

STATE OF RESEARCH IN THE EPILEPSIES 2013

CURE
Citizens United for Research in
EPILEPSY

www.CUREepilepsy.org



CURE

ABOUT CURE

Citizens United for Research in Epilepsy (CURE) is a nonprofit organization dedicated to finding a cure for the epilepsies by funding research and by increasing awareness of the prevalence and devastation of this disease.

CURE is proud to be the leading independent source of private funding of research in the epilepsies.

LETTER FROM THE CHAIR

Dear Friends,

Welcome to the State of Research in the Epilepsies 2013 report. Within these pages, we hope you will find information that is both useful and compelling. We are grateful to the many people who contributed to this project because they—like you—recognize the urgency of moving our collective agenda forward, faster.

Like our last report of 2010, the news is encouraging, but also very sobering.

It's encouraging because the last few years have brought a number of **promising trends**. Collaboration has increased throughout the field. On the whole, the community of epilepsy researchers is strong and growing. More young, bright scientific minds are joining our ranks, and we have witnessed an increase in epilepsy-related research publications and society memberships. And, most importantly, recent scientific advances have provided renewed hope that a disease modifying therapy or cure is within reach.

But, it is sobering because we continue to face **major challenges**. Per patient funding of epilepsy research continues to be inadequate to create long-overdue breakthroughs. Basic and clinical epilepsy research is still primarily focused on seizure control rather than preventing or stopping the progression of the disease. And, finally, for scientific discoveries to translate into cures, our community needs to come together to develop and implement the infrastructures needed to support novel clinical trials.

For the 65 million people worldwide with epilepsy, progress is unacceptably slow. Children with uncontrollable seizures frequently face a lifetime of intellectual and developmental disability. Mortality rates among people with epilepsy are three times the rate of the general population, and sudden death rates are more than twenty times higher.

In this country alone, one in 26 people will develop epilepsy in their lifetimes. For their sake, we must continue to be vocal advocates for making epilepsy research a national priority.

Our community is strong, energized and poised to make true strides towards eliminating seizures and their consequences. This collective commitment, along with a significant increase in funding, will help us to realize the true promise of research—transforming and saving lives.

Sincerely,



Susan Axelrod
Founding Chair
Citizens United for Research in Epilepsy

SUMMARY OF THE STATE OF RESEARCH IN THE EPILEPSIES 2013

The analyses we conducted for this report revealed a number of trends in epilepsy research that inspire hope that we are moving closer to a cure. However, a number of substantial challenges still impede our ability to take the most promising discoveries from the laboratory to the clinic.

Promising Trends in Epilepsy Research:

1. Collaboration has increased throughout the field.
2. The community of epilepsy researchers is strong and growing.
3. Important scientific advances provide renewed hope that a disease modifying therapy or cure is within reach.

Major Challenges Impeding Progress in Epilepsy Research:

1. Per patient funding for epilepsy research continues to be inadequate.
2. Basic and clinical epilepsy research is still primarily focused on controlling seizures rather than preventing or stopping the progression of the disease.
3. Translation of the most promising scientific discoveries into disease modifying therapies or cures requires an investment in infrastructure development.

PROMISING TRENDS IN EPILEPSY RESEARCH

COLLABORATION HAS INCREASED

A number of important projects, on an unprecedented scale, reflect a growing trend toward collaborative efforts. These include: (1) new or expanded consortiums bringing together professional, non-profit, and governmental agencies; (2) large scale, collaborative research projects; and (3) expanded 'Epilepsy Benchmarks' that promote multidisciplinary research with fields such as psychiatry and autism.

Consortiums

The **Interagency Collaborative to Advance Research in Epilepsy (ICARE)**, organized by the U.S. Department of Health and Human Services, consists of 20 federal agencies as well as research and advocacy groups. ICARE strives to increase communication and collaboration between non-profit and governmental organizations, focusing on advancing and coordinating research.

Vision 20-20 was founded by six epilepsy organizations in 2004. It now includes 32 nonprofit organizations, professional associations, and governmental agencies, who work together to advance epilepsy research.

The **Institute of Medicine's (IOM) report on Epilepsy Across the Spectrum: Promoting Health and Understanding**¹ was produced by a committee of 17 experts in the field and supported by 24 epilepsy agencies. Released in March 2012, it calls for further research that will lead to a shift from the symptomatic treatment of epilepsy to prevention and cures. Other research priorities were also suggested that will likely impact the long-term epilepsy research agenda.² The recommendations of the IOM report should be implemented expeditiously.

Large-Scale Collaborative Research Projects³

Several large-scale, collaborative, National Institute of Neurological Disorders and Stroke (NINDS)-supported planning grants have been awarded

since 2011 in targeted areas identified as critical to the field and potentially ripe for discovery. These may lead to funding of collaborative, multidisciplinary studies called "Centers Without Walls." To date, topics have included genetics, Sudden Unexpected Death in Epilepsy (SUDEP), disease modification or prevention in an epilepsy syndrome, and antiepileptogenesis. One important outcome of this effort could be the development of the infrastructure to support large-scale clinical studies focused on prevention, rather than symptomatic treatment, of epilepsy.

"The Epilepsy Phenome/Genome Project, Epi4K and the NIH Centers of Excellence are recent examples of broad-based collaborative research. These major projects, funded by NINDS and led by international teams of scientists, have set the stage for major advances in our understanding of the genetics of epilepsy. Scientists, clinicians, administrative personnel and the epilepsy community have joined together. They realize that the key to understanding the complex genetics of epilepsy and accelerating the path to cures is to take advantage of the tremendous power that comes when we all work together -- when committed and passionate people with a variety of talents and areas of expertise work collaboratively toward a common goal."

—Daniel H. Lowenstein, MD, Director of the Epilepsy Center at the University of California San Francisco, Medical Center

The International Epilepsy Electrophysiology Portal (IEEG-Portal) is also an important NINDS-sponsored resource that supports and enhances collaborative efforts. As a secure, cloud-based resource that provides a unique platform for sharing large datasets, computational resources, and tools, the IEEG-Portal provides an interactive social-networking like environment for collaborative groups, large projects, and "crowd-sourced" neuroscience, as well as for rigorously validating experimental results.

PROMISING TRENDS

The Curing Epilepsy Conferences and Epilepsy Research Benchmarks

The NIH Curing Epilepsy conferences provide an important venue where ground-breaking scientific advances can be highlighted and new collaborations forged. The Epilepsy Research Benchmarks, a comprehensive set of research goals established by the epilepsy research community in collaboration with the NINDS, arose from this conference in 2000. The Benchmarks underwent a revision and update in 2007 following the second Curing Epilepsy conference and again in 2012 in time for the third Curing the Epilepsies conference in April 2013. Collectively they represent an important community-based assessment of met and unmet needs in epilepsy research and serve as a measure for researchers, advocacy organizations, and legislative bodies of the work and resources still needed in the search for cures.⁴

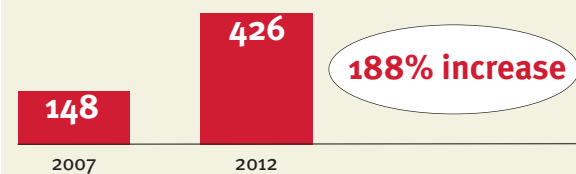
GROWTH IN THE RESEARCH COMMUNITY

Two pieces of evidence attest to the strength and growth of the epilepsy research community: (1) the number of investigators, as seen in membership levels in the American Epilepsy Society (AES) and in attendance at epilepsy-focused conferences and workshops, such as the Epilepsy Gordon Research Conferences; and (2) the number of research publications focused on epilepsy.

American Epilepsy Society (AES) Membership and the Epilepsy Gordon Research Conferences

Membership in the AES has shown strong growth. Particularly encouraging is the significant increase in the number of junior members, including graduate students, postdoctoral fellows and clinical fellows. Scientific interest in epilepsy research is also reflected by increased participation of epilepsy researchers in the Epilepsy Gordon Research Conferences. Attendance at the 2012 conference increased by 18% over that of the 2010 conference, and 44% of those in attendance were graduate students or postdoctoral fellows.

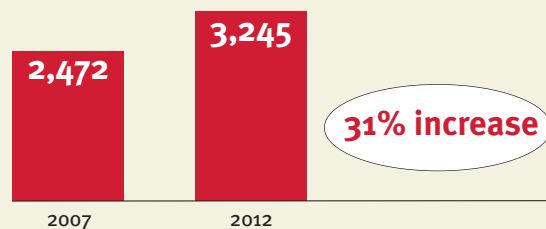
American Epilepsy Society
Junior Membership 2007 and 2012



Number of Epilepsy Publications and Authors

The number of epilepsy publications, average number of authors per publication, and number of unique authors have all increased since 2007, despite flat funding levels. These metrics indicate increased productivity and collaboration. There is, however, a crucial need to identify a mechanism wherein negative research findings can be more readily published; this is not easily achieved in the current environment.

American Epilepsy Society Total
Membership Rates 2007 and 2012



	Number of Publications	Average Number of Authors per Publication	Number of Unique Authors
2007	5,271	4.74	17,298
2012	6,035	5.26	21,482
Percent increase	15%	11%	24%

Source: <http://www.ncbi.nlm.nih.gov/pubmed>. Search term: epilepsy

SCIENTIFIC ADVANCES TOWARD DISEASE MODIFYING THERAPIES OR CURES

Greater Understanding of the Mechanisms of Epileptogenesis

In recent years, substantial advances have been made in animal modeling of acquired and genetic epilepsies that have led to greater understanding of underlying pathophysiological mechanisms. Evidence supports the growing hypothesis that many forms of epilepsy share convergent mechanisms of epileptogenesis, including mTOR signaling, activation of inflammatory pathways such as IL-1, perturbed blood-brain barrier integrity, and altered neuromodulation. There is also a greater appreciation of the mechanisms underlying autoimmune, antibody-mediated epilepsy and the role that reactive and defective glial cells play in ictogenesis and epileptogenesis. These discoveries are already impacting basic and clinical research in several ways that include new therapy development aimed at novel targets, screening for rare genetic mutations, and testing for the presence of autoantibodies in those epilepsies thought to be autoimmune in origin.

Notable Scientific Advances

- Greater understanding of the mechanisms of epileptogenesis
- More new therapies are now available for the treatment of epilepsy
- New lines of research suggesting that epilepsy and its comorbidities share common underlying mechanisms
- Greater insight into the mechanisms underlying pharmacoresistance
- Advances in identification of biomarkers of epileptogenesis
- Expanded focus of the NINDS Anticonvulsant Screening Project to include disease modification

More New Therapies Are Now Available for the Treatment of Epilepsy⁵

Since 2009, three mechanistically novel drugs have received FDA approval for the add-on treatment of partial epilepsy and two therapies have been approved for the treatment of infantile spasms and Dravet Syndrome, respectively. Moreover, the evidence demonstrates that: (1) several new therapies are in development; (2) many of the new drugs represent novel first-in-class therapies; (3) enhanced drug delivery therapies are emerging; and (4) a number of new devices for predicting, detecting, and controlling seizures are in development. Unfortunately, there is little evidence to suggest that these new drugs have led to improvement in seizure control for those patients with difficult to treat epilepsy. Novel therapies, i.e. those developed on the basis of evolving scientific discoveries, will hopefully lead to transformative improvement for patients tomorrow.

Drugs and Therapies Approved since 2009

- Ezogabine
- Lacosamide
- Perampanel
- ACTH (for infantile spasms)
- Stiripentol (for Dravet syndrome)
- Oxcarbazepine ER (extended release formulation)
- Topiramate ER (extended release formulation)

New Lines of Research Suggest that Epilepsy and its Comorbidities Share Common Underlying Mechanisms

The bi-directional nature of the comorbidities of epilepsy has led to the suggestion that certain other conditions may share a common mechanistic pathway with epilepsy. This information has led to new lines of experimental and clinical research that are increasing our understanding of the mechanisms underlying both epilepsy and several of the commonly experienced comorbidities.

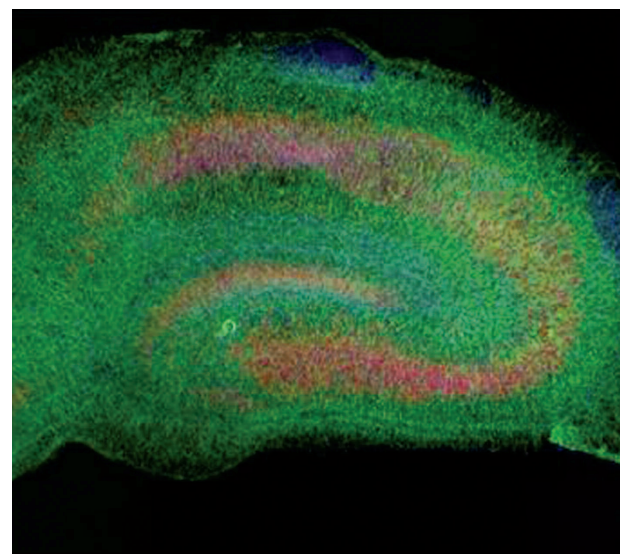
PROMISING TRENDS

Greater Insight into the Mechanisms Underlying Pharmacoresistance

Results obtained from animal models and human brain tissue suggest that overexpression of P-glycoproteins and multiple drug-resistant genes, altered network connectivity, and modification of a drug target can contribute to pharmacoresistance. This knowledge, when coupled with emerging animal models, provides a unique platform for testing and advancing novel therapies for the treatment of therapy-resistant epilepsy.

Advances in the Identification of Biomarkers of Epileptogenesis

In recent years, several promising biomarkers have emerged that may provide predictive insight into the process of epileptogenesis. These include alterations in hippocampal MRI images as suggested by the “Consequences of Prolonged Febrile Seizures in Childhood” (FEBSTAT) study, changes in white matter tracts in specialized MRIs, presence of interictal spikes and high-frequency oscillations in the EEG, and the presence of blood markers suggestive of brain inflammation. The continued development and validation of these and other emerging biomarkers are critical to future prevention studies.



Expanded Focus of the National Institute of Neurological Disorders and Stroke (NINDS) Anticonvulsant Screening Project (ASP) to Include Disease Modification

In May 2011, the National Advisory Neurological Disorders and Stroke (NANDS) Council convened a working group to evaluate the ASP. The working group clearly acknowledged the many contributions the ASP has made to facilitate therapy discovery and epilepsy research but found that the “magnitude of treatment-resistant epilepsy has not changed substantially” over the last 35 years and that “no treatment exists that modifies the course of the disease or prevents its development in those at risk.”⁶

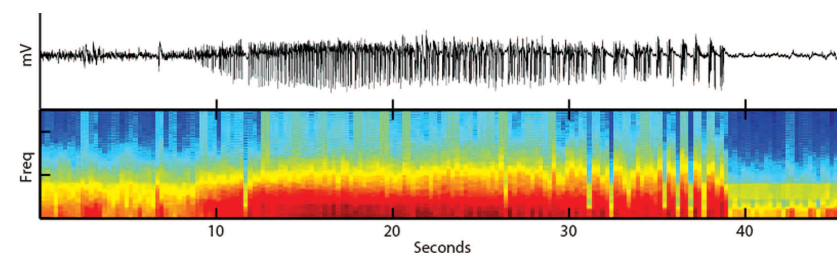
“NINDS expects to balance the clinical need that continues to exist for improved symptomatic therapies with the working group’s primary recommendation to shift the focus of the ASP toward disease modification, pharmacoresistant epilepsies, true comorbidities of epilepsy, and targeted and optimized interventions.”⁷

—Dr. Rajesh Ranganathan, Director of the NINDS Office of Translational Research

“Changes to the structure of the ASP are already being implemented that will directly address this important recommendation while remaining sensitive to the need to identify more effective and better tolerated anti-seizure drugs through a modified screening approach.”

—Dr. John Kehne, Director of the ASP

left Hippocampal slice culture, A.L. Pollock
below An EEG (top) and corresponding heat map showing the spectral power (bottom) of a seizure in an epileptic rat, K. Thomson



MAJOR CHALLENGES IN EPILEPSY RESEARCH

INADEQUATE PER PATIENT FUNDING

Compared to other neurological diseases, funding on a per patient basis for epilepsy research continues to be extremely low. NIH funding of epilepsy research has increased by only 5% since 2008. In comparison, NIH funding for autism has increased by 44% and for Alzheimer’s disease by 28%.

Disease advocacy organizations provide support of research in areas that complement and supplement public funding and are especially critical for stimulating novel, higher risk, translational research and for attracting and retaining talent. However, private dollars for epilepsy research continue to lag that for other common neurological diseases. Concerted efforts must be made to expand private support in this field in order to realize the promise of translational science.

RESEARCH FOCUSED ON SYMPTOM CONTROL RATHER THAN CURES

Since 2008, there has been a substantial increase in the number of epilepsy-related publications with a primary focus on basic mechanisms and potential cures. However, an analysis of the research suggests that the majority of epilepsy research is still focused on seizure control. Of the 1,532 articles analyzed, 67% were focused on the treatment of seizures, rather than disease modifications or cures.

Better tolerated and more effective therapies for the treatment of epilepsy are clearly necessary. However, as suggested by the NINDS Working Group review of the ASP, support for a more balanced approach is needed that

includes increased efforts focused on novel, out-of-the-box translational science that targets cures or disease modifying therapies.

INSUFFICIENT INFRASTRUCTURE FOR TRANSLATIONAL AND CLINICAL RESEARCH

A number of important scientific advances have led to an increased understanding of the mechanistic basis of epilepsy, but this information has been slow to move to the clinic. For example, a review of the titles of the “open” epilepsy clinical trials indicates that they have not yet evolved into evaluations of preventative or disease modifying therapies.

In order for there to be more rapid translation of key scientific discoveries into transformative therapies, further investment into patient registry development and novel trial design, recruitment, and conduct is needed.⁸ Further, clinical research design and execution do not currently include input from the very population they aim to help: the person with epilepsy or the parent of a child with epilepsy. The epilepsy community needs to seek the involvement of patients and their caregivers in the discussion and planning of clinical research.

“Among the many complex challenges is our ability to turn breakthrough scientific discoveries in the laboratory into accessible therapies that can improve – even save – patients’ lives. Too many scientific opportunities wither on the vine due to inadequate resources for well-designed clinical trials, leaving the potential for transformational advances to remain untapped.”

—Margaret Anderson, Executive Director of FasterCures

CURE'S IMPACT: AN UPDATE

ADVANCING INNOVATIVE EPILEPSY RESEARCH

Scientists and programs funded by CURE are making real advances toward cures. We highlight three:

Unravelling the Mystery of the Ketogenic Diet

For nearly a century, neurologists have known that a diet high in fat and low in carbohydrates can reduce seizures in some drug-resistant epilepsies, but the mechanism(s) by which this ketogenic diet works have remained a mystery. In May 2012, CURE Challenge Award recipients Gary Yellen, PhD, of Harvard Medical School and Nika Danial, PhD, of the Dana Farber Cancer Institute published a paper in *Neuron*⁹ revealing a potentially new mechanism by which the ketogenic diet may exert its protective effects. This multidisciplinary approach successfully linked seizure resistance to a protein that modifies cellular metabolism in the brain.

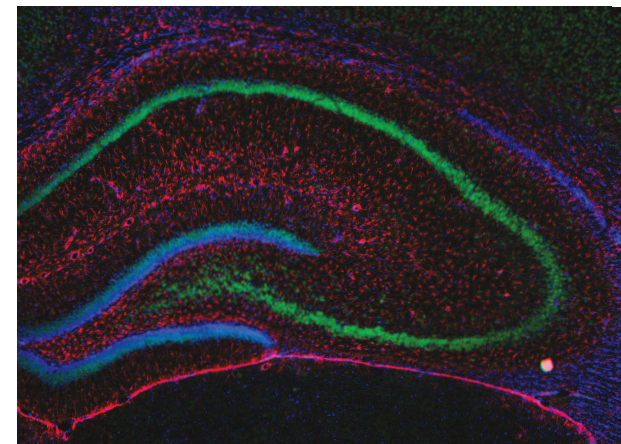
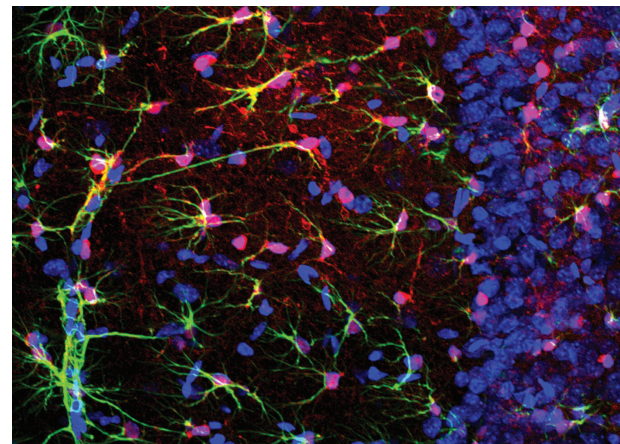
Discovering New Potential Causes of Childhood Epilepsy

Focal cortical dysplasia type IIb (FCDIIB) is a focal malformation of cortical development, and seizures in children with FCDIIB are often resistant to treatment with available drugs. In December 2012, CURE Challenge Award recipient Peter Crino, MD, PhD, of Temple University revealed his discovery of human papilloma virus (the most common cause of cervical cancer) in surgically

resected brain tissue from children with FCDIIB. These findings, published in *Annals of Neurology*,¹⁰ suggest that a common form of difficult to treat childhood epilepsy may be associated with maternal HPV infection. Dr. Crino's work has significant ramifications for how we think about this type of childhood epilepsy and could rapidly lead to new approaches to treatment and prevention of epilepsy caused by focal cortical dysplasia type IIb.

Pioneering a Targeted Program for SUDEP Research

CURE was the first organization to develop a targeted research program for Sudden Unexpected Death in Epilepsy (SUDEP), funding, to date, 18 awards totaling over \$1.7 million. As a result of CURE's leadership in SUDEP research, the community has witnessed unprecedented collaboration between basic and clinical investigators that has led to several important advances in the understanding of the potential mechanisms underlying SUDEP. These advances have led to further research initiatives, such as the SUDEP planning grants, now underway through NINDS. This effort will hopefully lead to the creation of a NINDS-sponsored "Center Without Walls" for SUDEP research. Additionally, CURE co-sponsored an inaugural conference, Partners Against Mortality in Epilepsy (PAME), which was held in June 2012 to great acclaim.



left
Network of
astrocytes,
D. K. Takahashi

right
Rat hippocampus,
K. S. Wilcox

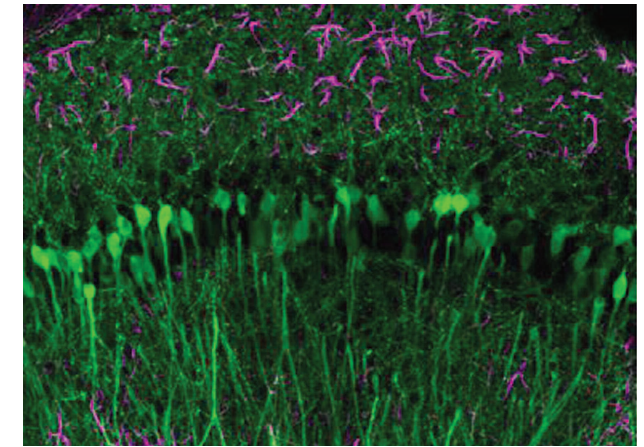
INCREASING INVESTMENT IN RESEARCH FUNDING AND CONFERENCE SUPPORT

Since its inception, CURE has awarded 141 grants totaling close to \$15 million. Despite the challenging economic climate of the past five years, CURE's investment in epilepsy research has grown by 105%. The number of applications for CURE grants continues to rise steadily each year, and as the leading independent source of private funding in epilepsy, CURE supports an increasing number of innovative research projects and concepts to push the field forward.

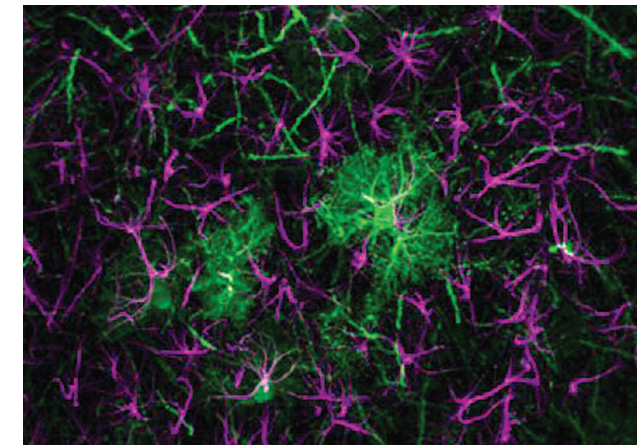
CURE also values the information sharing and networking that results from bringing scientists together at workshops and conferences. In 2012, CURE provided major support for six conferences and workshops. Some of these have been epilepsy-specific, others have fostered relationships between epilepsy researchers and researchers from other disciplines, such as a series of workshops co-sponsored with Autism Speaks.

LEADING THE WAY TOWARD GREATER COLLABORATION: THE INFANTILE SPASMS INITIATIVE

In a ground-breaking initiative, CURE is making a significant, multi-year investment in a team of investigators who, working together, will lead the way towards a cure for infantile spasms (a rare, but devastating form of epilepsy). The eight lead investigators in this initiative bring a wealth of expertise and perspectives to the team that spans adult and pediatric neurology, basic mechanisms of the epilepsies, animal modeling, human genetics and clinical trial design and execution.



GFP expression
in neurons (top)
and astrocytes
(bottom),
K.P. Flood



For more information about CURE's research programs and funding opportunities, please see:

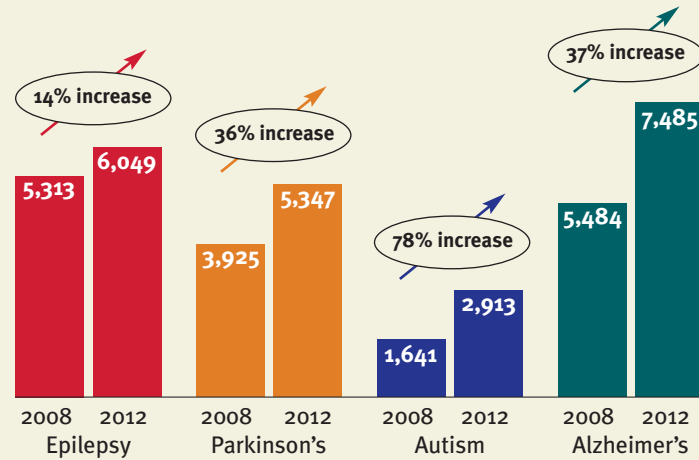
www.CUREepilepsy.org/research

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STATE OF RESEARCH IN THE EPILEPSIES 2013 DASHBOARD

Total Number of Research-Related Publications

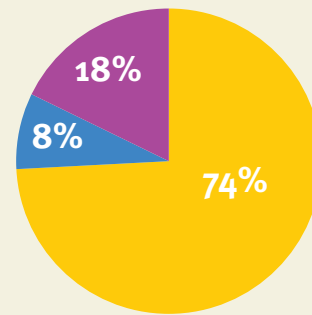
Number of publications
Percent growth



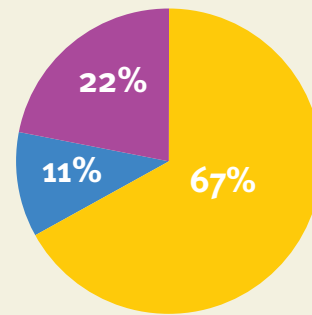
Source: <http://www.ncbi.nlm.nih.gov/pubmed>.
Searching on "Epilepsy," "Parkinson's disease," "Autism," and "Alzheimer's disease."
Data collected on March 4, 2013

Focus of Epilepsy Research Publications by Area Over Time

Breakdown for 2007
Percent
100% = 1,042 publications



Breakdown for 2012
Percent
100% = 1,532 publications



■ Treatment of epilepsy/seizures
■ Basic mechanisms of epilepsy
■ Disease modification/cure

Source: PubMed search for "treatment of seizures," "treatment of epilepsy," "basic mechanisms of epilepsy," "antipileptogenesis," "anti-epileptogenesis," "antipileptogenic treatment(s)," "antipileptogenic," and "cure."
Did not include those articles listed only under the broad heading "epilepsy"

Epidemiology of Epilepsy

United States Statistics from the IOM Report

Prevalence (number of people)	2,200,000*
Incidence (number of people per year)	150,000
Number of years of life lost with epilepsies of unknown origin	2 years
Number of years of life lost with epilepsies of known origin	10 years

Source: Committee on the Public Health Dimensions of the Epilepsies, Board on Health Sciences Policy, Institute of Medicine. *Epilepsy Across the Spectrum: Promoting Health and Understanding*. Washington, DC: The National Academies Press. 2012.

* According to the Centers for Disease Control, the prevalence numbers in the IOM report do not include people with disabilities or children. The CDC estimates the prevalence of epilepsy in the United States to be closer to 3 million people.

NIH Funding by Disease Over Time

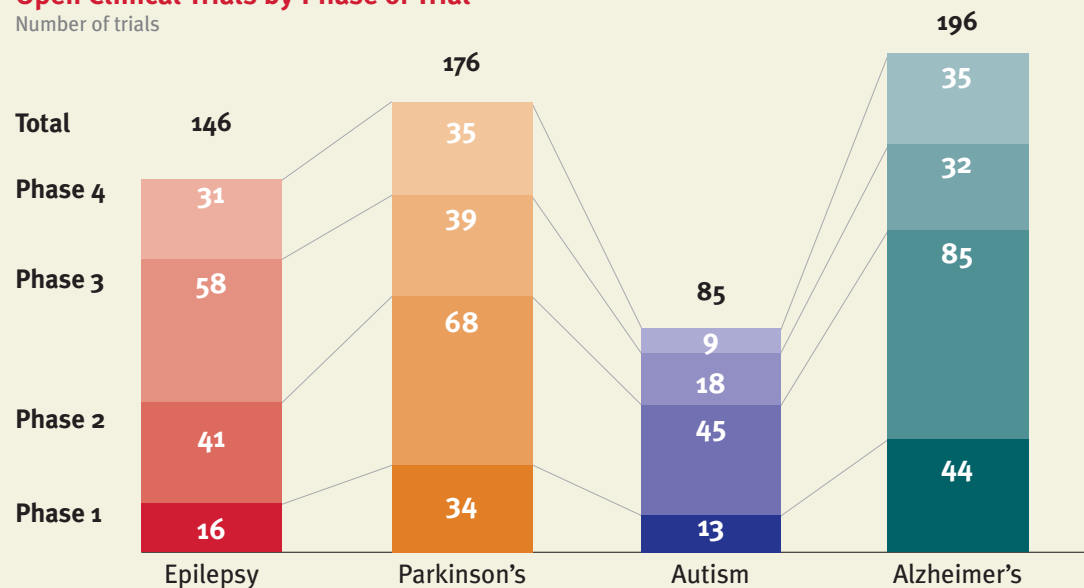
USD millions

	2008	2009	2010	2011	2012	2013 Estimated
Epilepsy	\$145	\$149	\$161	\$152	\$153	\$152
Parkinson's Disease	\$152	\$186	\$172	\$151	\$151	\$151
Autism	\$118	\$196	\$218	\$169	\$169	\$170
Alzheimer's Disease	\$412	\$534	\$529	\$448	\$498	\$529

Source: www.report.nih.gov/categorical_spending.aspx

Open Clinical Trials by Phase of Trial

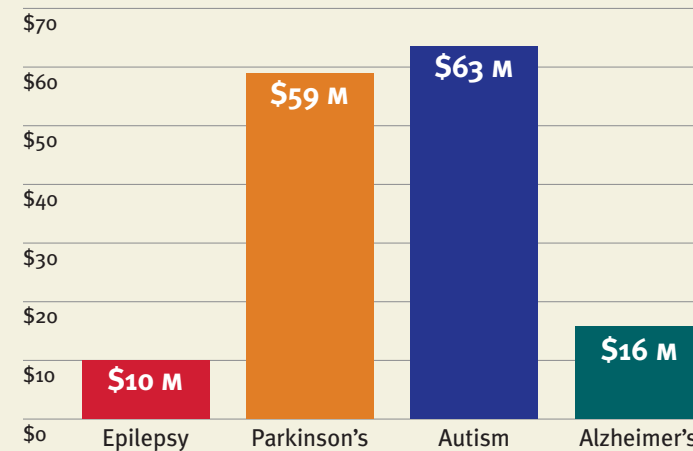
Number of trials



As of March 4, 2013, on www.clinicaltrials.gov. Used an advanced search, by phase, for "Epilepsy," "Parkinson's Disease," "Autism" and "Alzheimer's Disease."
Limited the search to include only currently open studies.

Estimated Private Funding for Research in Common Neurological Diseases

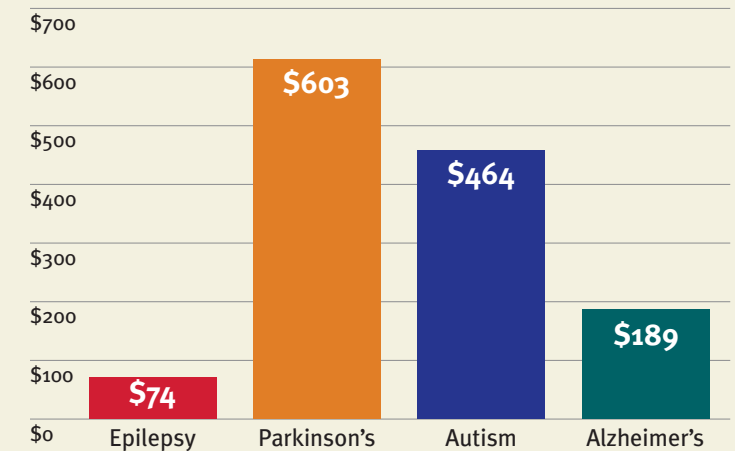
USD millions



Source: fconline.foundationcenterline.org; web search; interviews; Estimated from 2011 annual reports and other available information.

Estimated NIH and Private per Patient Funding for Research by Disease

USD/patient



Per patient estimates based on prevalence numbers in the IOM report of 2012. Research dollars include 2011 NIH and private funding only.

Source: www.report.nih.gov/categorical_spending.aspx; CURE estimates.

SOURCES AND ENDNOTES

1. Committee on the Public Health Dimensions of the Epilepsies, Board on Health Sciences Policy, Institute of Medicine. *Epilepsy Across the Spectrum: Promoting Health and Understanding*. Washington, DC: The National Academies Press, p.40. 2012.

2. Hesdorffer, DC, Beck, V, Begley, CE, Bishop, ML, Cushner-Weinstein, S, Holmes, GL, Shafer, PO, Sirven, JI, and Austin, JK. *Research Implications of the Institute of Medicine Report, Epilepsy Across the Spectrum: Promoting Health and Understanding*. *Epilepsia*, 54(2): 207-216. 2013.

3. For more information about these projects, see: <https://www.ieeg.org/>; <http://www.epgp.org/epi4k/index.htm>; <http://www.epgp.org/Pages/Default.aspx>; and <http://www.epilepsy.va.gov/EPILEPSY/ecoe.asp>

4. See: http://www.ninds.nih.gov/research/epilepsyweb/benchmarks_2007-2012progress.pdf

5. Bialer, M, Johannessen, SI, Levy, RH, Perucca, E, Tomson, T, & White, HS. *Progress Report on New Antiepileptic Drugs: A Summary of the Eleventh Eilat Conference (Eilat XI)*. *Epilepsy Research* 103(1), 2-30. 2013. Also: http://my.epilepsy.com/etp/pipeline_new_therapies.

6. http://www.ninds.nih.gov/research/asp/asp_working_group_report_022712.htm.

7. Ranganathan, R. The response of NINDS to the recommendations from the working group's 2012 review of the Program. *Epilepsia*, 53(10): 1839-40. 2012.

8. Two resources are now available to help facilitate the conduct of clinical studies: (1) The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT); and (2) The Epilepsy Common Data Elements (CDEs). The CDEs are periodically updated by a committee of experts on the basis of feedback from the epilepsy community and changes in clinical research. See <http://www.neuronext.org> and <http://www.commondataelements.ninds.nih.gov/epilepsy.aspx> for the most recent update (February 2013) of the CDEs as well as case report form (CRF) Modules and Guidelines.

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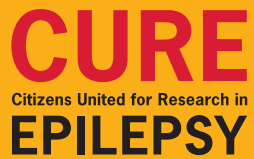
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223 West Erie Street
Suite 2sw
Chicago, Illinois 60654
Tel 312.255.1801
Fax 312.255.1809

www.CUREepilepsy.org