, debilitating symptoms and suicidal behavior. For patients **with treatment-resistant depression (TRD),** especially those with a high risk of suicide, other therapeutic options must be considered. Neurostimulation holds promise for patients with depression refractory to standard treatments.

Neurostimulation utilizes either electric current or application of a strong magnetic field to stimulate the brain. The various techniques used include **electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), vagus nerve stimulation (VNS**) and **deep brain stimulation (DBS).** Although ECT has been in use for decades, the technique is still being refined and improved in recent years.[5] The other neurostimulation treatments have been developed more recently and have efficacy profiles that are considered less well established than that of ECT.[6, 5] Two of theses five brain stimulation therapies with promise of antidepressant efficacy are reviewed here.

Vagus Nerve Stimulation

Since 1997 the US **Food and Drug Administration (FDA)** has approved VNS for refractory epilepsy.[7] More recently, VNS has been evaluated for treatment of depression and received FDA approval in July 2005. The device is now indicated for adjunctive, long-term use in chronic or recurrent major depression in adult patients with an inadequate response to at least 4 antidepressant treatments.

VNS accomplishes brain stimulation indirectly, via the vagus nerve (cranial nerve X). A generator about the size of a pocket watch is implanted subcutaneously into the left chest wall and is connected to bipolar electrodes that are attached to the left vagus nerve within the neck.[8] The generator is programmed to deliver mild electric pulses in continuous cycles, typically with 30 seconds of stimulation followed by 5 minutes off. The device can be programmed noninvasively by the treating physician, who uses an external telemetric wand to effect changes in "dose" (intensity or rate of stimulation).

Two published reports from a pilot study (Cyberonics Study D-01) have demonstrated both short- and long-term efficacy for VNS in a small, unblinded trial. In the short-term trial, 59 patients with TRD received VNS for 10 weeks.[9] Over 30% were responders (at least a 50% improvement), based on the primary efficacy measure, the Hamilton Depression Rating Scale (HDRS). In a long-term naturalistic follow-up to this D-01 pilot study, 30 patients received an additional 9 months of stimulation.[10] In these patients, response rates were sustained, and remission rates (HDRS score ≤ 10) were significantly increased (from 17% to 29%, $P = 0.045$).

Additionally, short- and long-term results from a "placebo"-controlled study of VNS in combination with usual standard-of-care have been described in a group of 225 patients with refractory depression.[11,12] Essentially, in the short-term (10-week) acute treatment phase (Cyberonics Study D-02) , the antidepressant effect of adjunct VNS was not confirmed, with response rates for active VNS similar to "sham" controls (15% vs. 10%, respectively).[11] However, analysis of the one-year follow-up D-01 study data from the first cohort of 30 TRD patients to receive adjunct VNS in an open-label fashion looked more promising (response rate of 46%, remission rate of 29%),[10] suggesting that adjunct VNS treatment exceeding the 10 weeks provided in the sham-controlled D-02 acute phase study may be necessary for more robust VNS effects.

Follow-up data were subsequently collected from the D-02 patients who received continued open-label adjunct VNS after the sham-controlled acute phase was completed. The most compelling VNS efficacy data published to date come from a nonrandomized study of two groups of TRD patients. One-year clinical outcomes of D-02 patients were compared with those measured in another sample of patients with TRD (Cyberonics Study D-04) who were treated with usual standard-of-care alone.[12] The mean improvement in **Inventory for Depressive Symptomatology-Self-Rated (IDS-SR)** scores per month was significantly greater in the VNS-treated patients than in those who received only the usual standard-of-care ($P < 0.001$). Response rates after 12 months were 27% for those who received adjunct VNS and 13% for those receiving "treatment as usual" ($p<0.011$).

The safety of VNS is well established because of its use in epilepsy. Over 32,000 patients worldwide have been implanted with the VNS device since the 1990s. Most side effects of VNS are associated with the actual stimulation, or the "on" phase of the cycle. Common stimulation-induced side effects include voice alteration, hoarseness, dyspnea, and cough. These side effects are typically mild and can be reduced or resolved by adjustments in the stimulation parameters (i.e., decreasing the intensity or pulse width of current). Cognitive side effects have not been reported.[7] Other issues to consider with VNS include a possible cosmetic change in the appearance of the chest after generator implantation, and the costs and risks associated with the surgery. An outpatient surgical setting and general anesthesia

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are typically used to implant the VNS device, followed by several weeks of postoperative wound healing before regular stimulation is initiated. Once programmed, the VNS system delivers continuous cycles of stimulation, 24 hours per day. Patients can use a handheld magnet to temporarily interrupt stimulation, if needed to temporarily manage stimulation-related side effects (i.e, vocal quality change while singing in a choir).

The cost of the VNS Therapy system and surgical implantation for cervical VNS is approximately $20,000 comparable to the cost of a course of ECT for depression in an inpatient setting. The battery life of the pulse generator models is approximately six to eight years, depending on stimulation parameters. A single surgical incision is needed in the chest wall to replace the entire pulse generator once the battery has expired. Data regarding the optimal stimulation parameters for antidepressant effects are limited, and the programming clinician typically customizes the VNS "dose" through adjustment of output current, signal frequency, pulse width, signal "on" time, and signal "off" time (duty cycle). Because of the potential for heating of the electrical leads, whole-body **magnetic resonance imaging** (**MRI**) is contraindicated in patients who have the VNS pulse generator implanted. Special ''send-receive coils'' have been used to concentrate magnetic fields away from the neck area when MRI of the brain is necessary. Patients with the VNS Therapy system are asked to carry identification cards and are educated about risks of being close to strong magnetic fields.

While it is tempting to imagine that VNS may someday replace psychotropic medications and their many undesirable side effects, it is important to bear in mind that VNS has been investigated as an adjunct therapy, rather than as a monotherapy, in the majority of cases. The clinical trials data in support of VNS efficacy for depression were derived from nonrandomized trials, and the FDA standard for proof of efficacy and safety for therapeutic devices has historically differed from that required for approval of new drugs. Patients' expectations for dramatic symptom recovery or even cure from severe psychiatric illness may be fueled by the introduction of new technology and the highly interventional nature of the device implantation surgery. Management of such expectations should be undertaken with great care, particularly in depressed patients who are at heightened risk for acting impulsively and self-destructively on feelings of disappointment and hopelessness.

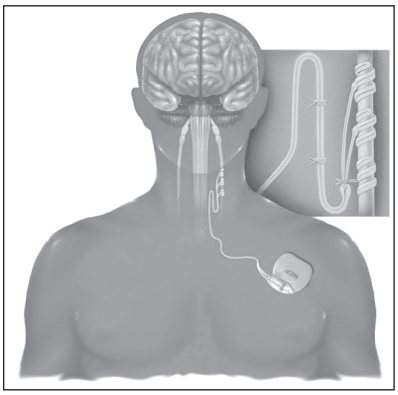

Figure 1. Vagus Nerve Stimulation (VNS) Therapy System for Treatment-Resistant Depression

With those caveats, it may be useful to consider the relationship of VNS to other somatic methods of therapeutic brain stimulation, such as ablative neurosurgery, gamma knife neurosurgery, DBS, ECT, MST, and rTMS. On a spectrum of relative invasiveness of the procedure, with ablative surgery at one end and rTMS at the other, VNS might be ranked in the middle.[8] Early success in establishing adequate terms of coverage and reimbursement by third party payors has contributed to the wide-scale availability of VNS for patients with epilepsy in the United States, but it is not yet clear that depressed patients will encounter a similar ease of access to VNS therapy for TRD. Development of specialized VNS clinics and other mechanisms for delivery of this novel adjunct treatment in the psychiatric community are in their initial stages.

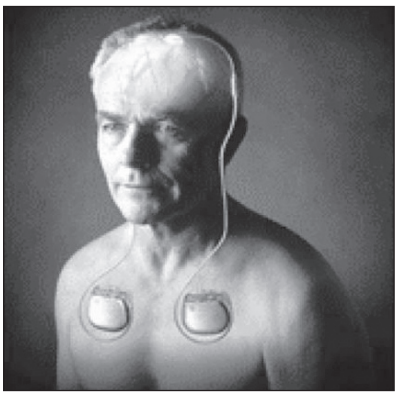

Figure 2. Deep Brain Stimulation

Deep Brain Stimulation

DBS, although FDA-approved for treatment of dystonia, essential tremor, and tremor in Parkinson's disease, is still in a highly exploratory phase of investigation for treatment of depression and other psychiatric disorders. Given the surgical risk associated with implantation of the electrodes, this procedure has been reserved for the most severe, debilitating, and chronic cases of depression that have failed several adequate courses of therapy from multiple treatment modalities (i.e., medication, ECT, and psychotherapy) during the current episode.[13,14]

Surgery to implant the DBS device is performed in 2 phases. Initially, implantation of electrodes is performed under local anesthesia through burr holes in the skull. A stereotactic frame and magnetic resonance images are used to guide placement of the thin metal electrodes into the targeted subcortical area. After successful implantation and testing of the electrodes, the electrodes are connected under general anesthesia via lead wires tunneled subdermally under scalp, neck, and chest wall areas to pacemaker-like pulse generators. As with VNS, DBS stimulation parameters are adjusted via a computer-controlled telemetric wand.

Only two publicly reported studies have evaluated DBS for depression. Our research group at Butler Hospital/Brown University studied 5 patients under blinded conditions (patient- and rater-blinded) for 3 months.[14] The brain area we targeted was the ventral portion of the anterior limb of the internal capsule and the adjacent dorsal ventral striatum. This area was chosen because it had been targeted in obsessive-compulsive disorder (OCD) patients who subsequently also showed improvement in comorbid depression symptoms.[14] All 5 patients with intractable depression showed some improvement with DBS of the ventral internal capsule in the first three months of stimulation therapy. Three of the five depressed patients were more than 50% improved on the HDRS, and the other 2 showed 23% and 17% improvement, respectively. Mean HDRS score for the group was 31.4 at baseline but improved to 15.8 after 3 months. **Social and Occupational Functioning Assessment Scale (SOFAS)** score improved over the same time frame from 41.2 to 57.6.

These patients continued successfully on open stimulation after the initial 3-month period.[14]

In a cohort with severe major depression lasting a year or more, DBS was evaluated in a different brain target region. Mayberg and colleagues implanted DBS electrodes into the white matter tracts adjacent to the subgenual cingulate in 6 patients.[13] After 2 months of stimulation, 5 of 6 patients achieved response defined as 50% or greater reduction in HDRS score. This response was maintained through study completion (6 months) in 4 patients. **Positron emission tomography (PET)** studies performed in 3 of the responders after 3 and 6 months of DBS found a normalization of blood flow in the subgenual cingulate (reduction from baseline) and in areas of prefrontal cortex (increase from baseline).

There are a number of risks and inconveniences associated with DBS therapy that will limit its use, even assuming that the efficacy of the technique becomes well proven. The risks of neurosurgery are significant and include intracranial hemorrhage, infection, and death.[16] Hardware malfunctions are not unusual, and batteries typically need to be replaced every 1 – 3 years.[16,14] As in VNS, small surgical scars and bulges from implantation of the generators into the chest wall can create cosmetic concerns for some individuals. Transient side effects of DBS may include dose-dependent light-headedness, insomnia, and psychomotor changes; however, persistent side effects are unusual. Transient hypomania has been reported but may be avoided by changes in stimulation parameters.[14]

Summary

Neurostimulation techniques are potentially useful options for severely depressed patients who have failed trial after trial of medication and psychotherapy. Cervical VNS therapy for chronic or recurrent depression which does not resolve with pharmacotherapy was recently approved by the FDA. DBS for severe intractable depression has been studied in two pilot studies with very few patients to date. Further investigations are currently underway in order to more fully evaluate both of these neurostimulation therapies, with the hope of substantially improving the treatment of refractory depression.

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References

1. Steffens DC, Krishnan KR and Helms MJ. *A Meta-analysis Depression* 1997; 6:10-8.
2. Greenberg P, Corey-Lisle PK, Birnbaum H, et al. *Pharmacoeconomics* 2004; 22:263-373.
3. Segal Z, Levitt A. *J Psychiatry Neurosci* 2002; 27:281-290.
4. Nirenberg AA, and Wright EC. *J Psychiatry* 1998; 60 Suppl 22:7-11.
5. Lisanby SH, Morales O, et al. CNS spectra 2003; 8: 529-36.
6. Bolwig TG., CNS spectra 2003; 8: 490-5.
7. Schachter SC. *Neurol* 2002; 59:S15-S20.
8. George MS, Sackeim HA, et al. *Biol Psychiatry* 2000; 47:287-95.
9. Sackeim HA, Rush AJ, et al. *Neuropsychopharmacology* 2001; 25:712-28.
10. Marangell LB, Rush AJ, et al. *Biol Psychiatry* 2002; 51:280-7.
11. Rush JA, Marengell LB, et al. *Biol Psychiatry* 2005; 58: 347-54
12. George MS, Rush JA, et al. *Biol Psychiatry* 2005; 58:364-73.
13. Mayberg HS, Lorano AM, et al. *Neuron* 2005; 45:651-60.
14. Greenberg B, Friehs G, et al. *Neuropsychopharmacology* 2005; 29:S32.
15. Abosch A. and Lozano A. *Can J Neurol Sci* 2003; 30 suppl.1:S72-SB2.

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Deep Brain Stimulation for Parkinson's Disease: Patient Selection and Motor Outcomes

Victoria C. Chang, MD, and Kelvin L. Chou, MD

Deep brain stimulation (DBS) of either the **globus pallidus interna (GPi)** or **subthalamic nucleus (STN)** is an FDA-approved treatment for **Parkinson's disease (PD)**. The development of DBS for the treatment of motor symptoms in PD, pioneered by Benabid and his colleagues in France, [1] has expanded the number of treatment options for patients suffering from this disorder. Over the last decade, the number of centers offering DBS worldwide has increased exponentially, and more PD patients in the future will be faced with the decision of whether or not to undergo the procedure. This article discusses some of the major considerations that go into determining appropriate DBS candidates and briefly reviews the literature regarding motor outcomes from DBS surgery for PD.

Patient Selection

One of the most important factors in ensuring a successful surgical outcome is patient selection. Only patients with a diagnosis of PD should be considered for DBS surgery because those with atypical parkinsonian syndromes, such as **progressive supranuclear palsy (PSP)** or **multiple system atrophy (MSA),** do not respond to DBS. Levodopa responsiveness is one of the best indicators of a good outcome from DBS ,[2, 3] and the atypical parkinsonian syndromes generally have a poor response to levodopa. Furthermore, in PD patients, only those symptoms that respond to levodopa will be improved by DBS [2, 3]; symptoms that are not helped by levodopa, such as speech and postural instability, do not improve with long-term stimulation [4, 5]. The one exception to this rule is parkinsonian tremor, which may be refractory to anti-PD medications but responds nicely to stimulation.

"The ideal candidate has idiopathic PD, suffers from complications of chronic levodopa therapy despite optimal medical management, and has no cognitive impairment or active psychiatric issues."

The ideal PD candidate for DBS (Table 1) is a patient who responds to levodopa, but despite optimal medical management, suffers from severe or incapacitating levodopa motor complications. These complications can include dyskinesias, wearing off, and on-off phenomena. DBS has regularly been shown to be effective in improving these motor complications for both the short and long term, [4-6] and patients with such advanced disease stand to benefit most from this procedure. Because PD tremor also responds to stimulation, patients with a tremor-predominant picture who are not controlled with medications are also good candidates for DBS surgery. However, because the DBS procedure is not without risk, patients should be optimized on antiparkinsonian medications prior to being considered for DBS. It has been proposed that DBS could potentially slow down the progression of the underlying disease, and there is considerable interest in operating on PD patients who are well controlled medically with the hope of delaying or preventing the motor complications. However, there is no evidence or justification to send patients for such "prophylactic" DBS surgery.

A younger age has also been reported to be predictive of a good outcome from DBS surgery. Many surgical centers have been using 70 years of age as a cutoff. Partly this is because younger patients recover from surgery more quickly, but patients under age 70 tend to show greater motor improvement than patients over 70. [2, 3] However, Russmann et. al.[7] showed that some patients over age 70 responded just as well as younger patients. Thus, a strict age requirement for DBS is insufficient, and cases should be evaluated on an individual basis. It will be important in the future to identify which preoperative factors will predict a good outcome in older patients.

DBS procedures can be associated with declines in cognition as well as psychiatric complications. While many neuropsychological studies have demonstrated that cognition remains generally stable post-DBS surgery, some PD patients with pre-existing cognitive problems have worsened irreversibly postoperatively. [8] Therefore, it is imperative for patients to undergo intensive neuropsychological testing before surgery to make sure that there is no dementing illness. This is also important because demented patients may lack insight into their own motor status and be unable to provide feedback intraoperatively and difficult to program postoperatively.

Finally, a number of surgical centers have reported depression following STN DBS surgery with a frequency ranging from 10-30%. [4, 9, 10] Some of these cases have been so severe that the patients attempted suicide. Unfortunately, it is difficult to predict which patients are at the greatest risk for developing severe depression. Nevertheless, it is important to make certain that there are no active psychiatric illnesses at the time of surgery by requiring preoperative psychiatric evaluation.

Mechanism of Action

Based on the original observations in patients with tremor who were treated with high frequency DBS of the thalamus, it appeared that DBS had an inhibitory effect, similar to lesions of the same structures. In the classical model of basal ganglia function in patients with PD, the STN and the GPi are overactive secondary to the loss of dopaminergic neurons in the substantia nigra pars com-

pacta. This ultimately leads to inhibition of the thalamus, decreased activity of the motor cortex, and the hypokinesia seen in PD. Based on this model, stimulation of the STN or GPi presumably disrupts their projections to the ventrolateral thalamus electrically and chemically and ultimately results in increased motor cortical activity facilitating movement. However, several other and more recent explanations for the mechanism of DBS have been hypothesized. Recent evidence suggests that the STN and GPi are not overactive, but instead have an altered firing pattern. It is now thought that DBS may silence this pathological activity and "reset" the normal activity of these structures.[11] While the exact mechanism of how stimulation produces its effects remains elusive, there is clear evidence supporting the clinical and therapeutic results of STN and GPi DBS on motor symptoms in PD.

Motor Outcomes of GPi and STN DBS

A successful surgical outcome depends upon a team comprised of neurologists, neurosurgeons, neurophysiologists, nurses and other professionals who are experienced with DBS. The DBS electrode is implanted by the neurosurgeon, usually with assistance from a neurophysiologist. The role of the neurophysiologist is to perform microelectrode recordings to help confirm that the DBS electrode is in the proper target. After the electrode is placed, it is connected via wires to a pulse generator implanted in a subcutaneous pocket overlying the pectoral muscle. Because PD is a bilateral disease, most patients will need electrodes placed bilaterally. The device is generally turned on and programmed 2-3 weeks after surgery by a neurologist, nurse practitioner, or nurse trained in DBS. Stimulation is then slowly increased on successive visits until the patient's symptoms are adequately controlled. Thus, each member of the DBS team contributes to the patient's outcome.

In short-term studies, both GPi and STN DBS appear to improve tremor as well as other cardinal symptoms of PD including bradykinesia and rigidity. The largest of these studies is a multi-center, non-randomized, prospective double-blinded crossover study conducted by the Deep Brain Stimulation for Parkinson's Disease Study Group in 2001. [6] DBS electrodes were placed bilaterally in the STN in 96 patients, and in the GPi in 38 patients. It showed an improvement of 49% ($p < 0.001$) for STN and 37% ($p < 0.001$) for GPi stimulation in the Unified Parkinson Disease Rating Scale (UPDRS) motor scores at three months. The UPDRS is used universally to evaluate severity of motor impairment in clinical trials of PD. This study also demonstrated that both STN and GPi stimulation prolonged the "on" time and shortened the "off" time experienced by patients. Similar effects were seen in various independent GPi and STN DBS studies which looked at various motor aspects, including limb akinesia, rigidity, bradykinesia, tremor, gait difficulty, levodopa induced dyskinesias, and freezing. [8, 12]

Table 1.

Characteristics of the Ideal PD Candidate for DBS
• The patient has a diagnosis of idiopathic PD without evidence of an atypical parkinsonian syndrome.
• Continued response to levodopa.
• Presence of complications from chronic levodopa therapy such as dyskinesias, wearing off, and on-off phenomena or, alternatively, a tremor predominant presentation.
• Absence of dementing illness or active psychiatric illnesses.

While it is now apparent that either STN or GPi DBS is effective in treating PD symptoms, there is no consensus on the target of choice. There has been a trend toward STN DBS in recent years, but in terms of motor improvement, neither site is clearly superior to the other. An early study by Burchiel et. al. showed no significant difference between the two targets.[13] Stimulation of both STN and GPi in this study demonstrated similar improvements in rigidity, tremor, and bradykinesia and exhibited a comparable improvement of 40% in the UPDRS in both groups when off medication. Krause et. al. placed stimulators in the GPi in six patients and STN in 12 patients, and found that GPi stimulation had no direct effect on bradykinesia or tremor.[14] In contrast, all parkinsonian symptoms improved with STN DBS and it was concluded that STN was the best choice for the treatment of advanced Parkinson's disease. In the Deep Brain Stimulation for Parkinson's Disease Study Group trial, the STN group seemed to have a greater benefit than the GPi Group, although the trial was not designed to compare the two sites. [6] Most recently, Anderson and colleagues found no significant differences in overall outcomes, although bradykinesia tended to be more improved in the STN group while dyskinesias were more improved in the GPi group. [15] Cognitive and behavioral problems were seen only in the STN group.

A recurring observation noted in a number of these studies appears to be the marked reduction in the levodopa dose seen with STN stimulation but not GPi stimulation.[4-6, 16, 17] This is one of the reasons that many surgical centers favor STN DBS over pallidal stimulation. It is unclear why GPi DBS patients cannot reduce the amount of their dopaminergic medications. It may be that GPi stimulation directly suppresses dyskinesias; therefore, decreasing levodopa post-operation is not necessary. [17] There has also been concern that selection bias may play a role in this particular outcome, since in one study patients who ended up receiving GPi stimulation had more dyskinesias with lower levodopa doses. [16]

As for long-term outcomes of DBS, GPi stimulation may not have as sustained an effect on the symptoms of PD as that of STN stimulation. The longest follow-up study for pallidal stimulation monitored eleven patients for five years and found that the initial benefit declined over time in both the "on" and "off" states. [18] Four patients in this series eventually underwent STN DBS because of the decreased efficacy of GPi stimulation. In a three-year study by Durif et. al., the mean improvement in the UPDRS scores

remained consistent over three years, but the amount of time spent in the off-state returned to baseline values after two years.[19] Conversely, STN stimulation appears to maintain its immediate post-operative motor improvements even at five years out from surgery, although non-motor components such as cognition and depression remained unchanged from the pre-operative state.[5] Shorter studies looking at results two years after STN implantation also supported this trend with improvements in tremor, rigidity, and bradykinesia more than axial motor symptoms.[4]

Adverse Effects

Although DBS has been determined to be a safe and effective treatment for PD, adverse motor and non-motor effects from DBS can occur postoperatively. They can be split into those related to surgery and those related to stimulation. Surgical complications include hemorrhage, stroke, infection of the device, seizures, and delirium. Stimulation-related side effects depend upon the stimulation site and are usually transient, or improve with adjustments in stimulation parameters. Common stimulation side effects seen with pallidal stimulation include dystonia, confusion, and paresthesias. In addition, GPi DBS produces variable effects on motor symptoms depending on the placement of the electrode. Stimulation of the ventral part of the GPi improves rigidity and levodopa induced dyskinesias but worsens bradykinesia, whereas stimulation of the dorsal aspect of the GPi improves bradykinesia but induces dyskinesia.[20] STN stimulation-related side effects can include worsening of dyskinesias, dysarthria, dystonia, paresthesias, and double vision. There is also accumulating evidence that STN stimulation may have cognitive and behavioral side effects (depression, mania, dementia) not seen with GPi stimulation.[15] It remains unclear whether this is a direct stimulation effect, but a possible explanation is that the STN is a much smaller target than the GPi, and therefore there is a greater chance for current to spread to nearby structures with limbic associations. The likelihood of spreading is increased if the electrode is not optimally placed.

Summary

DBS is a safe and effective option for the treatment of patients with advanced PD. To ensure a successful outcome, however, it is important to select the appropriate candidates. The ideal candidate has idiopathic PD, suffers from complications of chronic levodopa therapy despite optimal medical management, and has no cognitive impairment or active psychiatric issues. Although the exact mechanism of how DBS exerts its effects remains under investigation, it is clearly apparent that bilateral stimulation of either the GPi or STN effectively helps the motor symptoms of PD. While many surgical centers favor stimulation of the STN over the GPi, there is accumulating evidence that STN stimulation may result in adverse non-motor outcomes such as depression. Future studies will be needed in order to determine the best site of stimulation, the exact mechanisms of DBS, and the long-term outcomes of both motor and non-motor symptoms. As our understanding of these components becomes clearer, we will be able to optimize the treatment and management for those whose lives are affected by Parkinson's disease.

References

1. Limousin P, Pollak P, et al. *Lancet* 1995;345:91-5.
2. Charles PD, Van Blercom N, et al. *Neurol* 2002;59:932-4.
3. Welter ML, Houeto JL, et al. *Brain* 2002;125(Pt 3):575-83.
4. Kleiner-Fisman G, Fisman DN, et al. *J Neurosurg* 2003;99:489-95.
5. Krack P, Batir A, et al. *NEJM* 2003;349:1925-34.
6. Deep Brain Stimulation for Parkinson's Disease Study Group. *NEJM* 2001;345:956-63.
7. Russmann H, Ghika J, et al. *Neurol* 2004;63:1952-4.
8. Limousin P, Krack P, et al. *NEJM* 1998;339:1105-11.
9. Berney A, Vingerhoets F, et al. *Neurol* 2002;59:1427-9.
10. Funkiewiez A, Ardouin C, et al. *J Neurol Neurosurg Psychiatry* 2004;75:834-9.
11. Garcia L, D'Alessandro G, et al. *Trends Neurosci* 2005;28:209-16.
12. Kumar R, Lang AE, et al. *Neurol* 2000;55(12 Suppl 6):S34-9.
13. Burchiel KJ, Anderson VC, et al. *Neurosurg* 1999;45:1375-82; discussion 82-4.
14. Krause M, Fogel W, et al. *J Neurol Neurosurg Psychiatry* 2001;70:464-70.
15. Anderson VC, Burchiel KJ, et al. *Arch Neurol* 2005;62:554-60.
16. Minguez-Castellanos A, Escamilla-Sevilla F, et al. *J Neurol Neurosurg Psychiatry* 2005;76:34-9.
17. Vitek JL. *Stereotact Funct Neurosurg* 2002;78:119-31.
18. Volkmann J, Allert N, et al. *Ann Neurol* 2004;55:871-5.
19. Durif F, Lemaire JJ, et al. *Mov Disord* 2002;17:803-7.
20. Krack P, Pollak P, et al. *Ann Neurol* 1998;43:180-92.

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CEREBROVASCULAR DISEASE IN RHODE ISLAND: RISKS AND BURDEN

JOHN P. FULTON, PHD

The people of the United States experience about 700,000 strokes per year, of which about 500,000 are first attacks, and about 200,000 are recurrent attacks. Case fatality is relatively high, resulting in 157,000 deaths per year, or about one death per 4-5 attacks. In addition, an estimated 5.5 million Americans are stroke survivors, many coping with residual problems. About one-fifth of stroke survivors report some functional limitation as a sequela of stroke.[1]

The risk of stroke increases with smoking, high blood pressure, high blood cholesterol, and overweight, and decreases with physical activity.[2] Untreated atrial fibrillation also increases the risk of stroke.[1] Elevated plasma homocysteine has also been suggested as a risk factor for cerebrovascular disease,[3] but recent studies designed to clarify this relationship have not found convincing evidence that elevated plasma homocysteine precedes atherothrombotic stroke,[4] or that lowering homocysteine decreases the risk of recurrent stroke and death among victims of non-disabling cerebral infarction.[5]

The risk of stroke is not distributed evenly in the United States population. Risk increases with age, and is higher for men than for women. African Americans and Hispanics are at higher risk of stroke (incidence) than non-Hispanic whites, although Hispanics are at *lower* risk of age-adjusted mortality from stroke than non-Hispanic whites.[1] Most (perhaps all) of the elevated risk of stroke (incidence) experienced by African Americans and Hispanics *may* be attributable to lifestyle, high blood pressure, high blood cholesterol, and overweight, although a definitive understanding of the role of these factors in creating disparate stroke burdens awaits the results of future studies, perhaps designed as clinical trials.

Optimal treatment of stroke requires early intervention to avoid mass destruction of brain cells. The symptoms of stroke vary and may be subtle. Thus, public awareness of stroke's early warning signs and symptoms is essential to assure the earliest possible diagnosis and treatment in each case. A nationwide public health survey conducted in 2001 revealed substantial public recognition (85 percent or higher) of the three most important warning signs of stroke: "sudden numbness or weakness of the face, arm or leg;" "sudden confusion, trouble speaking or understanding;" and "sudden trouble walking, dizziness or loss of balance or coordination."[1]

Stroke is recognized by the federal government as a serious health problem amenable to several public health interventions. Accordingly, Healthy People 2010, "a framework for prevention for the nation"[2] incorporates two specific objectives for the reduction of stroke burden in the United States:

- 12-7. By 2010, reduce stroke deaths to 48 per 100,000 population (from 60 deaths per 100,000 in 1998).
- 12-8. Increase the proportion of adults who are aware of the early warning symptoms and signs of a stroke.

To assist with a new planning effort to reduce the risk of stroke and its sequelae in Rhode Island, basic data on health risks and stroke burden were assembled from the Rhode Island Behavioral Risk Factor Surveillance System,[6] the Rhode Island Hospital Discharge Data Set, and the National Center for Health Statistics.

METHODS

Health Risks

Trend data on smoking, blood pressure checks, blood cholesterol checks, leisure time physical activity, fruits and vegetables in the diet, and overweight (by body mass index) in Rhode Island were extracted from a web-based data query system developed and maintained by the **Behavioral Risk Factor Surveillance System (BRFSS)** of the Centers for Disease Control and Prevention.[6]

Table 1. Percentage of Rhode Island residents ages 18 and over with risk factors for stroke, 1990-2002, Rhode Island Behavioral Risk Factor Surveillance system.

Year	Current smoking	No blood pressure check in 2 years	No Cholesterol Check in 5 years	No leisure time physical activity	Insufficient fruits and vegetables in the diet	Overweight by body mass index
1990	26			26		37
1991	25			28		33
1992	22			26		33
1993	23	5	27		75	35
1994	25					
1995	23	5	25			35
1996	24			27	76	37
1997	23	4	25			38
1998	23			30	75	36
1999	22	3	24			37
2000	23			28	71	37
2001	24		19			38
2002	22			25	71	38
95% CI*	1.6	0.6	1.6	1.6	1.8	1.8

* 95 percent confidence interval for the latest estimate.

Table 2. Current membership of the Rhode Island Stroke Task Force established by the Rhode Island General Assembly.

Member	Affiliation
Matthew Blade	The Miriam Hospital
Maureen Claflin	Quality Partners of RI
Raymond Cord, PA	Hypertension & Nephrology, Inc.
Douglas DeOrchis, MD (**Chair**)	The Miriam Hospital Stroke Center
Curtis Doberstein, MD	Rhode Island Hospital / The Miriam Hospital
Frank Gallo	Stroke Survivor
Peter A. Hollmann, MD	Blue Cross / Blue Shield of Rhode Island
Arshad Iqbal, MD	Arshad Iqbal, MD, Neurology & Stroke
Brandon Klar	Saint Joseph's Health Services of Rhode Island
William Koconos	American Heart Association, NE Affiliate
Thomas Lawrence, NREMT-P, I/C	Rhode Island Hospital
Kathleen Locarno, RN	Our Lady of Fatima Hospital
Sharon Marable, MD, MPH	Rhode Island Department of Health
Peter Panagos, MD	Rhode Island Hospital
Esther Price	Saint Martin dePorres Senior Center
Walter Van Dyck, OTRL-L, BCN	Kent County Memorial Hospital
Kathleen Walden, RN	Rehabilitation Center at Kent Hospital

Hospitalizations

Trend data on hospitalizations for stroke in Rhode Island were constructed from electronic files of the Rhode Island Hospital Discharge Data Set developed and maintained by the Center for Health Data and Analysis, Rhode Island Department of Health. All hospitalizations whose first discharge diagnosis was coded in the range 430-438 using ICD-9 were extracted for the analysis of trends.

Deaths

Trend data on deaths from stroke in Rhode Island were extracted from a web-based data query system (SEER*Stat)[7] developed and maintained by **the Surveillance, Epidemiology, and End Results (SEER)** Program of the National Cancer Institute. Average annual age-adjusted stroke mortality rates were computed for whites and blacks by five-year period. The United States population of 2000 was used as the standard population for age-adjustment.

Results

Health Risks

With the exception of cholesterol checks, several risk factors for stroke (including very crude proxies for risk factors, like blood pressure checks) have not changed much since 1990. Smoking has declined slightly, and the consumption of fruits and vegetables has increased slightly. The proportion of people getting no leisure time physical activity hasn't changed perceptibly, and neither has the proportion overweight (by body mass index).

Hospitalizations

The number of hospital discharges in Rhode Island with stroke as the primary discharge diagnosis peaked in 1996, then declined slowly. In 2004, the last full year for which data are currently available, the number of hospital discharges of this type numbered 3137.

The number of hospital discharges in Rhode Island with stroke as a secondary discharge diagnosis jumped dramatically after 1998, peaked in 2000, then declined slowly. In 2004, the number of hospital discharges of this type numbered 3270.

Deaths

The age-adjusted death rate from stroke declined dramatically for both whites and African Americans in Rhode Island between 1969 and 2002. The age-adjusted stroke rate declined 59% for whites, 63% for African Americans. At present, about 600 Rhode Islanders die from cerebrovascular disease each year.

In Rhode Island, African Americans have a 26% higher risk of stroke death than whites, after adjusting for age differences in the two populations. This disparity has declined from an all time high of 72% in 1986-1990, but

Figure 1. Hospital Discharges for Stroke, Rhode Island, 1989-2004.

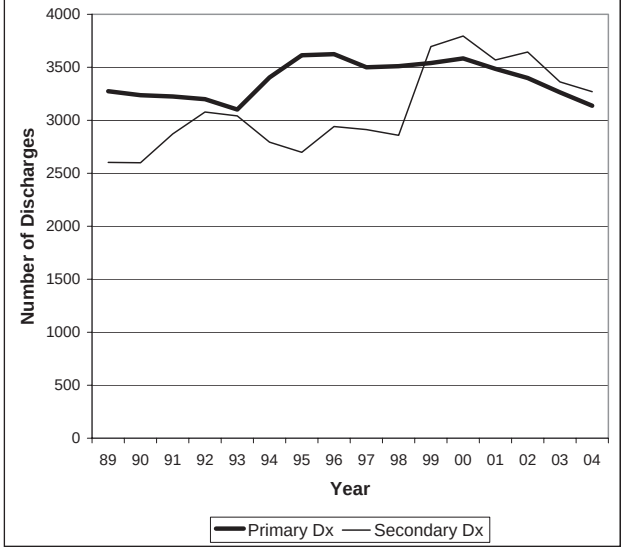
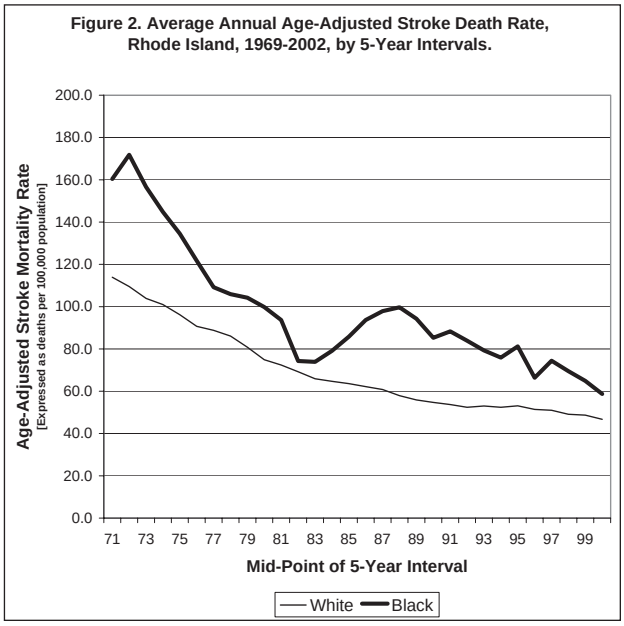


Figure 2. Average Annual Age-Adjusted Stroke Death Rate, Rhode Island, 1969-2002, by 5-Year Intervals.



is greater than the all time low of 7% in 1980-1984. At the present time, stroke death rates for African Americans and for whites appear to be converging.

Discussion

In 2004, the Rhode Island General Assembly enacted Chapter 23-77 of the Rhode Island General Laws, establishing the Rhode Island Stroke Task Force. (Table 2 lists current Task Force Members. The Task Force is expanding.) The Task Force is charged with 14 objectives in the legislation, itself. Not surprisingly, the first objective concerns data analysis: "Undertake a statistical and qualitative examination of the incidence and causes of stroke deaths and risks, including identification of sub-populations at highest risk for developing stroke and develop a profile of the social and economic burden of stroke in Rhode Island." The trend data in the present report were assembled to begin the statistical examination of cerebrovascular disease in Rhode Island, its risks and burden.

Rhode Island behavioral health risk data for smoking, physical activity, fruits and vegetables in the diet, and overweight show little improvement between 1990 and 2002. A quick check of preliminary figures from Rhode Island's 2005 BRFSS show no major changes in these trend lines.[8] Smoking continues to decline slightly, the trend in physical activity remains flat, and if any change in body mass index has occurred, we are heavier. As a state, we have much to do to reduce the risk of stroke (and cardiovascular disease, and diabetes, as well).

Given the flat trends in risk, the downward trends in hospitalization for stroke (as primary *and* secondary diagnoses) and in stroke mortality *must* be attributable to improvements in the medical management of stroke risks and stroke events. Further analysis of these interventions and their independent contributions to morbidity, disability, and mortality may be especially fruitful in guiding the work of the Task Force.

In the future, Rhode Island data on emergency department visits for stroke, available soon, may be used to construct a more comprehensive picture of stroke events, including those minor events (like transient ischemic attacks) that do not result in hospitalization. Potential enhancements to the Rhode Island BRFSS surveying blood pressure *control* and individual knowledge and understanding of lipid *profiles*, if affordable, would also help the Task Force track essential stroke risk factors and their distribution in the Rhode Island population.

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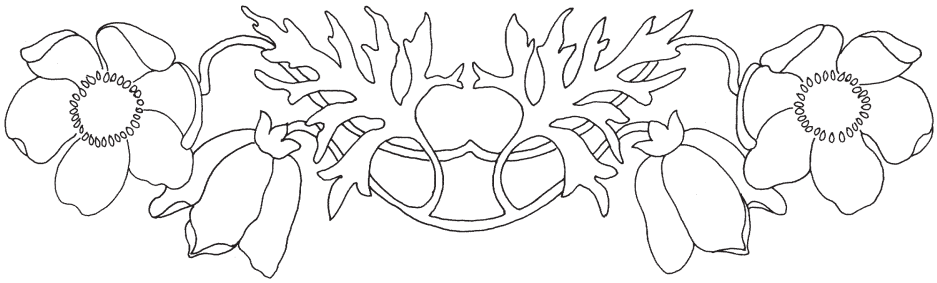
References

1. Thom T, Haase N, et al. Heart Disease and Stroke Statistics--2006 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Published online Jan 11, 2006; Circulation; DOI: 10.1161/CIRCULATIONAHA.105.171600
2. US Department of Health and Human Services. *Healthy People 2010. 2nd ed.* With Understanding and Improving Health and Objectives for Improving Health. 2 vols. Washington, DC: U.S. Government Printing Office, November 2000.
3. Malinow MR, Bostom AG, Krauss RM. Homocysteine, diet, and cardiovascular diseases. *Circulation* 1999; 99: 178 - 82.
4. Meiklejohn DJ, Vickers MA, Ret al. Plasma homocysteine concentrations in the acute and convalescent periods of atherothrombotic stroke. *Stroke* 2001; 32: 57 - 62.
5. Toole JF, Malinow MR, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. *JAMA* 2004;29:565-75.
6. Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [various years].
7. Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat)version 6.1.4.
8. Center for Health Data and Analysis. Rhode Island Behavioral Risk Factor Surveillance System Survey Data. Providence, Rhode Island: Rhode Island Department of Health, 2005 (Supported by the Centers for Disease Control and Prevention)



PUBLIC HEALTH BRIEFING
RHODE ISLAND DEPARTMENT OF HEALTH
DAVID GIFFORD, MD, MPH, DIRECTOR OF HEALTH
EDITED BY JOHN P. FULTON

COLORECTAL ALGORITHM GUIDELINES FOR SCREENING

ARVIN S. GLICKSMAN, MD

In the process of updating the State's Cancer Control Plan, the Rhode Island Department of Health asked the Rhode Island Cancer Council to develop statewide comprehensive guidelines for the management of colorectal cancer. To accomplish this goal, a Colorectal Cancer Care Task Force ("the Task Force") was assembled from all parts of the State and from a variety of medical disciplines. All are knowledgeable specialists in the screening and treatment of colorectal cancer. The full membership is listed in Table 1.

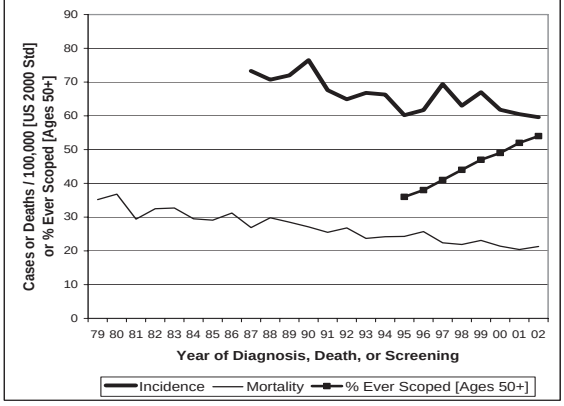
Thus far, the Task Force has developed *Screening Guidelines for Asymptomatic Individuals*. It is hoped that these *Guidelines* will support and enhance the upward trend in endoscopic screening for colorectal cancer in Rhode Island, observed since the mid-1990s. As Figure 1 shows, increased endoscopic screening is associated with decreased rates of colorectal cancer incidence and mortality. We are winning the war against this scourge, but we have a long way to go. According to current estimates, more than 40% of all Rhode Islanders ages 50 and over have never had any form of endoscopic screening for colorectal cancer.

Arvin S. Glicksman, MD, is Director, Rhode Island Cancer Council, Inc. and Professor of Radiology (Emeritus), Brown Medical School.

Table 1. Members of the Colorectal Cancer Care Task Force

Alyn Adrain M.D.	Thomas J. Miner M.D.
Leslie Cashel, M.D.	Brian Murphy M.D.
Robert Coli M.D.	Nicklas Oldenburg M.D.
Francis Cummings M.D.	Christopher Ottiano M.D.
Christy Dibble D.O.	Victor Pricolo M.D.
Thomas DiPetrillo M.D.	John Przygoda M.D.
Jorge Lagares-Garcia M.D.	Howard Safran M.D.
David Iannitti M.D.	Sundaresan Sambandam M.D.
Plakyil Joseph M.D.	William Sikov M.D.
Steven Lane M.D.	Michael Vezeridis M.D.
Robert Lev M.D.	Harold Wanebo M.D.
Sheldon Lidofsky M.D.	Daniel Wrobleski M.D.
Thomas McMahon M.D.	Orest Zaklynsky M.D.

Figure 1 - RI: Standardized Colorectal Cancer Rates and % Ever "Scoped" for Colorectal Ca Screening



Colorectal Cancer Screening Guidelines for Asymptomatic Individuals

Definition	Age at Onset of Screening	Type of Procedure	Frequency
Average Risk			
• Asymptomatic with no family history of Colorectal Cancer or Polyps	• 50 years	**Colonoscopy** is the preferred screening procedure. Although other tests exist, the accuracy and specificity are considerably lower than colonoscopy. The alternatives are listed with their associated shortcomings. • **FOBT** – Poor specificity • **Sigmoidoscopy** – Cannot examine the proximal colon.	**If no abnormalities are found** – return within 10 years. **If abnormalities are found** – frequency is dependent upon the number, size, location and pathology of the polyp. For small, tubular adenomas repeat colonoscopy within 5 years. If the abnormalities are > 1cm, multiple adenomas are found, or with a villous component, or high grade dysplasia – repeat colonoscopy within 3 years.
High Risk			
• Personal history of inflammatory bowel disease including Crohn's Disease, Ulcerative Colitis and Indeterminant Colitis	• After 8 years of disease in patients with pancolitis • After 15 years of disease in patients with left side colitis	**Colonoscopy** with biopsy 4 quadrants every 10 cm	**Every year when patient is quiescent**
• Early onset of Colorectal Cancer or colon polyps in a first degree relative	• 10 years before diagnosis or detection, or 40 years old, whichever is earlier	**Colonoscopy**	**If no abnormalities are found** – return within 10 years. **If abnormalities are found** -frequency is dependent upon the number, size, location and pathology of the polyp. For small, tubular adenomas repeat colonoscopy within 5 years. If the abnormalities are > 1cm, multiple adenomas are found, or with a villous component, or high grade dysplasia – repeat colonoscopy within 3 years.
• Clusters of same or related cancer in close relatives, family history of Classic Familial Adenomentous Polyposis, Attenuated Familial Adenomentous Polyposis, or Hereditary Non-Polyposis Colorectal Cancer ***See note below.***	• 10 years before diagnosis or detection, or 40 years old, whichever is earlier • Genetic counseling should be recommended for patients with a family history of colorectal cancer, or polyps plus family history of Endometrial or Ovarian Cancer, or other extra-colonic cancers in families with HNPCC (stomach, small bowel, biliary tract, uroepithelium, kidney and central nervous system).	**Colonoscopy**	
• Personal history of Uterine or Ovarian Cancer	• At diagnosis	**Colonoscopy**	

African-Americans are at higher risk than non-Hispanic whites and should begin screening at age 40-45.

[Developed by the Rhode Island Cancer Council's Colorectal Cancer Care Task Force for the Rhode Island Department of Health]

Sources: Cancer rates from the Rhode Island Cancer Registry; screening data from the RI Behavioral Risk Factor Surveillance System.

QUALITY PARTNERS™ OF RHODE ISLAND

Improving Nursing Home Culture Pilot

Marguerite McLaughlin, MA, and Gail Patry, RN C

Beginning in 2004, Quality Partners of Rhode Island led a national pilot project sponsored by the **Centers for Medicare & Medicaid Services (CMS),** called **Improving Nursing Home Culture (INHC).** The primary objective of the pilot was to help nursing homes implement a process of change to move from an institutionalized culture to an individualized culture of care. This model has been shown to improve the quality of care and life satisfaction for residents, families and staff as well as increase workforce retention.

More than 250 nursing homes volunteered to participate in this pilot, either working with their state **Quality Improvement Organization (QIO)** or the corporate office if they were part of a multi-facility chain. These pilot nursing homes committed to attendance at four learning sessions and an outcomes congress. Participants from the nursing homes included leadership, nurses and direct care staff. Individual QIOs and corporations were free to structure the learning sessions to best meet the needs of their customers. Thus, some offered 8 four-hour sessions, others held 4 eight-hour sessions, depending on their abilities to meet their individual staffing needs and concerns. These nursing homes received education, tools and exercises to help them challenge a long-standing institutionalized culture that often prevents residents from enjoying the freedom and daily activities that so naturally create home. The sessions included an overview of transformational change, leadership practices, clinical change concepts and information pertaining to workforce retention. The nursing home assumed all travel costs, staff time and costs associated with the changes they made to their systems.

The reality faced by many who move into a nursing home is a loss of control that can lead to psychic despair and depression in many older individuals and can create a multitude of other problems. Being checked for wetness every two hours throughout the night (if it is not necessary for the particular resident) interrupts sleep and can lead to sleep deprivation. To offset this problem, a resident might be given medication to either offset behaviors or to aid in sleep. This can contribute to falls, which sets the ball in motion for reduced mobility, strength, and appetite. The system is designed to create the outcome it achieves. In order to create better outcomes, there is a critical need to improve the system of care which impacts so critically on the lives of residents. For the many residents suffering from advanced dementia in our nation's nursing homes, this individualized approach to care acknowledges and incorporates the distinct knowledge of the resident that their caregivers and family are able to offer.

"Being involved in the pilot helped us to make changes in the delivery of services. By empowering and encouraging high involvement of residents and staff we have improved all of our lives in our home." – Nursing Home Pilot Participant

The pilot sought to assist nursing home teams initiate change and stop processes that reinforce institutional culture. The pilot led staff through a process known as the "Way of Inquiry" to discover for themselves what it was like to experience the harshness of their nursing home environment, systems and schedules and to find ways to create change based on these "irritants." The result was the adoption of new processes that put dignity and humanity back into many areas of nursing home life including but not limited to bathing, dining, relationships and dying.

The INHC pilot resulted in measurable gains among the 254 participating nursing homes. One hundred and sixty eight nursing homes saw a relative decline of 5.4% in their pain quality measure rates (chronic care population). More impressive, these same nursing homes experienced a 14.5% decline in their physical restraint quality measure rates.

Nationwide, nursing homes experience a 70% annual turnover rate of their nursing department personnel. Most long-term care experts agree that staff instability is the greatest barrier to significant breakthroughs in quality outcomes. Within seven months of participating in the INHC special study, four nursing home corporations (representing 51 nursing homes) experienced a 5.6% relative decline in their annualized turnover rates (from 55.2% to 49.6%) of their nursing departments (RN, LPN, CNA). The most significant decline occurred among the LPNs who typically serve in the capacity of unit charge nurse in a nursing home. LPNs experienced a 7.6% decline in their turnover rates. CNAs, who deliver 85% of the hands-on care nursing home residents receive, had 136 fewer terminations (annualized). Overall, nursing home participants re-

alized greater stability in their nursing departments, and saved approximately $490,000 in turnover costs. This estimate is based on industry research of the direct cost of an individual employee (working in the nursing area) leaving a nursing home.

The 86 nursing homes that focused exclusively on workforce retention also experienced some impressive improvements in their quality measure rates. They saw a 14% decline in their pain quality measure (chronic care population) from 6.32 to 5.44. In addition, these same nursing homes experienced a 9% decline in their use of physical restraints from 6.51 to 5.94. Among the post-acute care elders, a significant decline was noted in the delirium quality measure (25% decline).

Translating Quality Measures to People

As a result of the INHC pilot, approximately 143 elders were relieved of moderate to severe pain and 245 elders were released from physical restraints.

Additionally, homes reported greater satisfaction among families and employees. Anecdotal stories provide an extraordinary record of transformational change. In their own words, people working in nursing homes shared what they did, what it meant to them, and why they embraced the individualized model of care. Their efforts this past year changed life and work in their nursing homes. People now wake up, spend their days, and go to bed according to their own routines, and as they are restored to their own rhythms, they are thriving. So are those who care for them. As work is reorganized to follow the pace of each resident, instead of a rigid routine, workers are able to fulfill their intrinsic motivation to care for others, and to experience respect and care from their organizations.

For more information about the INHC pilot or nursing home culture change initiatives led by Quality Partners of Rhode Island, call (401) 528-3200.

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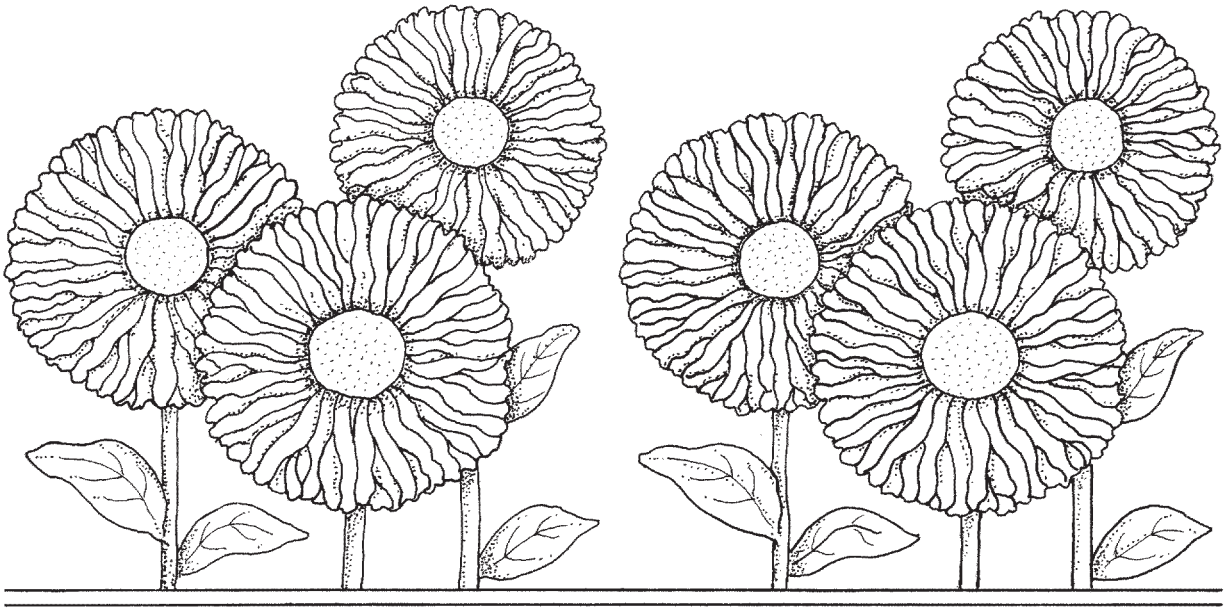

A Physician's Lexicon

A Skeletal Etymology, Part II

Stanley M. Aronson, MD

The word, vertebra, is derived from the Latin, *vertere,* meaning to rotate or turn, as in words such as vertigo or retroversion. It was the French naturalist, Pierre Lamarck [1744 - 1829], who first employed the word to describe the kingdom of animals with backbones [*les animaux vertebres*.] A synonym, the spine, comes from the Latin, *spina*, meaning thorn, prickle or backbone. The Latin, *spina*, evolved into the French, *epine*, which became the root of the word, porcupine [the spiny pig.]

The human vertebrae number 33 or 34 depending upon the anatomic text.

The cervical vertebrae, numbering five, derive their name from a fusion of two Latin words, *cerebrum* and *vinculum*, thus meaning "that which binds the head." Words cognate with *vincere* include invincible, convince, Vincent and victory. *Cervix uteri* defines the anatomic neck of the uterus. *Cervidae*, the zoological name for the deer, however, comes from the Latin, *cornu*, meaning horn as in words such as unicorn, capricorn and cornea [cornea tunica, a horny coat.]

The thoracic vertebrae, numbering 12, derive their name from a Greek word meaning breastplate. Homer uses the word frequently to describe the chest armor of the Greek warriors in the *Iliad*. The word, sternum, is also from the Greek, meaning that which is flat or stretched out.

The lumbar vertebrae, numbering five, derive their name from the Latin, *lumbus*, meaning loin as in the word, lumbago. The loins of a deer, called in Old English the *umbles*, were used for a peasant dish which formed the basis for its metaphorical use to signify humility [eating umble pie.] Lumber, as in furniture, comes from the word, *Lombard*, since many pawnbrokers were of Lombardic extraction and second-hand furniture was often sold in such shops.

The sacral vertebrae, often fused but numbering five, represent a mistranslation from the Greek. The word for 'strong' and the word for "holy" are identical in Greek; and hence "a strong backbone" was mistranslated as a "sacred backbone'"[*os sacrum*.]

The coccyx, numbering four or five fused bones, resembled, to the early anatomist, the beak of the cuckoo bird; hence they employed the Greek word for the bird to describe the lowest segment of the vertebral column. Ornithologists, to this day, stand in wonderment at the imaginative, fanciful powers of these classical osteologists.

Rhode Island Department of Health
David Gifford, MD, MPH,
Director of Health

Vital Statistics

Edited by Roberta A. Chevoya, State Registrar

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	April 2005	12 Months Ending with April 2005		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	258	3,059	286.5	4,673.0
Malignant Neoplasms	177	2,462	230.2	6,317.0
Cerebrovascular Diseases	37	499	46.6	825.0
Injuries (Accident/Suicide/Homicide)	39	427	39.9	6,705.5
COPD	49	519	48.5	562.5

Vital Events	Reporting Period		
	October 2005	12 Months Ending with October 2005	
	Number	Number	Rates
Live Births	1044	13,535	12.7*
Deaths	739	10,165	9.5*
Infant Deaths	(11)	(96)	7.1#
Neonatal deaths	(8)	(81)	6.0#
Marriages	892	7,527	7.0*
Divorces	285	3,254	3.0*
Induced Terminations	400	5,316	392.8#
Spontaneous Fetal Deaths	101	1,056	78.0#
Under 20 weeks gestation	(99)	(982)	72.6#
20+ weeks gestation	(2)	(74)	5.5#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,069,725

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population # Rates per 1,000 live births

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Ninety Years Ago, April 1916

An Editorial urged members to contribute papers to the Rhode Island Medical Journal: "Prominence in Providence…is not prominence in St. Louis, and the man who aspires to prominence in his home town must avail himself of local conditions. The reporting of interesting cases in a journal published a thousand miles away will avail little. Much better is it to acquaint ones' follow workers with the results of one's labors…."

A second Editorial praised Dr. Bernstein (the Pathologist of the State Laboratory, a position created 16 months earlier] for "successful achievement in the Westerly pie case." The case consisted of 60 cases of illness and 5 deaths, attributed to the paratyphoid bacillus.

Henry Dawson Ferriss, MD, from New York City read "Gynecological Urology," before the Providence Medical Assocation. The Journal reprinted the speech. He discussed pyelographs, phenol-sulphur-phthalien tests, ureter catheters, radiography, and blood pressure.

Harold G. Calder, MD, read "Spasmophilia," before the Providence Medical Association. The Journal reprinted that talk. He noted that the tendency to spasm, "practically confined to infants and young children," was "probably due to the relative deficiency of calcium as compared with sodium and potassium." For treatment, he recommended "phosphorus and cod liver oil and dietetic measures."

Fifty Years Ago, April 1956

Paul T. Welch, in "Post-Operative Shock Following Cortisone Treatment," urged surgeons to "be prepared to use preventive or emergency treatment against adrenal insufficiency if suspected." In this case from Rhode Island Hospital, a 59 year-old man had an appendectomy under spinal anesthesia. Four and a half hours after surgery, his blood pressure dropped to 80/60, his pulse was 120, and he reported chest pain. The patient stabilized once he was given Cortef. The surgeon later learned that the patient had been treated with cortisone 2 years earlier for Rhus dermatitis "in sufficient quantities to cause adrenal suppression."

Edward I. Seltzer, MD, and Stephen J. Maddock, MD, contributed "Technique for Supplementing Coronary Circulation by Means of a Splenic Graft." The authors transplanted the spleens of dogs to their hearts.

William P. Buffum, MD, in "Infantile Eczema," recommended topical medication and protection from scratching for immediate relief.

Twenty-Five Years Ago, April 1981

Robert G. Petersdorf, MD, Professor of Medicine, Harvard Medical School, discussed "The Prevention of Infection: A Brief History" at the Brown Medical Association fall seminar symposium. The Journal reprinted his remarks.

Antone A. Medeiros, MD, in "Expanding Spectrum of Antibiotic Resistance," noted "Constant surveillance is necessary for early detection."

Georges Peter, MD, in "New Development in Immunizations," noted, "Inadequate delivery of effective vaccines to targeted populations remains a challenge."

Gerald A. Faich, MD, in "A Public Health Perspective on Immunizable Diseases," advised physicians to "….examine their practices for opportunities to expand vaccine usage in adults and adolescents."