Published in final edited form as:

JAMA. 2014 April 23; 311(16): 1620–1621. doi:10.1001/jama.2014.4084.

Advancing Neurotherapeutics in the 21st Century

Roger N. Rosenberg, MD,

University of Texas Southwestern Medical Center at Dallas, Department of Neurology and the Alzheimer's Disease Center, Dallas, Texas

Jeffrey L. Saver, MD

University of California at Los Angeles, Neurology, Los Angeles, California

Neurology is emerging rapidly as a clinical discipline with new and effective therapies for major neurological disorders. This theme issue of *JAMA*, devoted to neurology, includes 5 original research investigations that provide new data on neurotherapeutic advances and 3 Viewpoints that discuss how therapeutic momentum in neurology must be focused and implemented in the future to ensure progress and effectiveness and to improve health outcomes.

In the first Viewpoint, Birbeck and colleagues[1] provide a global perspective of the immense challenge clinical neurology faces in providing basic neurological care to millions of persons worldwide with neurodegenerative, neurovascular, and infectious diseases. The authors project that by 2050, there will be 115 million people with dementia and note that stroke causes more deaths annually than AIDS, tuberculosis, and malaria combined. Their perspective is compelling, highlighting advances in medicine that are now producing a worldwide "epidemiologic transition from infections to chronic diseases." Addressing health needs will require the conduct of research in low and middle resource countries and global training in neurology.

Callaghan et al[2] in another Viewpoint draw attention to the great challenge of increasing health costs in the United States and the need to define the overall value of many of these expenditures. The authors endorse the Choosing Wisely campaign, which encourages dialogue between physicians and patients about the necessity of tests, procedures, and medications. They also point out that a critical assessment is needed to prioritize waste reduction targets and carefully but effectively provide the best care at the necessary but reduced cost. Their challenge to the neurological community is to eliminate unnecessary testing, procedures, and medications to help reduce the $210 billion spent on unnecessary services in the United States.

Pedley[3] strikes a positive note in his Viewpoint with examples of the transformative new therapies for autoimmune antibody-mediated diseases, new drugs for epilepsy, multiple sclerosis, deep brain stimulation for Parkinson disease, thrombolysis therapy for acute

Corresponding Author: University of Texas Southwestern Medical Center at Dallas, Department of Neurology and the Alzheimer's Disease Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9036 (roger.rosenberg@utsouthwestern.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

stroke, and widespread establishment of neurological intensive care units. On balance, however, he notes that the United States has an 11% shortfall in the number of neurologists needed and that this shortfall is projected to increase to 19% by 2015. Furthermore, with aging of the population, there will be an estimated increase of 60% in demand for neurological services by 2025.

The major impediment for continued development of new therapies, Pedley points out, is reduced National Institutes of Health (NIH) funding with the success rate of National Institute of Neurological Disorders and Stroke (NINDS) to fund grants at 16.8%. The therapeutic potential of the revolutionary advances in fundamental neurosciences of the past decades is only now beginning to be realized and, clearly, and the number and types of new treatments are increasing. However, with the US health care system and the NIH level of funding currently in flux, it is indeed a time of great challenge.

These Viewpoints set the stage for 5 original research articles in this issue of *JAMA*, all focused on neurotherapeutic advances. Two reports assess acute stroke management with intravenous thrombolysis. In Germany, Ebinger et al[4] report findings from a clinical trial demonstrating a shortened time for the administration of thrombolysis therapy in acute ischemic stroke. The investigators evaluated use of an ambulance equipped with a computed-tomography scanner, point-of-care laboratory and telemedicine connection, a stroke identification algorithm at the dispatcher level, and a specialized pre-hospital stroke team, which included on-site neurologists. The authors report that compared with usual care, starting thrombolysis before ambulance transport to hospital resulted in decreased time to treatment, without an increase in adverse events.

Fonarow et al[5] evaluated the success of a nationwide US quality improvement program to reduce door-to-needle time for administration of intravenous tissue plasminogen activator (tPA) to treat acute stroke. This study included 71 169 patients with ischemic stroke treated with tPA from 1030 participating hospitals. The authors report that median door-to-needle time declined from 74 minutes prior to implementation of the initiative to 59 minutes after implementation and was associated with lower in-hospital mortality and intracranial hemorrhage and more frequent independent ambulation at discharge and discharge to home. These beneficial therapeutic results are testimony to the commitment of physicians, nurses, and allied health professionals at stroke centers across the country to design and implement improved processes of care that resulted in clear clinical benefits achieved under complex circumstances.

The randomized trial by Wall et al[6] in this issue of *JAMA* illustrates the transition of neurology from an anecdotal to an evidence-based specialty. In a randomized trial involving 155 patients, the investigators evaluated acetazolamide, a long-standing component used to treat idiopathic intracranial hypertension. When added to a low-sodium, weight reduction diet, acetazolamide compared with diet alone, resulted in modest improvement in visual field function. Among the sub-group of patients with more serious visual impairment, the improvement was more substantial.

In another clinical trial involving 273 patients, Chamberlain et al[7] compared lorazepam to diazepam for treating pediatric status epilepticus. The authors found that lorazepam did not result in improved efficacy (in terms of cessation of seizures within 10 minutes without recurrence) or safety (in terms of requiring assisted ventilation) compared with diazepam, although patients in the lorazepam group were more likely to be sedated. This issue has been debated for some time and this randomized trial provides clear evidence to help inform clinical decision making for the selection of anticonvulsants for treatment of status epilepticus in children.

The outcome of unruptured arteriovenous malformations under conservative management or interventional treatment by any combination of the modalities of endovascular embolization, neurosurgical excision, and stereotactic radiosurgery was compared by Al-Shahi Salman et al[8] for unruptured arteriovenous malformations. In a population-based study, the investigators evaluated 204 patients and conclude that conservative management was associated with better clinical outcomes over 4 years than interventional treatment. These observational findings with long-term follow-up confirm and extend a recent randomized trial with a shorter period of observation.

Connolly and colleagues[9] provide a comprehensive review of the pharmacologic treatment of Parkinson disease. The authors include an evidence-based review of the initial pharmacologic management of the classical motor symptoms of Parkinson disease and also medication-related motor complications, such as motor fluctuations and dyskinesia, and other adverse effects stemming from medication including nausea, psychosis, impulse control disorders, and related behaviors. Included in the review is the management of nonmotor symptoms of Parkinson disease, including rapid eye movement sleep behavior disorder, cognitive impairment, depression, orthostatic hypotension, and sialorrhea. They cite evidence for using levodopa and dopamine agonists for motor symptoms, dopamine agonists and drugs that block dopamine metabolism for motor fluctuations, and clozapine for hallucination. Cholinesterase inhibitors may improve symptoms of dementia and antidepressants and pramipexole may improve depression.

What are some events currently under way that may offer potential positive major shifts in the trajectory of developing new therapies and thus favorable clinical outcomes for neurological research in the immediate future? Two come to mind.

First, the NIH and 10 of the world’s largest pharmaceutical companies have agreed to work together to discover therapies for Alzheimer disease, type 2 diabetes, rheumatoid arthritis, and lupus. This initiative, the Accelerating Medicines Partnership, recognizes that progress toward new therapies will require large-scale collaborations of this type. The synergism of the NIH and industry in a coordinated approach is the ideal model to develop therapeutic targets and then therapies for major neurological diseases.[10]

Second, in 2013, President Obama announced the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which will be a partnership between the NIH; the National Science Foundation; the Defense Advanced Research Projects Agency, an agency of the United States Department of Defense; private foundations; and researchers.[11]

Francis Collins, the NIH Director, stated that the charge of the BRAIN Initiative is “to accelerate the development and application of innovative technologies to construct a dynamic picture of brain function that integrates neuronal and circuit activity over time and space.” Cornelia I. Bargmann of the Rockefeller University and William T. Newsome of the Howard Hughes Medical Institute, Stanford University, are the co-chairs and will direct this major scientific program, which is expected to reach into the hundreds of millions of dollars in the next decade.

Defining the human brain connectome, documenting neuronal synaptic connections, and deciphering patterns of synaptic electrical activity with the conceptual tools of computational neuroscience for information storage and retrieval, as the basis for human behavior are desired products of the BRAIN Initiative. The goals are clear and will provide answers to the most complex question before all of medicine and science in the 21st century: How does the brain work?

The BRAIN Initiative is of direct interest to neurologists. From it will come a deep understanding of consciousness, cognition, language, speech, motor, sensory, visual, auditory, emotional, and autonomic functions. Its translational effect could lead to an appreciation of neurological diseases at the most basic level of genomic expression as well as to innovative and yet unexplored areas of neurotherapeutics.

REFERENCES

1. Birbeck GL, Hanna MG, Griggs RC. Global opportunities and challenges for clinical neuroscience. JAMA. 2014;311(16): doi:10.1001/jama.2014.2744.
2. Callaghan BC, Burke JF, Feldman EL. How neurologists can choose (even more) wisely. JAMA. 2014;311(16):doi:10.1001/jama.2014.1021.
3. Pedley TA. Neurology at a crossroads: opportunities and challenges. JAMA. 2014;311(16):doi: 10.1001/jama.2014.4081.
4. Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke. JAMA. 2014;311(16):doi:10.1001/jama.2014.2850.
5. Fonarow GC, Zhao X, Smith EE, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after initiation of a quality improvement initiative. JAMA. 2014;311(16):doi:10.1001/jama.2014.3203.
6. The NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss. JAMA. 2014;311(16): doi:10.1001/jama.2014.3312.
7. Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus. JAMA. 2014;311(16): doi:10.1001/jama.2014.2625.
8. Al-Shahi Salman R, White PM, Counsell CE, et al. Outcome after conservation management or intervention for unruptured brain arteriovenous malformations. JAMA. 2014:311(16): doi:10.1001/jama.2014.3200.
9. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease. JAMA. 2014;311(16):doi: 10.1001/jama.2014.3654.
10. Hyman SE. Time for new schizophrenia Rx. Science. 2014;343:1177. [PubMed: 24626901]
11. Bargmann CI, Newsome WT. The BRAIN Initiative [online April 7, 2014]. JAMA Neurol. doi: 10.1001/jamaneurol.2014.411.