

Global Care for People with Epilepsy
The ILAE President's Perspective

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Epilepsy: Facts and Figures

- 700 million: people having an epileptic seizure in their life
- 50 million: people with active epilepsy, more than multiple sclerosis, Parkinson, cerebral palsy and muscular dystrophy combined
- 9 600 new cases every day (300 people during the duration of this lecture)
- Co-morbidities in up to 80% of cases
- 60,000 deaths due to SUDEP every year
- Huge burden in terms of human suffering and cost to society

Fighting Epilepsy: Many Barriers to Overcome

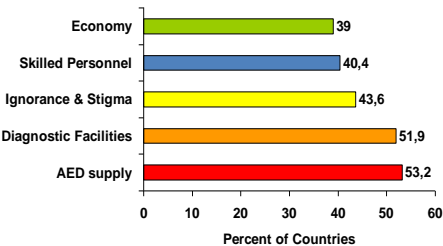
- Information
- Knowledge
- Diagnosis
- Treatment
- Legislation
- Social support
- Research



Major Challenges to Ensure Global Effective Epilepsy Care

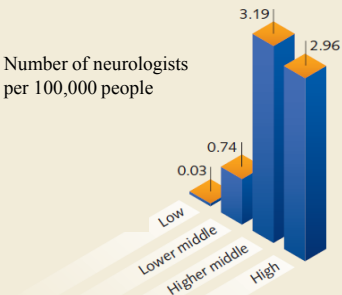
- Improve access to diagnosis and treatment
- Improve awareness and fight stigma, prejudice and discrimination
- Improve the quality of treatment
- Develop innovative and more efficacious treatments

Five Most Important Determinants of the Treatment Gap



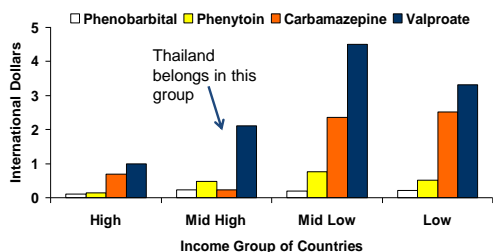
WHO: Atlas of Epilepsy Care, 2005
Meyer et al, Epilepsia 2012;53:2178-85

Number of Neurologists by World Bank Income Rating of Countries - an Index of Access to Care



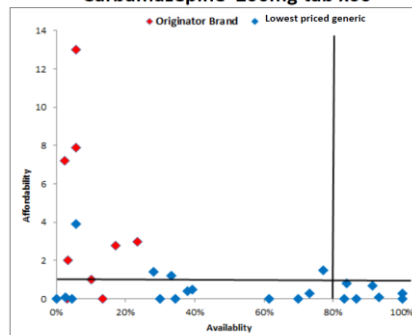
Neurology Atlas, WHO, 2004

Price of Drugs is Highest in the Countries with the Lowest Income



WHO: Atlas of Epilepsy Care, 2005

Availability & affordability: public sector Carbamazepine 200mg tab x60



Giving a Human Face to the Issues in The Philippines



A 2005 survey showed that the availability of medicines in the public sector was only about 15% and the prices excessive – 6 to 15 times the international reference prices.

Media and local community members produced a short video¹ that described the situation for an elderly couple dependent on medications.... The news coverage and the video, together with social mobilization and briefings of policy-makers led the Filipino Congress to pass a law to lower the prices of medicines

¹ (To view the video: <http://www.youtube.com/watch?v=hTVjZjGmyoQ>, accessed 7 February 2007)

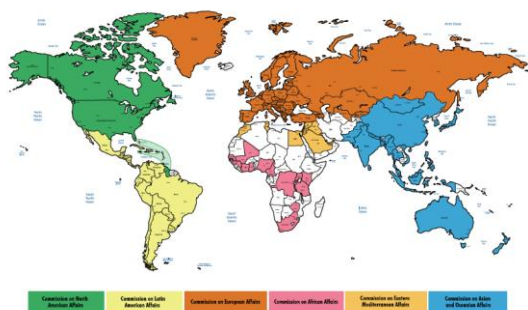
How Can We Address These Challenges?

By having all motivated people working together!

- professionals with an interest in epilepsy (ILAE)
- other professional societies
- IBE and other lay organizations
- international and national health organizations
- research funding bodies
- the public at large, and politicians

ILAE Chapters (2016)

The ILAE vision is a world where no person's life is limited by epilepsy



Making the ILAE Vision Come True: Priorities for the 2013-2017 Term

- Expand our educational agenda and our services to the epilepsy community
- Nurture the leaders of tomorrow
- Develop sustainable models to improve access to the medicines and quality health care -mobilize stakeholders!

What Does ILAE Do for Tomorrow's Leaders?

- A rich program of courses and summer schools, with extensive bursary support
- Training fellowships
- Mentorship initiatives, e.g. through participation in Commission and Task Forces
- Recognition programs, e.g. prizes for excellence in publications and the Harinarayan Young Neuroscientist Award
- Facilitated access to Regional and International Congresses

Improving Services to Our Younger Members:
Registration Fees (EUR) for IECs – 2009 to 2015

	2009 (Budapest)	2011 (Rome)	2013 (Montreal)	2015 (Istanbul)
Regular	625	655	545	545
Chapter Members	625	655	495	400
Junior	480	500	415	365
Jr Member	480	500	365	300



The Global Campaign against Epilepsy:
An ILAE / IBE / WHO Partnership

- Mission statement: to improve acceptability, treatment, services, and prevention of epilepsy worldwide
- Provide a platform for general awareness
- Assist governments in developing/improving access to epilepsy care, and quality of care



The GCAE China Project (2000-2006)

- Survey of 55,616 people in 5 provinces. Prevalence of epilepsy was 0.7%; treatment gap was 62.6%
- Awareness / education initiative was followed by treatment with phenobarbital in a pilot sample of 150 patients
- Seizure-free rate was 42%. Total 1-year healthcare costs per patient (Shanghai) decreased from 1,493 yuan to 92 yuan
- Intervention now being upscaled to other rural areas of China

Ding Ding et al, Epilepsia 2008; 49:525-538; Wang et al, Bull WHO 2008;86:964-9



World Health Organization

Approval of the Epilepsy Resolution by the
World Health Assembly: A Historical
Landmark | Tuesday 26th May 2015

Global burden of epilepsy and the need for
coordinated action at the country level to address its
health, social and public knowledge implications



Countries that Stood Up Supporting the Resolution

- | | | |
|--------------------------------|-----------------------|------------------------|
| • Albania | • India | • Poland |
| • Argentina | • Indonesia | • ep. of Korea |
| • Australia | • Iran | • Romania |
| • Azerbaijan | • Iraq ³ | • Russian Federation |
| • Bahrein | • Italy | • Saudi Arabia |
| • Benin ² | • Japan | • Suriname |
| • Brazil ¹ | • Lebanon | • Swazilan |
| • Canada | • Lithuania | • Taiwan |
| • Czech Republic, | • Malaysia | • Tanzania |
| • Dem. Rep. Congo ² | • Maldives | • Timor Leste |
| • Egypt ³ | • Malta | • Thailand |
| • Georgia | • Nepal | • United Kingdom |
| • Ghana | • Panama | • United States |
| • Greece | • People's Rep. China | • Uruguay ⁴ |
| | | • Venezuela |

¹Also speaking on behalf of the Americas; ²Also speaking on behalf of all the countries of the African region; ³Also speaking on behalf of all the countries of the Eastern Mediterranean region; ⁴Also speaking on behalf of all the countries of the Unisur Region

What Does the Resolution Call For?

- Recognize epilepsy as a major health priority, and implement actions to improve diagnosis and care – including actions at primary care level
- Improve access to epilepsy medicines
- Improve awareness and knowledge about epilepsy in the general population - step up the fight against stigma and discrimination
- Invest into prevention of epilepsy
- Make resources available for epilepsy research

Can the Resolution Improve Outcome for PWE?

- By itself, the Resolution is only a document – advocating for implementation is crucial
- It is a powerful tool to engage health authorities, governments and funding organizations
- Concrete actions are already taking place in many countries - often spurred by the initiative of ILAE chapters and associations
- Actions to be conducted jointly with WHO are being discussed, targeting mostly LAMIC countries

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Major Challenges to Ensure Global Effective Epilepsy Care

- Improve access to diagnosis and treatment
- Improve awareness and fight stigma, prejudice and discrimination
- **Improve the quality of treatment**
- Develop innovative and more efficacious treatments

Epilepsy Treatment: Can we Do Better?

- Large differences in prescribing practices across countries with similar economies
- Treatment strategies dictated by dogma, personal opinion and commercial pressure, not evidence
- Suboptimal treatment leads to failure to control seizures, and to unacceptable side effects
- The best treatment is not necessarily the newest drug!



Victims misdiagnosed by doctor paid £4m in compensation. The victims of a doctor who reduced children to "zombies" after misdiagnosing them have been paid more than £4m in compensation.
The Telegraph 11 February 2010

Hundreds of children wrongly diagnosed with epilepsy or incorrectly treated for the condition by a UK doctor are set to receive compensation after a High Court judge approved a multi-million pound settlement on June 15. Andrew Holton, a consultant paediatrician, was suspended from his post at Leicester Royal Infirmary in 2001 after colleagues became concerned about the number of children he was treating for epilepsy. In a case-by-case clinical review of almost 2000 children seen between 1990 and 2001, hospital bosses found that over 600 had been misdiagnosed. Many parents have described how their children were prescribed high doses of anticonvulsants and steroids and suffered traumatic side-effects as a result.

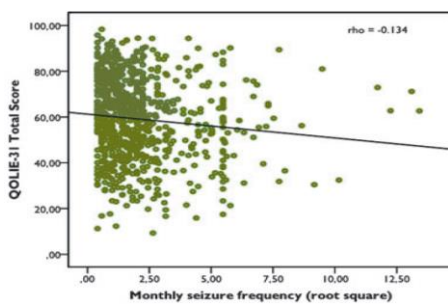
The Lancet Neurology, Volume 4, Issue 8, Page 451, August 2005

Overtreatment in Epilepsy

- Defined as a suboptimal balance between benefit and side effects, due to excessive AED dosages or unnecessary polypharmacy
- Highly prevalent, particularly among people with pharmacoresistant epilepsy
- A major determinant of poor quality of life

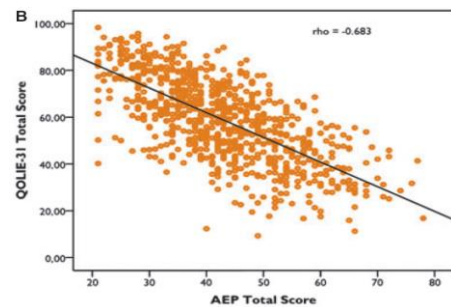
Perucca and Kwan, CNS Drugs 2005; 19: 897-908.

Seizure Frequency vs Quality of Life in 809 Patients with Refractory Epilepsy in Italy



Luoni et al, SOPHIE Study Group, Epilepsia; 2011;52: 2181-91

Adverse Drug Effects vs Quality of Life in 809 Patients with Refractory Epilepsy in Italy



Luoni et al, SOPHIE Study Group, Epilepsia; 2011;52: 2181-91

Treating Epilepsy in 2016: The Achievements

- ❖ Opportunities to adapt treatment choices to the individual needs have never been greater
- ❖ Most new AEDs are not enzyme inducers, and are less likely to cause adverse drug interactions
- ❖ We improved outcome through better recognition of indications, adverse effects and dose optimization

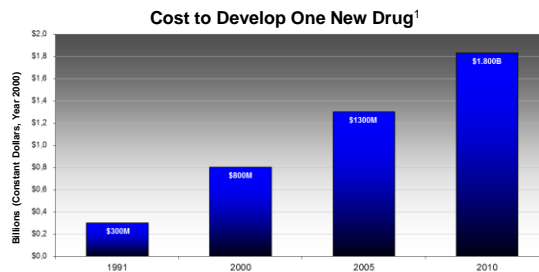
Treating Epilepsy in 2016: The Limitations

- ❖ We lack strong predictors of efficacy and side effects – treatment is still done by trial and error
- ❖ One third of patients are resistant to available AEDs – the same as in 1938
- ❖ Current treatments are symptomatic - none has been found to affect the underlying the disease

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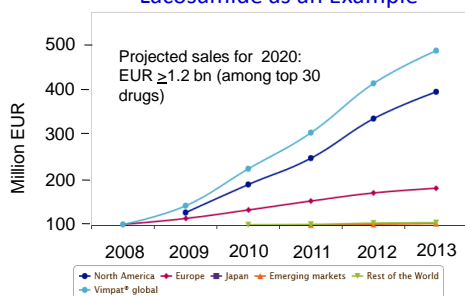
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The Increasing Cost of Drug Development



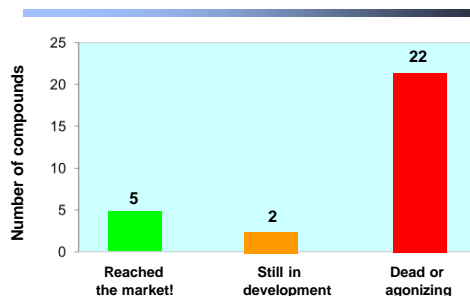
Sources: ¹ J. DiMasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics*, 2007; J. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 2003; Paul et al *Nature Rev Drug Discovery* 2010

Is AED Development No Longer Profitable? Lacosamide as an Example



<http://www.ucb.com/investors/UCB-today/Vimpat>

Fate of 29 Potential AEDs Which Were in Clinical Development in 1996



Potential AEDs Currently in Clinical Development

- | | |
|--------------------|------------------------|
| • Adenosine | • Huperzine A (INS001) |
| • Allopregnanolone | • Naluzotan (PRX 0023) |
| • Cannabidiol | • Selurapanel |
| • Cannabidivarin | • Tonabersat |
| • CNN 1014802 | • Valnoctamide |
| • CPP 15 | • VLB-01 (beprodone) |
| • 2-Deoxy-glucose | • YKP 3089 |
| • Ganaxolone | |

Targets of Potential AEDs Currently in Development

- | 'Traditional' targets | 'Novel' Targets |
|--|--|
| • AMPA receptors (selurampanel) | • Adenosine receptors (adenosine) |
| • GABA _A receptors (allopregnanolone, ganaxolone) | • CB receptors (cannabidiol, cannabidivarin) |
| • GABA transaminase (CPP 115) | • AchE (huperzine A) |
| • Potassium channels (ICA105665) | • Gap junctions (tonabersat) |
| • Sodium channels (YKP3089, CNN 1014802) | • Glycolysis (2-deoxy-glucose) |
| • SV2A (brivaracetam) | • H ₃ receptors (pitolisant) |
| | • 5-HT _{1A} receptors (naluzotan) |
| | • Melatonin receptors (VLB-01) |

The AEDs of the Future?

- Cation-chloride co-transporters (e.g., bumetanide)
- Inhibitors of the mTOR pathways (e.g. everolimus)
- Anti-inflammatory agents (e.g., anakinra and NSAIDs)
- Agents targeting the BBB and glial dysfunction (e.g., minocycline)
- Drugs reversing functional effects of epilepsy-causing mutations (e.g., quinidine for *KCNT1* mutations)
- Inhibition of TGF-beta signalling (e.g., losartan)
- Immunoactive treatments (e.g. steroids, IgG)

Precision Medicine: EIMS as an Example

- Epilepsy of infancy with migrating focal seizures is caused by a de novo mutation of the *KCNT1* gene in 50% of cases
- The mutation leads to gain of function of the affected potassium channels
- Quinidine, a KCN blocker, reverses the gain of function caused by the epileptogenic mutation
- Clinical observations confirm a positive effect of quinidine in some EIMS individuals

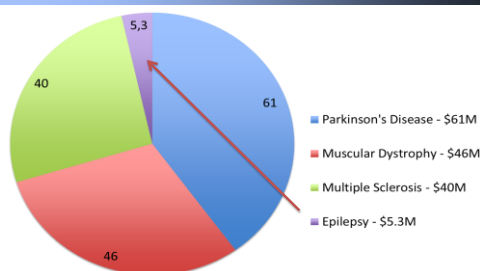
Milligan et al, Ann Neurol. 2014;75:581-90, 2014; Bearden et al, Ann Neurol 2014; 76:457-61; Mikati et al, Ann Neurol 2015;78:995-9

Technologies Beyond Drugs

- Gene or microRNA silencing (e.g., antagomirs)
- Gene therapy (e.g., studies with neuropeptide Y)
- Stem cell therapy
- Focal / biosensor-mediated drug delivery to the brain
- Drug delivery via nanoparticles / nanotherapeutics
- Neuromodulation



Annual Research Contributions of U.S. Non-Profits to 4 CNS Disease Areas (2011)

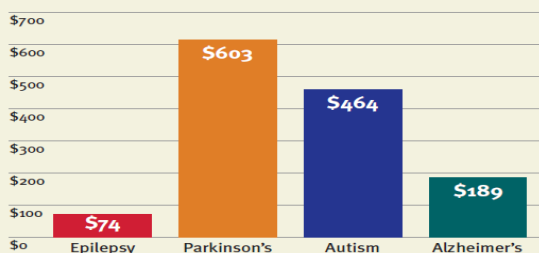


Data from 2011 990 Forms; some data are July-July; Epilepsy inc, CURE, EF, ERF, ETP.

Courtesy of Dr Roger Porter, May 2013

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.

CURE Report 2013 (<http://www.cureepilepsy.org/downloads/research/state-of-epilepsy.pdf>)

How Can we Promote a Radical Change in Support for Epilepsy Care and Research?

- By involving everyone – doctors alone cannot succeed without lay organizations and public support
- We need people with epilepsy and their families to come out and speak
- We need to improve awareness and dispel stigma through education of the general public

Champions who are Influencing the Political Agenda



Stand Up for Epilepsy!



STAND UP FOR EPILEPSY!



Conclusions

- Epilepsy is the most common serious neurological disease
- There are huge unmet needs that affect adversely the lives of people with epilepsy
- By working together and mobilizing governments and institutions, we can make a change

The time to act is now!

The Team - 2013-2017

