

Maximizing Antiseizure Medication to Save Lives and Save Costs

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28<sup>th</sup> Annual Meeting of the Epilepsy Society of Thailand, July 19<sup>th</sup>, 2024



DISCLOSURE

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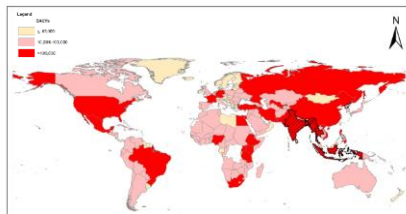
DISCLAIMER

Statements in this presentation about the properties of specific medications the presenter's interpretation of available evidence and do not represent the view of regulatory authorities. When prescribing, consult prescribing information in your country.

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 economic cost to individuals and society

Disability-Adjusted Life Years (DALYs) Due to Epilepsy Across The World

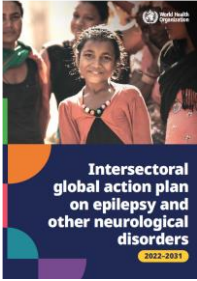


Singh et al. Lancet Regional Health Southeast Asia, published online 13 Jan 2023

Cost-Effective Approaches to Improve the Medical Treatment of People with Epilepsy: The Policy Makers' Perspectives

- Development of cost-effective sustainable policies needs to be adapted to the local setting
- Broad involvement of stakeholders essential
- Training health care professionals and providing access to medicines at affordable cost are only two components of an effective policy
- Policies should include broader strengthening of services, and a strategy to raise awareness and address stigma and discrimination
- Programs should incorporate impact assessment at a local level

Singh et al. Neurology 2020; 94:166-75; International Global Action Plan on Epilepsy and Other Neurological Disorders: 2022-2031 – Implementation Tool Kit, WHO, Geneva, 9 July 2024



<https://www.who.int/publications/i/item/9789240076624>



<https://www.who.int/publications/i/item/9789240096356>

**NEWS & REVIEWS**  
**Models of community-based primary care for epilepsy in low- and middle-income countries**

Gagandeep Singh, FRCP, Meenakshi Sharma, PhD, Anand Krishnan, PhD, Tarun Dua, MD, Francesco d'Aniello, Sara Mancini, and Jozeemir W. Sander, FRCP  
 Nidhiyogi<sup>1</sup> 2020;94:160-175. doi:10.1136/NNE.2000000000000039

Correspondence  
 Dr Sander  
 lsander@ucl.ac.uk

**Implementing WHO's Intersectoral Global Action Plan for epilepsy and other neurological disorders in Southeast Asia: a proposal**

The Lancet Regional Health - Southeast Asia 2023;10: 100135

Gagandeep Singh,<sup>1,2\*</sup> Meenakshi Sharma,<sup>3</sup> Gagan Singh,<sup>4</sup> Pabbi Maulik,<sup>5</sup> and Jozeemir W Sander<sup>6,7\*</sup>

**Cost-Effective Approaches to Improve the Medical Treatment of People with Epilepsy: The Physician's Perspectives**

- What are the goals of therapy for my patient?
- Which antiseizure medication (ASMs) provides the most cost-effective choice for my patient, taking the specific setting into account?
- Which formulation should I use (brand vs generics, immediate release vs modified release, etc)?
- How do I optimise dose, and how do I monitor clinical response?
- What else can I do to improve health outcomes for that individual?

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**The Goals of Therapy for Persons with Epilepsy**

- Ensure the best possible health-related quality of life taking into account the characteristics of the individual
- Complete seizure control without adverse effects impacting on quality of life is generally a primary goal. This involves measures to ensure adherence
- If seizure cannot be fully controlled, reducing seizure frequency and risk of seizure-related morbidity and mortality are among other major goals
- Any clinically relevant comorbidities need to be addressed

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- What else can I do to improve outcome for that individual?

Antiseizure Medicines (ASMs) in the 2023 WHO Essential Medicines List

ASMs for Chronic Treatment	ASMs for Emergency Use
<ul style="list-style-type: none"> <li>Carbamazepine</li> <li>Lamotrigine</li> <li>Levetiracetam</li> <li>Phenytoin</li> <li>Valproic acid</li> <li>Phenobarbital</li> <li>Phenytoin</li> </ul>	<ul style="list-style-type: none"> <li>Diazepam (injection, rectal gel/solution)</li> <li>Lorazepam (injection)</li> <li>Midazolam (injection/buccal)</li> <li>Phenobarbital (injection)</li> <li>Phenytoin (injection)</li> <li>Magnesium sulfate (injection, only for use in eclampsia and pre-eclampsia)</li> </ul>
Complementary list	Complementary list
Ethosuximide	<ul style="list-style-type: none"> <li>Levetiracetam (injection)</li> <li>Valproic acid (injection)</li> </ul>

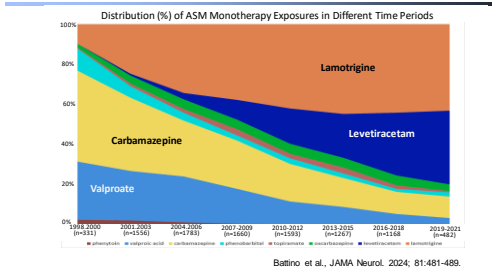


Key Properties to be Considered When Selecting an ASM for an Individual Patient

- Spectrum of efficacy and magnitude of efficacy
- Adverse effect profile
- Impact on co-morbidities
- Potential for adverse drug interactions
- Mechanism of action
- Ease of use
- Cost

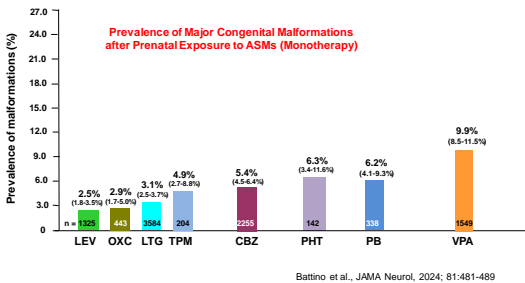
The management of epilepsy in women of childbearing potential as an example

EURAP Pregnancy Registry- Changes in Prescription Patterns Over the Years 1998 to 2021

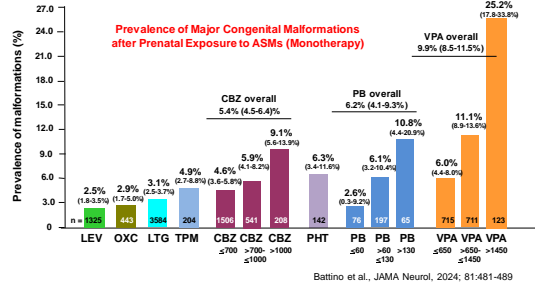


Leonardo da Vinci, Foetus in the Womb, ca 1510-12

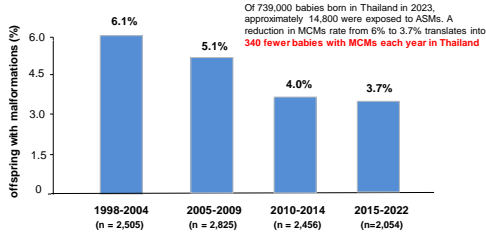
The Comparative Teratogenicity of ASMs – EURAP Registry Data 2024



The Comparative Teratogenicity of ASMs – EURAP Registry Data 2024



Changes in Prevalence of Major Congenital Malformations in the Offspring of Women Enrolled in the EURAP Registry over the Period 1998-2022



Tomson et al., Dublin IEC, September 2023      Battino et al., JAMA Neurol. 2024; 81:481-489

The Dilemma of Competing Risks: Findings from the U.K. MBRRACE Study



18 women died from SUDEP in 2016-18 in the UK and Ireland compared to 8 women in 2013-15. **This represents a more than doubling of the rate of SUDEP between 2013-15 and 2016-18 (RR 2.33, 95% 0.96-6.19, p=0.04).**

The statistically significant increase in maternal deaths from SUDEP – sudden unexpected death in epilepsy – **alongside new guidance on valproate use in women of reproductive age** - emphasises the importance of effective pre-pregnancy medication adjustment. This applies equally to women with pre-existing mental health problems – maternal suicide remains the leading direct cause of maternal death between six weeks and a year after the end of pregnancy.

Knight M, Bunch K, Tuffnell D, et al., eds. UK Maternal, Newborn and Infant Clinical Outcome Review Programme 2016-18 <https://www.hqip.org.uk/wp-content/uploads/2021/01/ef-202-mni-saving-lives-improving-mothers-care-2020-report.pdf>

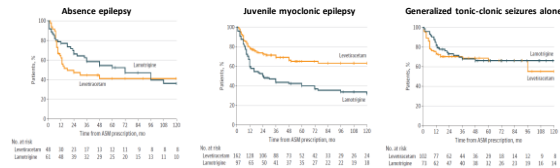
JAMA Neurology | Original Investigation

JAMA Neurol. 2023;80(11):1174-81.

Levetiracetam vs Lamotrigine as First-Line Antiseizure Medication in Female Patients With Idiopathic Generalized Epilepsy

Enayate Gaziul MD, PhD, Evencio Garcia MD, PhD, Alexander Moroni MD, PhD, Isaura Garcia MD, PhD, Roberto H. Caraballo MD, Susana Alvarez MD, PhD, Estrella Angulo MD, PhD, Cecilia Garcia MD, Estrella Alvarez MD, PhD, Angela Pereda MD, Sara Luciani MD, PhD, Priscilla Quaresima MD, Diana Pizarro MD, Priscilla Pizarro MD, Lorena Galarza MD, Verónica Ruiz MD, Beatriz Mendez MD, Estrella Parodi MD, Carolina Marín MD, Priscilla García de Sarmiento MD, PhD, Andrea Cardozo MD, PhD, Argem Latorre MD, PhD, Francisca F. Espinoza MD, María F. Coluberto MD, Benita Baskin MD, PhD, Christoph J. Bock MD, Carlos Schiavonetta MD, PhD for the Women With Idiopathic Treatment Resistant Epilepsy (WITRE) Study Group

- Multicenter retrospective follow-up study of 543 females of childbearing age diagnosed with IGE and started on levetiracetam (LEV) or lamotrigine (LTG) monotherapy
- LEV was more effective than LTG in JME, whereas a similar effectiveness between LEV and LTG was observed in other IGE syndromes



The Challenges of Selecting ASMs in a Non Expert Setting: Can We Get Help from a Smartphone?



Received: 12 May 2020 | Revised: 17 June 2020 | Accepted: 19 June 2020  
DOI: 10.1111/epi.16619

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

A pragmatic algorithm to select appropriate antiseizure medications in patients with epilepsy

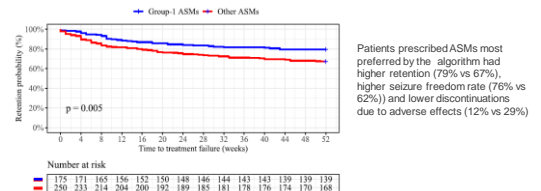
Ali A. Asadi-Pooya<sup>1,2</sup> | Sándor Beniczky<sup>3,4</sup> | Guido Rubboli<sup>5,6</sup> | Michael R. Sperling<sup>7</sup> | Stefan Rampp<sup>7,8</sup> | Emilio Perucca<sup>9,10</sup>

Epipick - <https://www.epipick.org>

- A freely available electronic tool to aid ASM selection in patients with epilepsy and seizure onset at age 10 or older
- Incorporates an algorithm for quick diagnostic validation
- Categorizes ASMs into 4 categories (from most desirable to least desirable)
- Categorization is based on consideration of individual variables (seizure types, age, gender, comorbidities, drug allergies, comedication)
- Underwent two external validations with positive outcomes
- Requires no more than 2 min for data entry and software feedback

Web-based decision support system for patient-tailored selection of antiseizure medication in adolescents and adults: An external validation study

Laventa Hadady<sup>1</sup> | Péter Kilyéni<sup>1</sup> | Emilio Perucca<sup>2</sup> | Stefan Rampp<sup>3,4</sup> | Daniel Fabó<sup>5</sup> | Csaba Bereczki<sup>6</sup> | Guido Rubboli<sup>7</sup> | Ali A. Asadi-Pooya<sup>8</sup> | Michael R. Sperling<sup>9</sup> | Sándor Beniczky<sup>10,11</sup>



Hadady et al. Eur J Neurol 2022;22:382-9

JAMA Neurol. 2022;69(10):1001-1011. doi:10.1001/jamaneurol.2022.2514  
 Published online August 29, 2022.

Research

JAMA Neurology | Original Investigation

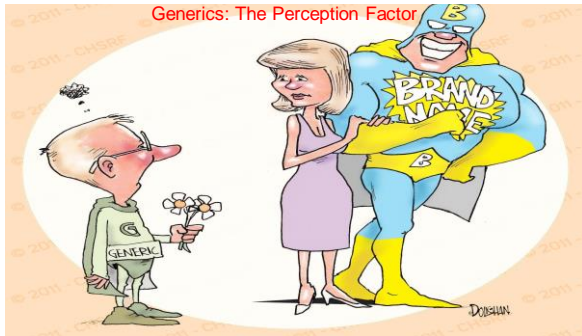
**Development and Validation of a Deep Learning Model for Predicting Treatment Response in Patients With Newly Diagnosed Epilepsy**

Hans Hillearn, MD, Wei Feng, MS, Zhibin Chen, PhD, CSat, Jun Choong, BEng, Martin J Brodie, MD, PhD, Si-Lin Feng, MBBS, Hong-Shang Lim, MBBS, PhD, Junhong Wu, MD, Xuefeng Wang, MD, Nicholas Laver, MSc, PhD, Guanghong Ni, MD, Xiang Gao, MSc, Mijian Luo, MD, Zyi Chen, MD, Zongquan Ge, PhD, Patrick Kwan, MD, PhD

<sup>1</sup>Although its current performance is modest, our model serves as a foundation to further improve clinical applicability to and comparison with expert consensus decision-making algorithms<sup>1</sup>

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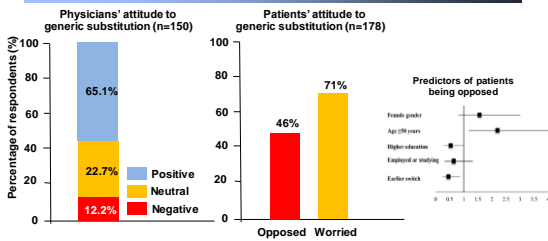


**ILAE Survey on Perceptions and Knowledge of Generic Substitution of ASMs**

- Survey among ILAE Chapter members; 800 respondents, mostly from Asia-Oceania (44%) and Europe (39%)
- The majority of responders had little or no education in bioequivalence and generic substitution
- Concern about level of regulatory control and quality of available generic products was expressed by most responders from low- and middle-income countries

Niyongere et al, on behalf of the ILAE Generic Substitution Task Force, Epilepsia Open 2022;7:260-70)

**A Swedish Survey of Physicians' and Patients' Attitude Towards Generic Substitution of ASMs**



Olsson et al, Acta Neurol Scand 2021;144:600-7; Olsson et al, Epilepsy & Behav 2021;114:107554

**Four Good Reasons for Supporting the Use of Generic ASMs**

- Currently approved generics meet rigorous quality standards
- Generics provide substantial cost savings to consumers, and to society – releasing resources for investment in health care
- Generics stimulate innovation, and the discovery of better medicines
- No properly controlled study has ever shown that generics are inferior to brand products - reports raising danger signals can have major bias!

### The Benefits of Generics Generic Drugs and Health Care Costs

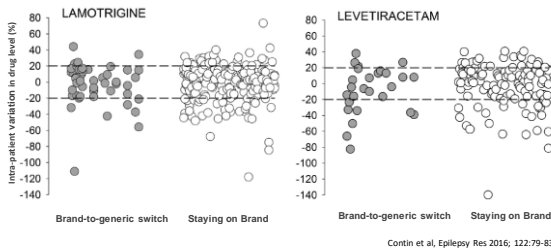
- In the US (where 8 out of 10 prescriptions are generics) generics saved consumers \$158 bn in 2010 alone.<sup>1</sup> For France, annual savings were €13.4 bn in 2012.<sup>2</sup>
- It is estimated that, in the U.S., \$1.16 billions could be saved for every 1% increase in the use of generic drugs<sup>3</sup>
- In low- & middle-income countries, **up to 89% of expenditure for medicines could be saved** by switching private sector purchases from originators to generics<sup>4</sup>

<sup>1</sup>[www.fda.gov/drugs/resourcesforyou/consumers/buyingsavingmedicinesafely/htm?2](http://www.fda.gov/drugs/resourcesforyou/consumers/buyingsavingmedicinesafely/htm?2); <sup>2</sup>Molinier et al, *Eur J Clin Pharmacol* 2017;73:471-77;<sup>3</sup> [www.ama-assn.org/ama/pub/category/15279.html](http://www.ama-assn.org/ama/pub/category/15279.html);<sup>4</sup>Cameron et al, *Value Health* 2012; 15: 664-73.



Is there any evidence justifying safety concerns with currently available generic ASMs?

### Day-to-Day Variation in Plasma Levels after Switching from Brand to Generic is Similar to That Observed in Patients Continuing on Brand



Contin et al, *Epilepsy Res* 2016; 122:79-83

### Are Generics Harmful? A Canadian Randomized Controlled Study

- 8-week randomized study of switching between brand valproic acid and generic in 64 patients
- Switch not associated with any significant difference in serum drug levels or seizure control
- Two previously seizure-free patients, however, showed recurrence of seizures
- **Both of these patients were in the group that continued to take the brand product !!!**

Vadney and Kraushaar, *Ment Retard* 1997;35:468-472

*Drugs*. 2010 March 26; 70(5): 605-621. doi:10.2165/0008530-000000000-00000.

### Seizure Outcomes Following Use of Generic vs. Brand-Name Antiepileptic Drugs: A Systematic Review and Meta-Analysis

Aaron S. Kesselheim, M.D., J.D., M.P.H.<sup>1</sup>, Margaret R. Stedman, Ph.D.<sup>1</sup>, Ellen J. Bubrick, M.D.<sup>2</sup>, Joshua J. Gagne, Pharm.D., M.S.<sup>3</sup>, Alexander S. Misono, B.A.<sup>1</sup>, Joy L. Lee, B.A.<sup>1</sup>, M. Alan Brookhart, Ph.D.<sup>2</sup>, Jerry Avorn, M.D.<sup>1</sup>, and William H. Shrank, M.D., M.S.H.S.<sup>1</sup>

<sup>1</sup>Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School

<sup>2</sup>Division of Epilepsy, Department of Neurology, Brigham and Women's Hospital and Harvard Medical School

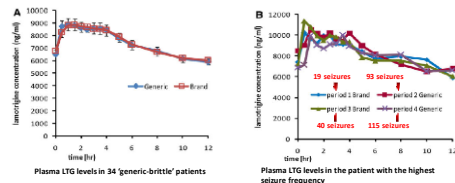
<sup>3</sup>Department of Epidemiology, UNC Gillings School of Global Public Health

**Conclusions**—Though most RCTs were short-term evaluations, the available evidence does not suggest an association between loss of seizure control and generic substitution of at least three types of AEDs. The observational study data may be explained by factors such as undue concern from patients or physicians about the effectiveness of generic AEDs after a recent switch. In the absence of better data, physicians may want to consider more intensive monitoring of high-risk patients taking AEDs when any switch occurs.



### Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard

\*Tricia Y. Ting, \*Wenhe Jang, †Robert Linsberger, †Jessica Wong, †Jace W. Jones, †Maureen A. Kane, \*Alfon Krumboltz, †Robert Tamura, and †James E. Poll  
*Epilepsia*, 56(9):1415-1424, 2015



Significance: Bioequivalence results in "generic-brittle" patients with epilepsy under clinical conditions support the soundness of the FDA bioequivalence standards.



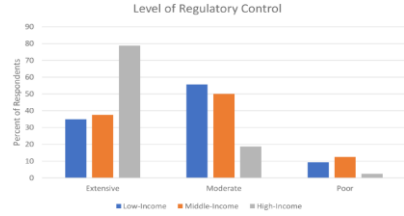
AES Revised Statement on Generic ASM Substitution

'Drug formulation substitution with FDA-approved generic products reduces costs without compromising efficacy'

'Patient counseling should not include descriptions of generic products as being a cheaper or lower-quality version of the brand product'

Vossler et al, *Epilepsy Curr.* 2016;16(3):209-11.

ILAE Survey on Barriers to Generic ASM Use: Percentage of Respondents Who Reported Extensive, Moderate or Poor Regulatory Control of Pharmaceutical Products in Their Country



Nyongere et al, on behalf of the ILAE Generic Substitution Task Force, *Epilepsia Open* 2022;7:260-70

Cost-Effective Approaches to Improve the Medical Treatment of People with Epilepsy: The Physician's Perspectives

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Consequences of Poor Adherence to the Prescribed ASM Regimen

**Nonadherence to antiepileptic drugs and increased mortality**  
Findings from the RANSOM Study

Neurology, 2008 Nov 11;71(20):1572-8.

**ABSTRACT**  
Objective: The primary objective was to investigate whether nonadherence to antiepileptic drug (AED) is associated with increased mortality, and the secondary objective to examine whether nonadherence increases the risk of serious clinical events, including emergency department (ED) visits, hospitalizations, motor vehicle accident (MVA) injuries, fractures, and head injuries.

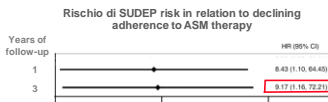
Evento	Risk Ratio (sarsa aderenza/ aderenza adeguata)
Emergency Department visits	1.50 (1.49-1.52)
Ospedalizz/hospitalizations	1.86 (1.84-1.88)
Injuries from road traffic accidents	2.08 (1.81-2.39)
Fractures	1.21 (1.18-1.23)
Traumatic brain injury	0.73 (0.72-0.75)
<b>Mortality</b>	<b>3.32 (3.11-3.54)</b>

RESEARCH ARTICLE

*Epilepsia*, 2023;64:641-653.

Adherence patterns in antiseizure medications influencing risk of sudden unexplained death in epilepsy: A data linkage study using dispensed prescriptions

Michael Tan<sup>1</sup> | Samuel S. Allemann<sup>1</sup> | Xiwen Simon Qin<sup>1</sup> | Wendy J. D'Souza<sup>1</sup>



\*Estimate based on Cox proportional hazard model, adjusted for age, sex, socioeconomic index, duration of epilepsy, concomitant ASMs, number of additional ASMs prescribed and comorbidity

*Epilepsia* & Behavior 32 (2014) 49-54

Seizure-related vehicular crashes and falls with injuries for people with epilepsy (PWE) in northeastern Thailand

Jiamjit Saengsuwan<sup>a</sup>, Wongsa Laohasirirong<sup>a</sup>, Suwanna Boonyaleepan<sup>b</sup>, Kittisak Sawanyawisuth<sup>c</sup>, Somsak Tiamkao<sup>d</sup>, Anoninara Talkul<sup>e,f,g</sup>, Integrated Epilepsy Research Group<sup>h</sup>

<sup>a</sup> Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand  
<sup>b</sup> Faculty of Nursing, Khon Kaen University, Khon Kaen, Thailand  
<sup>c</sup> Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand  
<sup>d</sup> Khon Kaen University, Khon Kaen, Thailand

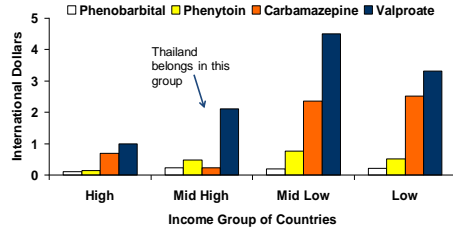
- Survey of 203 patients with epilepsy randomly selected at the university epilepsy clinic
- 84% of patients were operating regularly a vehicle. Of those, 22% had a vehicle accident. Of all patients surveyed 43% had been involved in a vehicle crash or a fall resulting in injury.
- Medication compliance was estimated at 66%, while 59% said they had little or no control over their seizures, and more than half did not feel confident about their ability to take care of themselves or to take their ASMs properly
- **'The results of this study suggest that patients' poor medication adherence and lack of confidence in managing their seizures may contribute to accidents**

### Some Major Causes of Poor Adherence to Prescribed ASM Treatment

- Suboptimal physician-patient communication
- Low educational status
- Perceived stigma
- Complex treatment regimens
- Memory dysfunction
- Depressed mood
- Adverse effects
- Problematic access to medication, including cost

Faught, *Epilepsy & Behav* 2012;25:297-30; Liu et al, *Epileptic Dis* 2013; 15:289-94; McAuley et al, *Epilepsy & Behav* 2015;43:61-6; Meevag et al *Acta Neurol Scand* 2016 Epub ahead of print

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

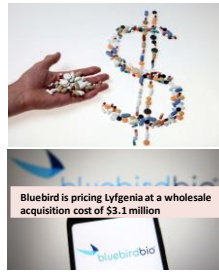


WHO: Atlas of Epilepsy Care, 2005

### Prices for new US drugs rose 35% in 2023, more than the previous year

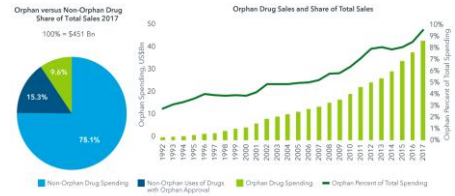
The median annual list price for a new drug was \$300,000 in 2023, according to the Reuters analysis of 47 medicines, up from \$ 222,000 a year earlier. In 2021, the median annual price was \$ 190,000

More than half of the new products approved by the FDA in 2023 and 2022 were for orphan diseases



Deena Beasley, February 24, 2024 <https://www.reuters.com/business/healthcare-pharmaceuticals>

### The Increasing Share of Orphan Medications in the Pharmaceuticals Market



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drug@FDA Database; FDA website, Accessed Sep 2018. Note: Volume is based on Extended US. Orphan Drug spending includes only orphan approved uses of drugs with orphan approvals. Report: Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments. IQVIA Institute for Human Data Sciences, Oct 2018

### The parents hoped an existing drug might keep their kids from having seizures. Then they saw the price

By Erika Check Hayden (Jan 3, 2015)



*Journal of Law and the Biosciences*, 158-166  
doi:10.1093/lawbio/lbu006  
Advance Access Publication 7 January 2015  
Peer Commentary

### Orphan drug incentives in the pharmacogenomic context: policy responses in the USA and Canada

Matthew Herder<sup>1</sup>

<sup>1</sup>Health Law Institute, Faculty of Medicine and Law, Dalhousie University, Halifax, Canada.  
<sup>\*</sup>Corresponding author. E-mail: Matthew.Herder@Dal.CA

- Sodium phenylbutyrate – a drug approved to treat urea cycle disorders – is a promising candidate for repurposing to treat epilepsies due to STXBP1 and SLC6A1 gene mutations
- Bench-to-market cost is estimated at ‘10% of that of a typical drug’, yet it was marketed at a price of \$45,000 per year in children. In Europe, another sodium phenylbutyrate product sells at EUR 11,000 per year.
- Glycerol phenylbutyrate (Ravicti), a derivative claimed to ensure better compliance and approved based on a non-inferiority trial over sodium phenylbutyrate now dominates the market for the same indications at a price of USD 740,000 per year

Batshaw et al. *JAMA* 2014;311:1729-30

Letter 2018; 392:792-94

### Outrageous prices of orphan drugs: a call for collaboration

Lucia Luzzatto<sup>1</sup>, Hanna H Hryg<sup>1</sup>, Anigo Schilling<sup>2</sup>, Enrico Costa, Steven Simons, Franz Schaefer, Jonathan C P Rice, Giampaolo Merlini, Hilma Kaatinen, Silvio Ganetti, Carlo E Hóflak, Giuseppe Bernuzzi, on behalf of the Second Workshop on Orphan Drugs participants

Few instances of a single act of legislation have shifted industrial policy in the pharmaceutical industry like the Orphan Drugs Act did when it was signed in the USA in 1983. The Act was written to facilitate the development of drugs for rare diseases and health conditions, and the diseases. So-called orphanisation of common disorders, which is a direct result of the genomics era, enhances the scope for precision medicine and is expected to expand the scope further. At present, 40% of drugs with OMP status are approved for specific types of cancer.



### Fair Pricing of Innovative Medicines: An EHA Position Paper

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