TEXAS NEUROLOGICAL SOCIETY WINTER 2018

Broca's Area

The Voice of Texas Neurology

A message from the President

What an eventful time we have had since I last wrote you.

Houston, in particular, has been through noteworthy highs and lows.

During one of the city's largest storms in its history, Houston suffered significant loss of life and property, but Houstonians showed the world what an amazingly resilient city we are. The people of Houston jumped into action to begin the process of rebuilding, recovering and healing. We were quickly surrounded by love and support from our friends and neighbors in Texas and beyond. The AAN was among those who raised funds to support those in need of assistance and we are truly grateful.

The Houston Astros gave us all reason to smile and to remember that above all, we are a team. We rallied together to heal our city and the Astros won the 2017 World Series. While the TNS represents all of Texas, I think it is fair to say, despite our uniqueness as Texans in medicine, we are a team.

TNS is a top-notch organization that provides continued education, opportunities for networking and collaboration while also supporting advocacy. This is an especially important branch of our efforts at the present moment. I would like to encourage our members to participate in advocacy work. We can make a difference for our patients and healthcare at large by speaking to our state representatives and making our voice heard.

During the regular 85th Texas Legislative session, thanks to a bill authored by Sen. Dawn Buckingham, MD (R-Lakeway), and sponsored by Rep. Greg Bonnen, MD (R-Friendswood), a new law will prevent the Texas Medical Board from using maintenance of certification (MOC) as a requirement for doctors to obtain or renew a medical license. This bill also prohibits hospitals and health plans from requiring physicians to obtain MOC for credentialing or contracts, although there will be a few exceptions. Thanks to our own Dr. Kim Monday for testifying on behalf of TNS and TMA in favor of this bill!

Another important win for us was the override of step therapy. This new law allows a physician to continue prescribing an effective medication even if an insurer's step therapy plan calls for a change.

I also encourage everyone to take advantage of continuing education. Thank you to Dr. Gina Jeter for an excellent educational and enjoyable summer conference at Hyatt Lost Pines. We are excited about the upcoming Winter Conference at the Hyatt in Austin led by Dr. Michael Soileau.

As my term as President winds down, I would like to thank

Erin Furr-Stimming, MD

my colleagues, past and present, on the TNS board who dedicate their time and efforts to keeping this society strong. I would also like to thank our consultants, Greg Herzog and Kristi Berrier, who have increased our awareness of legislative and socio-economic issues respectively. As always, a very special thank you to the one and only, Ky Camero. Ky is an outstanding Executive Director who works tirelessly to keep the TNS thriving.

As health care providers, we are a team. We work to promote and execute exceptional health care practices and patient outcomes. We are honored to have a spot on this team and we continue to always strive for the best.

I look forward to seeing all of you in February.

Sincerely,
Erin Furr Stimming, MD

We've gone digital!

OPEN THIS NEWSLETTER IN FIREFOX OR GOOGLE CHROME FOR THE BEST INTERACTIVE EXPERIENCE.

CONTENTS

Editor's Notes

Randolph W. Evans, MD

I thank our officers and other contributors for their excellent submissions to this issue. We look forward to seeing you at the 21st Annual TNS Winter Conference at the Hyatt Regency Austin. Michael Soileau, adult program director, Gary Clark, pediatric program director, Bob Fayle, education committee chair, and the education committee (Ed Fox, Aziz Shaibani, Katie Hendley, Mary Ellen Vanderlick, and Deborah Carver) have planned an excellent program.

MISOPHONIA ("HATRED OF SOUND")

Misophonia is an affective sound-processing disorder where strong negative emotions such as anger and anxiety are triggered by common sounds made by other people eating, drinking, chewing, and breathing. The prevalence is not known. Kumar et al (Kumar S, Tansley-Hancock O, Sedley W, et al. The Brain Basis for Misophonia. Curr Biol. 2017;27(4):527-533) performed a fMRI study of 20 misophonic and 22 controls finding that in misophonic subjects, trigger sounds caused hyperactivity of the left anterior insular cortex (AIC) which is a core hub of the salience network (first described by Greicius and Seeley in 2007) which select which stimuli are deserving of our attention (Menon V. (2015) Salience Network. In: Arthur W. Toga, editor. Brain Mapping: An Encyclopedic Reference, vol. 2, pp. 597-611. Academic Press: Elsevier). There was an abnormal functional connectivity of the AIC with a network of regions responsible for the processing and regulation of emotions including the ventromedial prefrontal cortex, posteromedial cortex (posterior cingulate and retrosplenial cortex), hippocampus, and amygdala.

MIRACLE CURE

If you have any interest in the history of medicine, I strongly recommend that you read William Rosen's brilliant and captivating book, "Miracle Cure. The Creation of Antibiotics and the Birth of Modern Medicine" (Viking, 2017, 358 pages; available on Amazon for as little as $7.99). Benjamin Rush's use of mercury for yellow fever in 1793 to Pasteur, Koch, Erhlich and the development of antibiotics in the 20th century including the early days of drug advertising. Will preview a few of the numerous fascinating stories.

SULFANILAMIDE AND THE 1938 FDA ACT

Sulfanilamide had been identified in 1908 and as an experimental drug and became instantly famous when it cured the President's son, FDR, Jr., of a near fatal strep infection in 1936. Although tablets were available, many patients preferred a liquid but sulfinilamide was poorly soluble. The SE Massengil company marketed their Elixir Sulfanilamide in 1937 using diethylene glycol as a solvent killing 71 adults and 34 children. The FDA (launched in 1906 as the Bureau of Chemistry and became the FDA in 1930) dealt with truth in claims but not safety. Samuel Massengill was prosecuted for mislabeling their product as an elixir which was required to contain alcohol which it did not and paid a fine of $26,100. Killing users of the drug was not illegal. The 1938 Federal Food, Drug, and Cosmetic Act was the result which required an application before marketing, required proof of safety, and listing of all ingredients.

FRANCES OLDHAM KELSEY, THALIDOMIDE, AND THE 1962 KEFAUVER-HARRIS AMENDMENTS

In 1960, Frances Oldham Kelsey, PhD, MD joined the FDA as a full time drug reviewer. Her first assignment was an application for thalidomide which had become extremely popular for use in Europe as a sedative safer than barbiturates and as an antiemetic especially useful during pregnancy and was available without prescription in Germany. She persistently asked for clinical and animal safety information which was not provided. By the time the drug was removed from sale at the end of 1961, over 10,000 infants were born to mothers who took thalidomide with phocomelia (grossly underdeveloped or absent limbs). Thanks to Dr. Kelsey's persistence, fewer than 30 were born in the United States whose mothers had received thalidomide in an investigational use trial (distributing more than 2.5 million pills to more than 1000 doctors) prior to FDA approval.

In 1962, the "Washington Post" published a front page story with the headline: "Heroine of FDA keeps bad drug off market." In 1962, the Kefauver-Harris Amendments were passed by Congress and signed into law by President Kennedy with Dr. Kelsey standing behind him (figure 1). The amendments required that the FDA specifically approve the marketing application, establish rules of investigation of new drugs including a requirement for the informed consent of study subjects, required reporting of adverse events, rate every drug introduced between 1938-1963 for effectiveness, and transferred the regulation of prescription drug advertising from the FTC to the FDA.

BRADFORD HILL, STREPTOMYCIN, AND RCTS

Statistician Sir Austin Bradford Hill (also known for his 1965 Hill's criteria for causation and for establishing the link between smoking and lung cancer with Doll; figure 2) pioneered the use of the first randomized controlled trial studying streptomycin for tuberculosis in 1947 in London. This trial showed less mortality for streptomycin at 6 months but about equal mortality at 3 years due to drug resistance. This led to a second RCT with the addition of PAS to streptomycin which had an amazing 80% three-year survival rate.

← BACK TO PAGE 1
NEXT PAGE →

DR. KELSEY AND THE BIRTH OF MODERN DRUG TRIALS IN 1963

Almost 10 years later, almost 50% of clinical trials in the U.S. and Britain did not have control groups. In 1963, Dr. Kelsey first proposed radical changes to new drug applications requiring phase 1, phase 2, and phase 3 trials before approval. Double blinded randomization with experimental and control arms became a de facto requirement. Before any human testing was begun, applicants for new drugs would have to guarantee that an independent committee at each institution would certify that the study was likely to have more benefits than risks, that any distress for experimental subjects would be minimized, and that all participants gave informed consent.

Figure 1. After signing the Kefauver-Harris Drug Amendments on October 10, 1962, President Kennedy presents his pen to Dr. Frances Kelsey (1914-2015).

CHLORAMPHENICOL AND APLASTIC ANEMIA

Parke-Davis' chloramphenicol was approved by the FDA in 1949 as safe and effective. (Parke Davis also launched Dilantin in 1953 and Neurontin in 1993). By 1951, chloramphenicol accounted for more than 36% of the total broad-spectrum antibiotic usage. By 1952, more than four million people had been given the drug with ostensibly no side effects. In 1952, numerous cases of aplastic anemia were reported . In 1953, the FDA issued a warning about the risk of aplastic anemia and sales decreased.

Parke-Davis aggressively utilized pharmacy sales reps (who they required to be phamacists) or detail men (the term was first used in the 1920s) and sales recovered. The president of Parke-Davis, Harry Loynd told his detail men at a sales meeting, "If we put horse manure in a capsule, we could sell it to 95 percent of these doctors." The FDA was outraged by the detailing and required warning labels advising physicians to use the drug only when utterly necessary. Prescriptions for colds, bronchial infections, gout, eczema, acne, UTIs, malaise, and iron deficiency anemia continued. In 1959, the first reports of gray baby syndrome appeared. After his daughter died from aplastic anemia prescribed for a sore throat, the prominent newspaper publisher, Edgar Elstrom, started a media crusade against chloramphenicol. The usage of the drug greatly declined. The chloramphenicol episode is largely remembered as a fable of lost innocence (the miracle of antibiotics came at a profound cost) or as a morality tale of greedy pharmaceutical companies, negligent physicians, and impotent regulators.

However, the real underlying subtext is appreciating risk vs benefit and appropriateness of use. Aplastic anemia developed in 1 in 20,000 patients who took chloramphenicol (due to inhibition of mitochondria) but 1 in 50,000 patients who took penicillin died from anaphylaxis. Chloramphenicol is now used in the U.S. for only life-threatening infection when a suitable safer antibiotic is not available but is widely used in developing countries. We face similar challenges with the safe use of many drugs in neurology including carbamazepine which has a risk of SJS/TEN of 1.4 cases/10,000 and fatal aplastic anemia in slightly under one in 50,000 (Verrotti A, Scaparrotta A, Grosso S, et al. Anticonvulsant drugs and hematological disease. Neurol Sci. 2014;35(7):983-93).

As a personal aside, I had a cousin who died in 1961 after developing aplastic anemia from chloramphenicol given to him at summer camp for a URI.

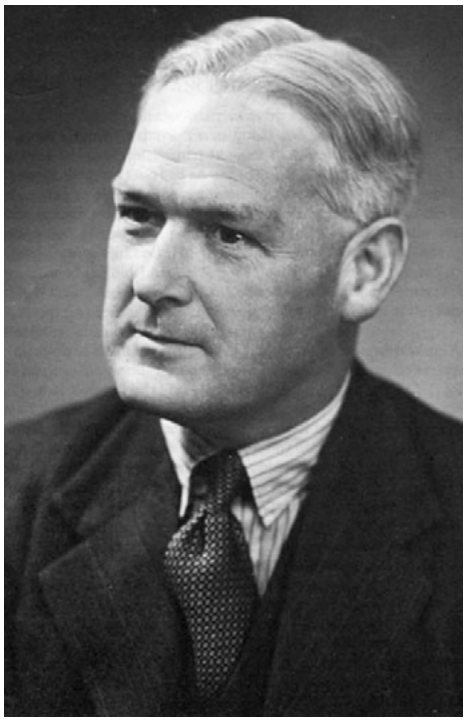


Figure 2. Austin Bradford Hill (1897-1991)

← BACK TO PAGE 1
NEXT PAGE →

Legislative and Public Policy

Sara Austin, MD, TNS Legislative Chair
Greg Herzog, TNS Lobbyist

As we look back on the 2017 Texas Legislative Session and look forward to 2018 and the 86th Legislature it is clear that TNS had a several successes and we face many challenges.

TNS was a leader on two bills last session that were priorities to our members. First, reforming the Maintenance of Certification (MOC) requirements bill, SB 1148, has been signed into law and went into effect January 1, 2018. This bill prohibits the weaponization of the MOC by Insurers, Hospital systems, and the Medical Board. Specifically, the bill prohibits third-party payers from using the MOC as a condition for credentialing, the bill prohibits the Texas Medical Board (TMB) requiring the MOC as a condition of licensure, and the bill prohibits hospitals from requiring MOC as a condition for privileges unless the facilities physician staff has voted in favor of that policy. Your Board is proud of its work on this issue and more importantly recognizes that this issue developed as a groundswell from within our membership.

TNS was also very active in passing SB 680 which reforms the practice by insurance company middlemen known as Step Therapy. This practice places barriers between you and your patients with regard to the pharmaceuticals you can prescribe to your patients. This law will provide transparency and due process into that practice. Specifically, the bill shortens the time insurance company has to respond to your request for an override step-therapy decision from 53 days to 3 days. Additionally, the bill prohibits a health plan from requiring a patient to re-enter a step therapy protocol in the event that the patient's insurance coverage changes. Our hope is that bill brings commonsense reforms to this practice and prevents insurance companies from making your prescription pad a 'suggestion pad'!

Looking forward to the coming year and next session, Hurricane Harvey has already changed the dialog in Austin. Moreover, the fiscal impacts to the state budget will be significant. Budget experts are already forecasting a bleak outlook. Some were already forecasting a $7.9 Billion dollars shortfall for Texas, before Hurricane Harvey! Those of us who practice in academic medical settings or provide services to a Medicaid population need to be aware of the potential for reduced state monies. This will be a very tight budget.

Additionally, the Texas Legislature is already studying issues for next session. Included on the list of items is the seemingly perineal issue of Balanced Billing AKA "surprise medical bills". This issue could directly impact how we are reimbursed for services provided to out-of-network patients. Obviously, this issue would impact all physicians and we will stand with TMA and others to protect our ability to be paid for services to out-of-network patients. The legislature will be reviewing a variety of issues this interim and TNS will be tracking any impacts to our specialty and our patients.

This election cycle will be very intense and dynamic. You Board strongly encourages you to engage your local elected officials and candidates for office. These people will craft the policies that impact your practice and your patients. As physicians, we are the best advocates for our patients and that includes public policy.

Thank you to our 2017 TNS Summer Conference Supporters

GOLD

Sunovion
UCB

SILVER

GE Healthcare
HealthSouth Rehabilitation Hospitals
Lilly, USA, LLC
Merz North America-Xeomin

BRONZE

Liva Nova
Silverado Memory Care

← BACK TO PAGE 1
NEXT PAGE →

Medical Economics–Axon Registry Discussed at Winter Conference

Stuart B. Black, MD, FAAN, Medical Economics Chair

The TNS is pleased to sponsor an important Medical Economics Breakfast Symposium as a feature of the Texas Neurological Society February 2-4, 2018 Seminar held at the Hyatt Regency, Austin. The Sunday Morning February 4 Breakfast will take place from 6:45 AM-8 AM. The guest speaker will be Dr. Lyell K. Jones, Jr., MD. Dr. Jones is a Consultant and Associate Professor of Neurology at the Mayo Clinic in Rochester, MN. In addition to his multiple clinical and academic accomplishments, Dr. Jones is a former Medical Director for the Mayo Clinic Office of Patient Experience and current Chair of Payment Model Operations at Mayo. He has been the program director of the Mayo Clinic-Rochester Adult Neurology Residency Program and also serves on numerous influential American Academy of Neurology committees including AAN Payment Alternatives Team, the AANEM Quality Committee and the AAN Medical Economics and Management Committee. Dr. Jones is also the Chair of the AAN Registry Committee, Axon.

The AAN Axon Registry is a clinical data registry focused on quality improvement and providing physicians with the tools they need to thrive in an era of evolving value-based care models. The most important national registries are the Quality Clinical Data Registries (QCDR) which are approved by the Centers for Medicare & Medicaid Services (CMS). In 2017 CMS approved the AAN Axon Registry as a QCDR. The QCDR designation not only helps neurologists meet Federal regulatory reporting and accountability requirements, but includes neurology-specific quality measures. Most national current quality measures that affect payment are designed to reflect primary care practices. As neurologists have learned, few of those measures are relevant to neurology. The Axon Registry provides neurology with measures that matter to neurologists; measures that are patient-centered, giving neurologists the necessary tools to measure and record quality care data in a clinically meaningful fashion. The Axon Registry is also approved by the American Board of Psychiatry and Neurology as a Maintenance of Certification Part IV Improvement in Medical Practice Clinical Module.

The benefits to neurologists participating in the Axon Registry are substantial. Currently participation in the Registry is without additional charge to AAN members. Not only does participation in the Registry provide neurologists with an unprecedented tool to assess the quality of care and to improve the care to our patients, but the Registry will also help satisfy many of the regulatory payment requirements from CMS, including those outlined in the Medicare Access and CHIP Reauthorization Act of 2015, MACRA. As the Merit-Based Incentive Payment System (MIPS) along with other Federal payment mandates replace PQRS, Meaningful Use (renamed Advancing Care Information) and the Value-Based Modifier, the Registry will help neurologists meet the various MACRA reporting requirements. Participation in Axon is of extreme benefit not only to small neurology practices, but also to large practices as well as academic practices. In addition, while the current emphasis is on Federal reimbursement programs, increasingly private payors are also requiring demonstration of quality metrics. As the entire health care system shifts its focus to a value based model, the neurologist will be mandated more and more to demonstrate and document quality outcomes within a cost-efficient environment. Participation in the Axon Registry's large database will provide neurologists the necessary data needed to demonstrate quality related to utilization and costs.

Dr. Lyell Jones in not only the AAN Chair of Axon, but is one of the most knowledgeable physicians/neurologists regarding the current medical economic environment. By the end of this special TNS Medical Economics Breakfast Symposium, participants should:

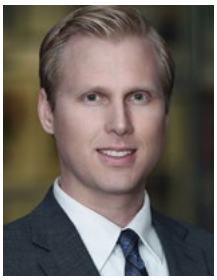
Guest speaker, Dr. Lyell K. Jones, Jr., MD

1. Have an overview of the rational, structure, and function of the AAN Axon Registry
2. Understand the upcoming major milestones in the development of the AAN Axon Registry
3. Better comprehend the utility of QCDR's for neurology practices, focusing on regulatory and economic benefits

To learn more about the AAN Axon Registry, TNS members are strongly encouraged to attend this very important and informative Medical Economics Breakfast Symposium on Sunday morning Feb. 4, 2018. The Axon Registry is an unprecedented program available to AAN members. It is predicted to be not only an indispensable tool toward helping neurologists provide the best possible care and outcomes for their patients but also, as a secondary benefit. to provide the vehicle necessary to assist neurologists toward satisfying the many regulatory requirements and mandates from CMS and private carriers.

← BACK TO PAGE 1

NEXT PAGE →



Advances in Endovascular Treatment of Cerebral Aneurysms

Jeremiah Johnson, MD, Assistant Professor,
Dept. of Neurosurgery, Baylor College of Medicine

Over the past 50 years, technology advances have driven rapid improvements in medical diagnosis and treatments. Taking advantage of leaps in material science, manufacturing capabilities and evolving radiology imaging capabilities, in 1964 the discipline of interventional radiology was founded with the stated goal of providing more minimally invasive treatments for vascular pathologies. The first catheterization of an intracranial vessel is credited to Luessenhop and Velasquez in 1964.1 However, it wasn't until the late 1960s that Serbinenko began the era of neurointervention using handmade detachable balloons inserted into the cervical carotid artery and floated intracranially to treat direct cavernous carotid fistulas and giant aneurysms (Fig. 1).2 In the mid-1980s, advances in flexible microcatheters and microwires ushered in the modern era of neurointervention by allowing direct endovascular access to intracranial vessels3. The first highly effective endovascular treatment of intracranial aneurysms was the detachable coil developed by the Italian neurosurgeon Guglielmi and first used clinically at UCLA in 1990 (Fig. 2).3 Since that time, endovascular treatments of brain aneurysms have advanced and there are many new tools allowing safe effective treatment intracranial aneurysms. Furthermore, new technologies are now allowing for the safe and effective obliteration of certain difficult cerebral aneurysm that were not previously treatable and as the population ages, is providing treatment options for older patients who would otherwise not be wise clipping candidates.

The 2000s saw a great leap in endovascular aneurysm treatment with the advent of intracranial balloon assisted coiling and the advent of flexible intracranial stents designed specifically to aid the coiling of wide necked aneurysms (Fig. 3). These tools jettisoned endovascular strategies to the forefront of aneurysm treatment and remain relevant and widely used part of the neuroendovascular armamentarium. However, in the past 5 years, powerful new endovascular aneurysm treatment modalities have emerged and several promising new treatment concepts are in the final stages of clinical data gathering. Although very important iterative advances have been made in catheter and coil technology, this article focuses on new endovascular treatment concepts within the past 5 years and devices in the late stages of clinical testing.

FLOW DIVERSION

Flow-diverting stents were first available in the United States when the Pipeline stent (Medtronic) was approved by the FDA in 2012. These stents have a higher metal surface area (30-35%) and decreased porosity compared with standard intracranial stents (6-9%); thus once placed in the parent vessel across the aneurysm neck, the flow-diverting stent directs intra-arterial flow away from the aneurysm sac while maintain parent vessel patency and importantly, also maintaining the patency of nearby sidewall artery branches covered by the stent (Fig. 4, 5). Over the course of months, the stents luminal metal surface area is covered with an endothelial layer, the aneurysm dome collapses and the parent vessel is completely remodeled.4 Flow-diversion has transformed the treatment of giant ICA aneurysms that were previously considered uncoilable and were traditionally treated with a relatively complex parent vessel sacrifice and high flow arterial extracranial to intracranial bypass surgery. The long-term effectiveness of flow-diversion treatment was recently reported in the 5-year follow-up of the initial Pipeline for Uncoilable or Failed Aneurysms trial that showed complete occlusion in 95% of treated aneurysms, and once occluded, there were no regrowths5. A recent prospective trial also showed safety and efficacy in smaller aneurysms. These devices have proven safe and effective for treating wide necked aneurysms of all sizes and complexity levels, but one drawback to these devices is the 2-5% risk of thromboembolic and hemorrhagic complications. Secondary to the high intraluminal metal surface area, patients treated with these devices require strict dual-antiplatelet regimens for 3-6 months after surgery and this also makes the use of this device for the treatment of acute ruptured aneurysms inadvisable. To address these issues, a new Pipeline version with phosphorylcholine coating called Pipeline Shield has been developed to decrease stent metal thrombogenicity and allow treatment without or with reduced antiplatelet requirements. Patients are currently being entered in an international, multicenter observational cohort trial to assess this device. Additionally, other novel flow diversion devices are being developed, most notably the Surpass

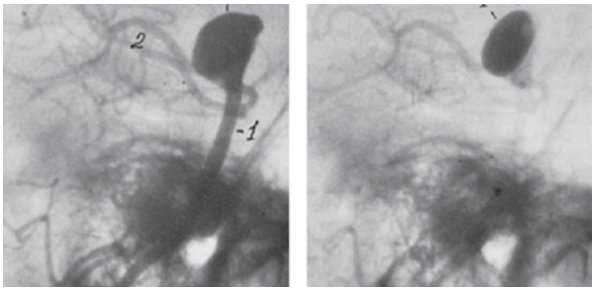


Fig. 1

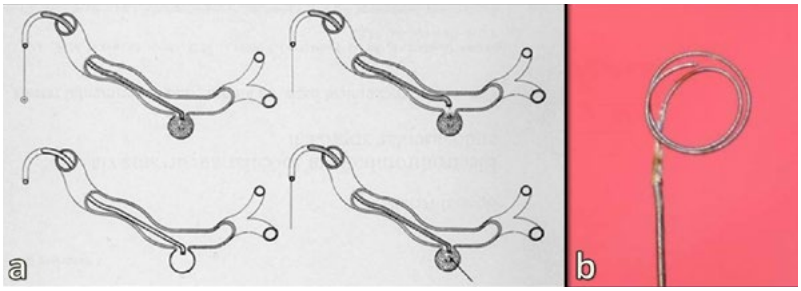


Fig. 2

← BACK TO PAGE 1
NEXT PAGE →

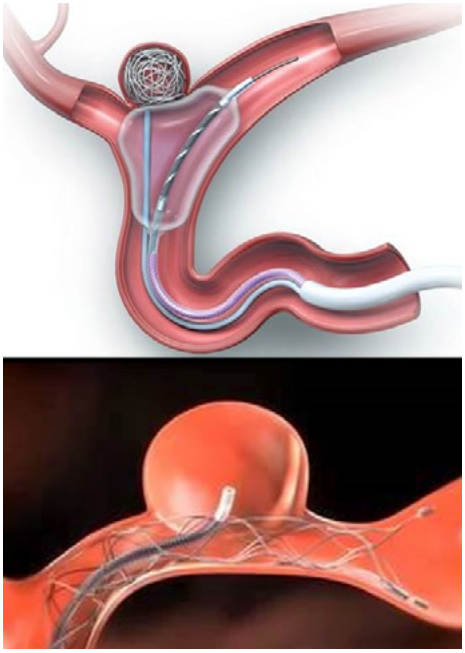


Fig. 3

device (Stryker) which is currently being tested in clinical trials.

BIFURCATION ANEURYSM COILING SUPPORT DEVICES

With the advent of stent-coiling and further advanced with flow-diversion, even the most challenging artery sidewall aneurysms can be effectively treated with endovascular methods. However, treating intracranial artery bifurcation aneurysms that have wide necks remains a challenge with current endovascular technology. However, new coiling support devices such as the PulseRider (Codman Neuro) and pCONus (phenox GmbH) and Barrel Stent (Medtronic) devices are entering the market with the design goal to improve the efficacy of coiling aneurysms at bifurcations by providing a scaffold to hold the coils in the aneurysm dome and protect the parent vessel (Fig. 6). Early experiences published thus far have been encouraging,6-7 and the PulseRider device has recently been approved for use in the United States.

INTRASACCULAR DEVICES

Another treatment paradigm entering the endovascular aneurysm space is the placement of intra-aneurysmal flow diverters. These devices have flow diversion properties, but in contrast to flow diverting stents, they are placed solely within the aneurysm. They are designed with a globular shape, are composed of a braided wire mesh providing 35%-45% neck metal coverage and a "stent-like" adherence to the inner walls of the aneurysm. These devices can be placed in vessel sidewall aneurysms or bifurcation aneurysms and hold nicely inside many wide-necked aneurysms. Since the device is contained completely within the aneurysm lumen, it has all the properties and advantages of flow diverting stents but without the thromboembolic risk; therefore, they can safely be used to treat ruptured aneurysms. Intrasaccular flow diversion devices currently being studied include, the Woven Endobridge or WEB (Sequent Medical, Inc.), Artisse (Medtronic) and Medina devices (Medtronic) (Fig. 7). Thus far, the most robust clinical data is available for the WEB device. In a recent systematic review and meta-analysis of 558 aneurysms treated with the WEB device (22% ruptured), the authors reported an 85% complete occlusion rate at 7 months which compared favorably for angiographic outcomes and complication rates with stent coiling.8-11 The WEB device is widely used in Europe and data is being collected for US approval.

CONCLUSION

Endovascular cerebral aneurysm treatment continues to benefit from rapid innovation. Novel devices and treatment strategies have greatly expanded the number and types of aneurysms that can be treated by endovascular means. While some aneurysms still are most appropriately treated with open surgical clipping, the advancing technologies available to neurointerventional surgeons is rendering aneurysms without excellent endovascular options ever less common.

REFERENCES

Luessenhop AJ, Velasquez AC. Observations on the tolerance of the intracranial arteries to catheterization. J Neurosurg. 1964;21:85-91.

Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974;41:125-145

Guglielmi G. History of Endovascular Endosaccular Occlusion of Brain Aneurysms: 1965-1990. Interventional Neuroradiology. 2007;13(3):217-224.Liou TM, Li YC. Effects of stent porosity on hemodynamics in a sidewall aneurysm model. J Biomech. 2008;41:1174-1183.

Liou TM, Li YC. Effects of stent porosity on hemodynamics in a sidewall aneurysm model. J Biomech. 2008;41:1174-1183.

Becske T, Potts MB, Shapiro M, et al. Pipeline for uncoilable or failed aneurysms: 3-year follow-up results [published online October 14, 2016]. J Neurosurg.

Bartolini B, Blanc R, Pistocchi S, et al. "Y" and "X" stent-assisted coiling of complex and wide-neck intracranial bifurcation aneurysms. AJNR Am J Neuroradiol. 2014;35:2153-2158.

Mukherjee S, Chandran A, Gopinathan A, et al. PulseRider-assisted treatment of wide-necked intracranial bifurcation aneurysms: safety and feasibility study [published online September 30, 2016]. J Neurosurg.

Asnafi S, Rouchaud A, Pierot L, et al. Efficacy and safety of the Woven EndoBridge (WEB) device for the treatment of intracranial aneurysms: a systematic review and meta-analysis [published online August 11, 2016]. AJNR Am J Neuroradiol.

Feng MT, Wen WL, Feng ZZ, et al. Endovascular embolization of intracranial aneurysms: to use stent(s) or not? Systematic review and meta-analysis. World Neurosurg. 2016;93:271-278.

Phan K, Huo YR, Jia F, et al. Meta-analysis of stent-assisted coiling versus coiling-only for the treatment of intracranial aneurysms. J Clin Neurosci. 2016;31:15-22.

Zhao B, Yin R, Lanzino G, et al. Endovascular coiling of wide-neck and wide-neck bifurcation aneurysms: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2016;37:1700-1705.

FIGURES LEGEND:

Figure 1. Lateral angiographic view of a basilar top aneurysm Pre (left) and Post (right) deployment of a detachable balloon into the aneurysm by Serbinenko.

Figure 2. Original illustration (a) of trans-catheter deployment of an original GDC aneurysm coil into an aneurysm. J Neurosurgery 75: 1-7, 1991. (b) an original GDC coil.

Figure 3. Illustration of balloon assisted aneurysm coiling (top) and stent-assisted aneurysm coiling (bottom).

Figure 4. Photograph of a standard intracranial stent (left) vs a Pipeline flow diverting stent (right) illustrating the difference in the stent porosity.

Figure 5. Giant, tri-lobed left ICA cavernous segment aneurysm pre-treatment (a) AP and (b) lateral angiographic views. Six months post-treatment with pipeline flow diverting stent shows complete obliteration of the aneurysm on (c) AP and (b) lateral views.

Figure 6. Illustrations of bifurcation aneurysm coiling support devices (a) pCONus (b) PulseRider and (c) Barrel stent.

Figure 7. Images of the Artisse (left) and WEB (right) intrasaccular embolization devices.

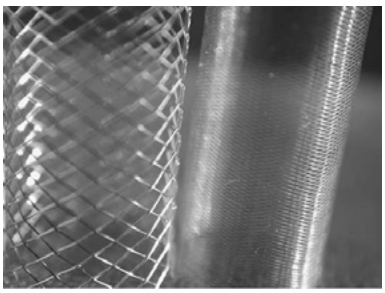


Fig. 4

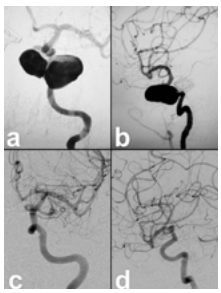


Fig. 5

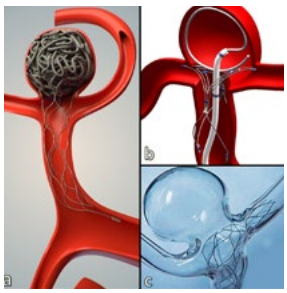


Fig. 6

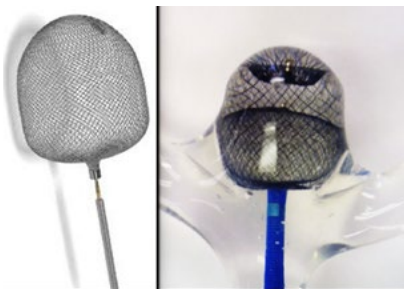


Fig. 7

← BACK TO PAGE 1
NEXT PAGE →

Lamotrigine Toxicity Causing Psychosis and Suicidal Ideation

Nancy Kuo, MD PGY3
Kent Ellington, MD
University of Texas Dell Medical School, Department of Neurology

INTRODUCTION

Lamotrigine is a commonly used medication for the treatment of epilepsy. Psychosis due to lamotrigine toxicity has been reported only twice before in the literature 1,2. In this case report, we describe an epileptic patient who developed visual hallucinations, confusion, and suicidal ideation due to an elevated lamotrigine level.

CASE REPORT

A 46-year-old male with a past medical history of right mesial temporal sclerosis and complex partial epilepsy since childhood was being treated on an outpatient basis. He had incomplete seizure control on levetiracetam and lamotrigine, so valproic acid was added to his regimen.

One week later, he developed confusion and visual hallucinations. He presented to the emergency department after he tried to grab a television that he saw floating in the air and then exhibited aggressiveness, cursing, and screaming when his family intervened. On initial assessment in the hospital, he appeared calm but stated that he saw lines in his vision, of which he could not provide further details. His neurological and physical exam was grossly normal. He was alert and oriented to time, place, and person. He did not exhibit any cranial nerve deficits and his strength, sensation, coordination, and gait were intact.

Routine EEG showed no epileptiform activity. A psychiatric consultation did not find a psychiatric cause for his behavior. His laboratory studies included a lamotrigine level, which was elevated at 15.6 (2.5-15.0), with a therapeutic valproic acid level of 55 (50-100) and levetiracetam level of 30 (12-46).

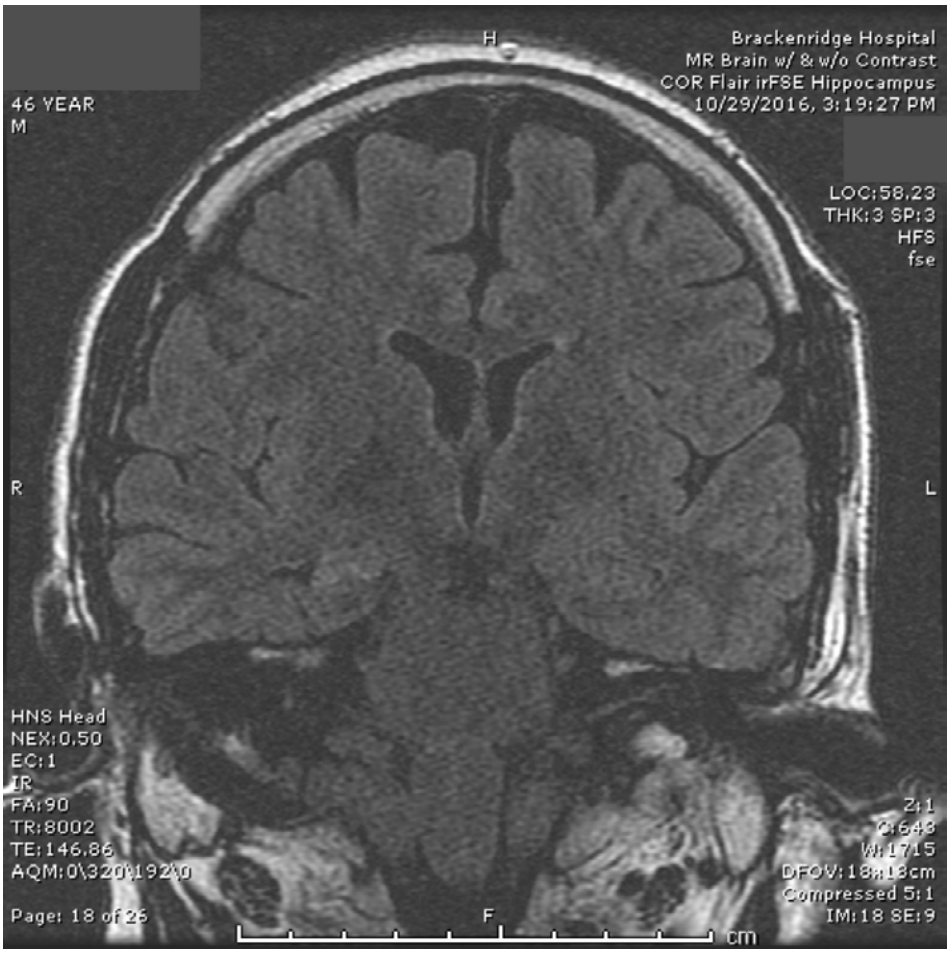


Figure 1. MRI brain, T2 FLAIR imaging. Subtle area of increased T2 signal within the right hippocampus. The right hippocampus is also smaller than the left. These two findings raise the possibility of right mesial temporal sclerosis.

His valproic acid was discontinued as it can increase lamotrigine levels. Ancillary testing including CSF studies were negative for West Nile virus, NDMA receptor antibody, HSV, VZV, and enterovirus.

His psychosis improved and he was started on zonisamide for seizure control in combination with his levetiracetam and lamotrigine.

Three days after discharge, the patient returned to the emergency department again with complaints of suicidal ideation. Once again, his lamotrigine level was drawn, which was elevated at 19.5. He was observed in the hospital and his lamotrigine dose was decreased by half. Zonisamide was discontinued per the family's request. His symptoms resolved 4 days later and his repeat lamotrigine level on the day of discharge was normal at 9.7.

DISCUSSION

Multiple drug regimen therapy is common in the treatment of seizures. Side effects may occur from interactions between antiepileptic drugs, and unusual side effects may be from drug toxicity.

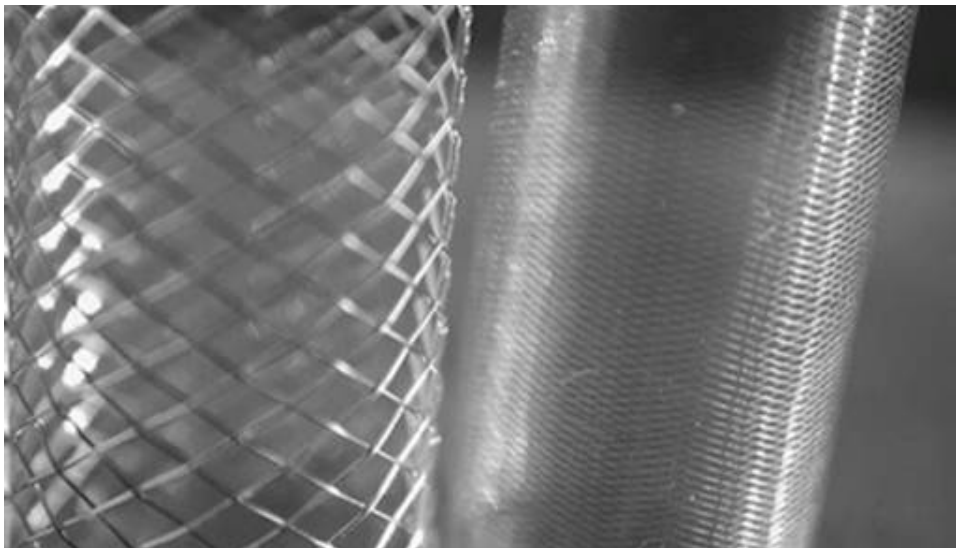
REFERENCES

1. Christian Brandt, Nora Fueratsch, Volker Boehme, Corinna Kramme, Maria Pieridou, Antonia Villagran, Friedrich Woermann, Bernd Pohlmann-Eden. Development of psychosis in patients with epilepsy treated with lamotrigine: Report of six cases and review of the literature. Epilepsy & Behavior. 2007;11:133-139.
2. Elisabetta Patorno, Rhonda L. Bohn, Peter M. Wahl, et al. Anticonvulsant Medications and the Risk of Suicide, Attempted Suicide, or Violent Death. JAMA. 2010;303(14):1401-1409.

← BACK TO PAGE 1
NEXT PAGE →

Recent happenings in neuro cognition and neural networks

Padma Kumar, MD and Yashwanth Garikiparthy



This is a brief article summarizing the happenings in the field of neural cognition and the neural networks, for the clinician.

Many questions arise in the field of cognition and the neural networks and the clinicians are not in the loo ,with advances made in these fields.

A brief synopsis is presented of selected papers to familiarize clinicians on the new thoughts in these fields.

Machine learning seems to be the main mechanism in the visual cortex, when f MRI was used and the extra striate body area seems to be the area which has a prominent role1.

Brain computation seems to be simpler in neuromudulatory neurons such as the dopaminergic neurons using simple logic in computation. A computational model in a clique of neurons called functional connectivity motif is the basis and a power of two is used as a computational logic in most of the 86 billion neurons2.

The synaptic network contains an abundance of cliques of neurons bound into cavities that guide the emergence of correlated activity. In response to stimuli, correlated activity binds synaptically connected neurons into functional cliques and cavities that evolve in a stereotypical sequence toward peak complexity. reconstructions consistently contained directed simplices of dimensions up to 6 or 7, with as many as 80 million directed 3-simplices 9(Dimensions in algebraic term). This is the first indication of the existence of such a vast number of high-dimensional directed simplices in neocortical microcircuitry, or in any neural network3.

The fact that each neuron belongs to many directed cliques of various dimensions explains in vivo observations that neurons can "flexibly join multiple ensembles". Braids of directed simplices connected along their appropriate faces could possibly act as synfire chains with a superposition of chains supported by the high number of cliques each neuron belongs to.

A stimulus may be processed by binding neurons into cliques of increasingly higher dimension, as a specific class of cell assemblies, possibly to represent features of the stimulus and by binding these cliques into cavities of increasing complexity, possibly to represent the associations between the features.

The above papers are dwelling into the complex neural architecture and complex neurophysiology which can be demonstrated by classical physics.

The other paper by fisher et al stands out in the fact of using quantum cognition.

Phosphorus is identified as the unique biological element with a nuclear spin that can serve as a qubit for such putative quantum processing - a neural qubit - while the phosphate ion is the only possible qubit-transporter. "Posner molecule", Ca9(PO4)6, has been identified as the unique molecule that can protect the neural qubits on very long times and thereby serve as a (working) quantum-memory. A central requirement for quantum-processing is quantum entanglement. It is argued that the enzyme catalyzed chemical reaction which breaks a pyrophosphate ion into two phosphate ions can quantum entangle pairs of qubits. Posner molecules, formed by binding such phosphate pairs with extracellular calcium ions, will inherit the nuclear spin entanglement. A mechanism for transporting Posner molecules into presynaptic neurons during a "kiss and run" exocytosis, which releases neurotransmitters into the synaptic cleft, is proposed. Quantum measurements can occur when a pair of Posner molecules chemically bind and subsequently melt, releasing a shower of intra-cellular calcium ions that can trigger further neurotransmitter release and enhance the probability of post-synaptic neuron firing.

Multiple entangled Posner molecules, triggering non-local quantum correlations of neuron firing rates, ca also be theorized as useful not only in the presynaptic area bot also in the cliques and as well as in the cavities. This might help in faster computing especially in processes involving critical or creative thinking.

REFERENCES:

Synced.In-Depth AI Technology & Industry Review www.synced-review.com | www.jiqizhixin.comJul 3.Using Human Brain Activity to Guide Machine Learning

2. Front. Syst. Neurosci., 15 November 2016 | https://doi.org/10.3389/fnsys.2016.000. Brain Computation Is Organized via Power-of-Two-Based Permutation LogicKun Xie1,2†, Grace E. etal

3. Front. Comput. Neurosci., 12 June 2017 | https://doi.org/10.3389/fncom.2017.00048Cliques of Neurons Bound into Cavities Provide a Missing Link between Structure and Function. Michael W. Reimann1†, Max Nolte1]

4. Fisher,Mathew. Neurons and Cognition (q-bio.NC); Biological Physics (physics.bio-ph); Quantum Physics (quant-ph). Journal reference: Annals of Physics 362, 593-602 (2015)

← BACK TO PAGE 1
NEXT PAGE →

Monoclonal Antibody Therapies in Multiple Sclerosis

Edward J. Fox, MD PhD
Director, MS Clinic of Central Texas
Central Texas Neurology Consultants, PA

INTRODUCTION TO MONOCLONAL ANTIBODIES

Monoclonal antibodies have been utilized in the therapy of a number of disease states, most notably neoplastic and autoimmune disorders. Based on the concept of the "magic bullet" proposed by Paul Ehlich a century ago, this form of therapy is designed as a very specific targeted attack against a given antigen. It was recognized that the B-cell cancer multiple myeloma may produce a monoclonal population of antibodies, but cellular manipulation was required in order to produce antibodies against a desired target. Transforming B-cells with Epstein-Barr Virus can sometimes lead to the production of a monoclonal antibody, but the most common technique now used is to fuse myeloma cells with splenic cells of mice that have been immunized with a particular protein. Hybridoma cells are then screened for antibody production against the desired antigen.

The nomenclature of monoclonal antibodies used in disease therapy is based on the origin of antibody proteins. Using genetic manipulation, antibodies can be chimeric, with approximately 2/3 of the structure being human, and the other 1/3 from the variable region of the murine antibody. Even greater genetic manipulation leads to humanized antibodies, which have greater than 90% human sequencing. Purely human monoclonal antibodies, although less likely to induce a neutralizing antibody, are much harder to produce. The generic name of a monoclonal antibody product will have the ending ximab if chimeric, such as rituximab, and will end with zumab if humanized, as in alemtuzumab and natalizumab. Fully human antibodies end in mumab, as in ofatumumab and zanolimumab.

MECHANISM OF ACTION OF MONOCLONAL ANTIBODIES

When monoclonal antibodies are targeted against an antigen located on a cell membrane surface, the result can be cellular death. Monoclonal antibodies can work by a number of mechanisms: compliment-mediated cytotoxicity, antibody-dependent cellular toxicity (ADCC), and phagocytosis of the bound cell. For any particular antibody product, its mechanism of action will be based primarily on its subgroup of antibody. IgG1 and IgG3 bind complement effectively, and also participate in ADCC and phagocytosis to a greater degree than IgG2 and IgG4. Monoclonal antibodies can also bind to antigen and block its biological effect.

MONOCLONAL AB USE IN MS

Available injectable and oral medications used for the treatment of multiple sclerosis have shown partial efficacy in the prevention of relapses and progression of disability. Safety, tolerability and efficacy limitations have also been noted, giving each of the products a unique risk:benefit profile. Development of newer therapies has led to a number of MoAb used in the treatment of relapsing MS, and the recent addition of treatment for primary progressive MS as well. The use of MoAb in the treatment of MS has allowed for less frequent dosing schedules, and various treatments have also explored the possibility of subcutaneous dosing rather than intravenous administration, also a potential benefit for those patients with poor access to infusion facilities.

Edward J. Fox, MD PhD

The initial MoAb developed for the treatment of MS was natalizumab, which acts as a selective adhesion molecule (SAM) inhibitor1. Natalizumab, a recombinant humanized antibody, binds to α4ß1-integrin and blocks its interaction with VCAM-1. As a result, leukocyte migration into brain tissue is inhibited, thereby reducing inflammation and preventing the formation of lesions2. Natalizumab may also inhibit ongoing CNS inflammation, mediated by leukocytes already present in the CNS, by interrupting the interactions between α4-integrin-expressing leukocytes and extracellular matrix proteins such as fibronectin and osteopontin3. Through these pathways, the inflammatory changes in MS are altered and prevented, leading to reduced disease activity that is seen throughout the course of treatment.

← BACK TO PAGE 1
NEXT PAGE →

Alemtuzumab was previously approved as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL), later approved as an agent generally used third-line for relapsing forms of MS. Alemtuzumab is a humanized monoclonal antibody (IgG1 subtype) directed against CD52, one of several specific antigens expressed during the leukocyte differentiation cascade and expressed in the cell membrane. In humans, CD52 is predominantly expressed on peripheral blood lymphocytes, monocytes, and macrophages4. Consequently, by binding to CD52, alemtuzumab is able to trigger targeted lysis of some or all of these cell types. Alemtuzumab acts by causing cell lysis through both complement fixation as well as antibody-mediated cytotoxicity (ADCC). It is the selective depletion of these cellular components and the sequential pattern of reconstitution of the lymphocyte population that is believed to mediate the durable reduction of clinical and radiographic activity in MS.

Daclizumab was approved in 2016 as an agent typically used third-line for relapsing MS. Daclizumab functions as an IL-2 receptor antagonist that binds with high-affinity to the Tac subunit of the high-affinity IL-2 receptor complex and inhibits IL-2 binding. Daclizumab binding is highly specific for Tac, which is expressed on activated, but not resting lymphocytes5. Prior to its approval for the treatment of MS, daclizumab received regulatory approval as add-on therapy to standard immunosuppressive regimen for the prevention of acute allograft rejection in renal transplantation. Mechanistic studies in MS demonstrated that the MOA of daclizumab is surprisingly broad and that the drug exerts unexpected effects on multiple components of the innate immune system. Specifically, daclizumab dramatically expands and activates immunoregulatory CD56(bright) NK cells, which gain access to the intrathecal compartment in MS and can kill autologous activated T cells. Daclizumab also blocks trans-presentation of IL-2 by mature dendritic cells to primed T cells, resulting in profound inhibition of antigen-specific T cells. Finally, daclizumab modulates the development of innate lymphoid cells.

Ocrelizumab received FDA approval for the treatment of relapsing forms and primary progressive MS in 2017. Ocrelizumab is a recombinant humanized antibody designed to selectively target cells that express the B lymphocyte antigen CD20 on their surface. The CD20 molecule is an activated glycosylated phosphoprotein expressed on a broad range of cells of the human B-cell lineage, with increasing concentrations from pre-B cell through naïve and memory B cell, whereas CD20 is not expressed on stem cells, pro-B cells, or differentiated plasma cells6. Although the role of activated T-cells in the pathogenesis of MS was long understood, the role of B cells in the disease process is a more recent discovery. B cells can produce proinflammatory cytokines and are potent antigen-presenting cells that are involved in the activation of proinflammatory T cells. Furthermore, ectopic lymphoid follicles resembling germinal centers containing B cells and plasma cells are present in the meninges of patients with progressive MS, indicating that B cells migrate to the brain. Given the increasing understanding of the role of B cells in MS pathology, it is therefore more understandable why significant clinical and radiographic outcomes have been met after B-cell depletion7.

Other B-cell depleting therapies have been investigated in clinical trials. Rituximab, previously approved for non-Hodgkin's lymphoma or chronic lymphocytic leukemia, and in combination with methotrexate for adult rheumatoid arthritis, was unsuccessfully tested for primary progressive MS in a trial reported in 20098. However, the data showed that younger patients, particularly those with active MRI lesions, were likely to receive some benefit from treatment. Newer therapies that are undergoing clinical trials are investigating whether MoAb products that can be administered subcutaneously, or with a faster administration protocol, would be of benefit in treating patients with MS.

FURTHER DIRECTIONS IN MOAB THERAPIES

MS is only one neurologic condition that has had remarkable advances in therapy utilizing MoAb technology. Current research of MoAb products for treatment of migraine headaches, Alzheimer's Disease, and other disease states ensures that the science will continue to advance. As biologic agents spread in utilization, a number of barriers may arise: access to infusion services can be limited, and referral to a hospital-based or private infusion facilities may result in personnel administering the medication who do not understand the disease state, therefore having an inability to differentiate between infusion reactions and the clinical symptoms of the condition itself. Properly trained infusion nursing services can add to the already good safety profile of this category of treatment.

The development of MoAb therapies has been the result of very intensive basic science followed by arduous pre-clinical and clinical trials. The cost of biological therapeutics has historically been high, and additional procedure-related healthcare expenses are incurred by IV nursing services. As both medical and pharmaceutical costs for chronic neurologic disorder have ballooned, access issues through managed care have also multiplied. Despite these burdens, utilization of biologic products will undoubtedly increase given the dramatic clinical responses observed both in research studies and in practice.

REFERENCES:

Léger OJP, Yednock TA, Tanner L, et al. Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis. Hum Antibodies. 1997;8:3–16.

Hutchinson, Michael. Natalizumab: A new treatment for relapsing remitting multiple sclerosis. Ther Clin Risk Manag. 2007 Jun; 3(2): 259–268.

Lobb RR, Hemler ME. The pathophysiologic role of α4 integrins in vivo. J Clin Invest. 1994;94:1722–8.

Hale G, Xia MQ, Tighe HP, Dyer MJ, Waldmann H. The CAMPATH-1 antigen (CDw52). Tissue Antigens. 35(3), 118-27 (1990).

Bielekova, B. Daclizumab therapy for multiple sclerosis. Neurotherapeutics. 2013 Jan;10(1):55-67.

Stashenko P., Nadler L., Hardy R., Schlossman S. (1980) Characterization of a human B lymphocyte-specific antigen. J Immunol 125: 1678–1685. PM: 6157744.

Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. Ther Adv Neurol Disord. 2016 Jan; 9(1): 44–52.

Hawker, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009 Oct;66(4):460-71.

← BACK TO PAGE 1
NEXT PAGE →

TNS Winter Conference

Feb. 2–4

Hyatt Regency • Austin

Hi fellow Texas Neurologists!

2017 has been a great year for the books. The Astros won the World Series, there have been some great developments for the field of neurology, and we watched thousands of Texans come together after devastating floods knocked down but did not crush our spirits. 2018 will be off to a great start in February with the TNS Winter Conference. This conference promises to be one of the best ever with some special changes you have asked for such as more resident involvement as they will introduce a clinical case prior to talks. We have special guests from top-tier neurological institutions such as the University of California – San Francisco and the University of Michigan flying in to lecture in the Lone Star State, each considered experts in their field. We also have for you a nice assortment of lectures from a variety of topics from Neuro-Oncology, Neuro-Opthalmology, Neuro-Otology, Headache Neurology, Movement Disorders, Neuro-Immunology, Behavioral Neurology, Sleep Neurology, Vascular Neurology, Physical Medicine and Rehabilitation, Neurosurgery, Neuromuscular, and Epilepsy.

As always, this conference serves as a cost-effective way to earn CME credit, great way to network with your peers, and a high-yield program well worth your time. I look forward to seeing all of you there so let's make this year's attendance the highest ever at the 2018 TNS Winter Conference!!

All the best,
Michael J. Soileau, MD
Winter Program Director

← BACK TO PAGE 1

NEXT PAGE →

AAN Members React to Opioid Emergency

Mike Amery, Esq.
AAN Senior Legislative Counsel

The opioid crisis has had a staggering impact on communities across the US, but few places have seen the challenges of this epidemic more than West Virginia. AAN Government Relations Committee members David Watson, MD, and Mitzi Payne, MD, practice in West Virginia and see their patients and community struggling. "This is a public health emergency in my state," said Watson.

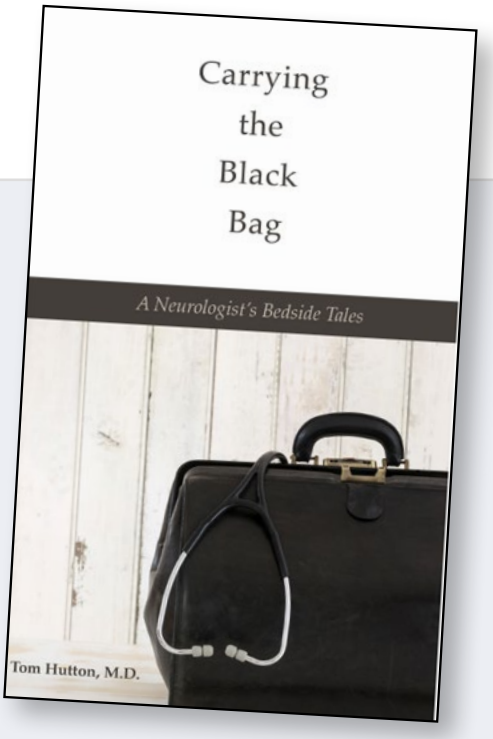
President Trump on October 26, 2016 declared the opioid epidemic as a national public health emergency. This declaration allows federal agencies to make resources available to reduce deaths related to opioid abuse, which include telemedicine services for opioid treatment and assistance for people with opioid addictions seeking housing or employment. The Department of Health and Human Services can also allocate additional staff and increase flexibilities in programs to prevent addiction and support recovery.

Neurologists like Drs. Watson and Payne have seen the devastating effects of opioid abuse in their practices and their communities. While most neurologists may not prescribe opioids, they treat many complications that result from opioid overuse and abuse. Babies diagnosed with neonatal abstinence syndrome (NAS) often visit pediatric neurologists to work through the symptoms of their condition and begin healing. Adults seeking help with addiction or working through recovery following an overdose may also see a neurologist as part of a care team. "The opioid crisis crosses all specialties," said Watson, "but as protectors of the brain it is a problem that neurologists must address head on. This includes not only rehabilitation but also finding new and safe treatments for people with pain."

Policy makers recognize the critical role that physicians, including neurologists, play in combating this epidemic and routinely ask AAN members and our lobbyists in DC about the impact this crisis is having on patients. The AAN supported 21st Century Cures, which allocated funding for the opioid crisis, and partnered with other physician organizations on sign-on letters supportive of more money to combat the epidemic. The Academy is working on the state and federal level to support actions that promote access to care for people struggling with opioid use disorders.

Membership News

Dr. J. Thomas Hutton, author of "Carrying The Black Bag: A Neurologist's Bedside Tales" has won several awards in 2017. One being "best new debut author." Dr. Hutton was also a finalist for the "Montaigne Medal" which carried the book to a five star rating on both Amazon and Goodreads. Congratulations!



← BACK TO PAGE 1