EPILEPSIAS

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Conflictos de interés

- ***Honorarios por Investigación clínica:***
- NOVARTIS
- JANSSEN-CILAG
- ESAI
- UPSHER-SMITH
- ***Honorarios por conferencias:***
- ABBOTT
- NOVARTIS
- GSK
- PFIZER
- JANSSEN-CILAG
- UCB PHARMA
- GADOR
- Raffo
- FAPASA
- ASOFARMA
- TECNOFARMA

OBJETIVOS

- Trata una primera crisis epiléptica ?
- Utilizan de drogas inductoras ?
- Que drogas utilizan en epilepsia de reciente comienzo?
- Que combinaciones se pueden utilizar en epilepsia resistente?
- En epilepsia resistente se utilizan 3-4 drogas antiepilépticas simultáneamente ?
- Status epiléptico.

Epilepsia

Afecta personas de todas las edades, razas y status socio-económico , prevalencia de 5 - 10 por 1000 habitantes .
Afecta aproximadamente más de 68 millones de personas en todo el mundo , 1.4 % de la población mundial (CDC: centro de prevención y control de enfermedades, USA, 2008)

Epilepsia es la primera enfermedad neurológica más común en niños y la segunda en adultos. Produce un gasto de salud (OMS) mayor al cáncer de mama en las mujeres e igual al de pulmón, en varones

64 % de las personas con epilepsia controlan las crisis hacen una vida normal

36 % de los pacientes son **RESISTENTES AL TRATAMIENTO** (Perucca 2007): estos tienen mayor morbilidad, mortalidad y peor calidad de vida (Wiebe 2007)

Comienza en cualquier momento de la vida
Dos momentos que es más frecuente su comienzo, primer año de vida y después de los 60 años.

Es 6 a 1 + frecuente que empiece **después de los 60 años con respecto al 1año de vida**.(Neurology 2005)

- Epilepsia segunda causa de muerte por causa neurológica por años de enfermedad luego del ACV

- 50 % de las personas que padecen epilepsia tienen trastornos psiquiátricos y trastornos cognitivos **(Epilepsia S2 (Suppl 1) 1,6 2011**

Epilepsias
Clasificación, 2017
ILAE

- **Crisis de inicio focal**
  - Conciencia conservada (CPS)=auras (20%)
  - Con pérdida de conciencia (CPC) (50%)

- **Crisis de inicio generalizado**
  - Motoras
    - tónico-clónicas
    - tónicas
    - clónicas
    - atónicas
    - mioclónicas
  - No motoras(ausencias)

- CF ⟶ EBTC

VIDEOS

Epilepsia, **46**(4):470–472, 2005
Blackwell Publishing, Inc.

Special Article

Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)

*Robert S. Fisher, †Walter van Emde Boas, ‡Warren Blume, §Christian Elger, ‖Pierre Genton, ¶Phillip Lee, and **Jerome Engel, Jr.

*Stanford University Medical Center, Department of Neurology, Stanford, California, U.S.A.; †Stichting Epilepsie Instellingen, Department of EEG and EMU, Heemstede, The Netherlands; ‡University of Western Ontario, London Health Sciences Centre, London, Ontario, Canada; §University of Bonn, Clinic of Epileptology, Bonn, Germany; ‖Centre Saint-Paul, Hôpital Henri Gastaut, Marseille, France; ¶British Epilepsy Association, Leeds, England; and **David Geffen School of Medicine at UCLA, Department of Neurology, Los Angeles, California, U.S.A.*

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014
doi: 10.1111/epi.12550

Robert S. Fisher
Department of Neurology & Neurological Sciences, Stanford University School of Medicine

Summary

Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The International League Against Epilepsy (ILAE) accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years. "Resolved" is not necessarily identical to the conventional view of "remission or "cure." Different practical definitions may be formed and used for various specific purposes. This revised definition of epilepsy brings the term in concordance with common use.

KEY WORDS: **Epilepsy, Seizure, Definition, Unprovoked, Recurrence.**

1) Por lo menos dos crisis no provocadas (o reflejas) separadas por más de 24 hs entre ellas.

2) Una crisis no provocada (o refleja) y una probabilidad de más crisis similar al riesgo de recurrencia después de dos crisis no provocadas (aproximadamente 60 % o más) que ocurren en un período de 10 años .

3) el diagnóstico de un Síndrome epiléptico

Propuesta de nueva definición resolución de la epilepsia

- Epilepsia resuelta: se considerará que no esté más presente en personas que tienen un Síndrome edad dependiente y que han pasado esa edad o permanecen libres de crisis epilépticas por lo menos 10 años , sin DAC en los últimos 5 años .
- Habiendo investigado que no hay factores de riesgo conocidos asociados con alta probabilidad de futuras crisis epilépticas

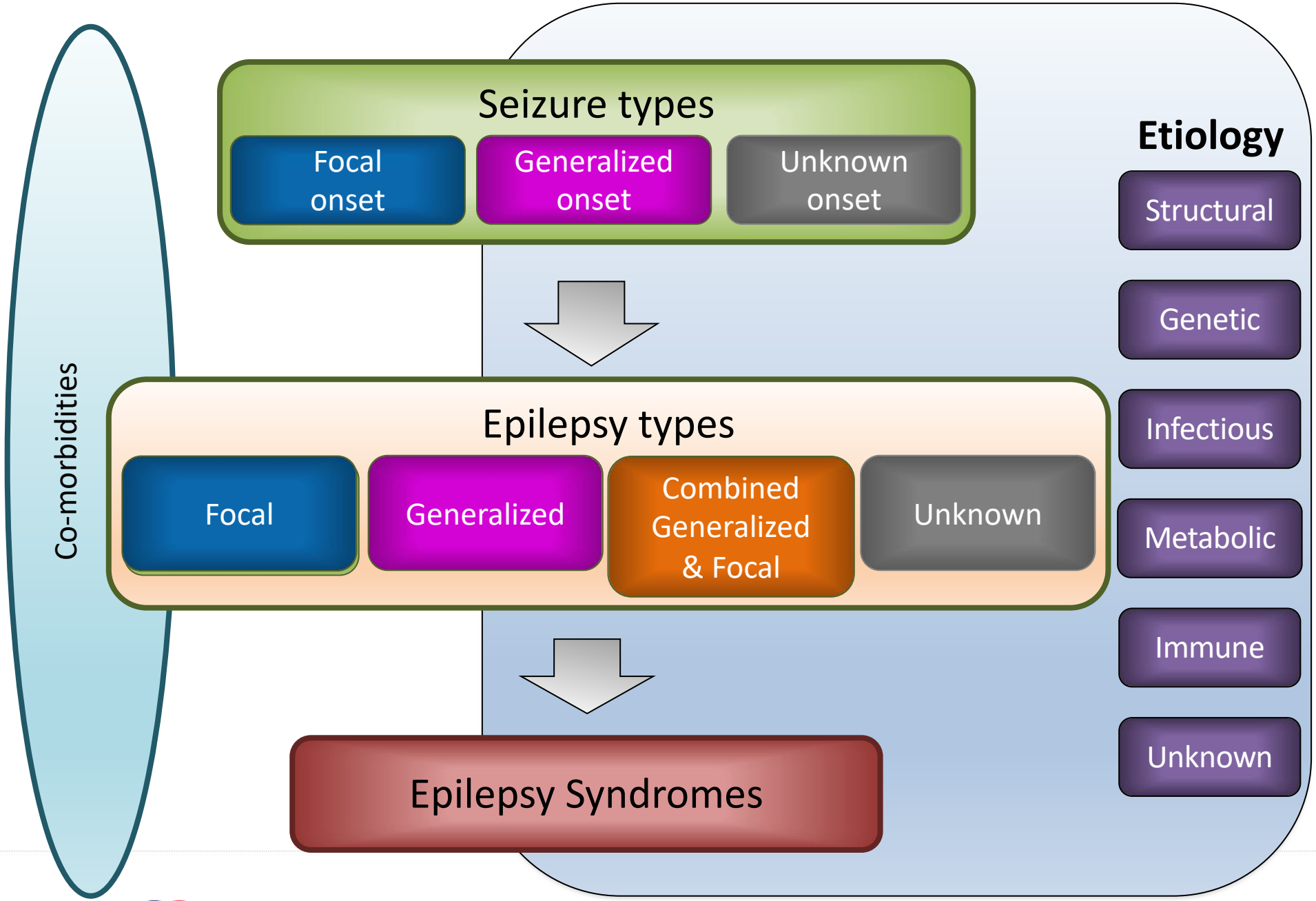
ILAE POSITION PAPER

ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

[1,2,3]Ingrid E. Scheffer, [1]Samuel Berkovic, [4]Giuseppe Capovilla, [5]Mary B. Connolly, [6]Jacqueline French, [7]Laura Guilhoto, [8,9]Edouard Hirsch, [10]Satish Jain, [11]Gary W. Mathern, [12]Solomon L. Moshé, [13]Douglas R. Nordli, [14]Emilio Perucca, [15]Torbjörn Tomson, [16]Samuel Wiebe, [17]Yue-Hua Zhang, and [18,19]Sameer M. Zuberi

Epilepsia, **(*):1–10, 2017
doi: 10.1111/epi.13709

SUMMARY



Scheffer et al, Epilepsia 2017;58:512-521

Original article

Epileptic Disord 2017; 19 (2): 178-85

Educational needs of epileptologists regarding psychiatric comorbidities of the epilepsies: a descriptive quantitative survey

Marco Mula [1], Esper Cavalheiro [2], Alla Guekht [3], Andres M. Kanner [4], Hyang Woon Lee [5], Cigdem Ozkara [6], Alfredo Thomson [7], Sarah J. Wilson [8]
on behalf of the Task Force on Education of the ILAE Commission on Neuropsychiatry

[1] Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust; Department of Neuropsychiatry, South West London & St George's Mental Health Trust; Institute of Medical and Biomedical Sciences, St George's University of London, United Kingdom
[2] Department of Neurology and Neurosurgery, Escola Paulista de Medicina/UNIFESP, São Paulo, Brazil
[3] Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department of Moscow, Pirogov Russian National Research Medical University, Moscow, Russia
[4] Comprehensive Epilepsy Center, Department of Neurology, University of Miami, Miller School of Medicine, Miami, USA
[5] Epilepsy and Sleep Center, Department of Neurology, Ewha Womans University Mogdong Hospital, Ewha Womans University School of Medicine and Ewha Medical Research Institute, Seoul, South Korea
[6] Department of Neurology, Medical Faculty, Istanbul University Cerrahpasa, Istanbul, Turkey
[7] Institute of Neurosciences at Favaloro University and Institute of Cognitive and Behavioural Neurology (INECO), Buenos Aires, Argentina
[8] Melbourne School of Psychological Sciences, The University of Melbourne, and Comprehensive Epilepsy Program, Austin Health, Melbourne, Australia

Received March 6, 2017; Accepted May 14, 2017

ILAE commission report

Epileptic Disord 2019; 21 (2): 129-40

Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy

Ingmar Blümcke [1], Alexis Arzimanoglou [2], Sandor Beniczky [3], Samuel Wiebe [4], the EpiEd Task Force[a]

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[2] Department of Clinical Epileptology, Sleep Disorders and Functional Neurology in Children, University Hospitals of Lyon, Member of the European Reference Network ERN EpiCARE and DYCOG team, Lyon Neurosciences Research Centre (CRNL), Lyon, France
[3] Department of Clinical Neurophysiology, Danish Epilepsy Centre, Dianalund and Aarhus University Hospital; Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[4] Department of Clinical Neurosciences and Clinical Research Unit, Cumming School of Medicine, University of Calgary, Canada

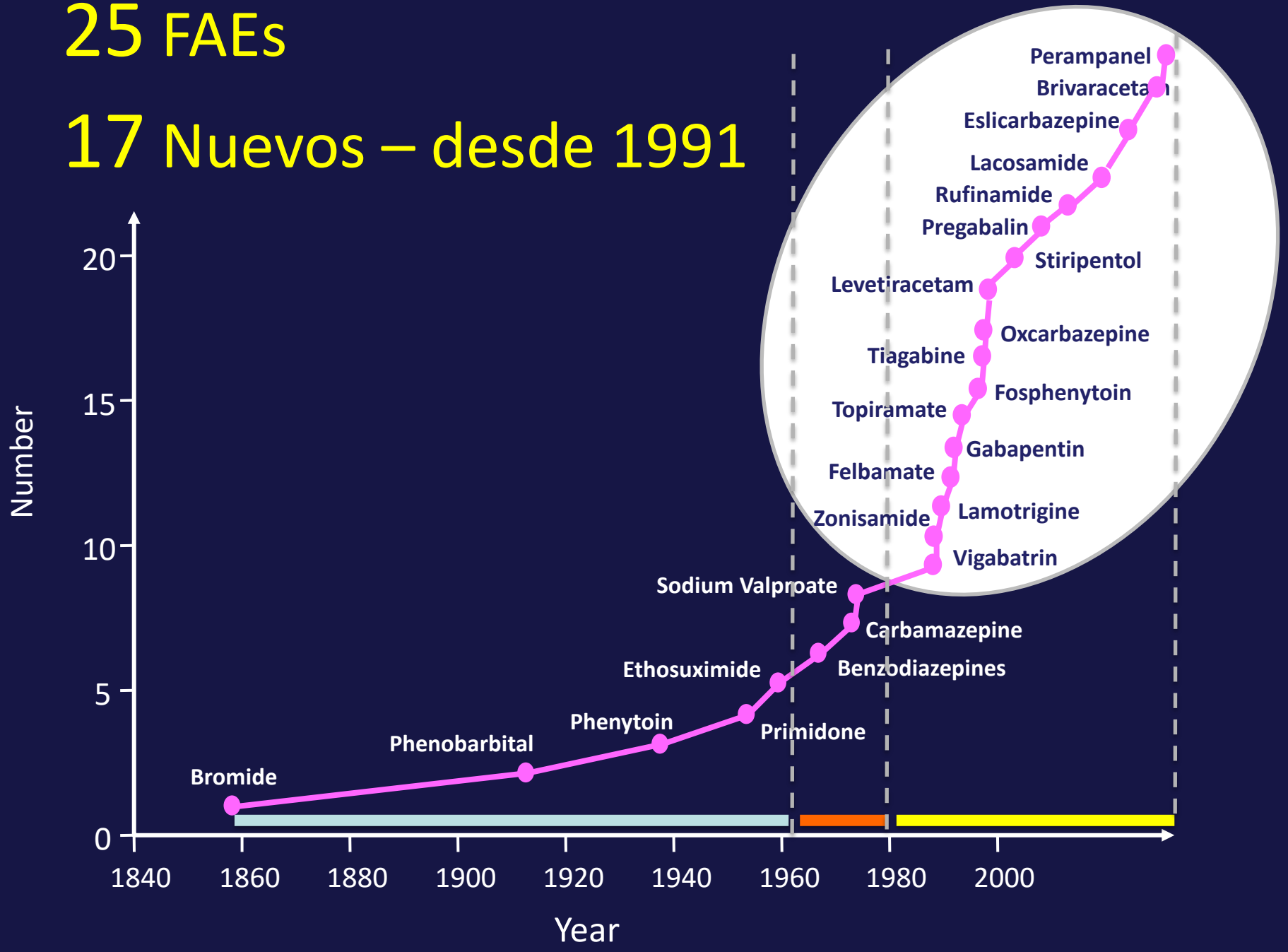
Received January 08, 2019; Accepted February 07, 2019

6.0 Comorbidities		
	6.1	**Demonstrate the ability to diagnose and manage cognitive and psychiatric comorbidities** 6.1.1 Recognize psychiatric comorbidities, such as depression, anxiety, attention deficit and hyperactivity disorder, psychosis and autism spectrum disorders 6.1.2 Appropriately manage or advise regarding psychiatric comorbidities 6.1.3 Adjust anti-seizure treatment as required for psychiatric comorbidities 6.1.4 Demonstrate the ability to recognize and manage the special needs of persons with epilepsy and intellectual disability 6.1.5 Manage cognitive changes in epilepsy and the cognitive effects of AEDs

Epilepsia de reciente comienzo

25 FAEs

17 Nuevos – desde 1991



Identificación Temprana de la Epilepsia Resistente

Estudio Glasgow

- Seguimiento prospectivo al inicio de DAC
- 525 pacientes consecutivos no tratados
- 470 nunca tratados previamente
- Edad promedio 29 años (rango 9-93)
- Seguimiento promedio 5 años (2-15.6)
- 1 año sin crisis : 64%
- **Kwan P and Brodie MJ. N Engl J Med 2000;342:314-319**

Epilepsia recientemente diagnosticada
Remisión al año

- Monoterapia de primera línea 47%
- Monoterapia de segunda línea 13%
- Monoterapia de tercer línea 1%
- Politerapia 3%
- Total sin crisis
  64%

Estudio de Glasgow
NEJM 2000

- 80 % de los pacientes libres de crisis (47%) con la primer droga :
- Carbamacepina: 600 mg/ día o <
- Valproato: 1000 mg/día o <
- Lamotrigina: 200 mg/día o <
- 20 % restante necesitó dosis altas.

Research

JAMA Neurology | Original Investigation

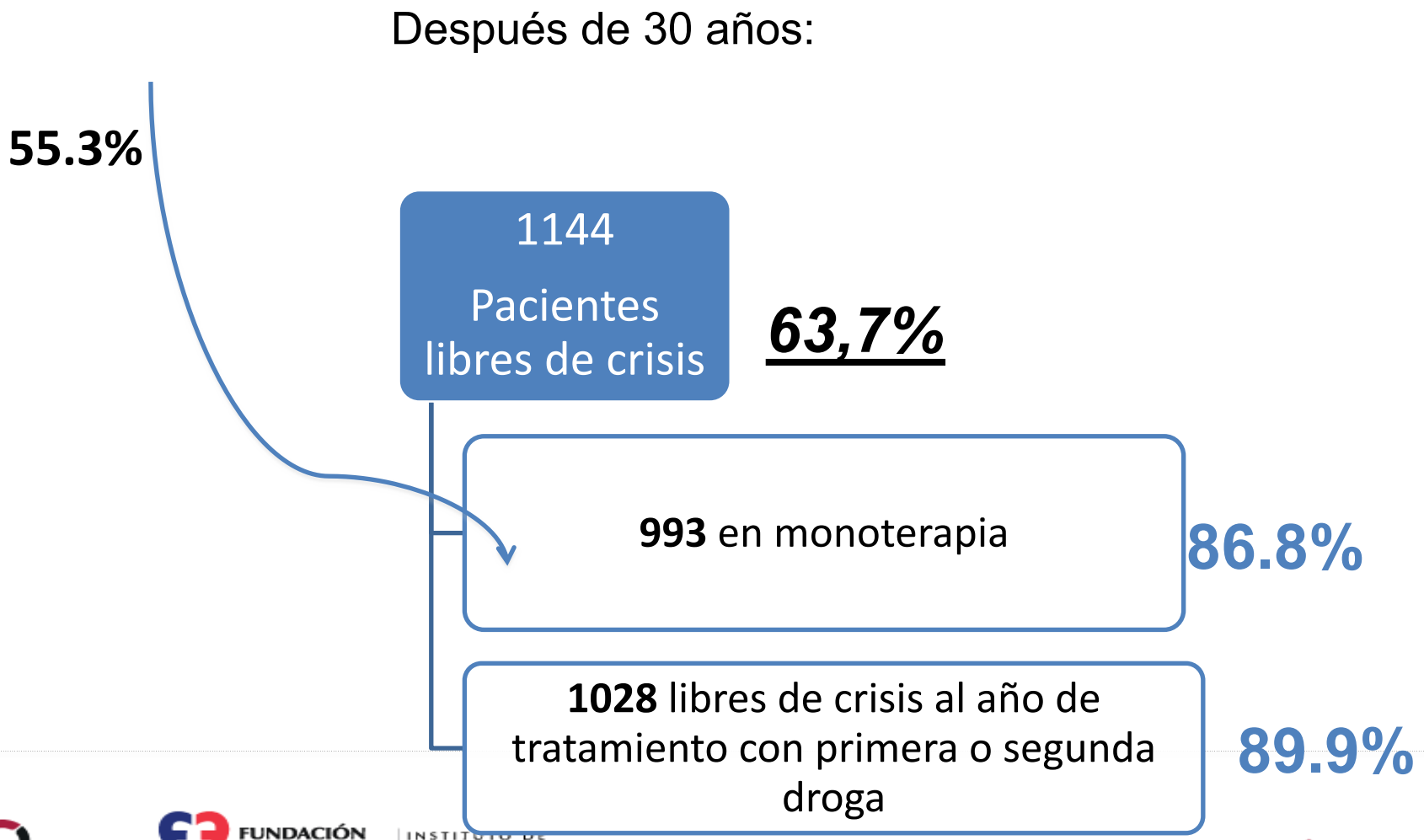
Treatment Outcomes in Patients with Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2017.3949
Published online December 26, 2017.

- **1975 pacientes**
- Promedio de edad: 33 años. Rango: 9 -93 años



- Probabilidad de estar libre de crisis con primera droga→ 50.5%
- Segunda o tercera, probabilidad adicional de 11.6 % y 4.1 % respectivamente.
- 2.1 % libres de crisis con esquemas subsiguientes
- **36,3% continúan con crisis**

- Antecedentes psiquiátricos: depresión (Epilepsy Res 2007)
- Pacientes con epilepsia generalizada demostraron mejor respuesta a las DAE que epilepsia focal

- **No hay evidencia confiable que sugiera alguna diferencia en la eficacia entre:**

-Carbamazepina y Fenitoína
-Carbamazepina y Ácido Valproico
-Fenitoína y Ácido Valproico.
-Fenobarbital y Carbamazepina.
-Fenobarbital y Fenitoína.
(ya sea en crisis focales o generalizadas motoras)

Kwan P, Brodie MJ. Expert Opin Emerging Drugs 2007;12:407–422

Manejo Racional
EAC con DACs modernas

Lamotrigina vs Carbamazepina [3] , Gabapentin [2] , Fenitoína [1]

Oxcarbazepina vs Fenitoína [2] , Carbamazepina, Valproato [1]

Vigabatrina vs Carbamazepina [1]

Gabapentin vs Carbamazepina [2] , Lamotrigina [1]

Topiramato vs Carbamazepina, Valproato [1]

Levetiracetam vs Carbamazepina liberación controlada [1]

Pregabalina vs Lamotrigina [2]

Zonisamida vs Carbamazepina liberación controlada [3]

[1]Stephen LJ, Brodie MJ. Neurol Clin 2009;27:967–992;
[2]Kwan P, et al. Lancet Neurol 2011;10:881–890;
[3]Baulac M et al. Lancet Neurol 2012; 11:579-588

Comparative Efficacy of Newer and Older ASDs in Newly Diagnosed Focal Epilepsy

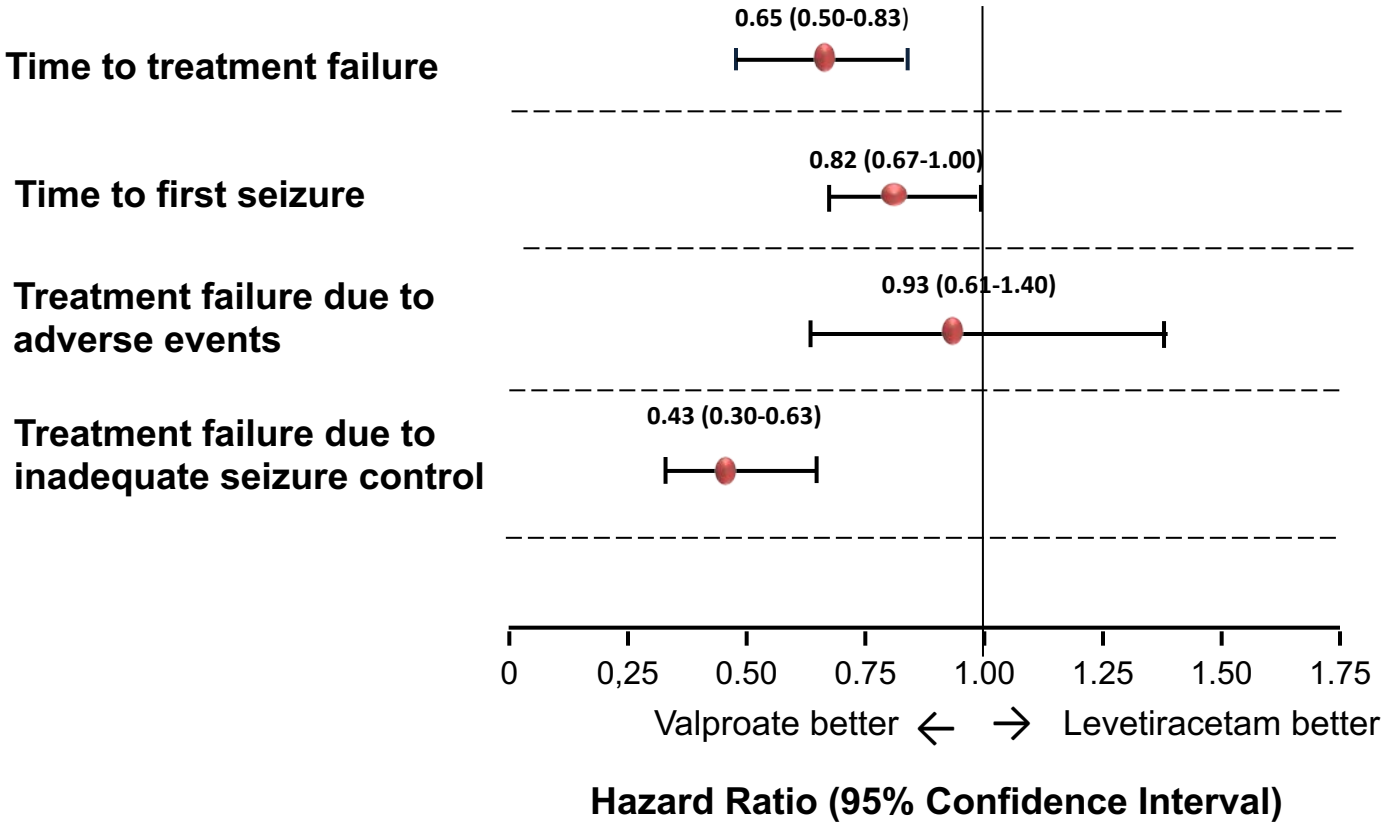
Systematic review of RCTs in newly diagnosed epilepsy – mostly patients with focal seizures

- Oxcarbazepine *vs* carbamazepine, valproate or phenytoin
- Lamotrigine vs carbamazepine, valproate or phenytoin
- Gabapentin vs carbamazepine
- Topiramate versus carbamazepine or valproate
- Levetiracetam vs carbamazepine
- Vigabatrin vs carbamazepine
- Zonisamide vs carbamazepine
- Lacosamide vs carbamazepine
- Eslicarbazepine acetate vs carbamazepine

Newer AEDs were not more efficacious than older drugs (and gabapentin and vigabatrin were less efficacious)

Glauser et al. Epilepsia 2013; 54: 551-63; Brodie et al. Neurology 2007; 68: 402-8.; Baulac et al, Lancet Neurol 2012;;11:579-88; Baulac et al, Lancet Neurol 2017;16:43-54; Trinka et al, Epilepsia 2018;59:479-91 ;

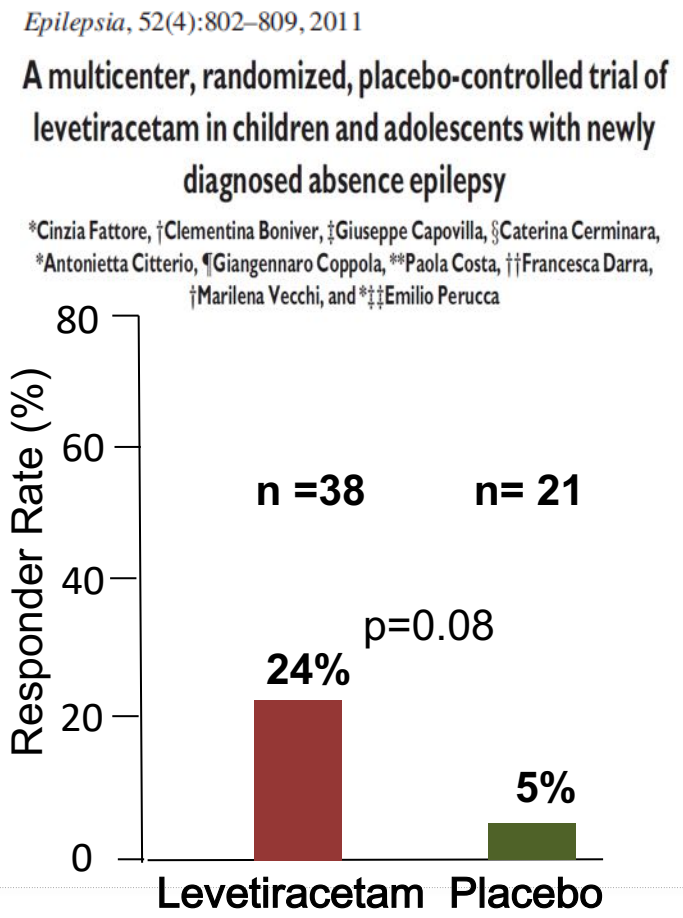
Valproate or Levetiracetam for Idiopathic Generalized (or Unclassified) Epilepsies? The SANAD II Trial Results

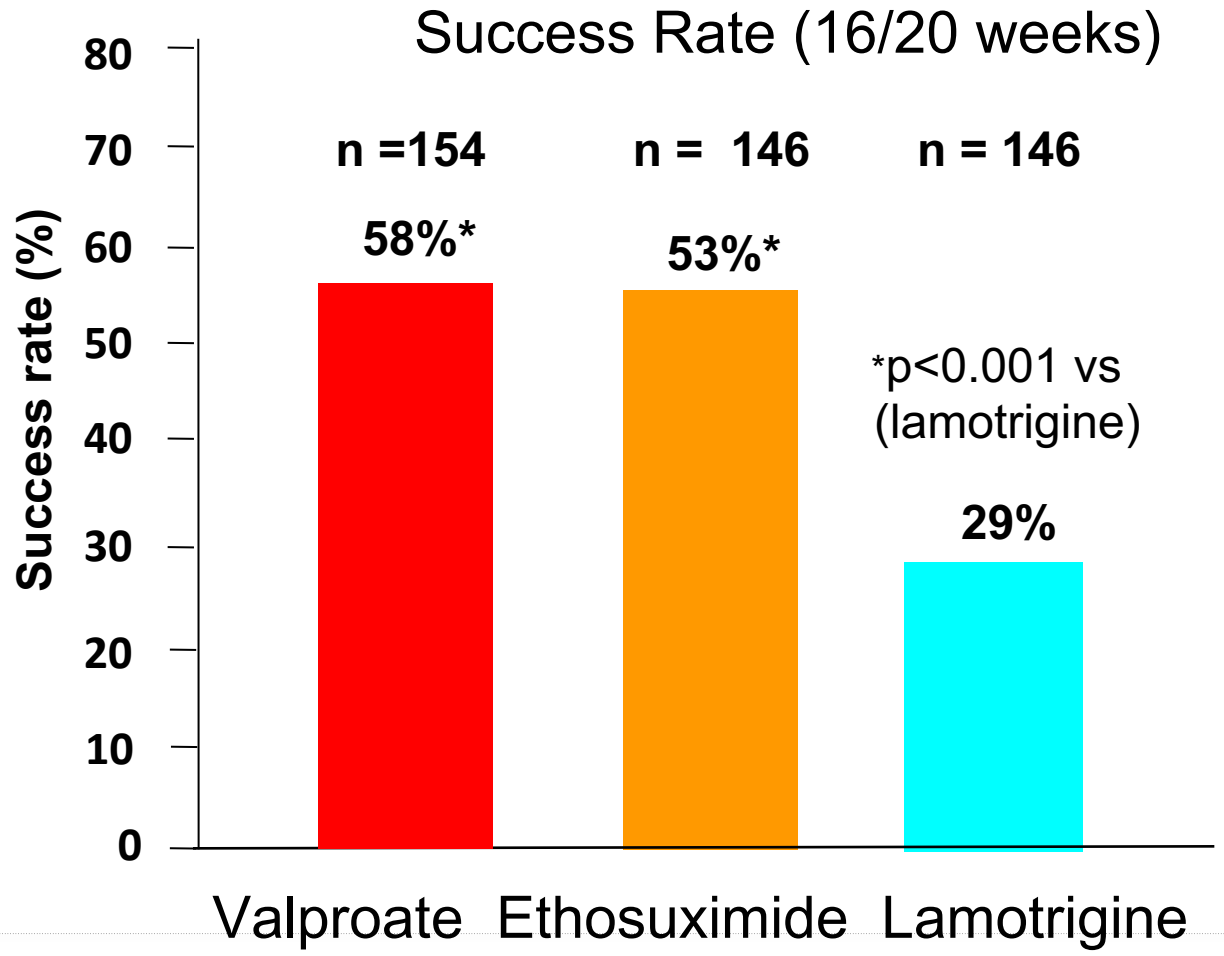


Valproate was also better for time to 24-month remission, and for proportion of patients achieving immediate 12-month remission (33% vs 24% on levetiracetam)

Marson et al International Epilepsy Conference; June 22-26; Bangkok, Thailand. Abstract: 1027.

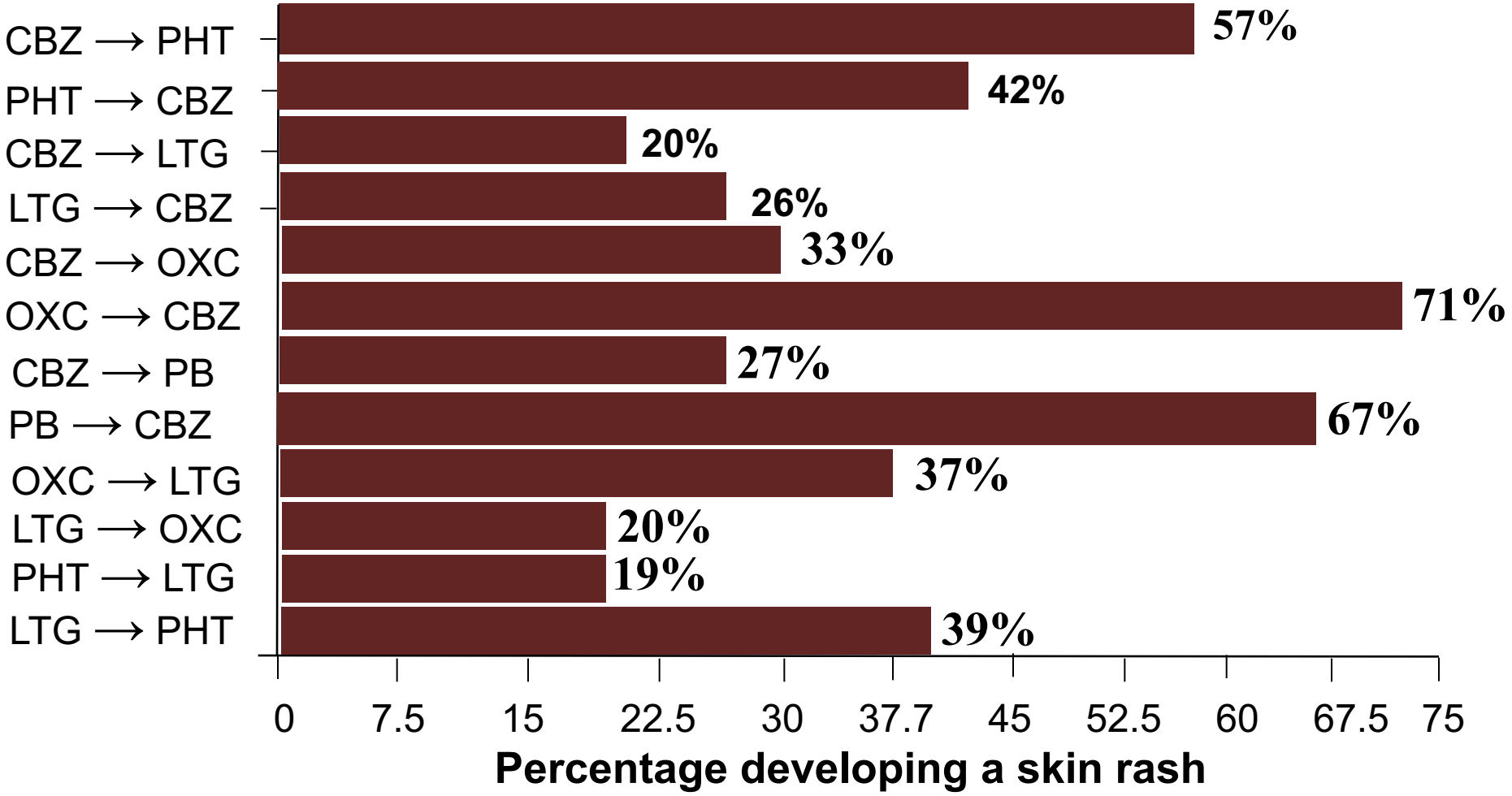
Lamotrigine vs Ethosuximide vs Valproic Acid in Children with Newly Diagnosed Absence Epilepsy





Glauser et al, *New Engl J Med* 2010; 362:790-9

Risk of Recurrence of a Skin Rash after Switching to Another AED in Patients who Had a Rash on the First Drug



Hirsch et al, Neurology 2008; 71:1527-1534

Fuente de la evidencia

- Estudios aleatorizados controlados (EAC) **LA MEJOR EVIDENCIA**
- 25 DAC
- Más de 299 combinaciones posible, más de 30 años para probarlas

EFECTIVIDAD

EFICACIA

+

TOLERANCIA

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE Subcommission on AED Guidelines

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Epilepsia, 54(3):551–563, 2013

- 1) “La decisión final para la terapia debe hacerse a la luz de todos los datos clínicos presentados por el paciente y por las opciones de tratamiento que están disponibles a nivel local para el paciente y su médico”
- 2)“Sin embargo, la decisión final recae en el médico; debe usar su juicio y experiencia para decidir sobre la DAE más adecuada para un paciente específico”

Combinaciones Sinergísticas

- Valproato + Lamotrigina

- Lacosamida + drogas no inductoras: Levetiracetam, Brivaracetam, etc.

DROGAS INDUCTORAS

Epilepsia, 50(Suppl. 8): 42–50, 2009
doi: 10.1111/j.1528-1167.2009.02235.x

REFRACTORY SEIZURES

Should enzyme-inducing antiepileptic drugs be considered first-line agents?

*Scott Mintzer and †Richard T. Mattson

*Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.; and
†Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

SUMMARY

Despite the introduction of a host of new antiepileptic drugs (AEDs) over the last 20 years, the older agents, which are potent inducers of the cytochrome P450 (CYP450) system, remain the AEDs most commonly prescribed throughout the world. At the same time, data have gradually and continuously emerged regarding the possible adverse consequences of CYP450 induction, such that it is now appropriate to pose the question of whether the inducing drugs should still be considered first-line agents for the treatment of focal epilepsy. In this article we review the evidence suggesting that these drugs may have many detrimental metabolic effects, along with the data concerning their relative efficacy compared to the newer, noninducing AEDs. We conclude that longer and better-powered studies are needed to truly establish whether the newer AEDs are equivalent in efficacy to the older, inducing agents. Pending this, however, the extant data are sufficiently concerning to suggest that it may be prudent to start with noninducing AEDs unless there is a clear indication for one of the inducing drugs.

KEY WORDS: Phenytoin, Carbamazepine, Cytochrome P450, Vitamin D, Cholesterol, Drug interactions.

Epilepsia, 54(1):11–27, 2013
doi: 10.1111/j.1528-1167.2012.03671.x

CRITICAL REVIEW AND INVITED COMMENTARY

Enzyme induction with antiepileptic drugs: Cause for concern?

*Martin J. Brodie, †Scott Mintzer, ‡Alison M. Pack, §Barry E. Gidal, ¶Charles J. Vecht, and #Dieter Schmidt

*Epilepsy Unit, Western Infirmary, Glasgow, United Kingdom; †Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.; ‡Department of Neurology, Columbia University, New York, New York, U.S.A.; §School of Pharmacy and Department of Neurology, University of Wisconsin, Madison, Wisconsin, U.S.A.; ¶Stichting Epilepsie Instellingen Nederland (SEIN) Epilepsy Foundation, Heemstede, The Netherlands; and #Epilepsy Research Group, Berlin, Germany

- **Inducción enzimática: Objetivos/blancos de los citocromos**

- - Carbamazepina → 1A2, 2B6, 2C9, 2C19, 3A4/5
- - Fenitoína→ 1A2, 2B6, 2C9, 2C19, 3A4/5
- - Fenobarbital→ 1A2, 2B6, 2C9, 3A4/5
- - Topiramato→ 3A4/5
- - Oxcarbazepina→ 3A4/5

- **Brodie MJ et al. Epilepsia 2013; 54: 11-27**

- **Inducción enzimática.**
- **Estudios en voluntarios sanos.**

- Carbamazepina 400 mg/día por dos semanas.

- Indujo el metabolismo de:

- -cortisol, testosterona y androstenediona
- -tiroxina y triiodotironina
- -y, por supuesto, de la propia carbamazepina!!!!!!!

- **t WG et al. Br J Clin Pharmacol 1983; 16: 133-7**
- **Connell JMC et al. Br J Clin Pharmacol 1984; 17: 347-51**
- **Connell JMC et al. Eur J Clin Pharmacol 1984 26: 453-6**

- **Inducción enzimática: Fármacos inducibles de uso común**

- Amitriptilina Metadona Omeprazol Donepecilo
- Clozapina Paclitaxel Citalopram Oxicodona
- Haloperidol Ibuprofeno Clopidogrel Propranolol
- Teofilina Glitizida Tamoxifeno Tramadol
- Verapamilo Losartán Progesterona Risperidona
- Warfarina Fluoxetina Simvastatina Ciclosporina
- Indinavir Diazepam Sildenafil Tacrolimus

-
  - ***Las isoenzimas del citocromo son responsables del metabolismo oxidativo de más del 80% de las drogas.***

- **Brodie MJ et al. Epilepsia 2013; 54: 11-27**

- **Inducción enzimática: sustratos exógenos.**

- Anticonceptivos orales.
- Anticoagulantes.
- Drogas citotóxicas.
- Analgésicos opioides.
- Antiretrovirales
- Estatinas
- Antihipertensivos.
- Antiarrítmicos.
- Inmunosupresores.
- Y otras DAEs
  - …. etc etc

Propieades a considerar cuando se selecciona una DAC

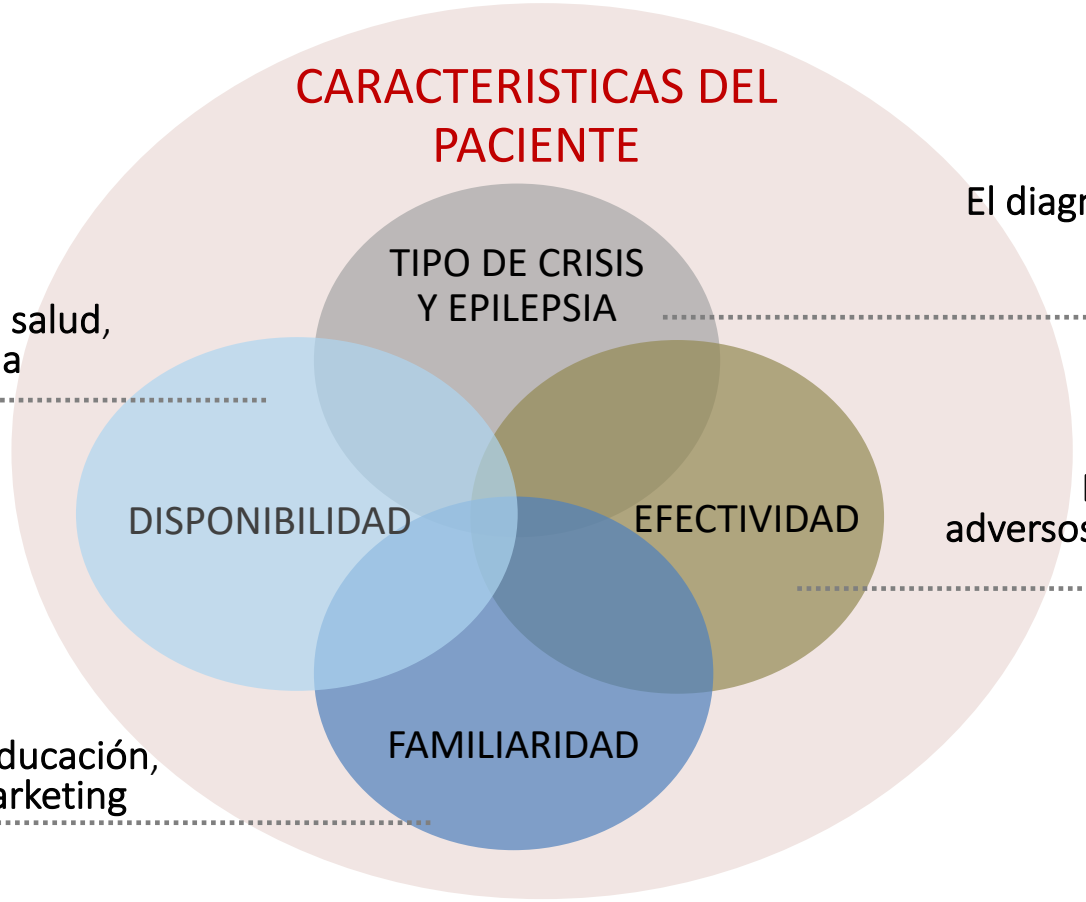
- Espectro de eficacia (tipo de crisis y sindrome)
- Magnitud de la eficacia
- Mecanismo de acción
- Perfil de efectos adversos (incluyendo teratogenicidad)
- Impacto en las comorbilidades
- Interacciones con otras drogas
- Fácil de usar
- Costo

Elección DAC

Dado que no existen grandes diferencias en la eficacia entre las DACs de primera línea, la tolerancia y seguridad a largo plazo deben ser las principales consideraciones a tener en cuenta en pacientes con epilepsia de reciente diagnóstico.

Kwan P, Brodie MJ. Neurology 2003; 60 (suppl 4): S2-S12

COMO SELECCIONAMOS DAC?



Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

Epilepsia fármaco resistente:

No responde luego de dos intentos de DACs bien toleradas y adecuadamente seleccionadas; se utilizan esquemas de DACs (ya sea monoterapia o combinada) para lograr el control de las crisis.

30 years of second-generation antiseizure medications: impact and future perspectives

Emilio Perucca, Martin J Brodie, Patrick Kwan, Torbjörn Tomson

Lancet Neurol 2020; 19: 544–56
Published Online February 25, 2020
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See Comment page 476

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Since 1989, 18 second-generation antiseizure medications have reached the market, resulting in a greatly increased range of treatment options for patients and prescribers. 30 years have passed and now is the time for an appraisal of the effect of these medications on clinical outcomes. Every antiseizure medication needs to be assessed individually, but overall second-generation drugs are less likely to cause pharmacokinetic interactions than their older counterparts. Some second-generation antiseizure medications have shown advantages in tolerability and safety, particularly in the treatment of older patients and women of childbearing potential. Disappointingly, however, none of these medications appear to be more efficacious than first-generation antiseizure medications, highlighting the need for novel strategies in epilepsy drug development. Although second-generation antiseizure medications have not substantially reduced the proportion of patients with pharmacoresistant epilepsy, their availability has enabled more opportunities to tailor treatment choice to the characteristics of the individual.

Introduction

Antiseizure medications introduced after 1989 are generally referred to as second-generation drugs. The development of these medications was primarily aimed at addressing the shortcomings of older, first-generation drugs (barbiturates, benzodiazepines, carbamazepine, ethosuximide, phenytoin, and valproic acid), such as their unfavourable pharmacokinetics and drug interaction profiles, ineffectiveness in controlling the seizures of a third of patients, and propensity to induce many adverse effects.[1]

Three decades after their introduction, we evaluate in this Review the overall effect of second-generation antiseizure medications on epilepsy management and the extent by which these drugs have overcome the short-

kinetics (phenytoin) and dose-dependent autoinduction (carbamazepine).[2] Furthermore, all first-generation antiseizure medications are extensively metabolised by enzymes sensitive to induction and inhibition, and their serum concentrations and resulting clinical responses can be affected by many interacting comedications.[3,4] Carbamazepine, phenytoin, and phenobarbital are potent enzyme inducers,[5,6] and valproic acid inhibits several metabolic pathways, particularly glucuronidation;[3] therefore, these medications are often a cause of clinically important drug–drug interactions.[7]

Although the literature often states that second-generation antiseizure medications have more favourable pharmacokinetics and lower interaction potentials than older agents,[8] available evidence suggests that this

Status epiléptico

Es la emergencia neurológica más frecuente con una mortalidad entre el 3% y 50 % que requiere un diagnóstico y
tratamiento precoz para disminuir potenciales complicaciones sistémicas y daño neuronal

Incidencia: entre 1.3 y 80 casos por 100.000 hab por año (USA) , 180.000 casos por año

Prevalencia: ***mayor*** en menores de 1 año y **mayores de 60 años**

Epidemiología del Status Epileptico

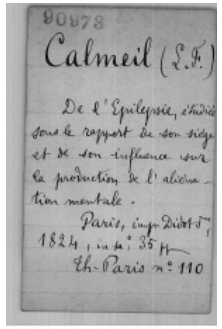
20% de mortalidad [2]

64 % de morbilidad 2

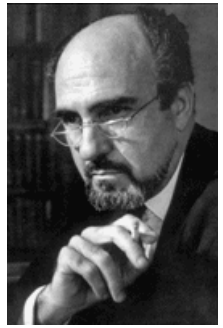
- < 50% con epilepsia [1,2]
  - Drogas bajas en sangre
- 50% sintomático agudo[1,2]
  - Enfermedad Cerebrovascular , trauma encefálico, encefalitis autoinmume, relacionado con el alcohol, metabolico
  - **2/3 de los pacientes responden al tratamiento inicial con Benzodiazepinas pero los otros necesitan una segunda droga de tratamiento. Trinka Agosto 2020. ILAE**

1 Coeytaux et al. Neurology 2000; DeLorenzo et al. Neurology 1996; Hesdorffer et al. Neurology 1998; Knake et al. Epilepsia 2001; Vignatelli et al. Epilepsia 2003

2 Logroscino et al. Epilepsia 1997; 2006; Shorvon 1994



Definition of Status Epilepticus



Traditional classification:

- There were as many types of status as there were types of epileptic seizures (draft 1962; final 1967)
- SE classification mirrored the seizure classification (1964, final 1970)

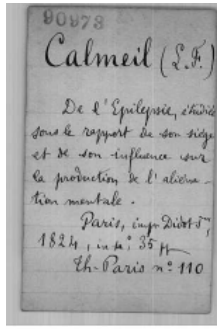
„a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur“ ILAE 1981[1]

Majority of GTCS < 2-3 min[3]

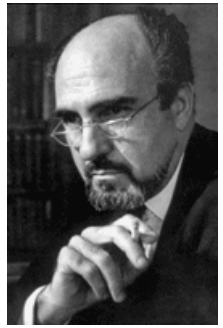
Operational definition: 5min[4]

…“Mechanistically, SE represents the failure of the natural homeostatic seizure-suppressing mechanisms for seizure termination.”…[2]

1 Commission on Classification ILAE, Epilepsia 1981; 2 Engel et al. Epilepsia 2006; 3 Theodore et al. 1994; 4 Lowenstein et al. 1999;



Definition of Non Convulsive Status Epilepticus



Traditional classification:

- There were as many types of status as there were types of epileptic seizures (draft 1962; final 1967)
- SE classification mirrored the seizure classification (draft 1964, final 1970)

„enduring epileptic condition with reduced/altered consciousness, behavioral and vegetative abnormalities or merely subjective symptoms, without major convulsive movements“

NCSE Definition 30 min

…“Mechanistically, SE represents the failure of the natural homeostatic seizure-suppressing mechanisms for seizure termination.”…[2]

1 Commission on Classification ILAE, Epilepsia 1981; 2 Engel et al. Epilepsia 2006; 3 Theodore et al. 1994; 4 Lowenstein et al. 1999;

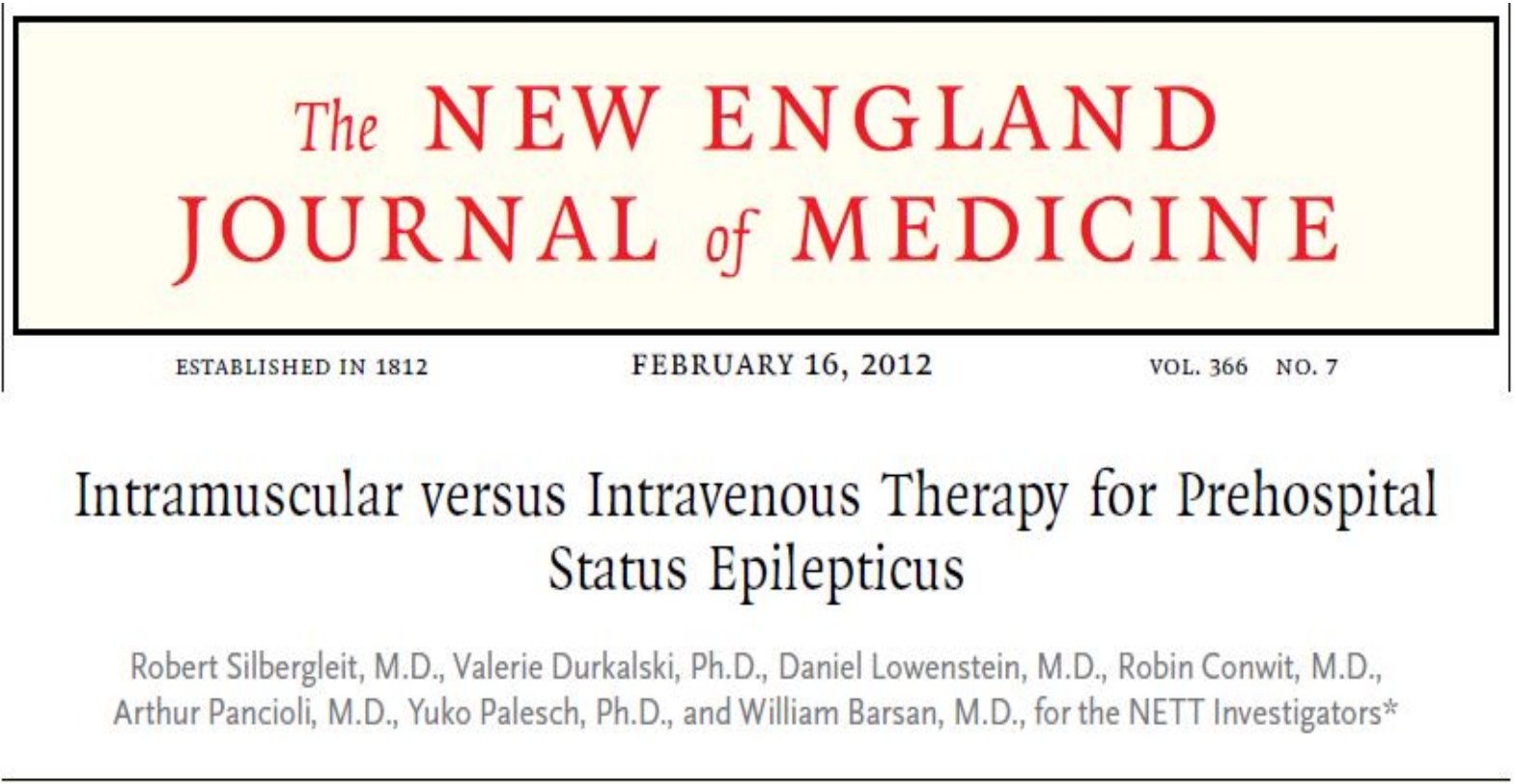
Benzodiacepinas

- Ventajas:
  - Potencia.
  - Rápida acción.
  - Duración de efecto variable entre cada una (MDZ 5-10 min; DZP 15-30 min; LZP 12-24 hs).

  60 % RESPONDEN!

- Desventajas:
  - Tolerancia.
  - Redistribución después de repetidas dosis.
  - Efectos adversos: depresión respiratoria, hipotensión arterial, reacción cutánea en IV.

LZP vs MDZ



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Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

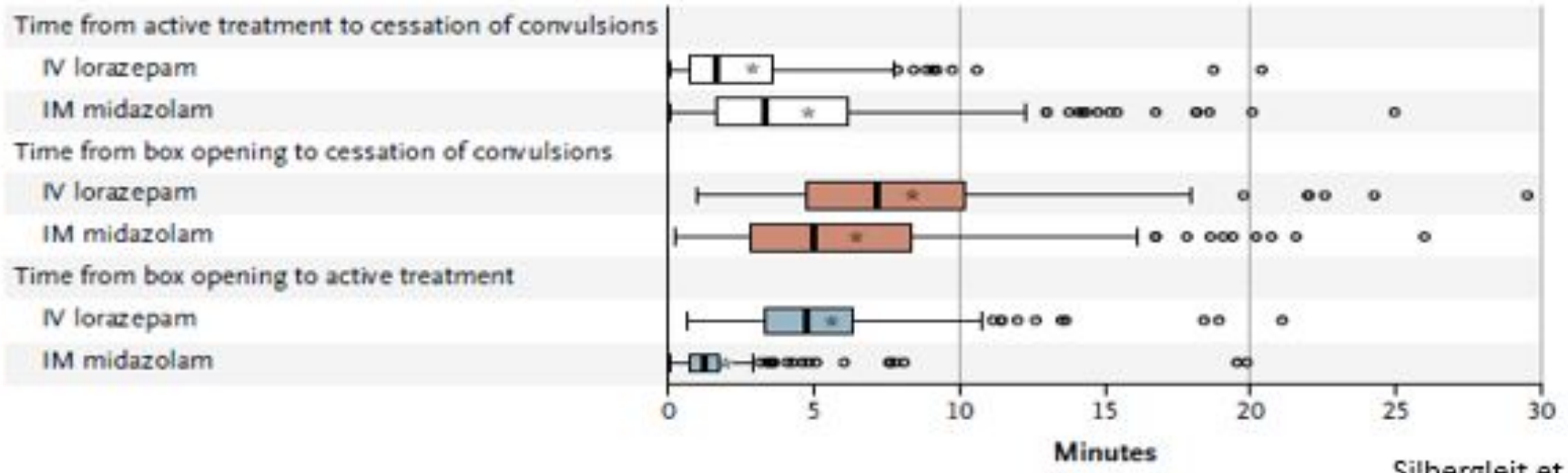
Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

- Estudio RAMPART (rapid anticonvulsivant medication prior to arrival trial).
- Doble ciego randomizado de NO-inferioridad.
- 893 pacientes (445 LZP y 448 MDZ).
- LZP 4 mg EV vs MDZ 10 mg IM (la mitad en niños).

LZP vs MDZ

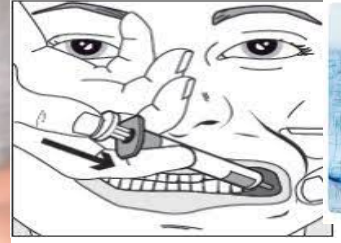
- **Conclusión:** 73% de MDZ IM y 63% de LZP EV con cese de crisis al llegar al DE (significativo). Tiempo medio desde tratamiento y cese de crisis 1,2 min MDZ y 4,8 min LZP.

Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Primary outcome				
Seizures terminated, no rescue therapy given				
No. of subjects	329	282	271	238
% of subjects (95% CI)§	73.4 (69.3–77.5)	63.4 (58.9–67.9)	74.9 (70.4–79.3)	64.3 (59.4–69.2)
Treatment failed — no. of subjects (%)	119 (26.6)	163 (36.6)	91 (25.1)	132 (35.7)
Seizures not terminated, no rescue therapy given	50 (11.2)	64 (14.4)	42 (11.6)	51 (13.8)
Seizures not terminated, rescue therapy given	22 (4.9)	42 (9.4)	14 (3.9)	38 (10.3)
Seizures terminated, rescue therapy given	47 (10.5)	57 (12.8)	35 (9.7)	43 (11.6)



Silbergleit et al. NEJM 2012





MDZ vs DZP

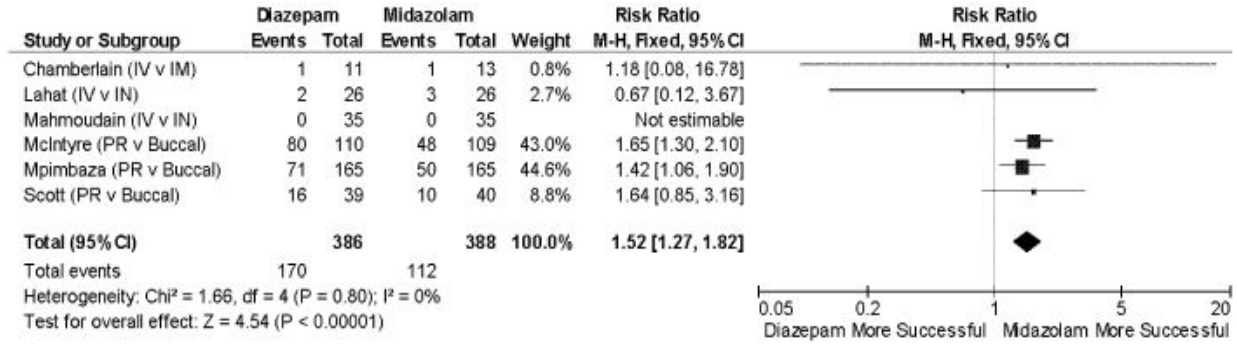


Figure 2. Diazepam versus midazolam in failure to achieve seizure cessation (all routes of administration). IV = intravenous; IM = intramuscular; IN = intranasal; M-H = Mantel-Haenszel; PR = per rectum.

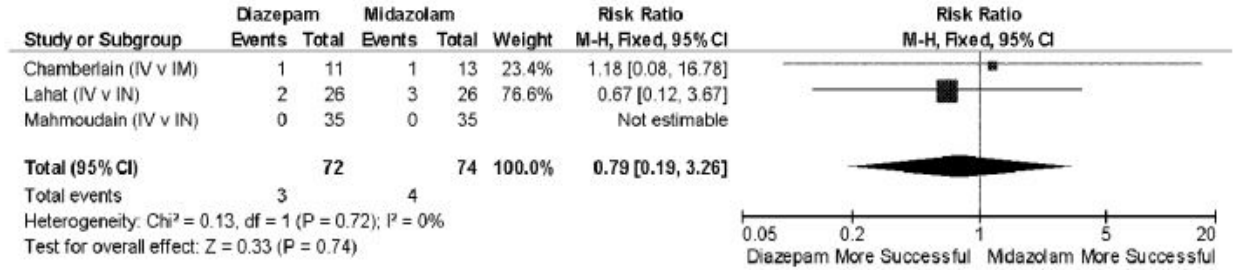


Figure 3. IV diazepam versus non-IV midazolam in failure to achieve seizure cessation. IV = intravenous; IM = intramuscular; IN = intranasal; M-H = Mantel-Haenszel.

- **Cese de crisis:** MDZ superior a DZP por cualquier vía (RR 1,52; CI 95% 1,27-1,82) (IM superior a rectal e IV?).
- Mismos EA.

INECO

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McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus Diazepam for the treatment of status Epilepticus in children and young adults: A meta-analysis. Acad Emerg Med. 2010;17(6):575-582. doi:10.1111/j.1553-2712.2010.00751.x

Conclusiones

- Las BZD son fármacos eficaces y seguros para tratar la emergencia en epilepsia en diferentes escenarios.
- En el status epiléptico como primera línea.

- **Misma eficacia entre todas las BZD en adultos…?**
  - MDZ IM superior a LZP EV
  - LZP igual a DZP (mínima tendencia que favorece al LZP).
  - MDZ superior a DZP? (bucal superior a DZP).
  - Y adultos con respecto a niños? (teoría de la lipofilia +- grasa corporal).

- Pensar en qué beneficios tiene cada BZD: MDZ no EV, LZP larga duración, DZP rápida entrada al SNC; y en qué desventajas: los no EV tienen 1er paso hepático, EV requerimiento de vía, rectal, LZP T°.

CASOS CLÍNICOS

- MUCHAS GRACIAS POR SU ATENCIÓN