NATIONAL ASSOCIATION OF EPILEPSY CENTERS
NAEC

PRESIDENT'S REPORT – 2011

It has been a very contentious and partisan year in Washington with Congress and the Obama Administration having little success in effectively addressing the country's stalled economy and high unemployment. Congress has focused its efforts on the federal budget and the size of the federal debt, but the Republican House and Democratic Senate have been unable to reach any sort of compromise on how to reduce federal spending other than setting stringent caps on all federal programs for the next ten years.

In spite of the standoff in Congress, the Administration and the states are steadily moving forward on the implementation of the Affordable Care Act, the healthcare reform legislation. Meaningful private insurance reforms are already in effect – no pre-existing condition limitations on children, coverage of children up to age 26 on their parents' plans, no caps on lifetime benefits and no rescissions of insurance benefits without cause. Federal funding has been provided to states to set up Affordable Insurance Exchanges, which will serve as marketplaces for individuals and small businesses to buy government-regulated insurance plans, which for many individuals will be significantly subsidized. Regulations for the exchanges to define "essential health benefits" and other aspects of the program are under development. As expected, the Supreme Court has decided to hear the cases on the ACA's mandate that individuals be required to have health insurance next year. The outcome is unclear, but will prove interesting because the decision will occur in the thick of an election year.

In contrast, the epilepsy community has collaborated on multiple fronts this year to all of our advantage. At the forefront is the Institute of Medicine's study of the *Public Health Dimensions of the Epilepsies* (described in greater detail in this report). NAEC joined eleven other epilepsy organizations in sponsoring the study, actively participated in IOM's hearings and conducted a survey of our centers for additional data for the panel to review. The final report and recommendations are expected in the spring and can help drive improvements in epilepsy care and our public policy agenda for many years.

This report also details the many other areas where we have worked closely with our sister organizations, especially the American Academy of Neurology (AAN), American Epilepsy Society (AES), and Epilepsy Foundation (EF), to improve access to and the quality of care provided to individuals with epilepsy and their families. Two significant successes are the development of epilepsy quality measures now recognized by Medicare and revisions made to the ICD-10 diagnoses codes for epilepsy, which will take effect in 2013.

In addition to the many policy activities we engage in and lead, NAEC is a membership organization and is expanding its efforts to support centers in their work. We will continue to assist centers with coding reimbursement questions and in dealing with private insurers on issues such as denials of EMU admissions, limitations on length of stay, and the utilization of ambulatory EEG and video EEG. NAEC has developed several documents for centers to use to educate insurers when faced with these challenges.

At the first of the year, the NAEC office will have moved to Washington, DC to the offices of our long-time policy advisor, Ellen Riker, who will now serve as Executive Director of the

Association. Ellen and her staff will be handling membership renewals and all member inquiries. Plans are underway to revise the NAEC website to make it more useful to the membership and to provide greater information to patients in search of nearby epilepsy centers. NAEC also plans to automate its self-designation survey for 2012, which should ease the completion of the survey in future years.

Please take note of the new address and phone. The e-mail address remains info@naec-epilepsy.org.

NAEC
c/o Cavarocchi Ruscio Dennis Associates
600 Maryland Avenue, SW, Suite 835W
Washington, DC
202-484-1100

Summary of NAEC Activities for 2011

NAEC has maintained its focus on identifying opportunities to promote the comprehensive specialized services provided by epilepsy centers and to improve coding, coverage and payment for these services by both public and private insurers. Throughout the year, NAEC responds to inquiries from private insurers and local Medicare Administrative Contractors (MACs), carriers and fiscal intermediaries on specialized epilepsy services and assists member centers with problems that may arise within their hospitals and with local insurers. This year NAEC worked in collaboration with other epilepsy organizations on several initiatives to promote access to better quality epilepsy care.

NAEC Actively Participated in Institute of Medicine Study on Epilepsy

Late last year NAEC, joined with 11 epilepsy-affiliated organizations and the Department of Health and Human Services to sponsor and participate in a study by the Institute of Medicine (IOM) on the Public Health Dimensions of the Epilepsies. Early in 2011, the IOM convened a panel of experts in epilepsy and other fields to assess current knowledge and make recommendations to improve the following aspects of epilepsy:

1) Public Health Surveillance, Collection, and Data Integration: To examine how existing or new surveillance systems could support a more accurate assessment of the public health burden of the epilepsies for patients and their families;

2) Population and Public Health Research: To identify what research questions or areas of focus should be priorities for future epidemiological and population health studies on the epilepsies that may inform the development of interventions or preventive strategies;

3) Health Policy, Healthcare and Human Services: To identify what constitutes adequate care and access to health and human services for people with epilepsy; what can be done to improve the consistency and quality of care for persons with epilepsy; what gaps and needs for improvement exist.

4) Patient, Provider, and Public Education: To define what needs exist to improve the education and training of health and other professionals who treat or support persons with epilepsy and explore how public education and awareness campaigns could best be

used to increase patient and public literacy, reduce stigma, and improve community support and participation for people with epilepsy.

NAEC participated in the three public hearings held over the year regarding the different aspects of the study. The first hearing in January was introductory in nature and included testimony from NAEC Board Member, Nathan Fountain, MD on the unique issues of caring for patients with epilepsy in rural communities. Former NAEC Board Member and Member of the IOM panel, Christi Heck, MD testified on her experience running a major inner city epilepsy center. At the second hearing in March, which focused on public health surveillance and population health research, NAEC Board Member Susan Herman, MD testified on primary epilepsy prevention strategies. At the final public hearing held in June on healthcare quality and access and education of patients and providers, NAEC President, Robert J. Gumnit, MD testified on the specialized epilepsy center model of care and NAEC Vice President, David Labiner, MD testified on the education of neurologists and epileptologists.

In addition, NAEC sponsored a site visit for the staff of the IOM panel to the F.E. Dreifuss Comprehensive Epilepsy Program at the University of Virginia Health System. The Center's Medical Director, Nathan Fountain, MD provided a full day experience for the staff, including a tour of the hospital's epilepsy monitoring unit. Over the summer, the IOM panel asked NAEC to survey its members to collect additional data on various parameters of epilepsy care. Specifically, the panel wanted information on outpatient visits, referral sources, waiting times for appointments and admissions to an EMU, and the care of patients following a referral to an epilepsy center. Forty-seven centers participated in the survey that NAEC distributed. The NAEC Board prepared a report to the IOM with an analysis of the data collected, which will be published as an appendix to the IOM's report.

The publication of the final IOM report is anticipated in the spring of 2012. NAEC is working with the IOM and co-sponsors of the study on a plan to disseminate and publicize the report and to develop an advocacy strategy based on the panel's recommendations. More information on the study can be found at: http://www.iom.edu/Activities/Disease/Epilepsy.aspx.

NAEC and AAN Present ICD-10-CM Coding Revisions for 2013 Implementation

In March, NAEC Vice President David Labiner, MD joined by AAN representative Laura Powers, MD presented multiple revisions to the proposed ICD-10-CM diagnosis codes related to epilepsy at the Center for Disease's Controls' ICD -9- CM Coordination and Maintenance Committee Meeting. The coding proposals seek to improve the categorization of the epilepsy disorders and syndromes and to assure that they conform to the International League Against Epilepsy (ILAE) classification. The coding proposal, which can be found on the NAEC website, will take effect in 2013 when ICD-10-CM is implemented.

NAEC Provides Input to Federal Agencies' Review of Bioequivalence, Effectiveness and Safety of Antiepileptic Medications

Agency for Healthcare Research and Quality (AHRQ): AHRQ initiated a comparative effectiveness review of the efficacy, safety and tolerability of antiepileptic medications in July 2010. The review titled *Effectiveness and Safety of Antiepileptic Medications in Patients with Epilep*sy looks at the existing literature as well as current studies and clinical trials to qualitatively and/or quantitatively compare older and newer medications and generic and innovator AEDs' impact on patient outcomes. As part of its review, AHRQ published and sought comments on the review's questions and findings. NAEC submitted comments (Attachment 1)

raising significant concerns with the review and its discussion of innovator versus generic medications.

More information on the AHRQ literature review on AEDs can be found at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=463.

FDA: In July, NAEC joined EF, AES, AAN, and ILAE in writing to the FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee, which was asked to review FDA's criteria for determining bioequivalence standards for AEDs. The letter (Attachment 2) encouraged FDA to create a more precise bioequivalence standard for AEDs and to undertake additional research to determine how this should be done. Following these efforts the Advisory Committee recommended that FDA review and revise its standards for bioequivalence and definition of narrow therapeutic index drugs. In addition, FDA recently awarded a small business innovation research grant to study bioequivalence.

NAEC President Asked to Serve on VA's Epilepsy Centers of Excellence (ECoE) Advisory Committee

Robert J. Gumnit, MD was invited to serve on the Department of Veterans Affairs ECoE Advisory Committee, which will hold its first meeting on December 1, 2011. The Committee was formed to provide guidance and direction to the VA's epilepsy centers as they develop protocols to identify veterans with epilepsy and develop referral networks to enable veterans to obtain specialized treatment. This is an excellent opportunity for NAEC to partner with the VA in epilepsy clinical care, education and research.

AES – Epilepsy Monitoring Unit Safety Project

This year NAEC made a donation of $50,000 to the AES for the production of an EMU safety educational program for epilepsy center personnel. Many NAEC members have been involved in the development of the program. The project will develop six web-based orientation and continuing education modules focused on how to assess patient safety and provide preferred practices on how to ensure greater patient safety in the EMU. The program will cover seizure observation, seizure provocation, acute seizures, and environmental and activity safety. Members of NAEC may be asked to participate in and evaluate the education modules as the testing phase proceeds.

2011 *US News and World Report's* America's Best Hospitals Ranking Released

This summer, the *US News and World Report* released its 2011 rankings of the best hospitals in America. Many NAEC member centers are included among the top neurology and neurosurgical centers. View the rankings on the *US News* website: http://health.usnews.com/best-hospitals/rankings/neurology-and-neurosurgery. Since 2004, the NAEC guidelines for adult Level IV epilepsy centers have been part of *US News'* criteria in ranking neurology and neurosurgery departments in U.S. hospitals. This raises national exposure for specialized epilepsy care and also offers many of our members an opportunity to rank among the top 50 neurology and neurosurgery centers in America.

Update on Medicare Regulations and Federal Epilepsy Programs

2012 Medicare Final Rule on the Physician Fee Schedule (PFS)

On November 28, 2011, the Centers for Medicare and Medicaid Services (CMS) published the final Medicare Physician Fee Schedule (MPFS) rule for 2012 in the Federal Register. The rule in its entirety can be found on the NAEC website along with a summary of the major provisions impacting epilepsy centers.

The total impact on Medicare payments to the average neurologist based on the changes made by the rule is estimated to be a 1% increase for 2012 and a 3% increase in 2013 although the impact on an individual physician will vary depending on the mix of services he or she provides. This impact analysis does not reflect a possible reduction in payment that would occur if Congress doesn't prevent a 27.4 percent reduction in the conversion factor (CF) in 2012. It is anticipated that Congress will enact a freeze in the current CF before the end of the year.

Attachment 3 includes several charts providing the 2011 and 2012 payment rates for epilepsy related medical and neurosurgical services and Evaluation and Management (E&M) services. A $34 conversion factor (the 2011 conversion factor) was used to calculate the payment in 2012. Overall, E/M services will either show no change or a change in the range of + or – 1 percent. The technical component and global service for most of the diagnostic testing procedures (EEGs, evoked potential, etc.) will see substantial increases in payment. For example, the TC for the highest volume EEG code, 95819, will see a 20 percent increase. Most professional component services are either flat for 2012 or will see a modest reduction (less than 1 percent). Epilepsy surgery services payments are relatively flat or modestly increasing.

CMS adopted three new epilepsy quality measures to be included in Medicare's Physician Quality Reporting System (PQRS) in 2012. These measures are:

- Documentation of Current Seizure Frequency(ies) of each current seizure type
- Documentation of Epilepsy Etiology or Epilepsy Syndrome
- Counseling for Women of Childbearing Potential with Epilepsy

Specific codes will be established for the epilepsy measures for claims reporting. A bonus payment of 0.5 percent of total allowed charges for services provided during the reporting period will be awarded to physicians that report each measure for at least 50% of their Medicare fee for service patients. NAEC had worked closely with AAN and AES to develop the epilepsy quality measures, with NAEC Board Members, Drs. Nathan Fountain and Paul Van Ness chairing the committee overseeing this effort. AAN had recommended a total of eight measures to CMS and in the proposed rule CMS had included 2 additional measures - Querying and Counseling about Anti-Epileptic Drug (AED) Side Effects and Counseling about Epilepsy Specific Safety Issues – in PQRS. CMS withdrew these measures in the final rule because they were not endorsed by the National Quality Forum.

2012 Medicare Final Rule on Hospital Outpatient Prospective Payment System (HOPPS)

On November 1, 2011, the Centers for Medicare and Medicaid Services (CMS) released the Hospital Outpatient Prospective Payment System (OPPS) final rule for 2012, which is available on NAEC's website, along with a summary of the rule.

The payments made under OPPS cover facility resources including equipment, supplies, and hospital staff, but do not include services of physicians or non-physician practitioners paid separately under the Medicare Physician Fee Schedule. Clinically-similar services that require similar resources are classified into payment groups called Ambulatory Payment Classifications (APCs) and a payment rate is established for each APC.

Overall, payments for hospital outpatient services will increase by 1.9 percent in 2012. Attachment 4 is an analysis showing a comparison of the 2012 to 2011 hospital outpatient payment rates for services provided by epilepsy centers. OPPS payment rates are relatively stable for services provided by epilepsy centers with payments for most APCs increasing slightly.

Medicare Shared Savings Program: Accountable Care Organizations (ACOs) Final Rule

On October 20, CMS announced the final rules for Accountable Care Organizations (ACOs) participating in Medicare's Shared Savings Program. Created by the Affordable Care Act, CMS' goal for the program is to incentivize providers to proactively coordinate care across care settings so that beneficiaries receive higher-quality care at a lower cost. ACOs can share in savings that they generate for Medicare as compared to CMS estimates of what their patient population was estimated to cost.

While the basic structure of the Medicare shared savings program remained as proposed, CMS made a number of revisions to respond to major criticisms of the rule and to encourage providers to participate. Although many stakeholders have praised the changes, it is still not clear how many organizations will ultimately decide to participate. The program will launch officially on January 1, 2012.

The Shared Savings Program final rule is available here. An analysis of the rule is available on the NAEC website.

Medicare Contractor Reform

Since 2004, CMS has been replacing its former claims payment contractors - fiscal intermediaries and carriers - with new entities called Medicare Administrative Contractors (MACs). While CMS originally planned to award a total of 15 MAC contracts to cover the majority of Part A and Part B services, it is now consolidating these contracts into 10 contracts.

Over the next several years, CMS will consolidate the following A/B MAC contracts to include the following states:

- **A/B MAC Jurisdictions 2** (Alaska, Washington, Oregon, Idaho) and **3** (North Dakota, South Dakota, Montana, Wyoming, Utah, and Arizona) – currently Noridian Administrative Services for both jurisdictions, but both contracts are under protest
- **A/B MAC Jurisdictions 4 (**Texas, Oklahoma, Colorado, and New Mexico) **and 7** (Louisiana, Arkansas, Mississippi) – currently TrailBlazer Health Services for jurisdiction 4 and jurisdiction 7's RFP was withdrawn
- **A/B MAC Jurisdictions 5 (**Kansas, Nebraska, Iowa, and Missouri) **and 6** (Minnesota, Wisconsin, and Illinois) – currently Wisconsin Physician Services and National Government Services, Inc., respectively
- **A/B MAC Jurisdictions 8 (**Michigan, and Indiana) **and 15** (Kentucky and Ohio)– currently Wisconsin Physician Services and CIGNA Government Services, respectively

- **A/B MAC Jurisdictions 13 (**New York and Connecticut) **and 14** (Massachusetts, Rhode Island, Vermont, Maine, and New Hampshire) – currently National Government Services and National Heritage Insurance Corporation, respectively

CMS also intends to re-compete five A/B MAC contracts/jurisdictions based on their present area boundaries, as the current A/B MAC contracts run their course. The five A/B MAC contracts/jurisdictions that will not be further consolidated are:

- **A/B MAC Jurisdiction 1** (California, Hawaii, Nevada, Pacific Islands) – currently Palmetto GBA
- **A/B MAC Jurisdiction 9** (Florida, Puerto Rico, US Virgin Islands) – currently First Coast Service Options, Inc.
- **A/B MAC Jurisdiction 10** (Alabama, Georgia, Tennessee) – currently Cahaba GBA
- **A/B MAC Jurisdiction 11** (North Carolina, South Carolina, Virginia, West Virginia) – currently Palmetto GBA
- **A/B MAC Jurisdiction 12** (Delaware, Maryland, Pennsylvania, New Jersey, Washington DC) – currently Highmark Medicare Services

CDC Epilepsy Program

The CDC's Epilepsy Program, with an annual budget of about $8 million, continues its efforts to improve care and treatment and increase public awareness and knowledge about epilepsy. Also, CDC has steadily built a research program in epilepsy. Opportunities exist for epilepsy centers to initiate and participate in studies on health outcomes, self-management and quality of life and epidemiologic and population studies. The links below provide an updated overview of the activities and research funded by the CDC Epilepsy Program.

CDC Epilepsy Program Activities: http://www.cdc.gov/epilepsy/program_activities.htm

CDC Epilepsy Research Projects: http://www.cdc.gov/Epilepsy/research_projects.htm

Objectives for 2012

In 2012, NAEC will continue to aggressively advocate for improved Medicare and private insurance reimbursement for epilepsy services, including physician services, hospital outpatient department payments and improved coverage for inpatient hospital care and new technologies. NAEC will also continue to assist member centers in working with their local insurers to ensure that adequate coverage for epilepsy services is maintained.

NAEC will also continue its efforts to:

- Improve coding and terminology for epilepsy diagnoses and procedural services.
- Provide its membership with coding and reimbursement information as well as other legislative and regulatory information affecting comprehensive epilepsy care.
- Participate in and provide support for federal research and public health programs in epilepsy funded by the NIH, CDC, and HRSA.
- Identify areas and projects of mutual interest to pursue in collaboration with other epilepsy organizations.

NATIONAL ASSOCIATION OF EPILEPSY CENTERS
NAEC

March 11, 2011

Carolyn Clancy, M.D.
Director
Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, MD 20850

Dear Dr. Clancy,

The National Association of Epilepsy Centers (NAEC) thanks you for the opportunity to submit comments on AHRQ's research review titled: "Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy." NAEC is an organization of over 130 specialized centers in the U.S. that diagnose and treat patients with complex and intractable epilepsy. NAEC is committed to improving the quality of care for individuals with epilepsy.

The NAEC is pleased that AHRQ funded this literature review as questions are frequently raised about the comparative effectiveness and safety of the various antiepileptic drugs (AEDs). At the same time our Association believes that it is important to recognize and understand the limitations of the evidence collected. In reviewing the report we also feel that some clarifications need to be made in the report.

New verses Older AEDs

We do agree with the conclusion that none of the newer medications have ever been proven to be more efficacious than carbamazepine. It is important to recognize, however, that all innovator drugs have been approved based on their ability to reduce seizure frequency in patients who are already on existing medications (add-on study design). Unfortunately, there are no head-to-head, well-controlled, comparative effectiveness studies of AEDs in common use and as such the existing data are not sufficient to distinguish a difference between these treatments. In the absence of such comparative data we caution against concluding there is no difference between old and new AEDs in regard to efficacy.

We would emphasize that as a group, as was mentioned in the report, the newer medications seem to have a more favorable safety profile. As with all evidence-based reviews, we realize that practical real world concerns of how best to use different medications in different groups of patients (Key Question 4) is presently not answerable due to lack of evidence.

Innovator verses Generic AEDs

Our greater concern with the review relates to the issue of innovator versus generic medications and the practical ramifications of the report's conclusions when considering potential public policies that may be derived, from this report. For this reason, we felt that it was important to provide a general view of pharmacological treatment of patients with epilepsy.

Epilepsy Drug Treatment - Epilepsy is a life-long chronic disease. Effective treatment is essential to the health and quality of life of individuals living with this disorder. The major issue in treating patients with epilepsy is to determine the AED that is most effective in controlling a patient's seizures without causing medical, psychological or cognitive side-effects. Most individuals living with epilepsy can be effectively treated with a single drug, which is often the first drug prescribed for the patient. Unfortunately, for 0.3% of the general population, or about 30% of epilepsy patients their seizures are difficult to control and are considered to have intractable epilepsy. These patients typically go on multiple drug trials and are often treated with more than one medication.

Once the optimal medication is determined for a patient with epilepsy, it is critical that the drug's pharmacokinetic behavior, especially absorption, is consistently maintained. To a high degree of probability, this will be the case when a brand drug is prescribed or if the patient is given the same manufacturer's generic version of the drug. Problems arise when patients are given variable and/or multiple generic formulations of the same drug. This is due to manufacturers' variations in product formulation which alter dissolution and can impact absorption. We do not believe that brand drugs are superior to their bioequivalent versions, but they provide the prescribing physician the assurance that the drug's absorption rate will be consistent This is typically not the case when a generic is provided to patients since the pharmacy will dispense whatever generic version of the drug is on hand.

The FDA Definition of Bioequivalence - Innovator vs Generic AEDs - For a generic product to be considered bioequivalent to a brand drug, FDA requires that the drug's absorption rate (the log-transformed ratios of AUC and Cmax between brand and generic products) fall within the range of 80% to 125%. Each generic is tested against the branded equivalent to make this determination, but not against other generic preparations. This can result in significant differences in absorption rates between two generics.

For example, a given generic can have a high but acceptable bioequivalence, while a second generic can have a low but also acceptable bioequivalence, potentially resulting in a 45% difference in the drug's absorption, as recently demonstrated by Krauss and colleagues[1] at a presentation at the American Academy of Neurology meeting (data not yet published). In this case, if the patient was started on the first generic and then switched to the second, the total decrease in delivered dose could be enough to result in seizure breakthrough and, of course, potentially devastating consequences. The opposite can also occur if the first generic given has low but acceptable bioequivalence and the second generic given has a high but also acceptable bioequivalence, resulting in an increase in delivered dose that could result in toxic symptoms. This problem is further amplified for patients with intractable epilepsy that require polypharmacy of two, three, four, or five antiepileptic drugs, often together with other classes of drugs such as antihypertensives, psychotropics, and oral hormones. In this case, the generic to generic drug changes combined with the interaction with these other medications (inducers and inhibitors) can have a dangerous impact.

Potential Results of Generic Substitution - Many patients with epilepsy can safely use generic medications, with accompanied financial savings. Unfortunately, there is little information available to determine which specific individuals might have problems with the switching of generic AEDs. There is a growing body of peer-reviewed data that suggests there might be problems associated with generic AED utilization. Retrospective studies such as the Claims Database Analysis done by Zachry et al.[2] studied the association between a recent substitution of an A-rated generic product and emergency care for a seizure-related event. In this analysis, patients requiring emergency care had 81% greater odds of having a generic AED formulation switched in the previous six months than controls (11.3% versus 6.2%).

In another retrospective analysis of data from Ontario, Canada, Andermann et al.[3] evaluated switchback rates of several classes of drugs including antiepileptic drugs (lamotrigine, Depakote) as well as several antidepressant and cholesterol-lowering drugs. Please be aware that in Canada, the physician has to write a letter of medical necessity before the patient can be switched back from a generic to an original product. In this analysis, a high switchback from generic to brand (12.9%-20.9%) was seen for AEDs as compared for non-AED classes of drugs (1.5%-2.9%).

Other more recent studies have shown that use of generic medications (compared with brand) lead to increased downstream healthcare utilization[4] as well as related increased costs[5].

One study cited in the report was the so called Express Scripts study[6]. This study has been widely used to refute the other observational studies. What is routinely ignored in these analyses and discussions is that the data in this study actually supports the concerns raised in the preceding paragraphs. There was in fact an increased hospitalization and emergency department utilization noted in the raw data that disappeared with adjustment for confounders. However there was significant increase in risk when the patient was on two or greater than three AEDs. This latter point was not addressed in the report.

The key issue, in our assessment, is not whether innovators are more efficacious that generics but rather the risk of formulation substitution (brand to generic, generic to generic, and generic to brand). It is assumed in the observational studies that individuals in the generic groups are likely receiving generics from different manufacturers. It is also very possible that these formulation substitutions are irrelevant in many patients. That said, we have no ability to determine *a priori* which patients would be negatively affected by such switching.

Conclusion

We at the NAEC applaud the AHRQ for funding a review of such importance to epilepsy patients. We ask the report more clearly emphasizes that absence of comparative effectiveness data (old versus new AEDs) does not prove an absence of difference. Further, we believe that the clinically relevant question regarding innovator versus generic questions, that of formulation substitution, was not addressed in the report and in fact couldn't be due to lack of data.

We caution against the use of this report for the development of clinical practice guidelines or quality standards. Well-designed comparative effectiveness studies of the AEDs in common use are needed to answer the questions raised in this research review. Until such studies are undertaken policy decisions should not be made based on inadequate data as they may result in harm to patients.

We would appreciate the opportunity to respond to any questions and discuss these issues further. Please contact Ellen Riker with NAEC at 202-257-6670 or ellen.riker@hklaw.com.

Sincerely,

David Labiner, MD
Vice President

END NOTES

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[3] Andermann F, Duh M, Gosselin A, Paradis P. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. *Epilepsia* 2007; 48: 464-469.

[4] Labiner DM et al. Generic antiepileptic drugs and associated medical resource utilization in the United States. *Neurology* 2010; 74: 1566-1574.

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July 19, 2011

Yvette Waples, Pharm.D.
Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002
SUBMITTED ELECTRONICALLY VIA E-mail: ACPS-CP@fda.hhs.gov

RE: Comments to the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting; responding to July 26, 2011 meeting notice

Dr. Waples:

The American Epilepsy Society, American Academy of Neurology, Epilepsy Foundation, International League Against Epilepsy, and the National Association of Epilepsy Centers are pleased to offer these joint comments to the Food and Drug Administration (FDA) Pharmaceutical Science and Clinical Pharmacology Advisory Committee. Collectively, our organizations represent a broad spectrum of the patients, providers, and researchers who seek to serve the health and welfare of the nearly three million Americans living with epilepsy and their families.

The issue of bioequivalence is important to all of our organizations, and concerns about bioequivalence for antiepileptic drugs (AEDs) and medication switching have been growing within our organizations and the epilepsy community for many years. [1] We offer the following comments to reinforce the steps that this Committee and the FDA have taken over the past year to address bioequivalence, and specifically the recognition by the FDA that this is an area of key concern within the epilepsy community. We applaud the steps the FDA has taken to address the Committee's recommendations from April 13, 2010. We encourage the FDA and the Committee to incorporate a definition of narrow therapeutic index (NTI) or critical dose drugs that allows for the inclusion of AEDs; and we continue to support the FDA in funding research that will best address the bioequivalence concerns for AEDs and epilepsy patients.

Definition of Narrow Therapeutic Index/Critical Dose Drugs:

Historically, the term Narrow Therapeutic Index was defined by pharmacokinetic and therapeutic criteria, and required definition of a minimum therapeutic and minimum toxic dose. Most of the AEDs do not have well defined minimum therapeutic and toxic doses. Our experts prefer the term critical dose drug, which would include those drugs where comparatively small differences in dose or concentration

[1] *See The substitution of different formulations of antiepileptic drugs for the treatment of epilepsy,* American Epilepsy Society Consensus Statement (Nov. 2007) http://www.aesnet.org/go/press-room/consensus-statements/drug-substitution
In Their Own Words: Epilepsy Patients' Experiences Changing the Formulation of the Drugs they Use to Prevent Seizures, Epilepsy Foundation (Mar. 2009)
http://www.epilepsyfoundation.org/medicationswitching/Consumer_Survey_Report%20_Recommendations.pdf
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may lead to serious therapeutic failures and/or serious adverse drug reactions. Based on this definition, most of the AEDs would be considered critical dose drugs
that require individualization in order to optimize treatment. In many patients, what may be seen as relatively modest changes in plasma concentration (~20%) decreases may result in either recurrent seizures, or clinically significant adverse effects; either seizures or critical adverse effects would be considered a serious therapeutic failure.

Current bioequivalence standards of FDA with formula-based 90% confidence intervals are based on the assumption that a 20% deviation of plasma concentration is not clinically significant. In the case of AEDs, our experts believe that many patients with epilepsy could experience clinical toxicity or loss of seizure control with a 20% change in plasma concentration, whether measured as peak concentration (Cmax) or total drug exposure (AUC).We believe that the current FDA bioequivalence standards may not be adequate for critical dose drugs. Additionally lot-to-lot variations, governed by the United States Pharmacopeia (USP) standards, may further add to differences in the amount of AED an individual receives over time. We encourage FDA to create a more precise definition of critical dose drugs, and to determine with evidence from clinical studies whether generic versions of critical dose drugs should be subjected to more rigorous standards for approval.

Recommendations for FDA Research on AEDs and Bioequivalence:

Many in the epilepsy community look to the FDA, as the agency that ensures the safety and efficacy of all medications for people in this country, to help guide the research on this topic. The epilepsy organizations we represent offer resources for outreach to patients, physicians and policymakers to ensure the FDA has all the tools it needs. Our organizations acknowledge that recent research contracts are just the first step, and we look forward to working with you to support this, and other scientific research projects, within the government and Congress.

Recent publications that are based on analyses of large databases, or on modeling of ANDA data provide a signal indicating concerns about widespread generic substitution of AEDs. However, we recognize that these studies do not provide the scientific rigor needed to change policy, but are rather an indication that prospective trials with rigorous pharmacokinetic analyses performed on people with epilepsy are needed. We are encouraged by the FDA's willingness to acknowledge the need for additional research and applaud the funding of an initial study in 2010 with rigorous pharmacokinetic methods, studying people with epilepsy who are randomized to receive chronic dosing of a single generic product or the brand AED. We suggest that the FDA consider the following studies for future research on this topic:

- A prospective, randomized trial in people with epilepsy comparing two generic products at the extremes of bioavailability, utilizing either chronic dosing or single doses.
- A study examining the "outlier" patients: use rigorous pharmacokinetic methods to determine whether patients who experience unexpected adverse effects or loss of seizure control with generic switches truly have differences in AED concentrations.
- Studies examining whether changes of 20% in AED plasma concentrations of people with epilepsy can produce clinically significant adverse effects or loss of seizure control.

Our organizations strongly support the efforts of the FDA to determine the ideal ranges for the confidence intervals, how to define critical dose drugs, and what factors might make a person absorb

different AED products differently. We believe that studies such as these will help address bioequivalence questions for AEDs and any concerns for people with epilepsy (or subpopulations) who switch between different manufacturer's products of an antiepileptic drug. Further, we realize that the research may result in further questions and necessitate additional studies before policy or regulatory changes could occur. We hope that the agency will see value to such studies, as they could guide outside research on other therapeutic questions or assist the agency with a variety of other consumer safety issues from quality to counterfeit drugs. In addition, we look forward to the FDA working closely with the epilepsy patient and provider community to collaborate on research outcomes.

The American Epilepsy Society, American Academy of Neurology, Epilepsy Foundation, International League Against Epilepsy, and the National Association of Epilepsy Centers strongly support the steps of the FDA and this Committee to address issues of bioequivalence and undertake research that could better inform the agency as it relates to AEDs. As you move forward with discussions about standards and make decisions about future research, we hope you will look to our organizations as partner for expertise and communications on bioequivalence and AEDs.

Sincerely,

Bruce Sigsbee, MD, FAAN
President, American Academy of Neurology

John M. Pellock, M.D.
American Epilepsy Society President 2011

Rich Denness
President & CEO, Epilepsy Foundation

Nico L. Moshé, M.D.
President, International League Against Epilepsy

Robert J. Gumnit, M.D.,
President, National Association of Epilepsy Centers

cc: Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA
Helen N. Winkle, Director, Office of Pharmaceutical Science, FDA
Keith Webber, PhD., Director, Office of Generic Drugs

Attachment

RESEARCH DATA ON MEDICATION SWITCHING

In 2009 the first case-control analysis to determine the odds of AED substitution among patients requiring emergency care was published in the journal *Epilepsia* (Zachry, et al). Using the Ingenix LabRX data base, the study reported that patients who had an epileptic event requiring emergency care, who had not required care for at least six months, had 81% greater odds of having an AED formulation switch.

The results of the Zachry study have been replicated using a different data base (PharMetrics) and an even larger control group. Published in the July 2009 issue of the journal *Pharmacotherapy*, Rascati and colleagues conclude: "Patients who had an epileptic event requiring acute care were about 80% more likely than matched controls without an acute event to have recently had an antiepileptic drug substitution. Replication of a previously published case-control analysis revealed a similar association between substitution involving A-rated antiepileptic drugs and subsequent epileptic events requiring acute care, thereby lending credibility to the findings."

Most recently, in an article titled "Antiepileptic drugs: the drawbacks of generic substitution," the journal *The Lancet Neurology* stated that "until firm evidence supporting the safety of generic switching becomes available, we should err on the side of caution and ensure that AEDs are excluded from any sweeping policies that promote automatic generic substitution."
In addition, the journal *Neurology* published a study by Labiner, et al., which found that with five common AEDs in the U.S., generic substitution was associated with significantly greater use of medical resources and risk of epilepsy-related medical events, compared to brand use.

For your reference, we are providing citations for these articles:

- Antiepileptic drugs: the drawbacks of generic substitution. *The Lancet Neurology*, Vol. 9; p. 227 (2010)
- Andermann, F., et al, Compulsory generic switching of antiepileptic drugs: Higher switchback rates to branded compounds compared with other drug classes. *Epilepsia*, 48(3); 464-469 (2007).
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- Burkhardt, R.T., PharmD, et al., Lower phenytoin serum levels in persons switched from brand to generic phenytoin. *Neurology* 63 (2004).
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2012 Final Physician Fee Schedule (CMS 1524-FC)					
Payment Rates for Medicare Physician Services - Epilepsy					
*We are assuming the retention of the current 2011 conversion factor through 2012.					
CPT Code	**Mod**	**Descriptor**	**2011 CF = $33.9764**	**2012 CF = $33.9764***	**% CHANGE 2011-2012**
95812		EEG, 41-60 minutes	$316.66	$366.27	15.67%
95812	TC	EEG, 41-60 minutes	$262.30	$312.24	19.04%
95812	26	EEG, 41-60 minutes	$54.36	$54.02	-0.63%
95813		EEG, over 1 hour	$356.41	$424.37	19.07%
95813	TC	EEG, over 1 hour	$270.11	$338.07	25.16%
95813	26	EEG, over 1 hour	$86.30	$86.30	0.00%
95816		EEG, awake and drowsy	$292.88	$336.37	14.85%
95816	TC	EEG, awake and drowsy	$238.17	$282.00	18.40%
95816	26	EEG, awake and drowsy	$54.70	$54.36	-0.62%
95819		EEG, awake and asleep	$326.85	$381.89	16.84%
95819	TC	EEG, awake and asleep	$272.49	$327.87	20.32%
95819	26	EEG, awake and asleep	$54.36	$54.02	-0.63%
95822		EEG, coma or sleep only	$305.45	$348.26	14.02%
95822	TC	EEG, coma or sleep only	$251.09	$294.24	17.19%
95822	26	EEG, coma or sleep only	$54.36	$54.02	-0.63%
95824	26	EEG, cerebral death only	$38.05	$37.71	-0.89%
95827		EEG, all night recording	$561.97	$670.01	19.23%
95827	TC	EEG, all night recording	$507.61	$615.65	21.29%
95827	26	EEG, all night recording	$54.36	$54.36	0.00%
95829		Surgery electrocorticogram	$1,500.06	$1,669.26	11.28%
95829	TC	Surgery electrocorticogram	$1,190.53	$1,361.09	14.33%
95829	26	Surgery electrocorticogram	$309.53	$308.17	-0.44%
95830	Hospital	Insert electrodes for EEG	$86.64	$86.30	-0.39%
95830	Office	Insert electrodes for EEG	$191.29	$200.80	4.97%
95950		Ambulatory eeg monitoring	$271.81	$297.63	9.50%
95950	TC	Ambulatory eeg monitoring	$195.36	$221.87	13.57%
95950	26	Ambulatory eeg monitoring	$76.45	$75.77	-0.89%
95951	26	EEG monitoring/videorecord	$310.54	$308.51	-0.66%
95953		EEG monitoring/computer	$414.51	$428.78	3.44%
95953	TC	EEG monitoring/computer	$257.20	$273.17	6.21%
95953	26	EEG monitoring/computer	$157.31	$155.61	-1.08%
95954		EEG monitoring/giving drugs	$311.22	$405.00	30.13%
95954	TC	EEG monitoring/giving drugs	$197.40	$287.44	45.61%
95954	26	EEG monitoring/giving drugs	$113.82	$117.56	3.28%
95955		EEG during surgery	$168.52	$193.67	14.92%
95955	TC	EEG during surgery	$118.24	$143.04	20.98%
95955	26	EEG during surgery	$50.29	$50.62	0.68%
95956		EEG monitoring, cable/radio	$1,013.86	$1,176.94	16.09%
95956	TC	EEG monitoring, cable/radio	$836.50	$999.93	19.54%
95956	26	EEG monitoring, cable/radio	$177.36	$177.02	-0.19%
95957		EEG digital analysis	$340.44	$385.97	13.37%
95957	TC	EEG digital analysis	$239.87	$286.42	19.41%
95957	26	EEG digital analysis	$100.57	$99.55	-1.01%
95958		EEG monitoring/function test	$454.94	$494.36	8.66%

2012 Final Physician Fee Schedule (CMS 1524-FC)					
Payment Rates for Medicare Physician Services - Epilepsy					
*We are assuming the retention of the current 2011 conversion factor through 2012.					
CPT Code	**Mod**	**Descriptor**	**2011**	**2012**	**% CHANGE 2011-2012**
			CF = $33.9764	**CF = $33.9764***	
95958	TC	EEG monitoring/function test	$240.55	$281.32	16.95%
95958	26	EEG monitoring/function test	$214.39	$213.03	-0.63%
95961		Electrode stimulation, brain	$252.10	$270.45	7.28%
95961	TC	Electrode stimulation, brain	$99.89	$119.60	19.73%
95961	26	Electrode stimulation, brain	$152.21	$150.86	-0.89%
95962		Electrode stim, brain add-on	$226.62	$235.80	4.05%
95962	TC	Electrode stim, brain add-on	$63.88	$74.41	16.49%
95962	26	Electrode stim, brain add-on	$162.75	$161.39	-0.84%
95965	26	MEG, spontaneous	$419.27	$414.17	-1.22%
95966	26	MEG, evoked, single	$209.29	$206.58	-1.30%
95967	26	MEG, evoked, each addÏl	$181.77	$180.07	-0.93%
95970	Hospital	Analyze neurostim, no prog	$23.10	$23.10	0.00%
95970	Office	Analyze neurostim, no prog	$59.12	$63.54	7.47%
95971	Hospital	Analyze neurostim, simple	$40.09	$39.75	-0.85%
95971	Office	Analyze neurostim, simple	$57.76	$57.42	-0.59%
95972	Hospital	Analyze neurostim, complex	$77.47	$77.47	0.00%
95972	Office	Analyze neurostim, complex	$106.69	$108.04	1.27%
95973	Hospital	Analyze neurostim, complex	$47.23	$47.91	1.44%
95973	Office	Analyze neurostim, complex	$60.14	$61.84	2.82%
95974	Hospital	Cranial neurostim, complex	$154.59	$153.57	-0.66%
95974	Office	Cranial neurostim, complex	$185.17	$189.93	2.57%
95975	Hospital	Cranial neurostim, complex	$87.32	$86.98	-0.39%
95975	Office	Cranial neurostim, complex	$100.23	$102.27	2.03%

2012 Final Physician Fee Schedule (CMS 1524-FC)				
Payment Rates for Medicare Physician Services - Epilepsy Surgery				
*We are assuming the retention of the current 2011 conversion factor through 2012.				
CPT Code	**Descriptor**	**2011 CF = $33.9764**	**2012 CF = $33.9764***	**% CHANGE 2011-2012**
61531	Implant brain electrodes	$1,215.34	$1,227.57	1.01%
61537	Removal of brain tissue	$2,458.87	$2,467.03	0.33%
61538	Removal of brain tissue	$2,660.01	$2,673.60	0.51%
61539	Removal of brain tissue	$2,361.36	$2,370.19	0.37%
61540	Removal of brain tissue	$2,190.12	$2,195.89	0.26%
61541	Incision of brain tissue	$2,150.71	$2,158.86	0.38%
61542	Removal of brain tissue	$2,244.14	$2,208.81	-1.57%
61543	Removal of brain tissue	$2,164.30	$2,177.21	0.60%
61566	Removal of brain tissue	$2,259.43	$2,262.83	0.15%
61567	Incision of brain tissue	$2,579.15	$2,581.87	0.11%
61720	Incise skull/brain surgery	$1,241.50	$1,263.24	1.75%
61735	Incise skull/brain surgery	$1,513.31	$1,579.22	4.36%
61750	Incise skull/brain biopsy	$1,404.92	$1,411.72	0.48%
61751	Brain biopsy w/ct/mr guide	$1,370.61	$1,381.14	0.77%
61760	Implant brain electrodes	$1,563.59	$1,579.56	1.02%
61770	Incise skull for treatment	$1,598.59	$1,616.60	1.13%
61790	Treat trigeminal nerve	$860.96	$872.85	1.38%
61791	Treat trigeminal tract	$1,105.93	$1,116.46	0.95%
61796	Srs, cranial lesion simple	$968.67	$992.79	2.49%
61797	Srs, cran les simple, addl	$218.81	$218.13	-0.31%
61798	Srs, cranial lesion complex	$1,293.48	$1,338.33	3.47%
61799	Srs, cran les complex, addl	$301.71	$301.37	-0.11%
61800	Apply srs headframe add-on	$151.53	$152.21	0.45%
61867	Implant neuroelectrode	$2,290.69	$2,296.80	0.27%
61868	Implant neuroelectrde, add'l	$509.99	$505.57	-0.87%
61870	Implant neuroelectrodes	$1,185.10	$1,191.21	0.52%
61875	Implant neuroelectrodes	$1,025.41	$1,034.92	0.93%
61880	Revise/remove neuroelectrode	$556.19	$570.46	2.57%
61885	Insrt/redo neurostim 1 array	$541.92	$532.75	-1.69%
61886	Implant neurostim arrays	$826.99	$848.39	2.59%
61888	Revise/remove neuroreceiver	$390.05	$390.73	0.17%
63620	Srs, spinal lesion	$1,058.03	$1,089.96	3.02%
63621	Srs, spinal lesion, addl	$251.09	$250.75	-0.14%

2012 Final Physician Fee Schedule (CMS 1524-FC)							
Payment Rates for Medicare Physician Services - Evaluation and Management							
*We are assuming the retention of the current 2011 conversion factor through 2012.							
CPT Code	**Descriptor**	**NON-FACILITY (OFFICE)**			**FACILITY (HOSPITAL)**		
		2011 CF = $33.9764	**2012 CF = $33.9764***	**% CHANGE 2011-2012**	**2011 CF = $33.9764**	**2012 CF = $33.9764***	**% CHANGE 2011-2012**
99201	Office/outpatient visit, new	$41.45	$42.47	2.46%	$25.82	$25.82	0.00%
99202	Office/outpatient visit, new	$71.01	$72.37	1.91%	$48.93	$48.93	0.00%
99203	Office/outpatient visit, new	$103.29	$104.99	1.64%	$74.75	$74.75	0.00%
99204	Office/outpatient visit, new	$158.67	$160.37	1.07%	$126.39	$126.73	0.27%
99205	Office/outpatient visit, new	$197.74	$199.10	0.69%	$162.41	$162.41	0.00%
99211	Office/outpatient visit, est	$19.71	$19.71	0.00%	$9.17	$9.17	0.00%
99212	Office/outpatient visit, est	$41.45	$42.47	2.46%	$25.14	$25.14	0.00%
99213	Office/outpatient visit, est	$68.97	$70.33	1.97%	$49.61	$49.61	0.00%
99214	Office/outpatient visit, est	$102.61	$103.97	1.32%	$75.77	$76.11	0.45%
99215	Office/outpatient visit, est	$137.94	$139.64	1.23%	$107.03	$107.03	0.00%
99221	Initial hospital care	N/A	N/A	N/A	$97.17	$98.19	1.05%
99222	Initial hospital care	N/A	N/A	N/A	$132.17	$132.85	0.51%
99223	Initial hospital care	N/A	N/A	N/A	$194.01	$195.02	0.53%
99231	Subsequent hospital care	N/A	N/A	N/A	$38.39	$38.05	-0.88%
99232	Subsequent hospital care	N/A	N/A	N/A	$69.65	$69.65	0.00%
99233	Subsequent hospital care	N/A	N/A	N/A	$99.89	$99.89	0.00%
99291	Critical care, first hour	$264.68	$266.71	0.77%	$217.45	$216.77	-0.31%
99292	Critical care, add'l 30 min	$118.92	$119.26	0.29%	$109.06	$108.72	-0.31%
99471	Ped critical care, initial	N/A	N/A	N/A	$775.34	$767.87	-0.96%
99472	Ped critical care, subseq	N/A	N/A	N/A	$390.05	$390.39	0.09%

2012 Final Hospital Outpatient Prospective Payment System (HOPPS) Regulations
Epilepsy-Related APCs

2012 Final APC	HCPCS	Descriptor	2011 Final Payment Rate	2012 Final Payment Rate	% Change
0209	**Level II Extended EEG, Sleep, and Cardiovascular Studies**		**$780.77**	**$795.16**	**1.84%**
	95805	Multiple sleep latency test			
	95807	Sleep study, attended			
	95808	Polysomnography, 1-3			
	95810	Polysomnography, 4 or more			
	95811	Polysomnography w/cpap			
	95950	Ambulatory eeg monitoring			
	95951	EEG monitoring/videorecord			
	95953	EEG monitoring/computer			
	95956	Eeg monitoring, cable/radio			
0213	**Level I Extended EEG, Sleep, and Cardiovascular Studies**		**$166.64**	**$170.12**	**2.09%**
	95800	Slp stdy unattended			
	95801	Slp stdy unatnd w/anal			
	95806	Sleep study unatt&resp efft			
	95812	Eeg, 41-60 minutes			
	95813	Eeg, over 1 hour			
	95816	Eeg, awake and drowsy			
	95819	Eeg, awake and asleep			
	95822	Eeg, coma or sleep only			
	95827	Eeg, all night recording			
	95958	EEG monitoring/function test			
0216	**Level III Nerve and Muscle Tests**		**$186.17**	**$185.46**	**-0.38%**
	92584	Electrocochleography			
	95961	Electrode stimulation, brain			
	95962	Electrode stim, brain add-on			
0218	**Level II Nerve and Muscle Tests**		**$80.78**	**$84.19**	**4.22%**
	95954	EEG monitoring/giving drugs			
	95975	Cranial neurostim, complex *(moved from APC 0692)*			
	95970	Analyze neurostim, no prog			
0692	**Level II Electronic Analysis of Devices**		**$110.95**	**$115.65**	**4.24%**
	93271	Ecg/monitoring and analysis			
	95971	Analyze neurostim, simple			
	95972	Analyze neurostim, complex			
	95973	Analyze neurostim, complex			
	95974	Cranial neurostim, complex			
	95978	Analyze neurostim brain/1h			
	95979	Analyz neurostim brain addon			
	95982	Io ga n-stim subsq w/reprog			
0065	**Level I Stereotactic Radiosurgery, MRgFUS, and MEG**		**$977.12**	**$902.53**	**-7.63%**
	95966	Meg, evoked, single			
	95967	Meg, evoked, each addl			
	G0251	Linear acc based stero radio			
0039	**Level I Implantation of Neurostimulator Generator**		**$14,743.58**	**$15,188.78**	**3.02%**
	61885	Insrt/redo neurostim 1 array			
0220	**Level I Nerve Procedures**		**$1,317.77**	**$1,322.75**	**0.38%**
	61790	Treat trigeminal nerve			
0221	**Level II Nerve Procedures**		**$2,567.33**	**$2,529.61**	**-1.47%**
	61720	Incise skull/brain surgery			
	61770	Incise skull for treatment			
0203	**Level IV Nerve Injection**		**$881.28**	**$896.18**	**1.69%**
	61791	Treat trigeminal tract			
0315	**Level II Implantation of Neurostimulator Generator**		**$18,850.77**	**$19,995.82**	**6.07%**
	61886	Implant neurostim arrays			
0687	**Revision/Removal of Neurostimulator Electrodes**		**$1,496.15**	**$1,450.72**	**-3.04%**
	61880	Revise/remove neuroelectrode			
0688	**Revision/Removal of Neurostimulator Pulse Generator Receiver**		**$2,003.33**	**$2,177.51**	**8.69%**
	61888	Revise/remove neuroreceiver			