Importance and Hurdles to Drug Discovery for Neurological Disease

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This is a critical time in neurotherapeutics. The prevalence of neurological disease, such as dementia, stroke, and peripheral neuropathy, is large and growing consequent to the aging population. The personal and societal impact of these disorders is enormous, and the number of novel therapies in the pipeline for these disorders has been contracting. Support for the development of neurotherapies must continue from the bench to their ultimate place at the bedside. Academic medicine must continue to play a critical role, in league with industry and government, in the development of novel neurotherapies desperately needed by an ever-expanding population. Critical steps include the identification and adoption of reliable, valid, and reproducible biomarkers to serve as primary endpoints in clinical trials of neurological disease.

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The burden of neurological disease is remarkable in both its impact on the quality of life and its cost. This has been particularly true in developed countries where an increasing life expectancy has resulted in substantial increases in the prevalence of diseases that chiefly afflict the elderly, such as stroke and dementing disease. Were a critical prospective analysis to be done on the elderly population, it is likely that few would escape some form of neurological ailment, with many individuals suffering from more than one.

The nature of neurological disorders varies with age. Autistic spectrum disorders (ASDs), cerebral palsy, and Tourette syndrome are among many disorders that present in childhood. A conservative estimate of the frequency of ASDs is 27.5 per 10,000, with newer surveys suggesting that it is as high as 60 per 10,000 individuals.[1] A surveillance study of ASDs during 2008 from 14 sites in the United States found a prevalence of 11.3 per 1,000 (1 in 88) children aged 8 years old.[2] With respect to cerebral palsy, studies from Europe and the United States reveal a median prevalence of 2.4 per 1,000.[3] An increase in preterm births, which has been occurring in the United States in the recent past,[4] is associated with an even higher prevalence of cerebral palsy. The reported prevalence of Tourette syndrome is age-dependent and has varied widely from study to study, but a median estimated prevalence of 3.5 per 1,000 has been proposed.[3] One in 5 children experience transient tics, and 1 in 100 develop Tourette syndrome.[5]

Among the more common neurological disorders across the age spectrum are migraine headache and epilepsy. The 1-year prevalence per 1,000 for migraine derived from an analysis of multiple epidemiological studies was 121.[3] The 1-year prevalence in a study conducted in Philadelphia revealed that 17.2% of women and 6.0% of men were migraineurs, with the highest prevalence between the ages of 30 and 49 years.[6] The economic impact of migraine is substantial, with indirect costs outweighing the cost of treatment.[7] Approximately 1% of the US population will have epilepsy by age 20

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years, with >2/3 having onset in childhood.[8,9] The incidence of seizures is high in the first year of life, but highest in individuals age 75 years or greater,[9] which represents an increasing percentage of the population of the developed world. The 1-year prevalence per 1,000 for epilepsy in the United States is estimated at 7.1,[3] and the cumulative incidence of all unprovoked seizures through age 74 years is 4.1%.[10]

Traumatic brain injury (TBI), spinal cord injury (SCI), and multiple sclerosis (MS) lead to the highest rate of neurologic disability among young adults. TBI has a median annual incidence in the United States of 101 per 100,000[3] and is notably frequent among veterans returning from the Iraq and Afghanistan wars. In a Veterans Administration study of 327,388 veterans of these 2 recent wars, 6.7% had been diagnosed with TBI, and 89% of those patients carried a psychiatric diagnosis.[11] Similarly, chronic traumatic encephalopathy has been recognized with increased frequency in individuals engaged in contact sports.[12,13] SCI from trauma resulting in complete or incomplete functional interruption of spinal pathways has a median annual incidence of 4.5 per 100,000 and a prevalence of 72 per 100,000 in the United States.[3] The median estimate of the annual incidence of MS in the United States is 4.2 per 100,000 (range = 0.8–12.0), with prevalence estimated between 47.2 and 109.5 per 100,000.[14] Both the incidence and prevalence are twice as high in women as in men, and the peak age of onset is approximately 30 years.[3]

In the 20th century, the age-adjusted death rate of Americans declined by about 74% and the life expectancy increased 56%.[15] The aging population has been accompanied by an increase in neurological disorders, particularly stroke and neurodegenerative conditions, such as Alzheimer and Parkinson disease. In 2009, the life expectancy at birth in the United States was 78.5, and for a person age 65 years old, 19.2 years.[16] In 2010, the Department of Health and Human Services estimated that there were >40 million individuals in the United States >65 years old, constituting 13.0% of the total population.[17] By 2030, that number will nearly double to >71 million and represent 19.7% of the population.[17] Data collected from 17 series with >15,000 persons aged 60 years or more revealed a mean incidence of moderate to severe dementia of 4.8%.[18] The incidence rate for dementia in Rochester, Minnesota was 187 per 100,000 and for Alzheimer disease was 123 per 100,000.[19] The frequency of Alzheimer disease increases with advanced age; for those 60 to 69 years old, the prevalence approximates 300 per 100,000, for those 70 to 79 years old, the prevalence is 3,200, and for those >80 years old, the prevalence is 10,800.[20] In 2010, 4.7 million people aged 65 years or older in the United States had Alzheimer disease,[21] accounting for 42% of the chronic conditions among persons living in residential facilities.[22] By 2050, it is estimated that there will be 13.8 million people with Alzheimer disease in the United States.[21]

Estimates from several studies of the incidence and prevalence of Parkinson disease indicate that the median incidence is 160 (range = 62–332) per 100,000 for persons aged 65 or older, with a prevalence rate of 9.5 per 1,000 (range = 7.0–43.8).[3] It is estimated that Parkinson disease affects about 1 million people in the United States.[20]

Regarding cerebrovascular disease, the median annual incidence of first-ever stroke is 183 per 100,000, with the rate roughly doubling every decade during adulthood. The prevalence of stroke, as determined in a study from Rochester, Minnesota, was 1% of the population,[23] and nationwide studies suggest that it approaches 2% for persons aged 25 to 74 years.[24] Annually, 700,000 people in the United States suffer a stroke, about 1 person every 45 seconds, and >1/2 die within 8 years of their stroke.[25] In 2010, there were 4.7 million people living with stroke in the United States.[25] Stroke accounted for 11% of the persons living in residential facilities.[22]

The neurological disorders described above are but a short list of some of the more common neurological afflictions. Disorders of the peripheral nervous system, such as Guillain–Barré disease, chronic inflammatory demyelinating peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia and other pain syndromes, and myasthenia gravis, as well as other central nervous system (CNS) disorders, such as amyotrophic lateral sclerosis, are not encompassed in this review. It also does not address the 20% of orphan diseases that are neurological; neurological disease has the third-highest number of orphan product designations.[26] When all these conditions are considered in aggregate, it reveals a substantial burden of neurological disease, with a significant impact on health and well-being coupled with enormous direct and indirect financial costs. Neurological disorders accounted for a substantial amount of the $2.1 trillion dollars of direct cost of personal health care expenditures in the United States in 2009.[16]

Difficulties of Bringing Drugs to Market

About 85% of all drug therapies fail in clinical trial, and on average only 25 to 30 new molecular entities are approved in the United States annually.[27,28] Data collected by the US Food and Drug Administration indicate that over the past 20 years there was a spike in new drug approvals in the mid-1990s (53 in 1996), with a

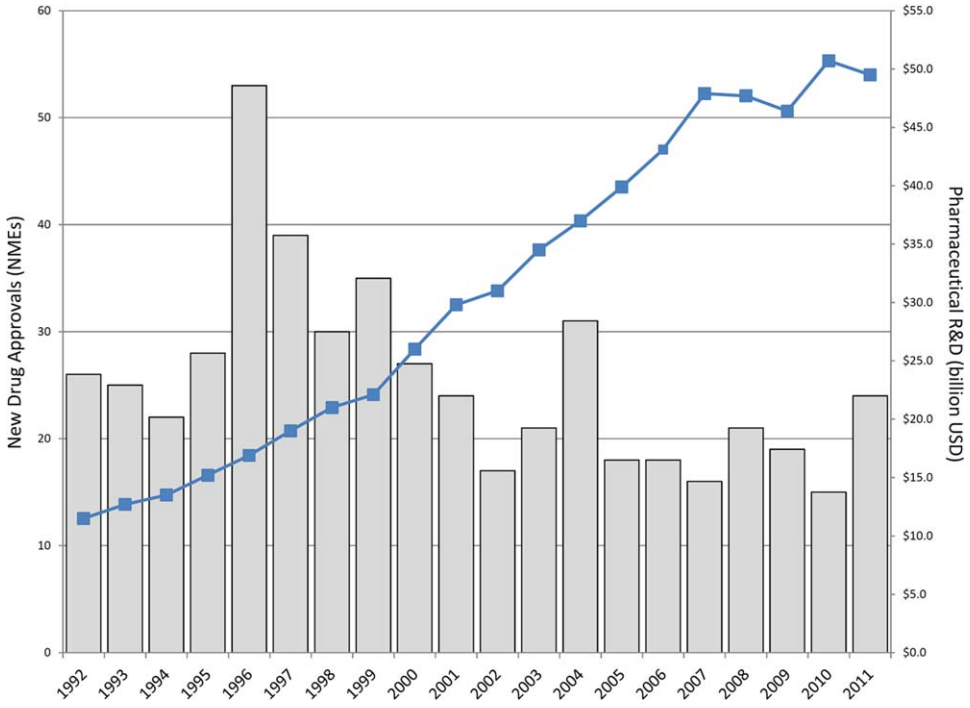

FIGURE 1: Annual research and development (R&D) spending versus new drug approvals over the past 20 years. The number of new drug approvals, reported in number of new molecular entities (NMEs; *gray bars*), is plotted against the amount of money spent on pharmaceutical R&D, reported in billions of United States dollars (USD; *blue line*). [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

flattening out in the past decade.[29] In the past 3 years, the number of annual new drug approvals has averaged approximately 1/3 of the approval rate of the preceding 2 decades.[29] Nonetheless, the cost of research and development has continued to increase during this time, with an inverse relation to the number of approved new drugs. The expense of research and development in 1996 was $16.9 billion, compared to $49.5 billion in 2011, roughly a 3-fold increase (Fig 1).[30] The capitalized clinical development costs for CNS drugs is higher than drugs in any other category[31]; estimates for the cost of research and development for bringing a new medical entity to market averages as much as $1.8 billion.[32] In 2005 in the United States, industry contributed $7.8 billion US dollars for the development of neurotherapeutic agents, exceeding the contributions for any other therapeutic area.[33,34]

The process of drug development is complex and costly. The initial phase is exploratory research for drug discovery. In this phase, efforts are made to identify biological pathways important to disease pathogenesis that can be modified by a specific drug. Once such a pathway and targeting agent is identified, it must be demonstrated that the drug reaches the appropriate target tissue, that it affects the pathway of interest, and that there is a therapeutic window for the drug. Clinical research must also determine the pharmacokinetics and pharmacodynamics for the drug to identify its optimal dosing. Following testing in animals, a sequential series of clinical trials with increasing numbers of human volunteers is undertaken.

New neurological therapies have a higher attrition than therapies in any other area, other than oncology.[35] Only 8% of CNS drugs ever make it to clinical trials, roughly 1/2 the rate of drugs in other fields.[31] Furthermore, CNS drugs tend to fail late in development,[31] substantially increasing their cost and the financial risk to companies working in the CNS drug space. The probability of success for a new neurotherapeutic agent has been calculated at 2.85%.[35]

The approval success rate for therapies varies widely by discipline. For instance, systemic anti-infectious disease therapies have nearly 3× the likelihood of making it to the market as therapies for neurological disorders.[36] Additionally, the time to market for CNS drugs from clinical trials (Fig 2) through the approval process averages 10.0 years (8.1 in clinical trials and 1.9 years in the approval phase), substantially exceeding that for any other therapeutic area.[36] Therefore, there are economic disincentives for industry to pursue neurological therapies, and as such, neurological therapies are considered a high-risk investment with long, costly development phases and low probabilities of approval. Because of these considerations, in the past 3 years, many large pharmaceutical companies, including AstraZeneca, GlaxoSmithKline, Pfizer, Merck, Sanofi, and Novartis, have significantly downsized their neuroscience commitment.[37,38]

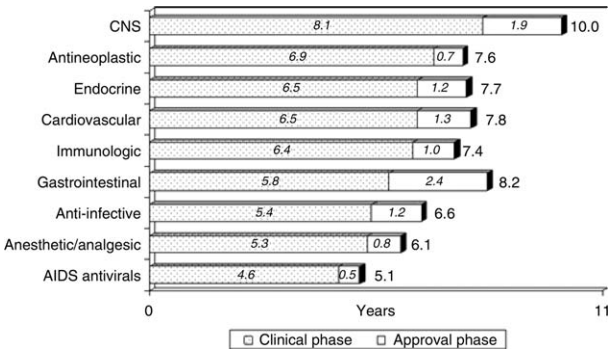

FIGURE 2: Mean clinical and approval phase times for approved new molecular entities and significant biologicals, 2005–2009, grouped by therapeutic class. Note that the anti-infective group does not include acquired immunodeficiency syndrome (AIDS) antivirals. CNS = central nervous system. Reprinted by permission from Macmillan: Clin Pharmacol Ther 2011;89:183–188, copyright 2011.[36]

Decreasing the time and financial investment in bringing neurological therapies to the marketplace will likely require the development and support of biomarkers. For instance, biomarkers could potentially assist in identifying particular populations that are at high risk of disease activity or rapid disease advancement. Biomarkers may also enrich study populations by increasing their homogeneity. Biomarkers could potentially provide not only more objective measures of disease activity than clinical batteries, but also more sensitive measures for early presymptomatic disease (eg, magnetic resonance imaging in MS).[39] Biomarkers may also play a role in drug safety (for example, JC virus antibody testing to identify risk of progressive multifocal leukoencephalopathy with natalizumab treatment for MS) and may predict the rapidity of disease progression. The outcome measures for clinical trials need to be validated, sensitive to change, reliable having low inter- and intrarater variability, and practical. Identification of meaningful biomarkers will be important for achieving those goals.

Solutions for Increasing the Drugs Available for Neurological Disorders

Increasing drug discovery for neurological disorders requires a multifaceted approach. Academic neurological societies must play a leading role in this neurotherapeutic endeavor and support the domain of neurologists who have contributed to the discovery of these agents, their clinical testing, and their use at the bedside. Scientists must first identify the hurdles in shepherding a novel neurotherapy from the bench to the patient's bedside, and then implement measures to overcome these challenges.

Direct measures to promote neurotherapeutics by the academic neurological community (Table 1) include targeting meeting programs for drug discovery, developing and training fellows for translational neuroscience, and promoting publications that advance the field. Additionally, academic neurological societies can advocate prioritizing translational neuroscience within academia. Academic leaders may also serve at the forefront of developing public–private partnerships to develop disease models, outcome assessment tools, biomarkers, and therapies. To facilitate the development of neurological therapies, these individuals must engage with many entities, including funding agencies, such as the National Institutes of Health and private foundations, with regulatory agencies, such as the US Food and Drug Administration, and with industry. In addition, the neurological academic leadership needs to play a pivotal role in informing governmental policy makers that support of investigations in neurotherapeutics has high value regarding quality of life, survival, and societal costs.

As appropriately addressed by Leppert and Glanzman,[40] among the greatest challenges for neurological therapies is determining reliable and measurable

TABLE 1. Recommendations to Improve Neurotherapeutic Development

Engagement of neurological societies
Promote educational programs for therapeutic discovery during national meetings
Develop training programs in translational neuroscience for early career neurologists
Advocate for translational research
Academic leaders
Support development of public–private partnerships
Fundraising
Enhance communication among National Institutes of Health, US Food and Drug Administration, and industry
Political advocacy to educate policy makers
Research focus
Enhance clinical trial endpoints
More rigorous clinical endpoints
Biomarker discovery
Other approaches
Promotion of federal and industry partnerships specific for therapy development
Tax incentives for neurotherapeutics
Increased patent length for neurotherapeutics

endpoints for clinical trials. The endpoints for neurological and psychiatric disease often lack the precision and validity observed with those employed for other forms of therapy. These endpoints are often dependent on soft psychophysical measures, rater dependency, and clinical phenomenology, and may be affected by culture and language.[40] Substituting biomarkers as primary endpoints, such as the use of magnetic resonance imaging for MS, may decrease the expense and improve the facility and speed with which studies can be performed. Academic neurology should consider strongly encouraging regulatory agencies to permit neurotherapeutic trials to utilize such biomarkers when they have been proven scientifically valid, reliable, reproducible, and predictive of disease activity.

Other approaches that might be considered for fostering neurological therapies include encouraging partnerships between federal funding agencies and industry for the performance of clinical trials, providing tax incentives to pharmaceutical companies engaged in neurotherapeutic development, and increasing the patent length on therapies to assist in the financial viability for the initial investment.

Conclusions

This is a critical time in neurotherapeutics. The imperative for agents that treat neurological disorders is large and expanding. Continued research is needed to identify the most sensitive and specific clinical outcome measures and biomarkers of safety and efficacy. A concerted commitment by academic medicine, industry, and government will fulfill the promise of new, effective, and safe therapies for many neurological diseases.

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Potential Conflicts of Interest

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