Sílabo

International League Against Epilepsy

Educational Program

2ª Escola Latino-americana de Verão em Epilepsia
2ª Escuela Latino-americana de Verano en Epilepsia
2nd Latin American Summer School on Epilepsy

"Epilepsia: Aumentando o conhecimento e solucionando o problema do tratamento"
"Epilepsia: Aumentando el conocimiento y solucionando el problema del tratamiento"
"Epilepsy: Increasing knowledge and decreasing the treatment gap"

Fev. 7-16, 2008
São Paulo, Brasil

LASSE

ILAE

Liga Brasileira de Epilepsia

INTERNATIONAL LEAGUE AGAINST EPILEPSY
ACADEMIA LATINO-AMERICANA DE EPILEPSIA
ALADE

ALADE Mission: To provide and promote epilepsy education and research with excellence, quality, efficiency and humanistic approach for medical and non-medical professionals in Latin America.

ALADE Vision: To be a Latin American Institution, a logistic Branch of the ILAE Latin American Commission and the ILAE Education Commission, established to promote and provide epilepsy education and research, aiming to improve the health care of people with epilepsy in the region.

Goal: The goal of ALADE is to promote epilepsy education and research in the Latin American region in order to improve health care of people with epilepsy.

SECOND LATIN AMERICAN SUMMER SCHOOL ON EPILEPSY
LASSE
Epilepsy. Increasing knowledge and decreasing the treatment gap

LASSE is one annual educational activity of the ALADE

On behalf of the Organizing Committee and the Scientific Advisory Committee, it gives us great pleasure to welcome you to São Paulo. The main topic of this second LASSE is Treatment of Epilepsy with a broad approach of the Antiepileptic Drugs and Surgical Treatment aiming to reduce treatment gap in Latin America.

Welcome, enjoy your stay in São Paulo and thank you all who cooperate for the success of this program.

Programa – 07.02.2008

Morning session – 9:00 – 13:00

- Welcome – Group formation – Research topic distribution – Esper Cavalheiro (Brazil)
- LASSE-ALADE and the ILAE-Educational Program – Elza Márcia Yacubian (Brazil) and Marco Tulio Medina (Honduras)
- Transcultural aspects of the neuropsychiatric disorders – Naomar Monteiro de Almeida Filho (Brazil)
- History of neuroscience research – Marina Bentivoglio (Italy)

Afternoon session – 14:30-18:30

- Epidemiology of the Epilepsies in Latin America – Carlos Acevedo (Chile)
- Classification of epileptic seizures – Vera Terra Bustamante (Brazil)
- Classification of the epileptic syndromes – Americo Sakamoto (Brazil)
- Epilepsy in Mesopotamia – Mario Fales (Italy)

Welcome – Group formation – Research topic distribution

Esper Cavalheiro (Brazil)

LASSE-ALADE and the ILAE-Educational Program

Elza Márcia Yacubian (Brazil) and
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Transcultural aspects of the neuropsychiatric disorders

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History of neuroscience research
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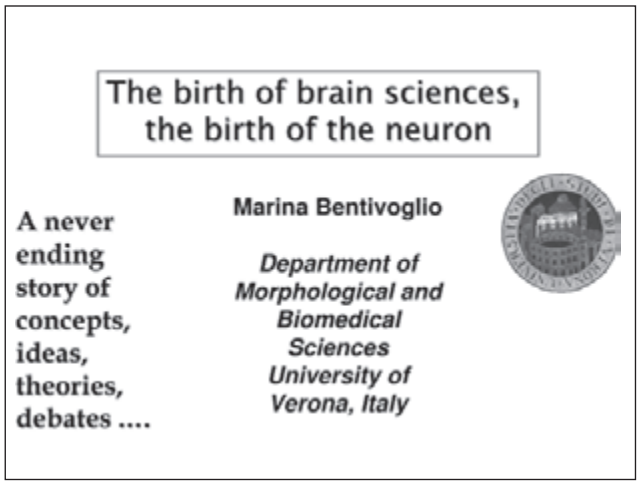
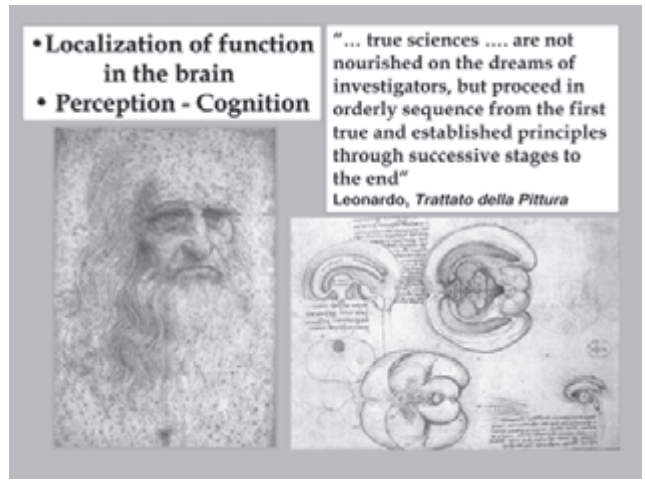
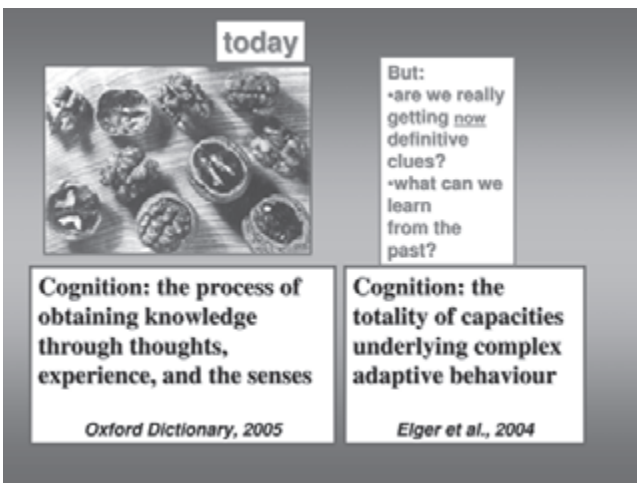
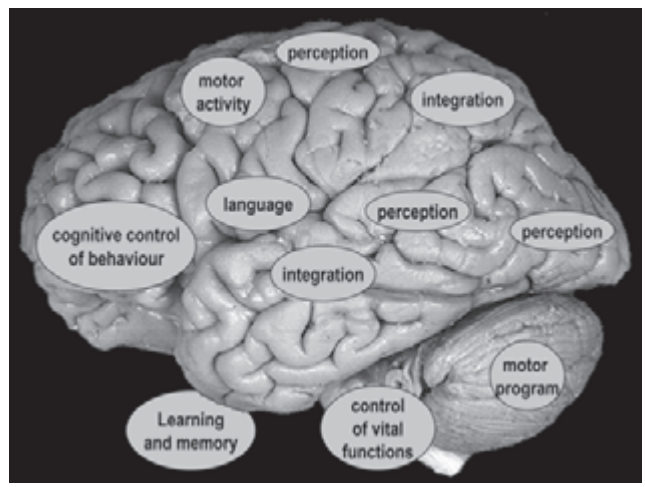
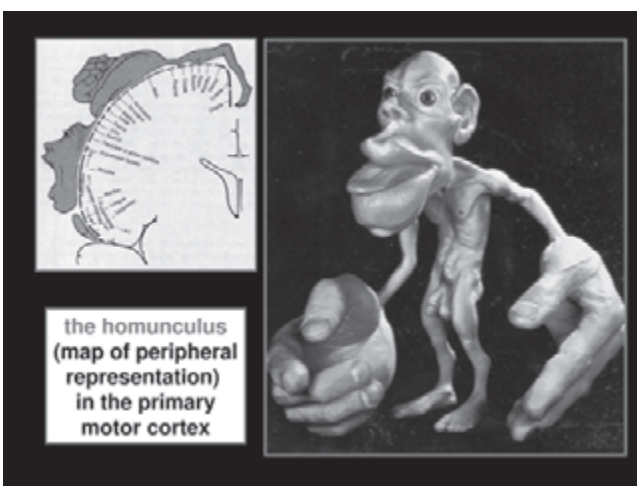
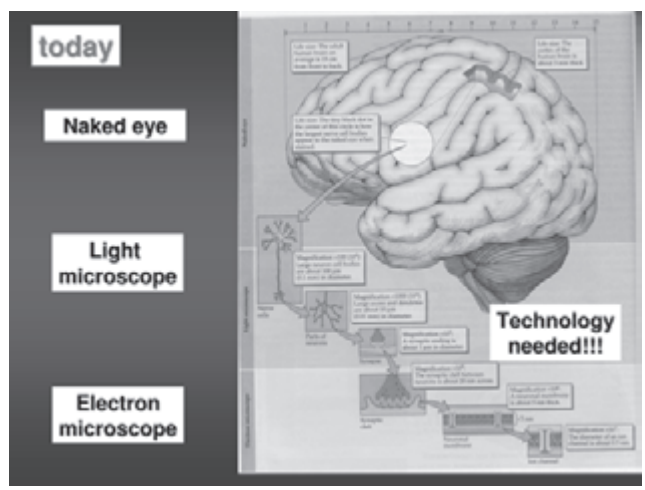












In the past

5th century BC
pre-Socratic ideas

Empedocles
492-432 BC

•4 elements: fire, air, water, earth
composed in various proportions all the parts of the body

•The ingredients of the blood determined intelligence
•The heart was the basis of the intellect

5th century BC
pre-Socratic ideas

Democritus

•Each of the 4 elements is composed by a different kind of particle

•The psyche or soul is composed of the lightest, fastest moving and nearly spherical particles, especially concentrated in the brain

•Particles of lesser quality are found in the heart, giving it a role in emotion

•The most coarse particles are located in the liver

Plato
427-347 BC

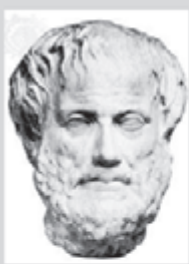
•assigned specific geometrical shape to each of the 4 kinds of particles

3 different kinds of psyche
•Rational thought and bevahior associated with the head

•That involved with passion and the emotions associated with the breast and heart

•That concerned with desires associated with the liver

•Describes the psyche or soul as bonded to a substance found in its purest form in the cranial and spinal cavities where it appears as "marrow"



Aristotle 384-322 BC (student of Plato)

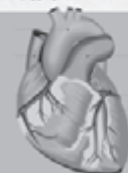
•Vital pneuma: ether which filled all space, taken in by the lungs, transformed to vital pneuma in the heart, conducted in the blood stream to be transmitted to muscles

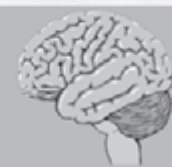
•The vital pneuma then initiated the final phase of muscle's psyche, that is, its contraction leading to locomotion

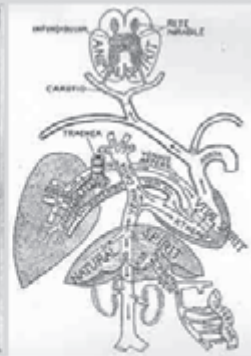
From C. Gross, 1995

Table 1. Aristotle's Arguments for the Heart and against the Brain as the Center for Sensation and Movement

Heart	Brain
1. Affected by emotion (PA669a)	1. Not affected (PA652b, 656a)
2. All animals have a heart or similar organ (GA771a, PA665b)	2. Only vertebrates and cephalopods have one, and yet other animals have sensations (PA652b)
3. Source of blood, which is necessary for sensation (PA667b)	3. Bloodless and therefore without sensation (HA494a, 514a, PA765a)
4. Warm, characteristic of higher life (S543bb)	4. Cold (PA652, HA495a5)
5. Connected with all the sense organs and muscles, via the blood vessels (GA744a, HA492a, 469a, GA781a)	5. Not connected with the sense organs or the connection irrelevant (PA652b, HA503b)
6. Essential for life (YO468a, Pa647a)	6. Not so (HA532a, GA741b)
7. Formed first, and last to stop working (GA741b)	7. Formed second (GA674b)
8. Sensitive (S543ba, PA669a)	8. Insensitive. If the brain of a living animal be laid bare, it may be cut without any signs of pain or struggling (PA652b, 656a)
9. In a central location, appropriate for its central role (PA670a)	9. Not so







2nd and 3rd centuries: Galen and his students

Vital pneuma delivered by blood vessels to the brain is converted there into psychic pneuma, and from there transmitted along nerves to muscles

15th century drawing illustrating pre-Cartesian theories which followed the views of Aristotle

- The sense of touch and taste are connected to the heart
- the boxes on the head are the "cerebral cells" where mental faculties such as memory and fantasy are located.

1517

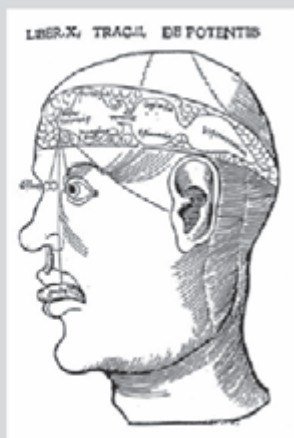
Connections departing from sensory organs converge to the anterior cerebral ventricle, divided into 3 faculties:
- *sensus communis*
- *fantasia*
- *imaginativa*

(common sense, imagination)

Second ventricle, 2 faculties:
- *cogitativa*
- *estimativa*

Third ventricle:
- *Memorativa*

(memory)

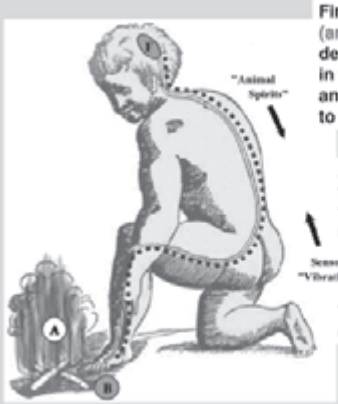


"Cogito, ergo sum"

René Descartes
1596-1650

Replaces pneuma by mechanical corpuscles

The psyche as elaborated by Aristotle is abandoned



Fine highly volatile particles (animal spirits) derived from the blood in the brain, are conducted and transmitted along nerves to enter the muscles

Animal spirits enter therein they cause the whole body of the muscle to inflate and shorten and so pull

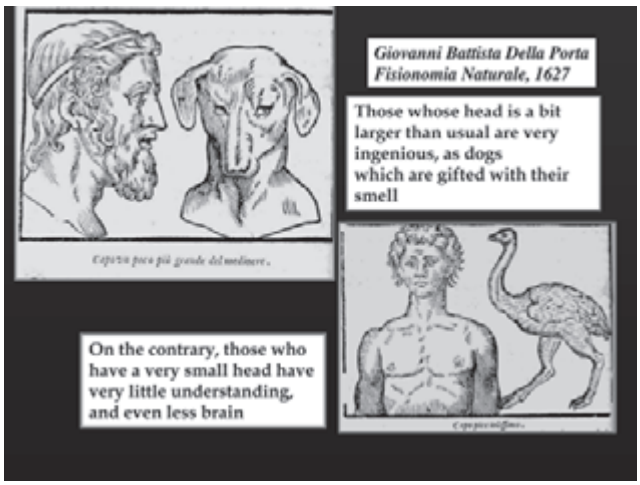
When they withdraw the muscle disinflates and elongates again

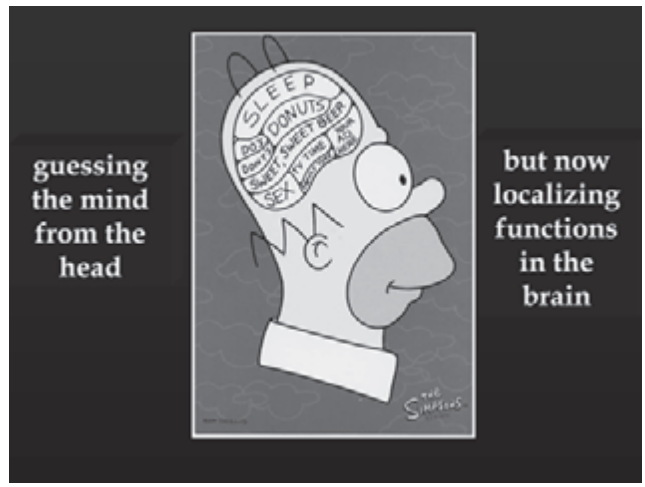
Guessing the mind from the head

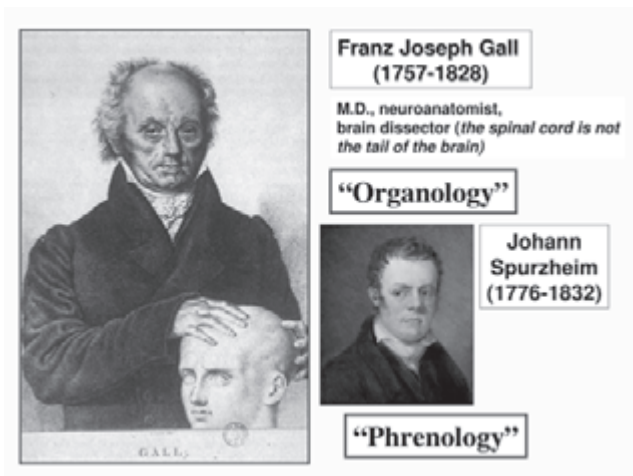
Giovanni Battista Della Porta
Fisionomia Naturale, 1627

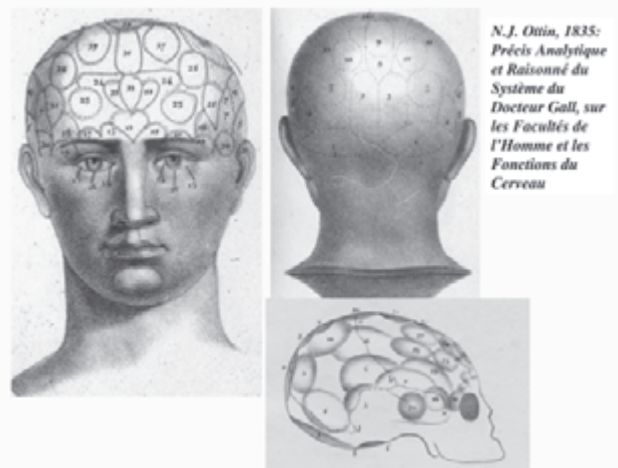
large forehead

square forehead

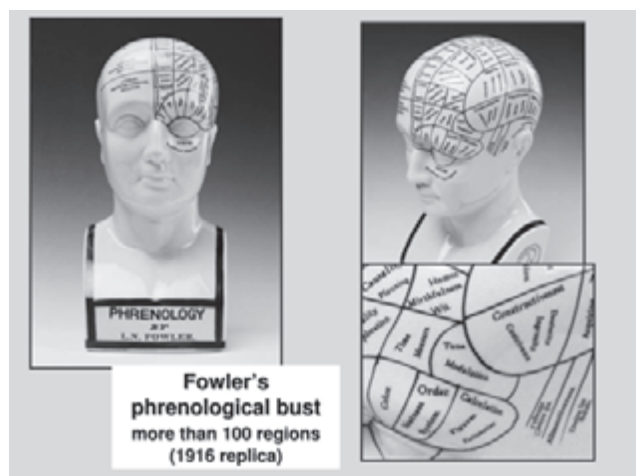

Giovanni Battista Della Porta
Fisionomia Naturale, 1627
Those whose head is a bit larger than usual are very ingenious, as dogs which are gifted with their smell
On the contrary, those who have a very small head have very little understanding, and even less brain

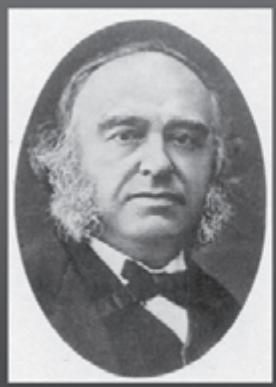

guessing the mind from the head
SLEEP
DONUTS
SWEET, SWEET BEER
SEX
but now localizing functions in the brain


Franz Joseph Gall
(1757-1828)
M.D., neuroanatomist,
brain dissector (the spinal cord is not the tail of the brain)
"Organology"
Johann Spurzheim
(1776-1832)
"Phrenology"

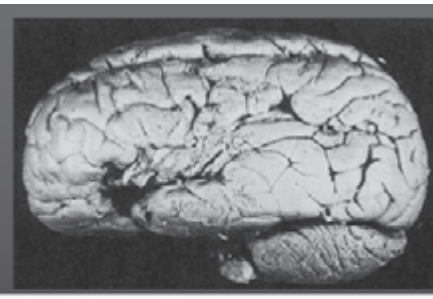

N.J. Ottin, 1835:
Précis Analytique et Raisonné du Système du Docteur Gall, sur les Facultés de l'Homme et les Fonctions du Cerveau


The Phrenologic Museum of Fowler and Wells,
New York Illustrated News, February 18, 1860


PHRENOLOGY
Fowler's phrenological bust
more than 100 regions
(1916 replica)



Paul Broca
(1824-1880)



Monsieur Leborgne ("Tan"): hospitalized for 21 years, epileptic, suffered from loss of speech

P. Broca: Perte de la parole, ramollissement chronique et destruction partielle du lobe antérieur gauche du cerveau (Sur la siège de la faculté du langage). Bull. Soc. Antropol. Paris 2, 235-238, 1861.

John Hughlings Jackson (1835-1911)

Study on Convulsions
1870

today

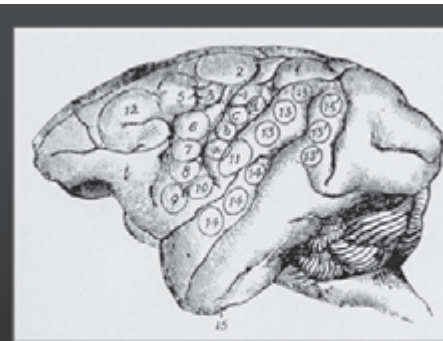
Epilepsy gave an important contribution to the discovery of localization of function in the brain!

Electrophysiological mapping

- Gustav Fritsch (1838-1927)
- Eduard Hitzig (1838-1907)

Individualization of the motor centers in the brain of a dog
1870

- Proved using electrical stimulation that cortical ares control certain movements
- Proved that the cortex can be stimulated directly
- Electricity became since then an instrument of major importance for the exploration of brain functions



Influenced by the work of Fritsch and Hitzig, David Ferrier mapped the primate cortex
(Numbers 1-12, a-c: areas of motor function; 13: areas of vision)

The birth of the neuron

"Nothing can be found in nature that is not a part of science"

Leonardo, *Trattato della Pittura*

... and the birth of the synapse

Michelangelo, Sistine Chapel

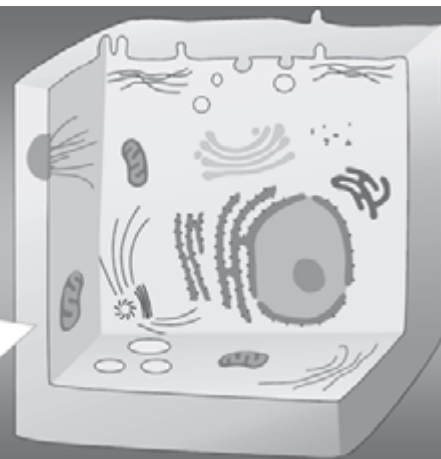
today

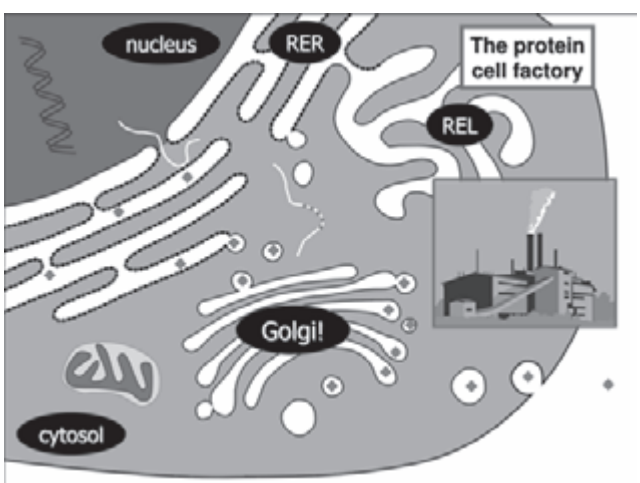
The brain, as all other parts of the body and as other parts of living organisms, is made up by cells

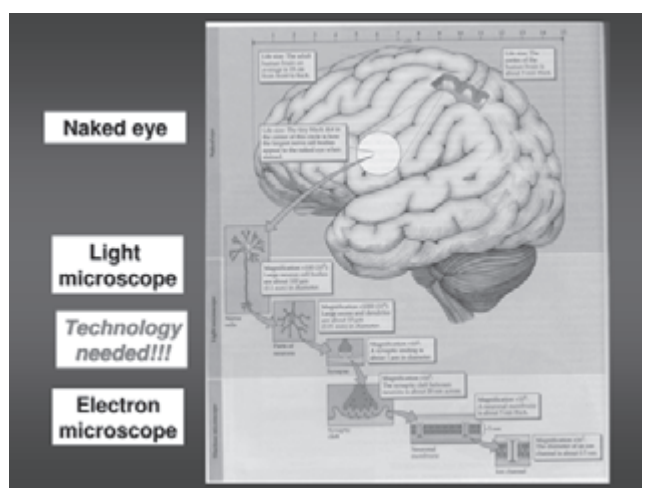
today

The cell

Cells have nuclear and cytoplasmic compartments, the latter containing organelles







In the past

Robert Hooke (1635-1703):

"cella" "cell"

(the units composing a cork)

Micrographia
(London, 1665)

The Latin word *cella* means "a small room", and the Latins applied this word to the cells of a honeycomb

Cell theory
enunciated in 1838-1839

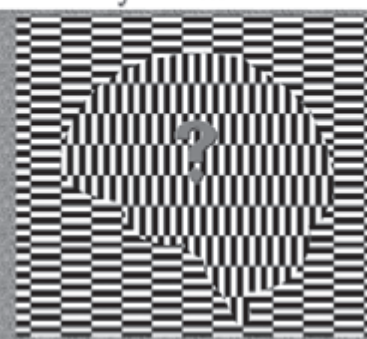
1838: Matthias J. Schleiden (1804-1881)

1839: Theodor Schwann (1810-1882)

"All plant and animal organisms are composed of individual cellular elements"

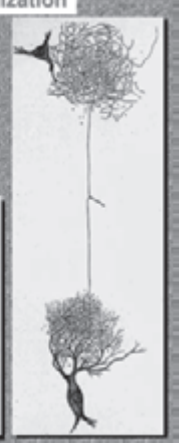
1858: Rudolph Virchow (1821-1902)
"omnis cellula e cellula"
(every cell derives from a cell)

And what about the nervous system?



Reticular theory of nervous system organization

Gerlach, 1872

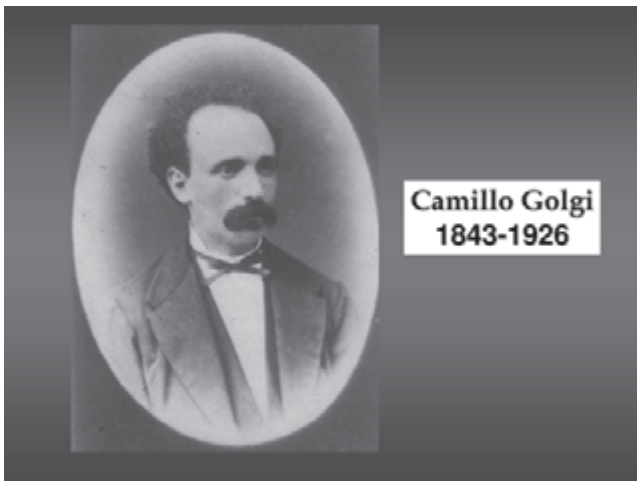


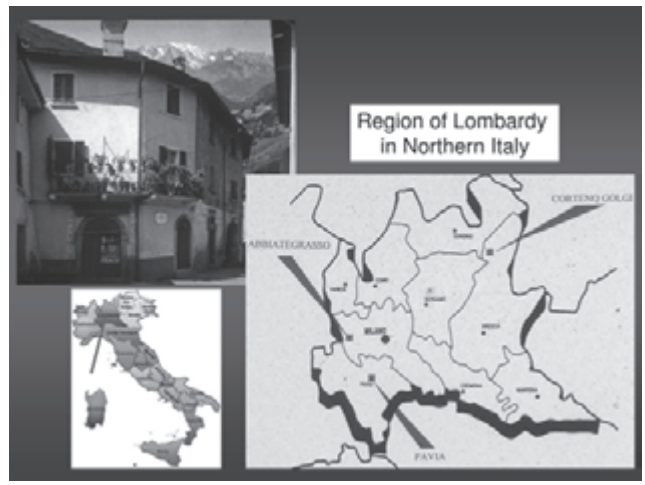
The rain in Spain falls mainly in the plane

"Pigmalion" – George Bernard Shaw
the musical "My Fair Lady"

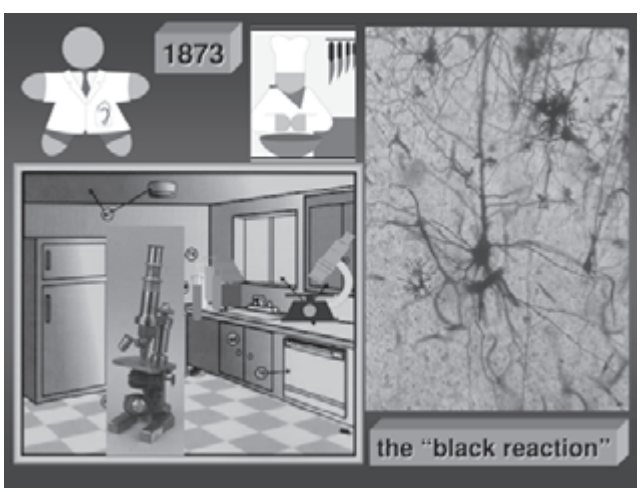
*The gain in the brain is mainly in the **stain***

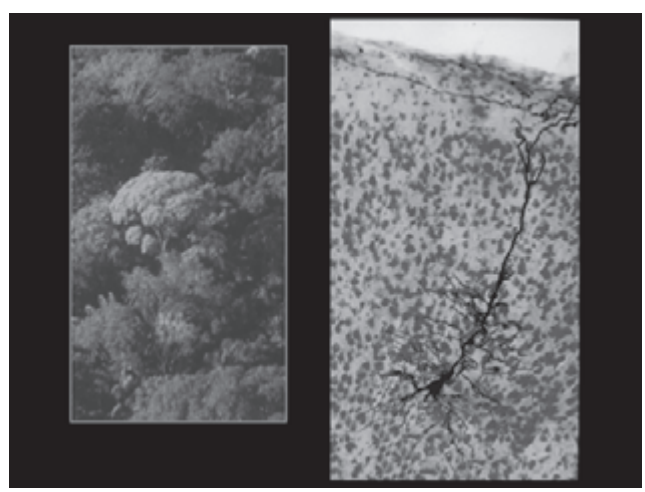
Floyd Bloom


Camillo Golgi
1843-1926

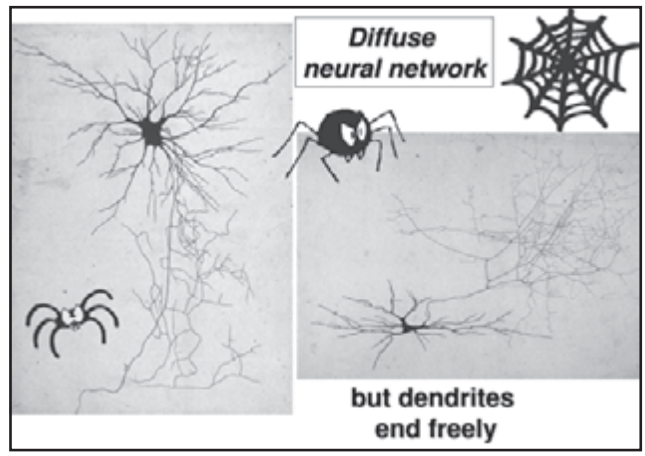

Region of Lombardy
in Northern Italy
ABBIATEGRASSO
CORTENO GOLGI
PAVIA

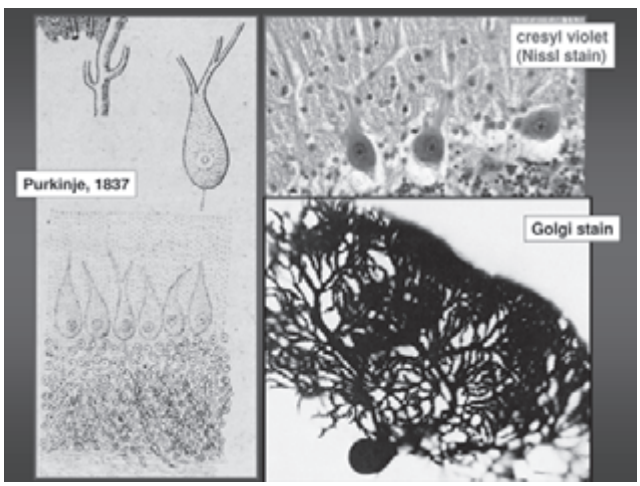

NEW TECHNICAL CAPABILITIES?
LET'S SEE NOW...
R&D
DEPT.

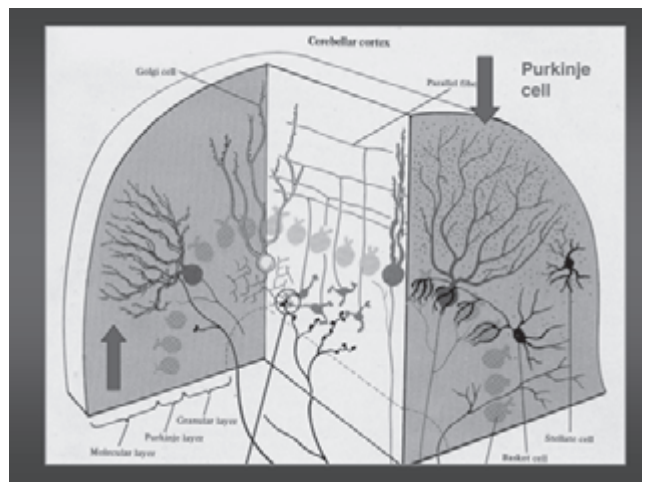

1873
the "black reaction"

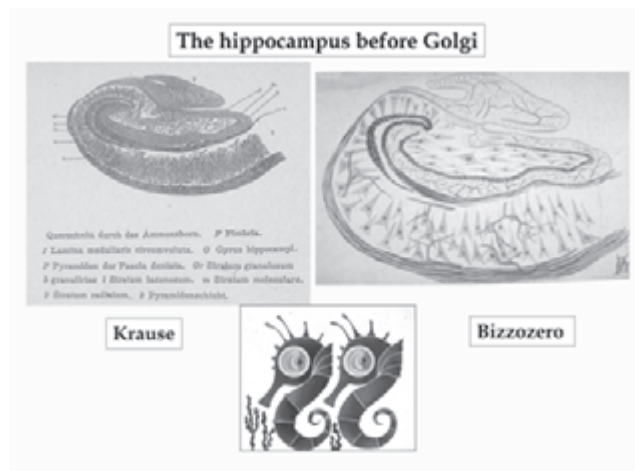


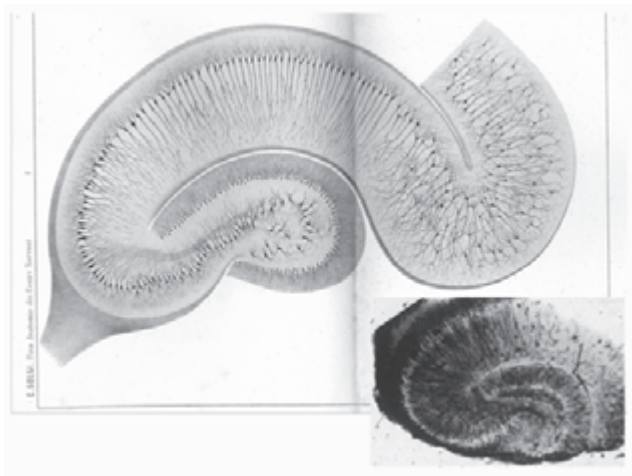

SULLA FINA STRUTTURA
DEGLI
BULBI OLFATTORII
MEMORIA
DEL
DOTT. CAMILLO GOLGI

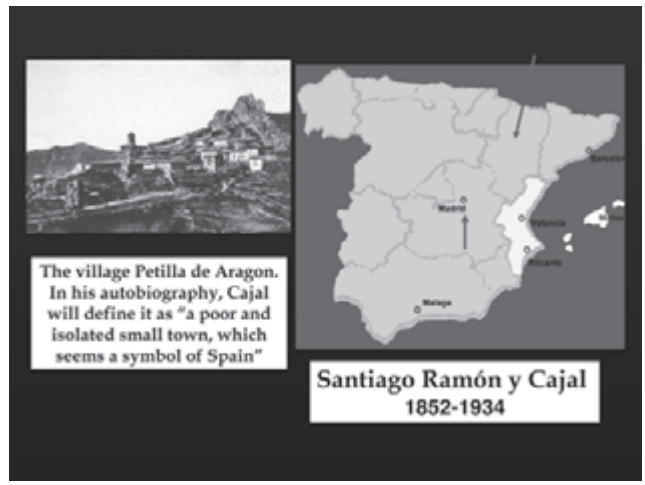

Diffuse
neural network
but dendrites
end freely

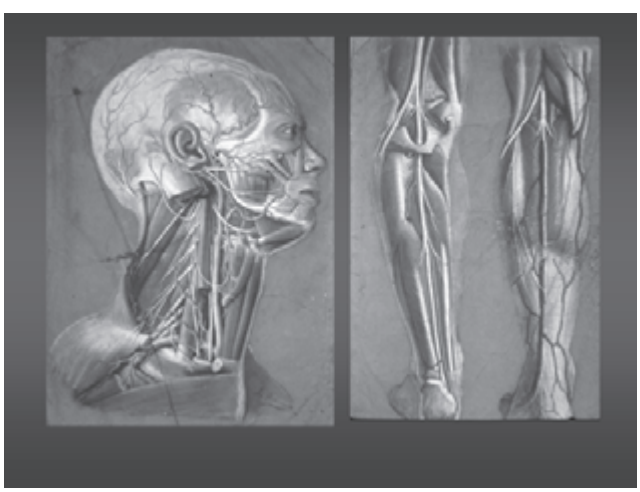

Purkinje, 1837
cresyl violet
(Nissl stain)
Golgi stain

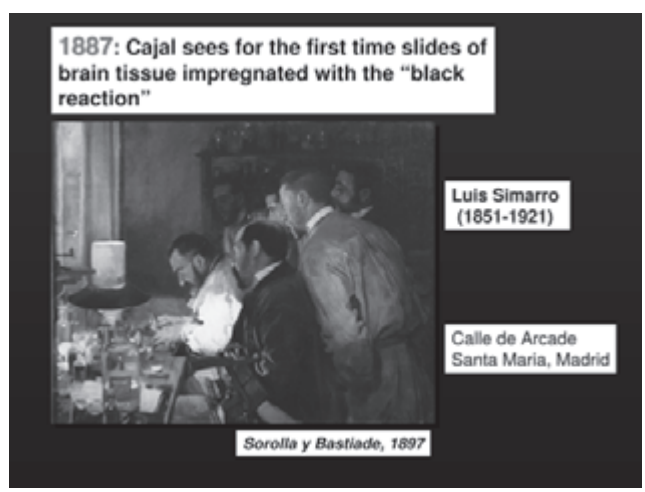

Cerebellar cortex
Golgi cell
Purkinje
cell
Granular layer
Purkinje layer
Molecular layer
Stellate cell
Basket cell

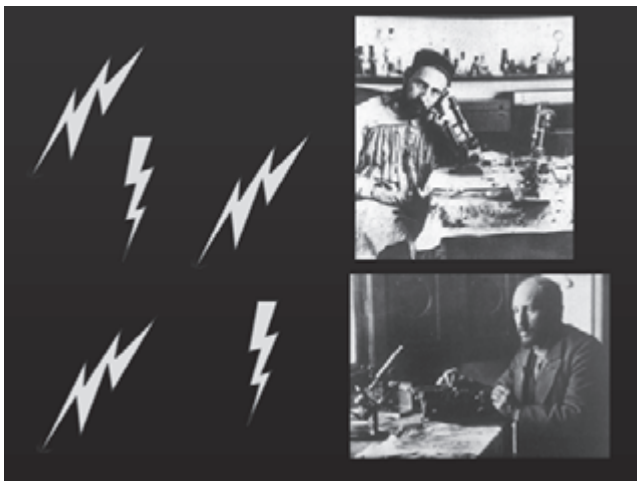

The hippocampus before Golgi
Krause
Bizzozero

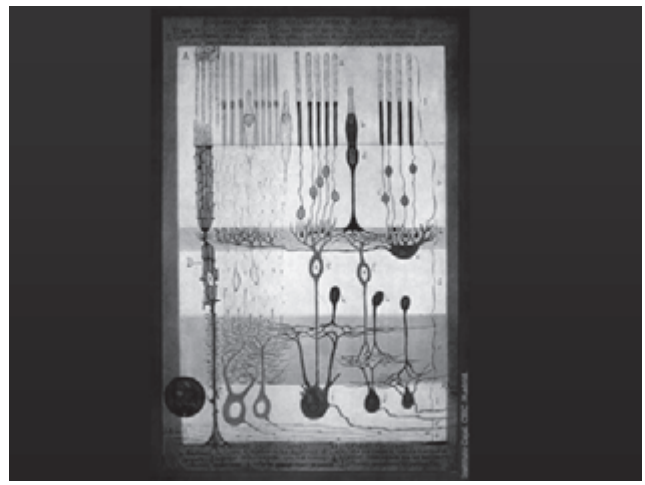


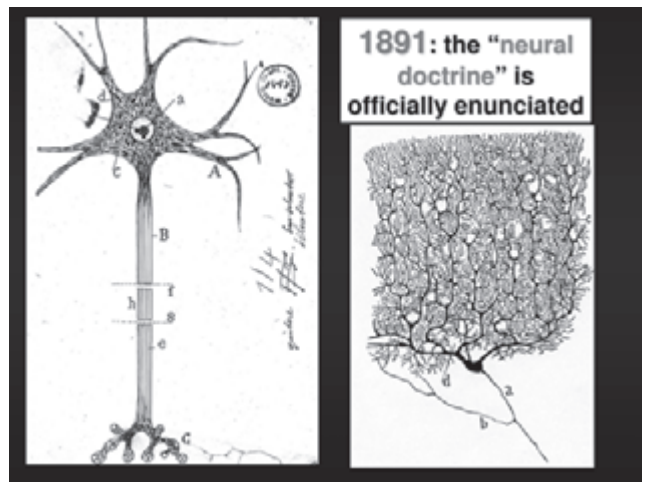

The village Petilla de Aragon. In his autobiography, Cajal will define it as "a poor and isolated small town, which seems a symbol of Spain"
Santiago Ramón y Cajal
1852-1934

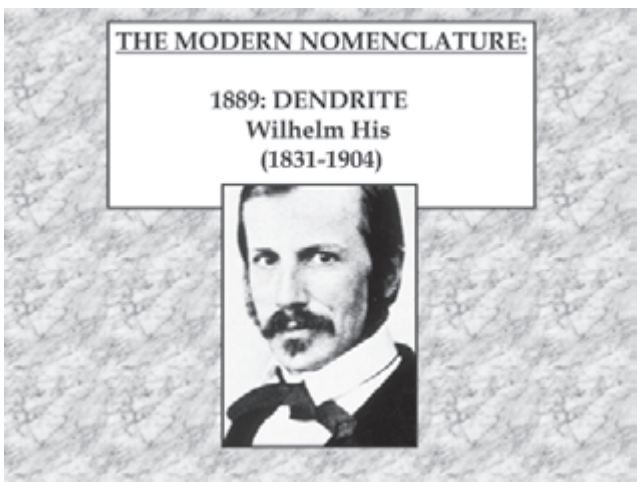


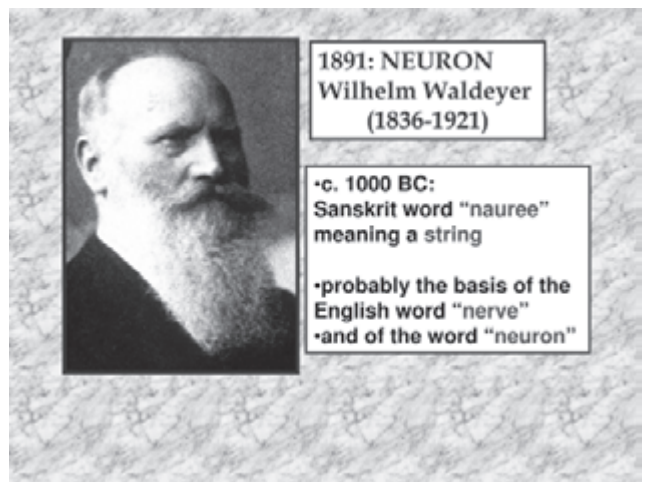

1887: Cajal sees for the first time slides of brain tissue impregnated with the "black reaction"
Luis Simarro (1851-1921)
Calle de Arcade Santa Maria, Madrid
Sorolla y Bastiade, 1897






1891: the "neural doctrine" is officially enunciated

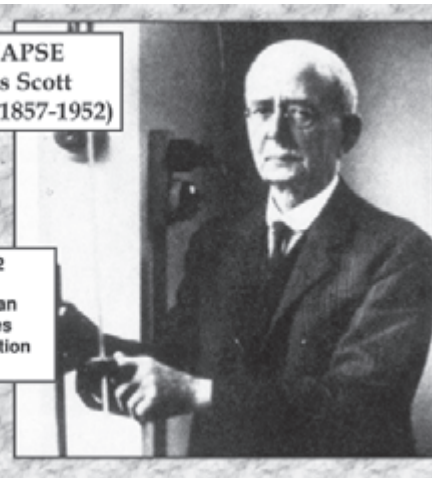

THE MODERN NOMENCLATURE:
1889: DENDRITE
Wilhelm His
(1831-1904)


1891: NEURON
Wilhelm Waldeyer
(1836-1921)
•c. 1000 BC:
Sanskrit word "nauree"
meaning a string
•probably the basis of the
English word "nerve"
•and of the word "neuron"

1896: AXON
(axis cylinder)

Rudolph Albert
von Kölliker
(1817-1905)

1897: SYNAPSE
Sir Charles Scott
Sherrington (1857-1952)



Nobel Prize in 1932

with Edgar D. Adrian
for their discoveries
regarding the function
of neurons

Sherrington writes: "You enquire about the introduction of the term 'synapse'; it happened thus. M. Foster had asked me to get on with the Nervous System part(Part iii)of a new edition of his 'Text of Physiol.' for him. I had begun it, and had not got far with it before I felt the need of some name to call the junction between nerve-cell and nerve-cell(because the place of junction now entered physiology as carrying functional importance). I wrote him of my difficulty, and my wish to introduce a specific name. I suggested using 'syndesm'(σύνδεσμος). He consulted his Trinity friend Verrall, the Euripidean scholar, about it, and Verrall suggested 'synapse' (from συνάπτω-ἅπτω[clasp])and as that yields a better adjectival form, it was adopted for the book."

Euripides

The word Sherrington introduced in Foster's Textbook was actually *synapsis*. As it is a Greek word, the plural would be *synapses*, from which the Anglicized singular *synapse* readily derived

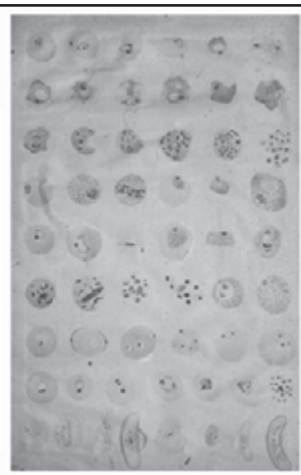
18 THE SIMPLE REFLEX [LECT.

As to the existence or the non-existence of a surface of separation or membrane between neurone and neurone, that is a structural question on which histology might be competent to give valuable information.

Studies on malaria:
1885-1893

Golgi's discoveries on malaria
("verifica dei seguenti fatti fondamentali"):

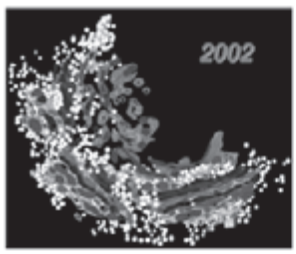
- Cycle of development of the parasite in the tertian and quartan forms of malaria
- Parasite differences in the two forms
- Correspondence between the cycle of development of the parasite and febrile bouts
- Action of quinine

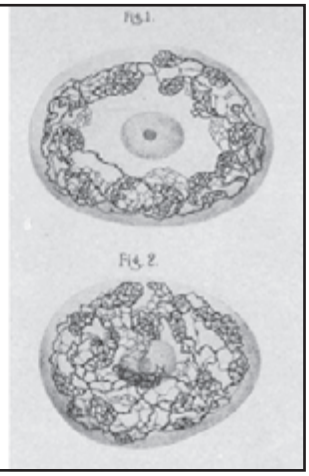


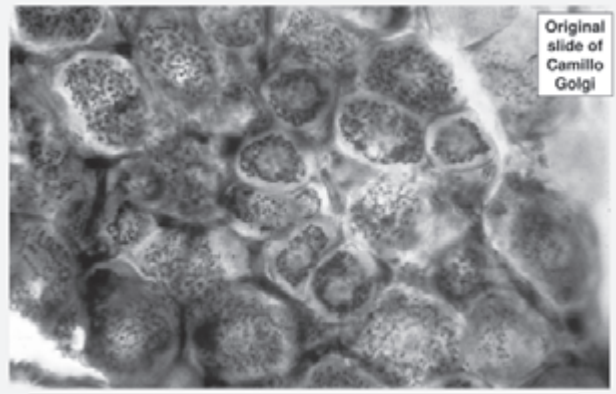
1898

Discovery of the "internal reticular apparatus"

Golgi apparatus







A heated debate followed: artifact or organelle?

1901: the Nobel Prize is instituted

Alfred Nobel 1833-1896

1866: **Nobel invents dynamite, and then creates companies and labs in more than 20 countries worldwide**

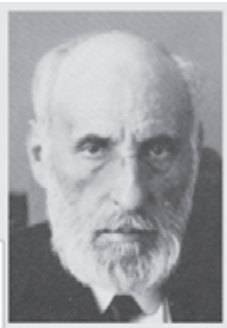
27 November 1895: **Nobel signs his will**

10 December 1896: **dies due a stroke in Sanremo (Italy).**

Stockholm, 1906

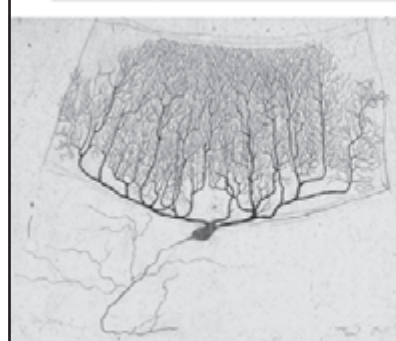
"WHAT A CRUEL IRONY OF FATE TO PAIR, LIKE SIAMESES TWINS UNITED BY THE SHOULDERS, SCIENTIFIC ADVERSARIES OF SUCH CONTRASTING CHARACTER!"

Cajal, Recollections of My Life

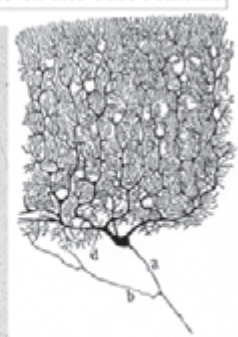


Stockholm, 1906
"In recognition of their work on the structure of the nervous system"

Drawings of the Purkinje cells of the cerebellum



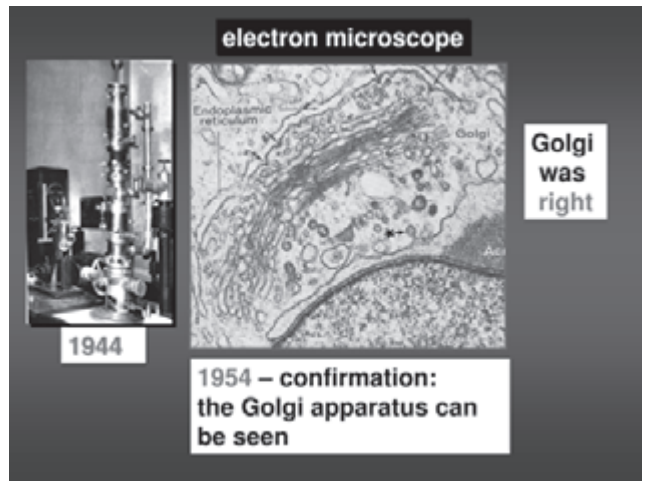
Golgi

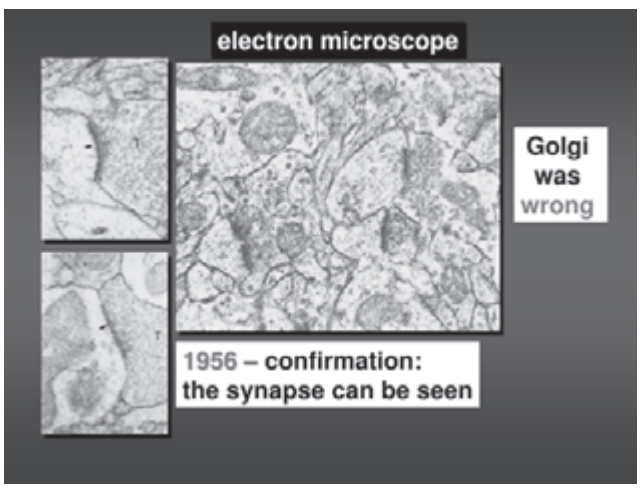


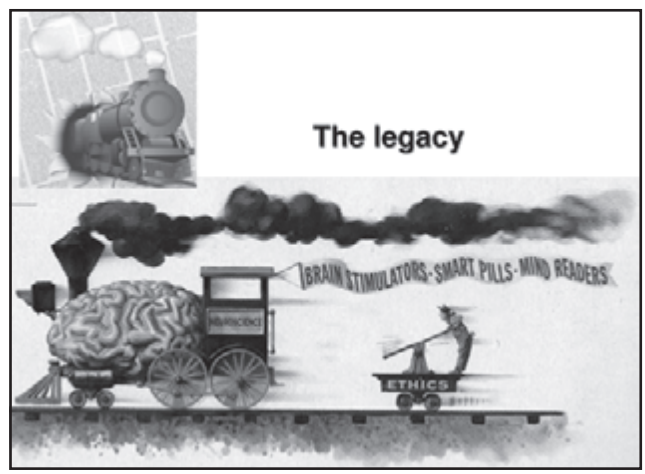
Cajal

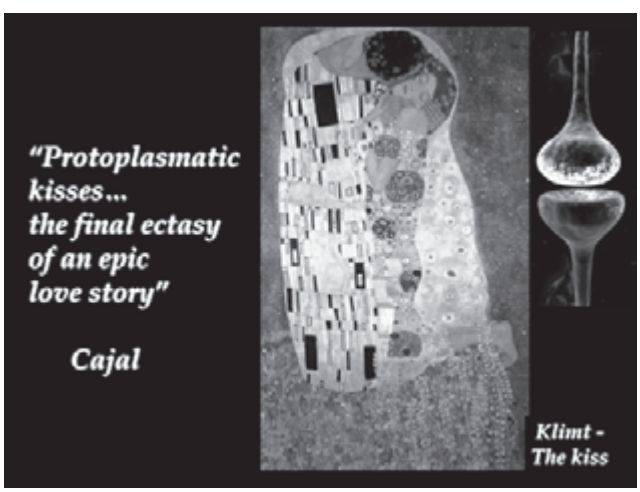
They saw (and depicted) the same findings!

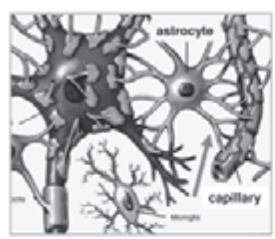

Otto Loewi
(1873-1961)
Sir Henry Hallett Dale
(1857-1961)
Nobel Prize in 1936 for their discoveries relating to chemical transmission of nerve impulses

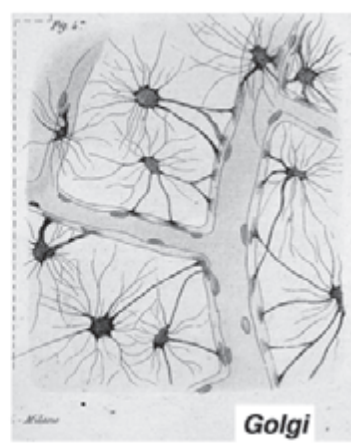

electron microscope
Endoplasmic reticulum
Golgi
Golgi was right
1944
1954 – confirmation: the Golgi apparatus can be seen


electron microscope
Golgi was wrong
1956 – confirmation: the synapse can be seen


The legacy
BRAIN STIMULATORS · SMART PILLS · MIND READERS
ETHICS

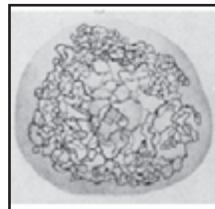

"Protoplasmatic kisses... the final ectasy of an epic love story"
Cajal
Klimt - The kiss


astrocyte
capillary

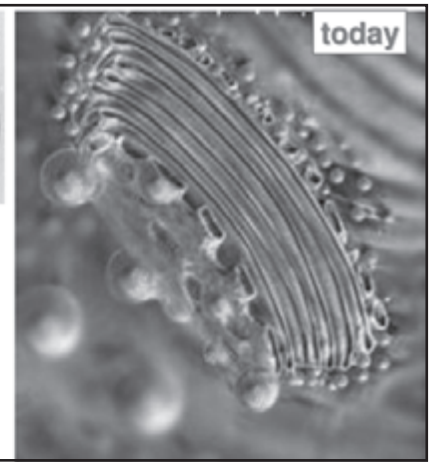

Golgi

"La gloire consiste à devenir un thème, ou un nom commun, ou un épithète… …"

Paul Valéry



today

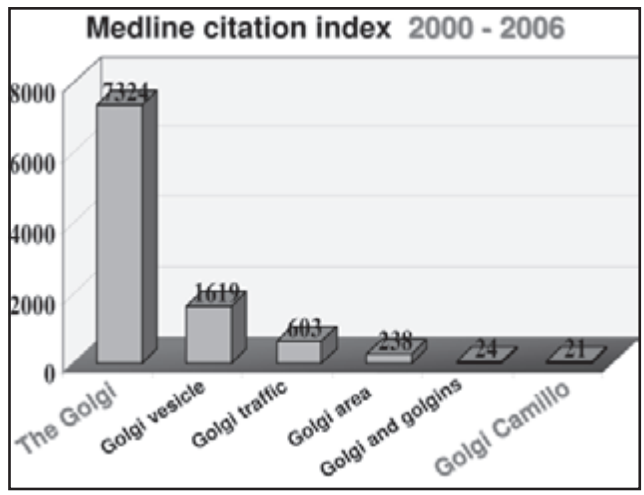


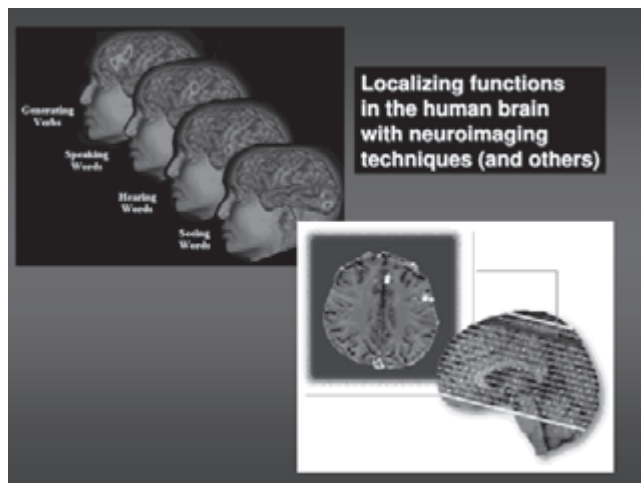
"the Golgi"

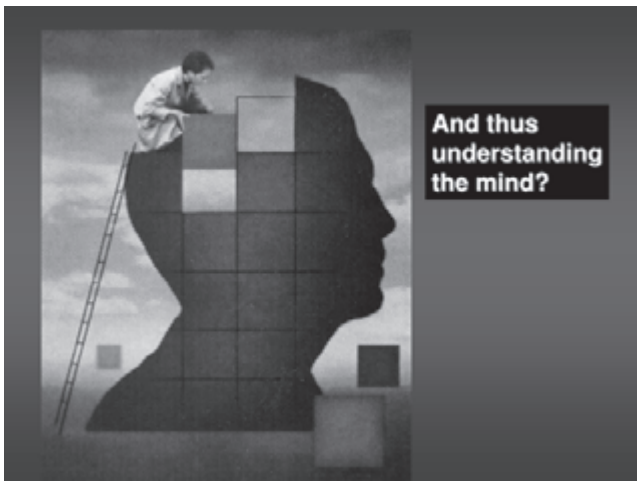
"Golgi"

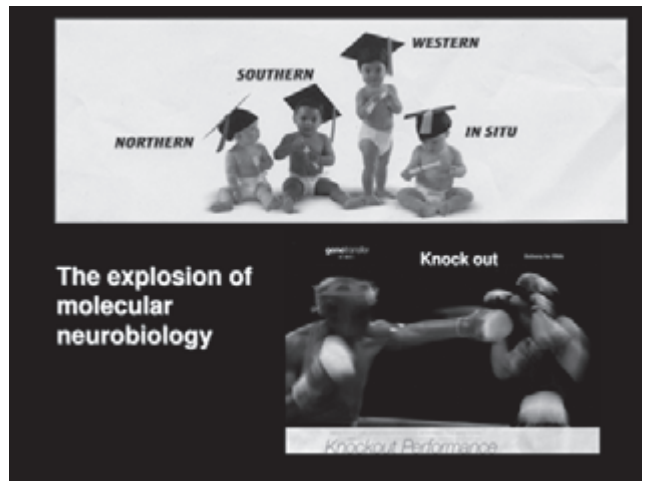
VARIETY OF TERMS COMMONLY USED IN THE SCIENTIFIC LITERATURE ON THE GOLGI APPARATUS

anti-Golgi	Golgi network	Golgi transport
Golgi accentuation	Golgi organelle	Golgi tubules
Golgi area	Golgi pool	Golgi vacuolation
Golgi autoantigen	Golgi precursors	Golgi vesicles
Golgi body	Golgi receptor	Golgi zones
Golgi chaperone	Golgi recycling	Golgi-associated
Golgi cisternae	Golgi region	Golgi-bound
Golgi cluster/s	Golgi reporter	Golgi-derived
Golgi compartments	Golgi retention	Golgi-enriched
Golgi elements	Golgi retrieval	Golgi-modified
Golgi enzyme	Golgi ribbon	Golgi-processed
Golgi figures	Golgi route	Golgi-resident
Golgi fraction	Golgi saccules	Golgi-restricted
Golgi ghosts	Golgi sites	Golgi-rich
Golgi lamellae	Golgi skeleton	Golgi-targeted
Golgi localization	Golgi spots	intra-Golgi
Golgi lumen	Golgi stacks	para-Golgi
Golgi lysosome	Golgi stage	peri-Golgi
Golgi marker	Golgi storage	post-Golgi
Golgi membranes	Golgi structures	pre-Golgi
Golgi modifications	Golgi system	trans-Golgi
Golgi morphology	Golgi trafficking	









Examples of debates:

today

•Mossy fiber sprouting
•Hippocampal sclerosis
Consequence or cause of epilepsy?

•Amyloid deposition in plaques
Consequence or cause of Alzheimer's disease?

•Prion diseases
A yet undiscovered microbe or
a mutant protein replicating
without nucleic acids? *(20 years of debates)*

today

•Adult neurogenesis
Stupid or intelligent?

But the neurons that will be born in your brain tomorrow will not have listened to today's lectures...

"For all those who are fascinated by the bewitchment of the infinitely small, there wait in the bosom of living being millions of palpitating cells which, for the surrender of their secret, and with it the halo of fame, demand only a clear and persistent intelligence to contemplate, admire, and understand them".

Last sentence of Cajal's autobiography

Epidemiology of the epilepsies in latin america

Carlos Acevedo (Chile)

Epidemiología de las Epilepsias

Dr. Carlos Acevedo Schwartzmann

Vice-Presidente Latinoamericano IBE

Epidemiología de las Epilepsias

- Epidemiología es el estudio de la distribución y determinantes de una enfermedad dada en Poblaciones humanas.
- Entrega información sobre incidencia, prevalencia, mortalidad, factores de riesgos.
- Importante en diseño de políticas de salud, investigadores, industria farmacéutica.

Epidemiología de las Epilepsias

Requisitos de un estudio epidemiológico.

- Diseño acorde con la hipótesis y sus objetivos.
- Calidad del muestreo de la población en riesgo.
- Concordancia entre numerador y denominador.
- Validación de los instrumentos y procesos utilizados.
- Definiciones conceptuales y operativas.
- Formas de asegurar el diagnóstico.
- Controles de calidad.

Epidemiología de las Epilepsias

Dificultades metodológicos en estudios epidemiológicos en LA y el Caribe.

- Organización fragmentada de los sistemas de salud.
- Sistemas de salud sin complementaridad.
- Baja cobertura de sistemas de salud.
- Coexistencia de modelo de atención publica y privada.

Epidemiología de las Epilepsias

Fuentes epidemiológico. de origen para estudios

1 Estudios basados en los registros de los servicios de Salud. Dificiles de realizar por requerir sistemas de salud muy bien organizados.

2 Estudios directos de la población basados en encuestas. Son la mayoría de los estudios regionales. De alto costo, observacionales.

Epidemiología de las Epilepsias

Incidencia

Definición: Número de casos nuevos que se presentan en un intervalo de tiempo dado (1 año), en una población determinada y expresada como tasa ajustada a 100.000 habitantes por año. Es un buen predictor del riesgo de padecer esa enfermedad.

Dificil de realizar.

Epidemiología de las Epilepsias

Incidencia Cruda

114x100.000 personas año (Chile)

190x100.000 (CME Ecuador)

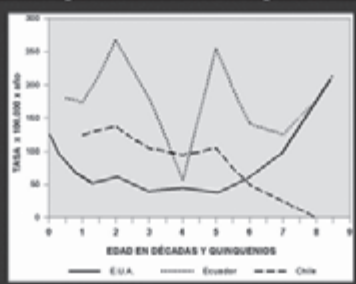
(122x100.000)

24-53x100.000 Hauser, Rochester USA.

26-70x100.000 Hauser, Rochester USA (agrega crisis únicas)

Epidemiología de las Epilepsias

Incidencia específica de edad en población entera



Epidemiología de las Epilepsias

Prevalencia

Definición: Es el conjunto de enfermos de un espacio y tiempo determinados, usualmente se la presenta como tasa ajustable a 1000 habitantes. Es la base para planificar la prevención secundaria y terciaria. La prevalencia de las epilepsias depende de la incidencia, remisión y mortalidad.

Epidemiología de las Epilepsias

Prevalencia Cruda en toda la población.

Existencia de una gran variabilidad mundial

Hauser,Goodridge 4 - 8x1000

LA y el Caribe 3,4 Cuba(Naranjo) y 57x1000 Panamá(Gracia)

Revisión 49 estudios a nivel internacional según edad de la población y nivel de desarrollo de los países(Placencia 1992)

- Infancia en países en desarrollo.32,8±10,6x1000:4 estudios.

-Infancia países desarrollado:19 ± 13,3x1000:6 estudios.

Toda edad países en desarrollo:20,9 ± 10,4x1000:16 estudios

Toda edad países desarrollados:9 ± 9,3x1000: 23 estudios

Epidemiología de las Epilepsias

¿Por qué tantas diferencias entre estos estudios?

- Diferentes definiciones
- diferentes etiologías
- calidad del diagnóstico
- diferentes factores de riesgo
- metodología utilizada

} Encuestas

- Sub- registro, ocultamiento: Estudios de registro de servicios

Países muy heterogéneos.

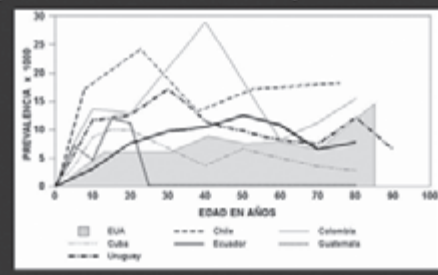
Epidemiología de las Epilepsias

Diferencias por sexos de prevalencia específica

- A nivel internacional no hay diferencias significativas entre los sexos.
- En LA y el Caribe las tasas específicas en la mayoría de los estudios son mayores en el sexo femenino. No hay explicación científica: ocultamiento? ¿migración?
- (Alves 2001, Carpio 1986, da Motta-Gomes 2002, Nicoletti 1999, Placencia 1992)

Epidemiología de las Epilepsias

Prevalencia específica de edad, en población completa.
Comparación Estudios Prevalencia LA y el Caribe con USA.



Epidemiología de las Epilepsias

Magnitud global del problema.

Definición: Cifra absoluta de enfermos (casos prevalentes totales)en un espacio y tiempo.

- 50 millones de personas con epilepsias en el mundo
- 40 millones de personas con epilepsia en los países en desarrollo.
- 5 millones viven en LA y el Caribe.

Grupos de mayor riesgo: niños, mujer, anciano.

(Atlas Epilepsy care in the World 2005 WHO, ILAE, IBE)

Epidemiología de las Epilepsias

Tasas probables de Incidencia y Prevalencia

Incidencia: 100-120 x 100.000

Prevalencia epilepsia activa: 5-9x1000

Se requieren mayores estudios.

Epidemiología de las Epilepsias

Prevalence, Incidence and Etiology Epilepsies in Rural Honduras: The Salamá Study)

Area rural Honduras, puerta a puerta. 6473 habitantes

Incidencia 92,7x100.000

Prevalencia activa 15,4x1000

- Prevalencia > en la mujer
- 50% de los casos de epilepsia activa < 20 años edad
- 92,2 de los casos crisis parciales.

– M.T.Medina et cols (Epilepsia 2005)

Estudio de Salamá

Epidemiología de las Epilepsias

Prevalence and Pattern of Epilepsy in different Social-Economic Classes in Brazil (Campinas and Sao José de Rio Preto)

- Estudio puerta a puerta
- Población total de 96.300 personas
- Prevalencia epilepsia activa 5,4x1000
- Prevalencia en población con mayor deprivación social 7,4x1000
- Prevalencia en población con menor deprivación social 1,6x1000
- Prevalencia en el adulto mayor: 8,5x1000
- Tratamiento inadecuado 38% de los casos

Ana L.A. Noronha et cols, Epilepsia 2007 in press

Epidemiología de las Epilepsias

Mortalidad en epilepsia

- Esta descrito desde mediados del siglo XIX un mayor riesgo de muerte asociado a la epilepsia (Bacon 1868)
- SMR (standardized mortality ratio:2-3 veces comparado con la población general)
- Compara el riesgo de morir de las personas con epilepsia con el riesgo de morir de la población general
- Gran margen de error en su cálculo
- Existe menor información en la población infantil

Epidemiología de las Epilepsias

Causas de muerte en epilepsia

1 Relacionada con la epilepsia

- Estado de mal epiléptico
- Muerte por accidente: traumatismo, asfixia por inmersión, quemaduras, aspiración de contenido gástrico, accidente automovilístico
- Atribuible al tratamiento de la epilepsia: fármacos antiepilépticos(FAE), cirugía de la epilepsia

Epidemiología de las Epilepsias

Causas de Muerte en epilepsia

2 Enfermedades médicas: Cáncer, enfermedad cerebrovascular, enfermedades respiratorias, enfermedades digestivas

3 Suicidio

Epidemiología de las Epilepsias

Mortalidad en epilepsia.Estudios en países desarrollados: Forsgren, Hauser(2005): SMR 1,6 a 3,0

- Epilepsia remota sintomática: SMR 2.2 6.5 en pacientes con crisis frecuentes y severas. Sube a 50 veces mas si es de inicio neonatal y si hay RM y/o PC
- Epilepsia idiopáticas: No hay mayor riesgo
- Mayor riesgo: Daño cerebral y epilepsia:causas precisas de muerte son: convulsiones, neumonía por aspiración, asfixia por inmersión (Day 2002)
- Expectativa de vida: baja 2 años en epilepsias idiopáticas/criptogénicas y 10 años en epilepsias sintomáticas (Gaitatzis, UK 2004)

Epidemiología de las Epilepsias

Mortalidad en Epilepsia: Estudios en países desarrollados en niños (Berg and Shinnar 2004)

Seguimiento en 613 casos nuevos de epilepsia en niños. Se detectan 13 muertes, de las cuales 10 están relacionadas con la causa subyacente de la epilepsia y dos a convulsiones

SMR 7.54 para la población total de pacientes

SMR 33.46 en epilepsias sintomáticas

SMR 1.43 en epilepsias no sintomáticas

Conclusión: los niños con epilepsia presentan un riesgo mayor de muerte

Epidemiología de las Epilepsias

Mortalidad en epilepsia

Estudios en países en vías de desarrollo

- Estudio de S.Kochen; Argentina

SMR 2,45 Mejor pronóstico en las epilepsias idiopáticas y peor pronóstico en los casos de epilepsias sintomáticas

- G. Diop(2005): Africa. SMR 6
- Ding (2006) China: SMR 3,9 en la población general. SMR 23 población entre 15 a 29 años

Epidemiología de las Epilepsias

Mortalidad en epilepsia

Suicidio

Sujeto a controversias. Estudio Rochester 3 casos en 8233 personas año

- Riesgo de muerte por suicidio es 4-5 veces mayor comparado con la población general.(Lina Nashef 2000)
- Subgrupos de mayor riesgos: adolescentes, depresión, conductas psicoticas, epilepsia del lóbulo temporal
- Es indispensable atención psiquiátrica de los pacientes de mayor riesgo, por ser potencialmente prevenible

Epidemiología de las Epilepsias

Mortalidad en epilepsia

Definición SUDEP: Muerte súbita e inesperada, con o sin testigos no traumática, en ausencia de sofocación, en un paciente con epilepsia en el cual una autopsia acorde o protocolo especifico no revela una causa de muerte

Tasa SUDEP muy variable dependiendo de que subgrupo se trate

Epidemiología de las Epilepsias

Mortalidad en epilepsia

- Tasa SUDEP: 1x500 a 1x1000

Bruselas: 0,4x1000

Canfield: 1-2x1000

- Riesgo en Epilepsia idiopáticas: similar al de la población general

Riesgo SUDEP: Daño neurológico, epilepsias sintomáticas de dificil control, crisis TC generalizados, politerapia, edad joven, durante el sueño, irregularidad FAE

Epidemiología de las Epilepsias

Mortalidad en epilepsia

Conclusión:

- La mortalidad en epilepsia es mayor comparado con la población general y es mayor aún en los países en vías de desarrollo
- Se requiere mejorar la calidad de la certificación de muerte y la preocupación de los neurólogos por este aspecto de las epilepsias

Epidemiología de las Epilepsias

- El riesgo es mucho mayor en epilepsias sintomáticas que en epilepsias idiopáticas
- El riesgo es mayor el primer año después del diagnostico
- La posibilidad de prevenir muertes es limitada y la medida de mayor utilidad es un mejor control de las crisis

Epidemiología de las Epilepsias

Etiología de las epilepsias

Existen pocos estudios

- Causas mas frecuentes: secuelas de patologías perinatales, neuroectodermosis, asociado a retardo mental y/o parálisis cerebral, enfermedades metabólicas y neurodegenerativas, tumores cerebrales, TEC grave, malformaciones del desarrollo cortical cerebral, Alzheimer, patologías cerebrales asociadas al envejecimiento

Epidemiología de las Epilepsias

Etiología de las epilepsias Atlas 2005 OMS

- Información de 17 países de LA y el Caribe
- En un 30-60% de los casos no se identifica la etiología
- Etiologías más frecuentes reportadas en el cuestionario:
- TEC: 16 países
- Secuelas de patologías perinatal: 13 países
- Accidentes cerebrovascular: 13 países
- Infecciones del SNC: 10 países
- Neurocisticiscosis: 8 países
- Tumores: 7 países

Epidemiología de las Epilepsias

Etiología de las epilepsias

Estudio de Salamá:

Etiología idiopatica/criptogénica: 37,8% De los casos

Etiología Sintomática: 62,2%

- Neurocisticercosis 36,6 de los casos
- Muchos de los casos de epilepsia en los países de LA y el Caribe tienen prevención

Etiología de la epilepsia activa Estudio Salamá

TABLE 3. *Etiology of active epilepsy in the patients studied by age groups*

Etiology/Age groups	0–9	10–19	20–29	30–39	40–49	50–59	60+	Total	%
Cryptogenic	7	8	3	3	2	3	1	27	30.0
Idiopathic	3	4						7	7.8
All symptomatic	7	21	8	6	9	3	2	56	62.2
Neurocysticercosis	4	13	5	3	6	1	1	33	36.6
Perinatal brain damage		5	1	1				7	7.8
Poststroke					1		1	2	2.2
Cortical dysplasia	1			1				2	2.2
Post-traumatic	2	1						3	3.3
Postmeningitis/encephalitis			1		1			2	2.2
Multifactorial		1			1			2	2.2
Other*		1		1	1	2		5	5.6
All etiologies	24	55	18	15	21	9	5	90	100.0

*The "Other" category includes a tumor (probable meningioma), noncysticercotic granuloma, chronic alcoholism sequelae, chronic hydrocephalus, progressive myoclonic epilepsy (probable Unverricht-Lundborg disease).

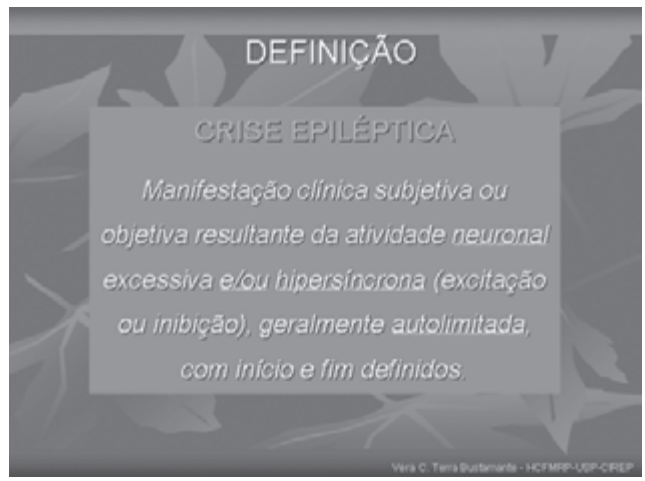
Epidemiología de las Epilepsias

Conclusiones del Reporte

1 Es esencial identificar la etiología de las epilepsias
2 La información obtenida es crucial para diseño de planes y estrategias de prevención y manejo
3 Hay una enorme carencia de recursos diagnósticos y humanos
4 Las 5 causas más frecuentes reportadas en LA y el Caribe tienen prevención

Classification of epileptic seizures

Vera Terra Bustamante (Brazil)



CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

- CLASSIFICAÇÃO VIGENTE: a classificação atual ainda encontra-se vigente e só será substituída quando uma nova classificação for amplamente aceita.

Engel, 2006.

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

- ANAMNESE:
  - História Clínica (testemunha).
  - Relação com ciclo menstrual, ciclo sono/vigília.
  - Fatores desencadeantes.
  - Exame clínico.
  - Exames complementares: EEG/VEEG, neuroimagem.

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

- DIVISÃO EM **EIXOS:**
  - Permite a descrição dos sintomas da crise e seu tipo.
  - Definição da síndrome epiléptica.
  - Descrição etiológica.
  - Impacto das crises/epilepsia.

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

ESQUEMA PARA A CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

- Eixo 1: Fenomenologia ictal - Glossário descritivo da fenomenologia ictal (Epilepsia 42(9):1212-1218, 2001).
- Eixo 2: Tipos de crises - Lista das crises epilépticas (Epilepsia 42(6): 1-9, 2001).
- Eixo 3: Síndromes epilépticas - Lista das síndromes epilépticas.

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

ESQUEMA PARA A CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

- Eixo 4: Etiologia - Classificação das doenças frequentemente associadas a crises ou síndromes epilépticas.
- Eixo 5: Grau de comprometimento (adaptada da OMS).

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DEFINIÇÃO

EIXO 1

Descrição do evento ictal, sem referências à etiologia, anatomia ou mecanismos. Pode ser breve ou extremamente detalhada.

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DEFINIÇÃO

EIXO 2

Tipo ou tipos de crises epilépticas apresentadas pelo paciente, originadas de uma lista diagnóstica pré-estabelecida (classificações de 1981, 2001, 2006).

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DEFINIÇÃO

EXEMPLO

EIXO 1: sensação de mal-estar epigástrico, perda da consciência, seguida de automatimos gestuais e oroalimentares.

EIXO 2: crises parciais complexas (crise focal com automatimos típicos).

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

CRISES EPILÉPTICAS

FOCAIS OU PARCIAIS

Simples X Complexas

Focais com Generalização Secundária

GENERALIZADAS

INCLASSIFICÁVEIS

Commission on Classification and Terminology of the ILAE. Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures. *Epilepsia* 1981, 22: 489-501

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

O TERMO FOCAL SUBSTITUI OS TERMOS *PARCIAL* OU *RELACIONADO COM LOCALIZAÇÃO*

ILAE - 2001

Epilepsia 2001, 42 (Suppl 6): 1 -8.

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

CRISES FOCAIS

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

CRISES GENERALIZADAS

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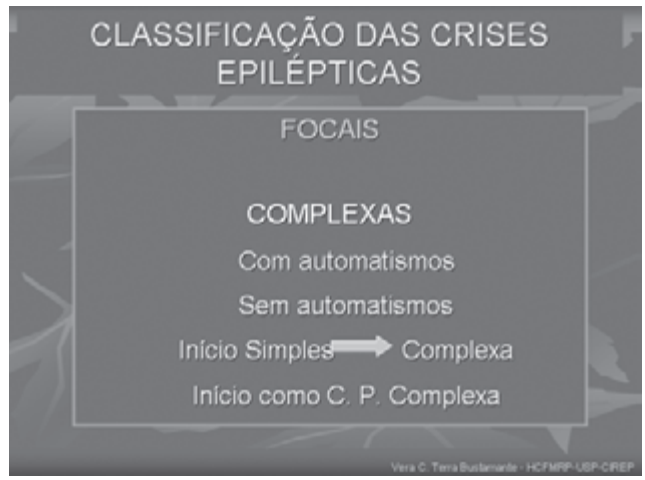
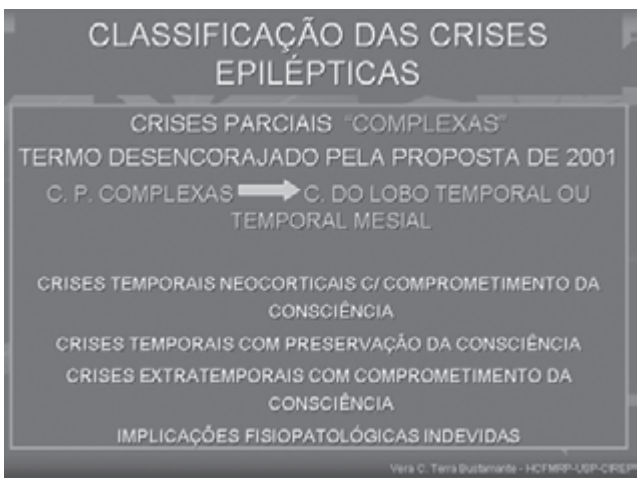
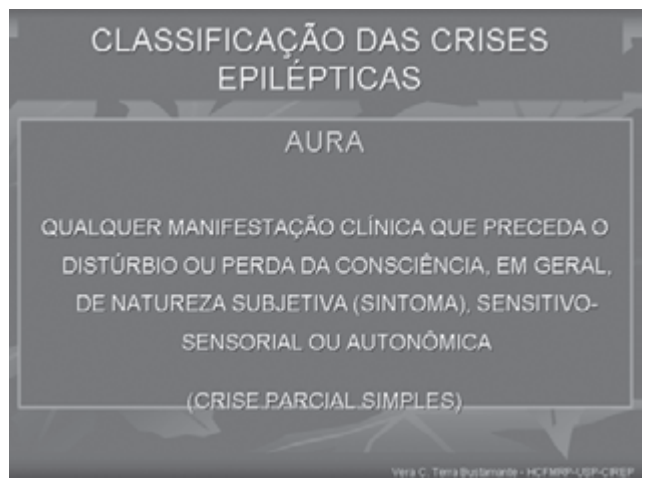
CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS
FOCAIS
SIMPLES
Motoras (tônicas, clônicas, mioclônicas, atônicas, versivas)
Somato-sensitivas e Sensoriais (gustativas, olfativas, vertiginosas, auditivas, visuais)
Com Sintomatologia Psíquica
Autonômicas ou Vegetativas


CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS
FOCAIS
COMPLEXAS
Com automatismos
Sem automatismos
Início Simples → Complexa
Início como C. P. Complexa


CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS
CRISES PARCIAIS "COMPLEXAS"
TERMO DESENCORAJADO PELA PROPOSTA DE 2001
C. P. COMPLEXAS → C. DO LOBO TEMPORAL OU TEMPORAL MESIAL
CRISES TEMPORAIS NEOCORTICAIS C/ COMPROMETIMENTO DA CONSCIÊNCIA
CRISES TEMPORAIS COM PRESERVAÇÃO DA CONSCIÊNCIA
CRISES EXTRATEMPORAIS COM COMPROMETIMENTO DA CONSCIÊNCIA
IMPLICAÇÕES FISIOPATOLÓGICAS INDEVIDAS


CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS
AURA
QUALQUER MANIFESTAÇÃO CLÍNICA QUE PRECEDA O DISTÚRBIO OU PERDA DA CONSCIÊNCIA, EM GERAL, DE NATUREZA SUBJETIVA (SINTOMA), SENSITIVO-SENSORIAL OU AUTONÔMICA
(CRISE PARCIAL SIMPLES)


CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS
GENERALIZADAS
TÔNICO-CLÔNICA
TÔNICA
CLÔNICA
MIOCLÔNICA
ATÔNICA
AUSÊNCIA


CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS
CRISES EPILÉPTICAS GENERALIZADAS
AUSÊNCIA
SIMPLES
COMPLEXA
COM COMPONENTES MIOCLÔNICOS BRANDOS
COM COMPONENTES TÔNICOS
COM COMPONENTES AUTONÔMICOS
COM AUTOMATISMOS

CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

CRISES EPILÉPTICAS GENERALIZADAS
ILAE/ 1981

MIOCLONO-ASTÁTICAS ?

ESPASMOS INFANTIS ?

Vera C. Terra Bustamante - HCFMRP-USP-CIREP

CLASSIFICAÇÃO DAS EPILEPSIAS E SÍNDROMES EPILÉPTICAS - PROPOSTA ILAE 2001

CRISES QUE NÃO REQUEREM NECESSARIAMENTE O DIAGNÓSTICO DE EPILEPSIA

CRISES NEONATAIS BENIGNAS

CRISES FEBRIS

CRISES REFLEXAS

CRISES INDUZIDAS POR DROGAS OU OUTRAS SUBSTÂNCIAS QUÍMICAS

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CLASSIFICAÇÃO DAS EPILEPSIAS E SÍNDROMES EPILÉPTICAS - PROPOSTA ILAE 2001

CRISES QUE NÃO REQUEREM NECESSARIAMENTE O DIAGNÓSTICO DE EPILEPSIA

CRISES DA ABSTINÊNCIA ALCOÓLICA

CRISES PRECOCES PÓS-TCE

CRISES OU CLUSTER DE CRISES ISOLADOS

CRISES COM REPETIÇÃO ESPORÁDICA (OLIGOEPILEPSIA)

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CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS

EXEMPLOS DE CRISES EPILÉPTICAS

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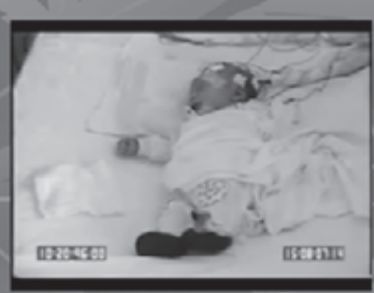
CRISES MIOCLÔNICAS NO LACTENTE



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CRISE MIOCLÔNICAS NO LACTENTE

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CRISES HIPOMOTORAS
CRISES PARCIAIS COMPLEXAS???
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CRISE FOCAL MOTORA – PARCIAL COMPLEXA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


ESPASMOS INFANTIS
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

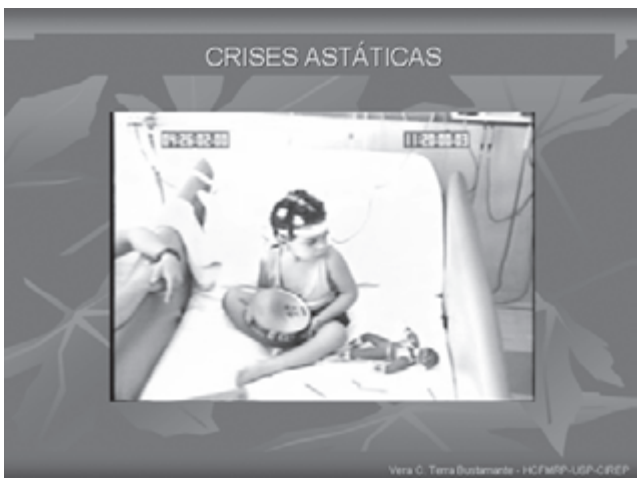

AUSÊNCIA INFANTIL TÍPICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


AUSÊNCIA INFANTIL ATÍPICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

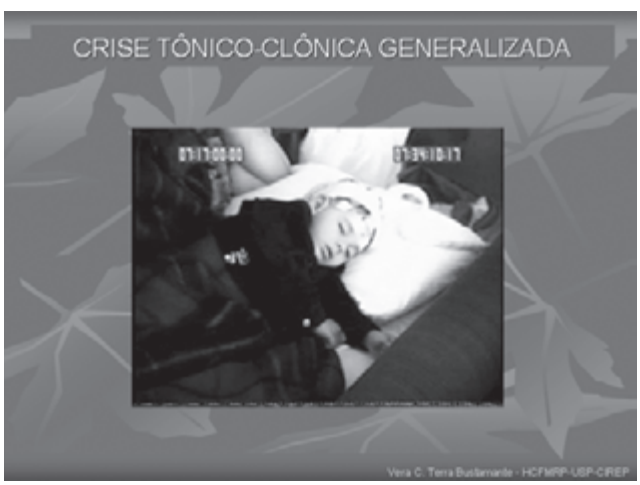

CRISE MIOCLÔNICA-TÔNICO-CLÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISES DE AUSÊNCIA MIOCLÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

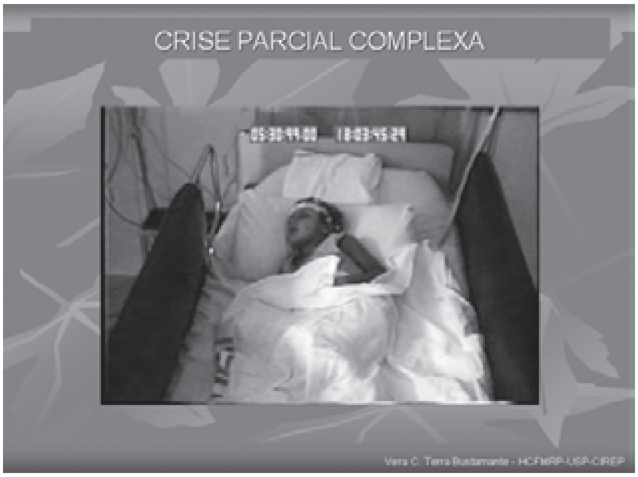

AUSÊNCIA ATÍPICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

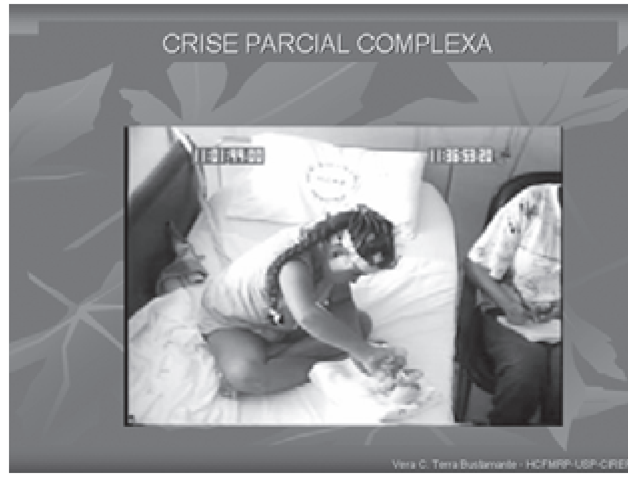

CRISES ASTÁTICAS
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISES ASTÁTICAS
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE TÔNICO-CLÔNICA GENERALIZADA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISES TIPO STARTLE
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE PARCIAL COMPLEXA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

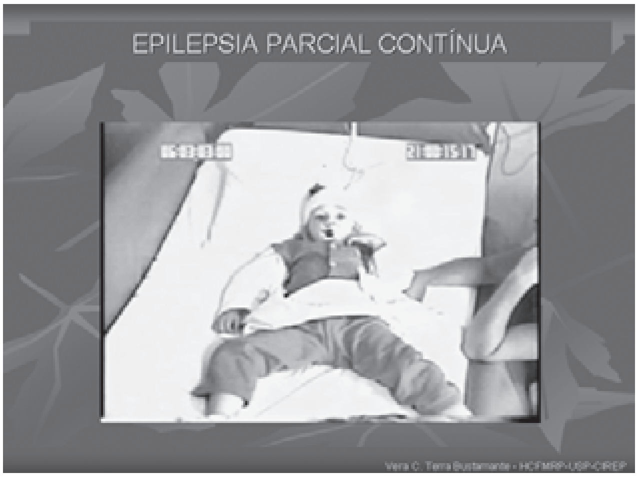

CRISE PARCIAL COMPLEXA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE PARCIAL COMPLEXA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE PARCIAL COMPLEXA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

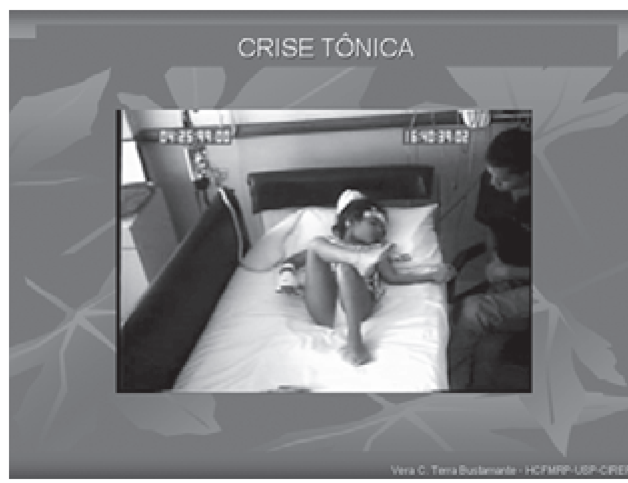

CRISE PARCIAL COMPLEXA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE FOCAL MOTORA – CLÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


EPILEPSIA PARCIAL CONTÍNUA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE TÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE TÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE TÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP


CRISE TÔNICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

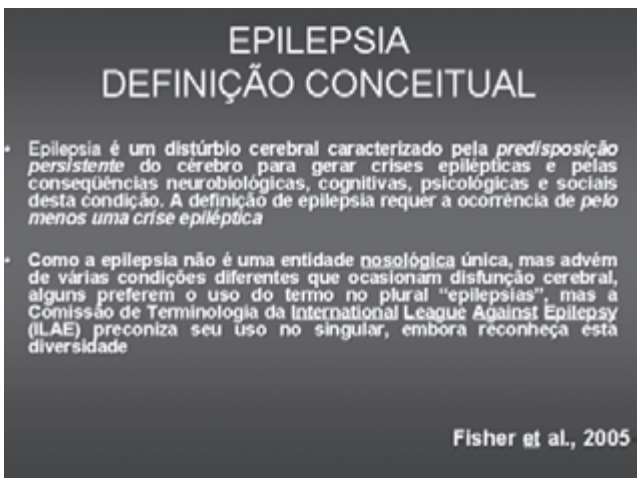

CRISE GELÁSTICA
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

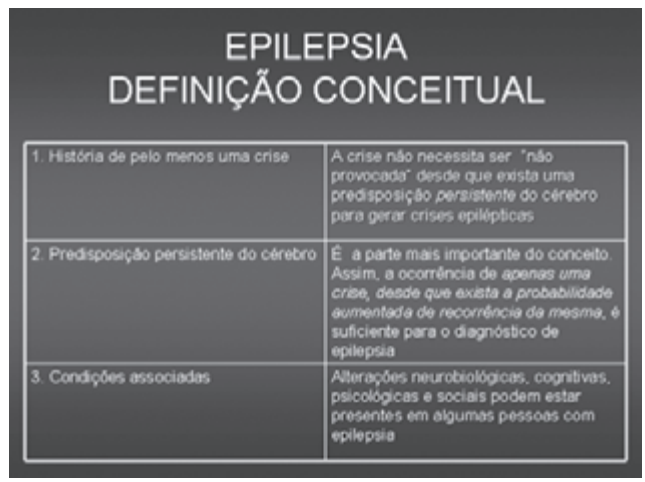

CRISE FOCAL MOTORA COM SINTOMAS VEGETATIVOS
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

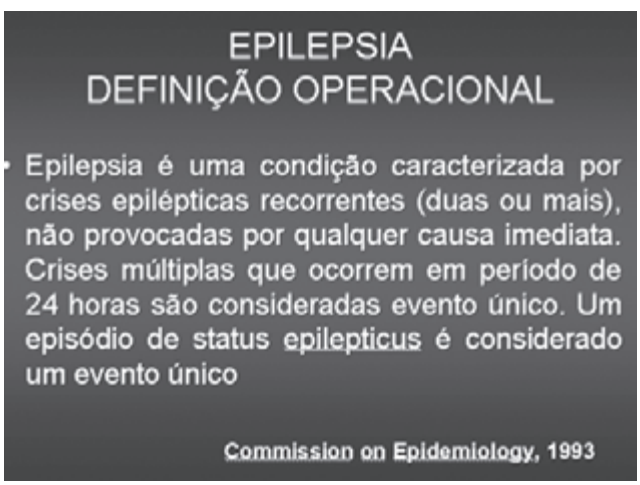

CRISE FOCAL MOTORA COM SINTOMAS VEGETATIVOS
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

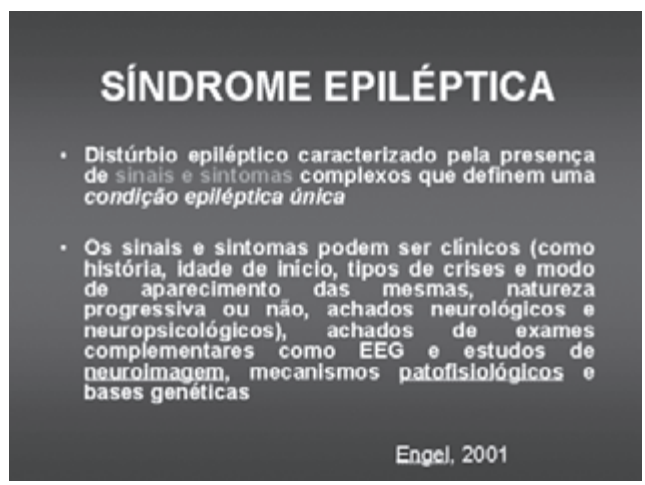

PERDA DE FÔLEGO
Vera C. Terra Bustamante - HCFMRP-USP-CIREP

Classification of the epileptic syndromes
Americo Sakamoto (Brazil)









SÍNDROME EPILÉPTICA

- Idade de início
- Eventos precipitantes
- Antecedentes familiares
- Tipo (s) de crise (s) epiléptica (s)
- Características eletrencefalográficas
- Neuroimagem estrutural
- Avaliação funcional
- Patologia

CLASSIFICAÇÃO INTERNACIONAL DAS SÍNDROMES EPILÉPTICAS (1989)

- Epilepsias e síndromes relacionadas à localização, parciais ou focais
  - idiopáticas
  - sintomáticas
  - criptogênicas
- Epilepsias e síndromes generalizadas
  - idiopáticas
  - criptogênicas ou sintomáticas
  - sintomáticas
    - ✓ etiologias não específicas
    - ✓ etiologias específicas
- Epilepsias e síndromes indeterminadas se focais ou generalizadas
  - com sinais e sintomas de crises generalizadas e focais
  - sem sinais inequívocos de crises generalizadas ou focais
- Síndromes especiais
  - crises relacionadas à situações

ESQUEMA PARA A CLASSIFICAÇÃO INTERNACIONAL DAS CRISES E SÍNDROMES EPILÉPTICAS *UMA NOVA PROPOSIÇÃO*

ILAE 2001

ESQUEMA PARA A CLASSIFICAÇÃO INTERNACIONAL DAS CRISES EPILÉPTICAS E EPILEPSIAS

- Eixo 1
  - Fenomenologia ictal: Glossário descritivo da fenomenologia ictal
- Eixo 2
  - Tipos de crises: Lista das crises epilépticas
- Eixo 3
  - Síndromes: Lista das síndromes epilépticas
- Eixo 4
  - Etiologia: Classificação das doenças freqüentemente associadas a crises ou síndromes epilépticas
- Eixo 5
  - Grau de comprometimento (adaptada da OMS)

CLASSIFICAÇÃO INTERNACIONAL DAS SÍNDROMES EPILÉPTICAS *UMA NOVA PROPOSIÇÃO – ILAE 2001*

CLASSIFICAÇÃO INTERNACIONAL DAS SÍNDROMES EPILÉPTICAS *UMA NOVA PROPOSIÇÃO – ILAE 2001*

✓ Classificação das síndromes epilépticas

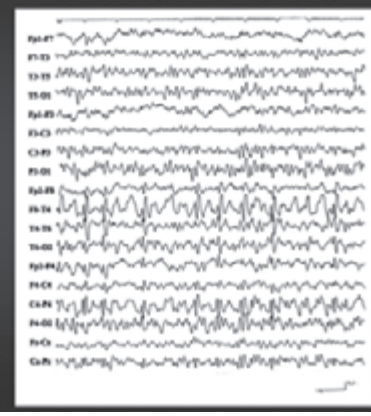
1. Epilepsias focais idiopáticas
2. Epilepsias focais familiares
3. Epilepsias focais sintomáticas
4. Epilepsias generalizadas idiopáticas
5. Epilepsias reflexas
6. Encefalopatias epilépticas
7. Epilepsias mioclônicas progressivas
8. Crises que não obrigam o diagnóstico de epilepsia

A Classificação das Síndromes Epilépticas

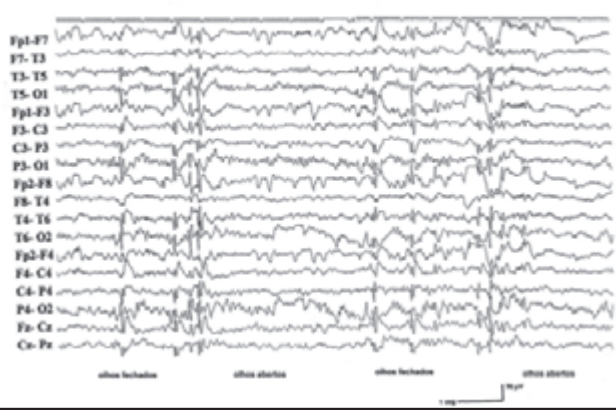
1. Epilepsias focais idiopáticas do lactente e da criança

- Crises neonatais benignas
- Epilepsia benigna da infância com descargas centrotemporais
- Epilepsia com paroxismos occipitais
  - ✓ Tipo Gastaut (início tardio)
  - ✓ Tipo Panayiotopoulos (início precoce)

EPILEPSIA COM DESCARGAS CENTROTEMPORAIS



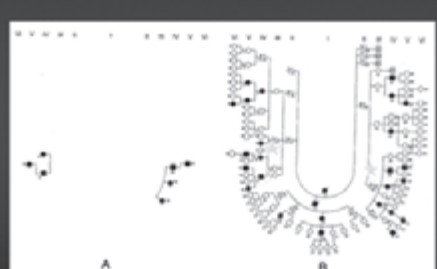
EPILEPSIA COM PAROXISMOS OCCIPITAIS



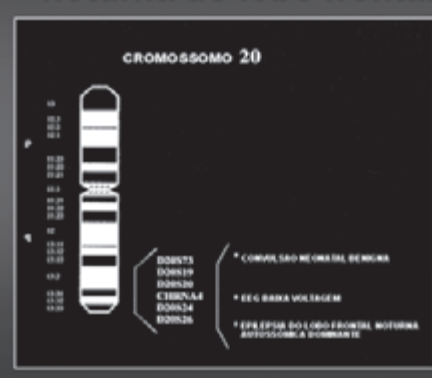
A Classificação das Síndromes Epilépticas

2. Epilepsias focais familiares
   - Crises neonatais benignas familiares
   - Epilepsia autossômica dominante noturna do lobo frontal
   - Epilepsia familiar do lobo temporal
   - Epilepsia autossômica dominante com focos variáveis*
   - Epilepsia autossômica dominante com manifestações auditivas

Epilepsia autossômica dominante noturna do lobo frontal



Epilepsia autossômica dominante noturna do lobo frontal



A Classificação das Síndromes Epilépticas

3. Epilepsias focais provavelmente ou indubitavelmente sintomáticas
   - Epilepsias límbicas
     - Epilepsia medial do lobo temporal por esclerose hipocampal
     - Epilepsia medial do lobo temporal definida por etiologias específicas
   - Epilepsias neocorticais
     - Síndrome de Rasmussen
     - Síndrome de hemiconvulsão-hemiplegia
     - Outros tipos definidos pela localização e etiologia
     - Crises parciais migratórias da infância precoce

A Classificação das Síndromes Epilépticas

4. Epilepsias generalizadas idiopáticas
   - Epilepsia mioclônica benigna do lactente
   - Epilepsia com crises mioclono-astáticas
   - Epilepsia ausência da infância
   - Epilepsia com ausências mioclônicas
   - Epilepsias generalizadas com fenótipos variáveis
     - Epilepsia ausência juvenil
     - Epilepsia mioclônica juvenil
     - Epilepsia com crises tônico-clônicas generalizadas
   - Epilepsias generalizadas com crises febris plus *

A Classificação das Síndromes Epilépticas

5. Epilepsias reflexas
   - Epilepsia fotossensível idiopática do lobo occipital
   - Outras epilepsias sensíveis a estímulos visuais
   - Epilepsia primária da leitura
   - Epilepsia do sobressalto

A Classificação das Síndromes Epilépticas

6. Encefalopatias epilépticas
   - Encefalopatia mioclônica precoce
   - Síndrome de Ohtahara
   - Síndrome de West
   - Síndrome de Dravet (epilepsia mioclônica severa da infância)
   - Status mioclônico em encefalopatias não progressivas *
   - Síndrome de Lennox-Gastaut
   - Síndrome de Landau-Kleffner
   - Epilepsia com ponta-onda contínua durante sono lento

A Classificação das Síndromes Epilépticas

7. Epilepsias mioclônicas progressivas
   - Doenças específicas

A Classificação das Síndromes Epilépticas

8. Crises que não exigem necessariamente o diagnóstico de epilepsia
   - Crises neonatais benignas
   - Crises febris
   - Crises reflexas
   - Crises da retirada de álcool
   - Crises induzidas por drogas ou substâncias químicas
   - Crises pós-traumáticas imediatas ou precoces
   - Crises únicas ou cluster isolado de crises
   - Crises raras (oligoepilepsias)

A Classificação das Doenças que são freqüentemente associadas à crises ou síndromes epilépticas

1. Epilepsias mioclônicas progressivas
2. Distúrbios neurocutâneos
3. Malformações do desenvolvimento cortical
4. Tumores do sistema nervoso
5. Anormalidades cromossômicas
6. Doenças mendelianas monogênicas com mecanismos patogênicos complexos

A Classificação das Doenças que são freqüentemente associadas à crises ou síndromes epilépticas

7. Doenças metabólicas hereditárias
8. Lesões isquêmicas pré ou perinatais ou infecções causando encefalopatias não progressivas
9. Infecções pós natais
10. Outros fatores pós natais
11. Miscelânea

CLASSIFICAÇÃO DAS SÍNDROMES EPILÉPTICAS

- Em setembro de 2006, o Grupo de Trabalho em Classificação e Terminologia da ILAE publicou um novo comunicado no qual apresenta a lista das síndromes epilépticas de acordo com a idade de início das crises e outras condições a elas relacionadas
- Estas síndromes foram graduadas pelos participantes da Comissão de forma preliminar de 1 a 3, sendo 3 as síndromes melhor definidas

Engel, 2006

Lista das Síndromes Epilépticas por Idade de Início (Engel, 2006)

Período neonatal	Crises neonatais benignas familiares (3) Encefalopatia mioclônica precoce (3) Síndrome de Ohtahara (3)
Lactentes	Crises migratórias parciais do lactente (3) Síndrome de West (3) Epilepsia mioclônica do lactente (3) Crises infantis benignas (3) Síndrome de Dravet (3) Encefalopatia mioclônica em desordens não progressivas (3)
Infância	Epilepsia occipital benigna da infância de início precoce (tipo Panayiotopoulos) (3) Epilepsia com crises mioclono-atônicas (3) Epilepsia benigna da infância com descargas centrotemporais (3) Epilepsia occipital da infância de início tardio (tipo Gastaut) (1) Epilepsia com ausências mioclônicas (2) Síndrome de Lennox-Gastaut (3) Encefalopatia epiléptica com descargas de espículo-onda contínuas durante o sono incluindo a síndrome de Landau-Kleffner (3) Epilepsia ausência da infância (3)

Lista das Síndromes Epilépticas por Idade de Início (Engel, 2006)

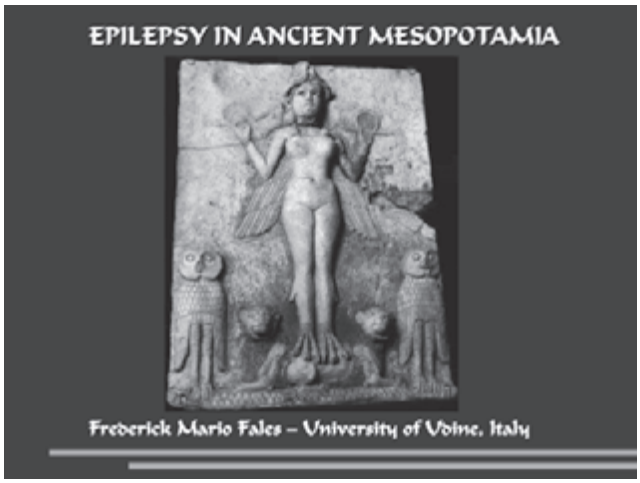
Adolescência	Epilepsia ausência juvenil (3) Epilepsia mioclônica juvenil (3) Epilepsias mioclônicas progressivas (3)
Relação com idade menos específica	Epilepsia do lobo frontal noturna autossômica dominante (3) Epilepsias do lobo temporal familiar (3) Epilepsia do lobo temporal mesial com esclerose hipocampal (2) Síndrome de Rasmussen (3) Crises gelásticas com hamartoma hipotalâmico (3)
Condições epilépticas especiais	Epilepsias focais sintomáticas não especificadas de outra forma Epilepsia apenas com crises tônico-clônicas generalizadas Epilepsias reflexas - Epilepsia occipital fotossensível (2) - Epilepsia primária da leitura (3) - Epilepsia da água quente em lactentes (3) Crises febris plus Epilepsia focal familiar com focos variáveis (3)
Condições com crises epilépticas que não requerem o diagnóstico de epilepsia	Crises neonatais benignas (2) Crises febris (3)

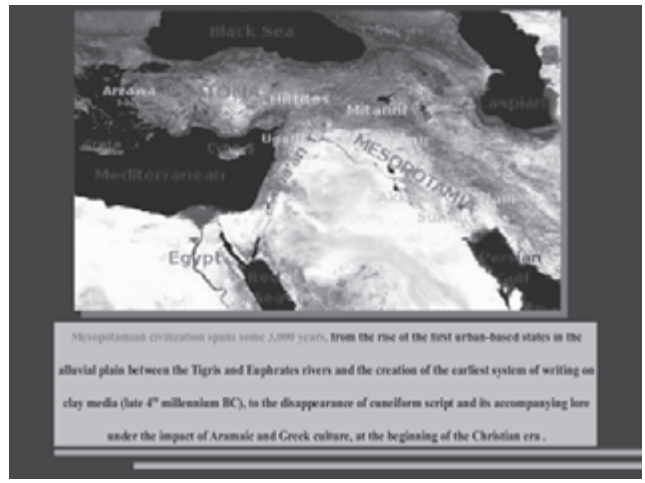
CLASSIFICAÇÃO INTERNACIONAL *A PROPOSIÇÃO DA ILAE 2001*

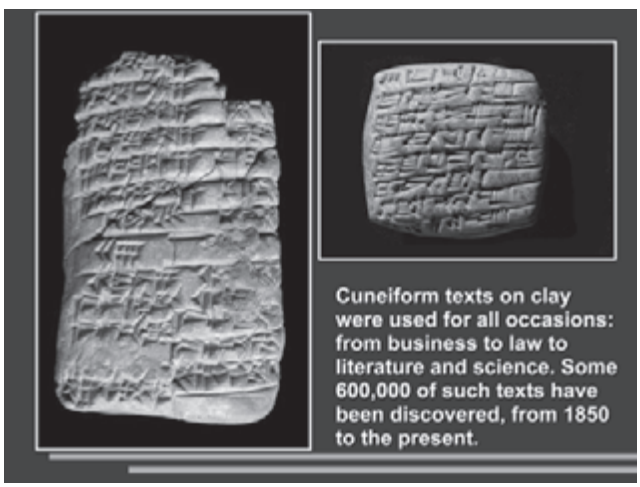
http://www.epilepsy.org//ctf

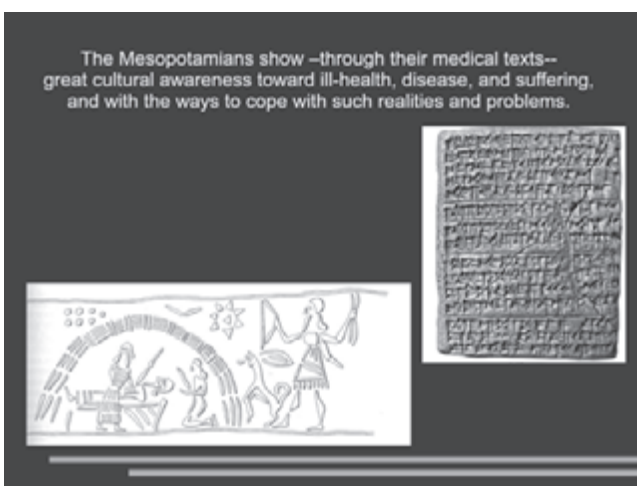
Epilepsy in Mesopotamia

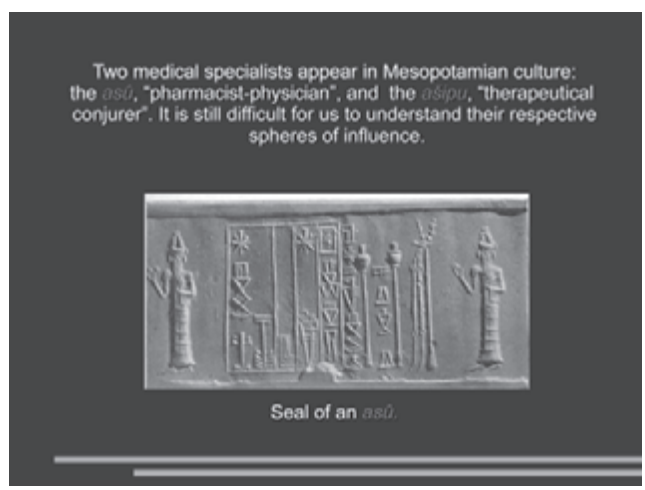
Mario Fales (Italy)











Traditionally, Mesopotamian medicine is traced back to the influence of the "supernatural": but as modern anthropological thought shows, the various gods, demons, celestial influxes, and other agents of illness were all considered to be part of the fully *natural* world.

Most recently, it has been suggested that the various divine or demonic "hands" in Mesopotamian medical prognoses could have begun to represent different individual illnesses –with a development that brings Mesopotamia very close to the Greek concept of healing before Hippocrates.

Mesopotamian medical literature has left us a vast array of texts dealing with symptoms. These texts are construed in the "if...then" mode: if a certain symptom appears, then its diagnosis must be such-and-such.
Sometimes a prognosis, in terms of life/death/recovery was also attempted.

In difficult cases, the exorcist was called to help, with a decided recourse to apotraopaic or liberatory *magic*.

Seal depicting an exorcism.

Seizures of various types are well documented in Mesopotamia: thus, the Code of Hammurabi states that

"If a man purchases a slave or a slave woman,

and within his one-month period seizure

(*bennu*) then befalls him, he shall return him to his seller,

and the buyer shall take back the silver that he has weighed and delivered"

The following are symptoms relevant to the general field of seizure and/or epilepsy, and specifically to forms of generalized seizure (nowadays defined as *petit mal*, *grand mal*, etc.), which went under the name of AN.TA.ŠUB.BA, "(that which has) fallen from heaven":

- If a sick man's neck turns to the right, time and again, while his hands and feet are paralysed (*awēlū*), his eyes are now closed, now rolling, saliva flows in/from his mouth, he makes ... sounds (*ḫurāṣu*): (it is) a.n.t.a.š.u.b.b.a.
- If his heart is awake (= he is conscious) when it seizes him, it will be eradicated (*nasāḫu*).[9]
- If he does not know himself (= he is unconscious) when it seizes him, it will not be eradicated.
- If he turns his neck to the left, time and again, while his hands and feet are stretched, his eyes are wide open, (turned) to the sky, saliva flows in/from his mouth, he makes ... sounds; he does not know himself (= he is unconscious); in the end of [....] it (= the disease) overwhelms (*ḫâṣu*) him time and again: (it is) a.n.t.a.š.u.b.b.a; the Hand of Sin.

Of particular interest

is also the recording of the well-known "aura"

(unfamiliar odors, sensory illusions, hallucinations)

which accompanies an incoming seizure:

"If, when a confusional state comes over him,

his torso feels heavy and stings him,

and afterward it comes over him and he forgets himself

– (this is) AN.TA.ŠUB.BA-seizure.

If this happens in the middle of the day

--it will be difficult for him".

In sum,

among the signs and symptoms observed by Mesopotamian medical practitioners, those associated with disorders of the nervous system, and specifically seizures of various types (among which epilepsy) prove to be among the most focused, due to the rich technical vocabulary employed, and to the careful characterization of the clinical picture involved .

More widely, Mesopotamian diagnostic texts,

in connection with written material of other --medical or non-medical--

nature, may be said to offer a remarkable insight into ancient mankind,

as observed through its illnesses, sufferings,

and destinies (by the prognostication of recovery or death).

Programa – 08.02.2008

Morning session – 9:00 – 13:00

- Focal epilepsies – EEG-clinical correlation – Tonicarlo Velasco (Brazil)
- Generalized epilepsies – EEG-clinical correlation - Elza Márcia Yacubian (Brazil)
- Catastrophic epilepsies in the childhood – Maria Chiara Stefanini (Italy)
- West Syndrome – Patricia Campos Olezabal (Peru)

Afternoon session – 14:30-18:30

- Experimental Models/Basic mechanisms of the epilepsies – Giuliano Avanzini (Italy)/ Luiz Mello (Brazil)/ João Pereira Leite (Brazil)
- Febrile status epilepticus: a translational approach – Solomon Moshé (USA)

Evening session

- Epilepsy-Neurotrasmitters-Neuroreceptors and comorbidities – Harry Stokes (Guatemala)
- Cognitive deterioration in epilepsy – Salvador Gonzales Pal (Cuba)

Focal epilepsies – EEG-clinical correlation

Tonicarlo Velasco (Brazil)

GENERALIZED EPILEPSIES – EEG-CLINICAL CORRELATION

ELZA MÁRCIA YACUBIAN (BRAZIL)

LASSE

GENERALIZED EPILEPSIES

Elza Márcia Yacubian
Unidade de Pesquisa e Tratamento das Epilepsias UNIFESP-EPM

Proposal for Revised Classification of Epilepsies and Epileptic Syndromes

Commission on Classification and Terminology of the International League Against Epilepsy

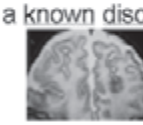
CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

1. **Localization-related (focal, local, partial) epilepsies and syndromes**
2. **Generalized epilepsies and syndromes**
3. **Epilepsies and syndromes undetermined whether focal or generalized**
4. **Special syndromes**

2. Generalized epilepsies and syndromes

2.1 Idiopathic- Greek *idios* self, own, or personal

2.2 Symptomatic- a consequence of a known disorder of the central nervous system



2.3 Cryptogenic- a disorder whose cause is hidden or occult

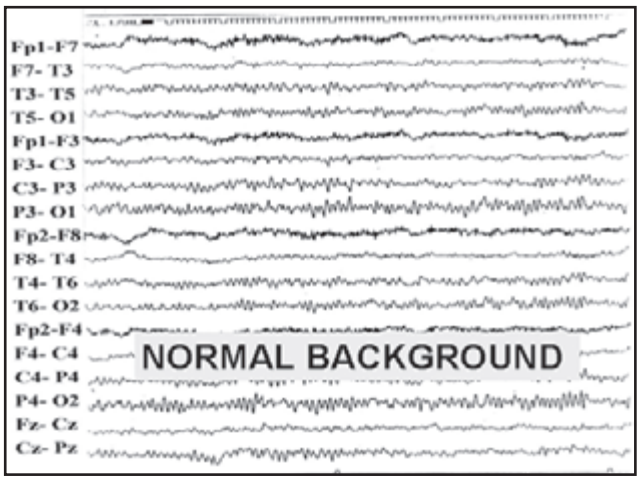
2. Generalized epilepsies and syndromes

2. 1. Idiopathic
(with age-related onset- listed in order of age)

- Infancy
- Childhood
- Adolescence

2. 1. Idiopathic (with age-related onset - listed in order of age)

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation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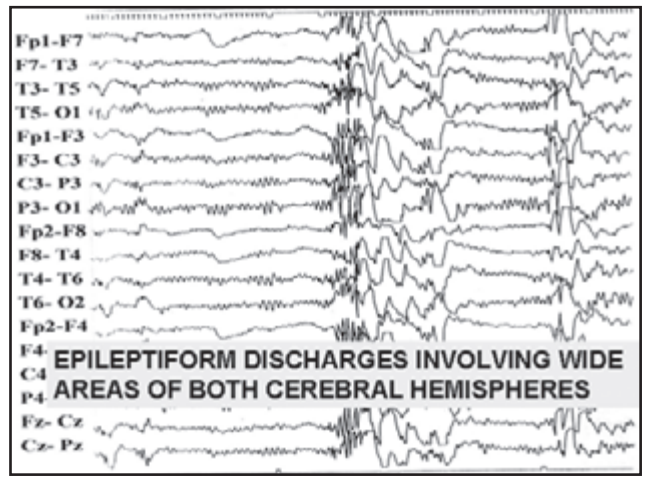
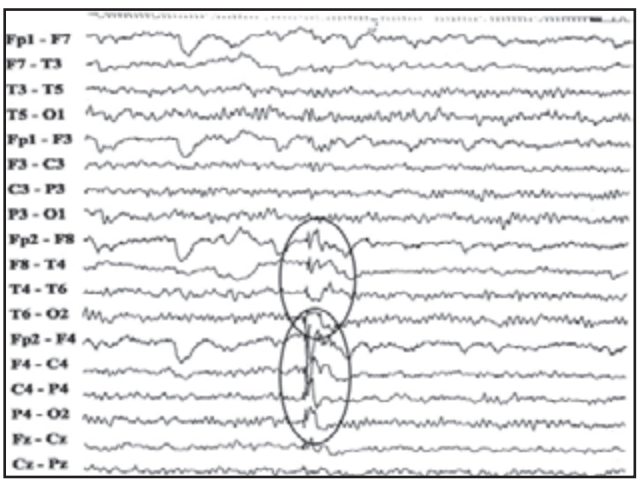
F7- T3
T3- T5
T5- O1
Fp1-F3
F3- C3
C3- P3
P3- O1
Fp2-F8
F8- T4
T4- T6
T6- O2
Fp2-F4
F4- C4
C4- P4
P4- O2
Fz- Cz
Cz- Pz
NORMAL BACKGROUND


Fp1-F7
F7- T3
T3- T5
T5- O1
Fp1-F3
F3- C3
C3- P3
P3- O1
Fp2-F8
F8- T4
T4- T6
T6- O2
Fp2-F4
EPILEPTIFORM DISCHARGES INVOLVING WIDE AREAS OF BOTH CEREBRAL HEMISPHERES
Fz- Cz
Cz- Pz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F7 - T3
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C3 - P3
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F8 - T4
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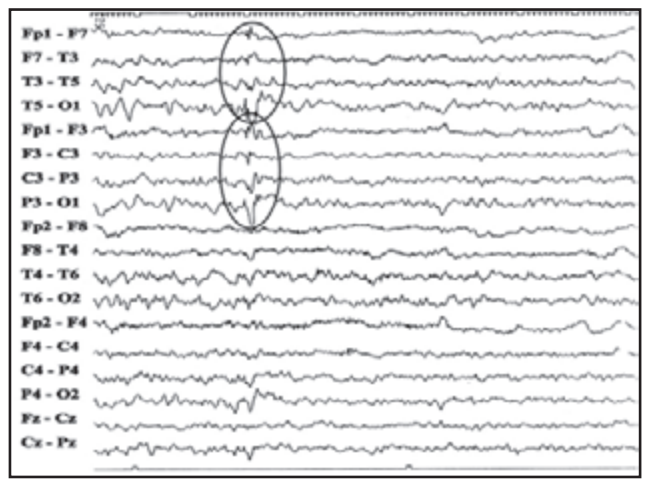
P4 - O2
Fz - Cz
Cz - Pz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P3 - O1
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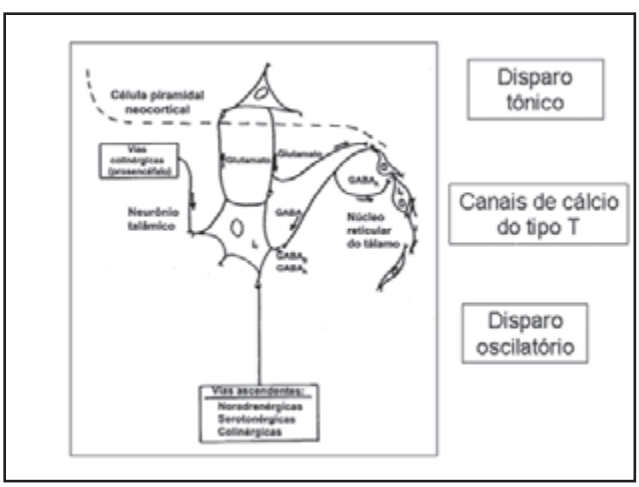
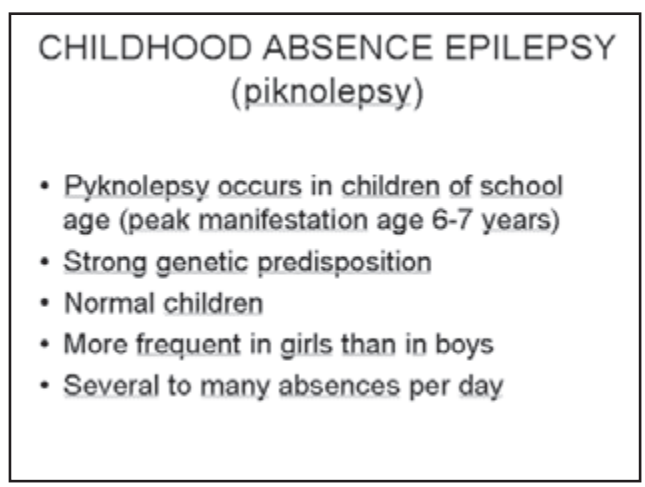
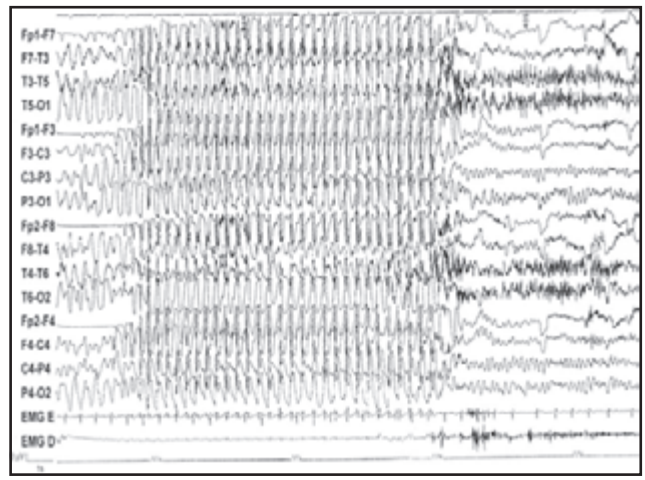
F8 - T4
T4 - T6
T6 - O2
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fz - Cz
Cz - Pz

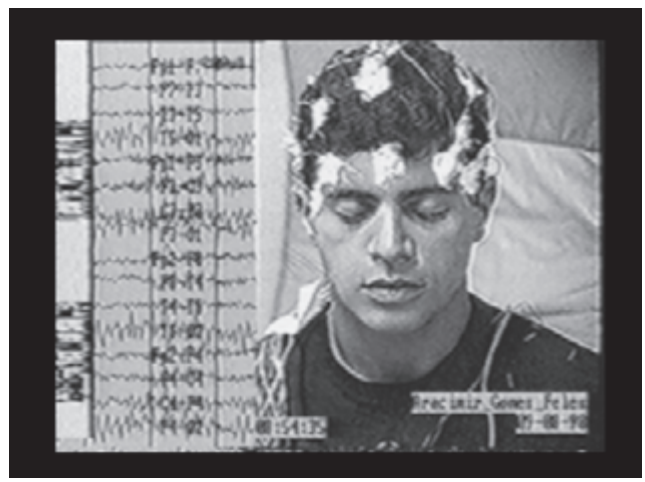

Célula piramidal neocortical
Via colinérgica (presença/falta)
Glutamato
Glutamato
GABA
Neurônio talâmico
GABA
Núcleo reticular do tálamo
GABA
GABA
Vias ascendentes:
Noradrenérgicas
Serotonérgicas
Colinérgicas
Disparo tônico
Canais de cálcio do tipo T
Disparo oscilatório

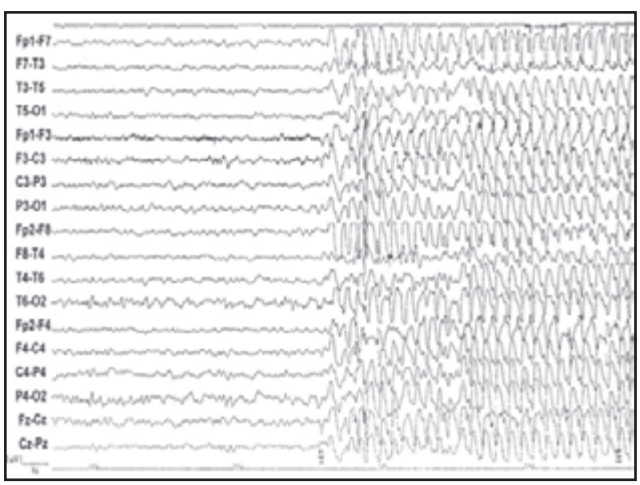

CHILDHOOD ABSENCE EPILEPSY
(piknolepsy)
• Pyknolepsy occurs in children of school age (peak manifestation age 6-7 years)
• Strong genetic predisposition
• Normal children
• More frequent in girls than in boys
• Several to many absences per day

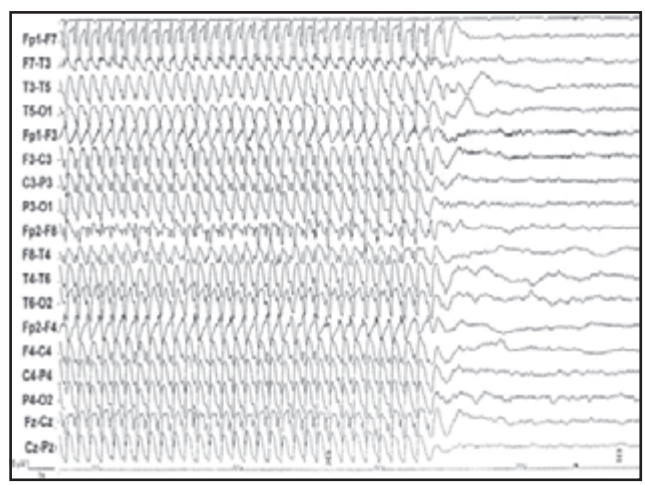


JUVENILE ABSENCE EPILEPSY

- Manifestations around puberty
- Sex distribution is equal
- Absences occurring less frequently than every day, mostly sporadically
- Association with GTCS
- Not infrequently, the patients also have myoclonic seizures

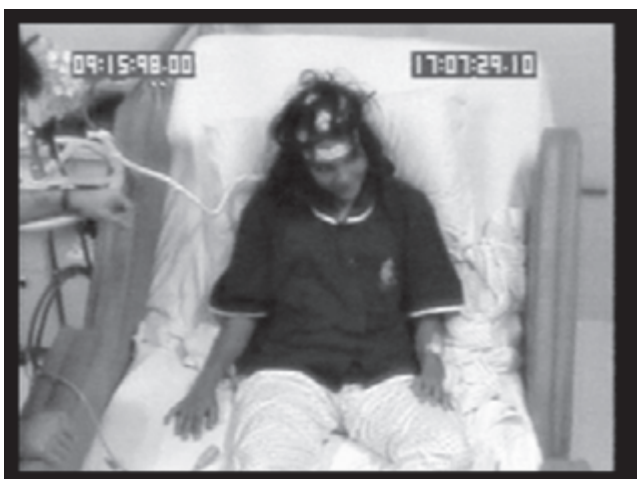


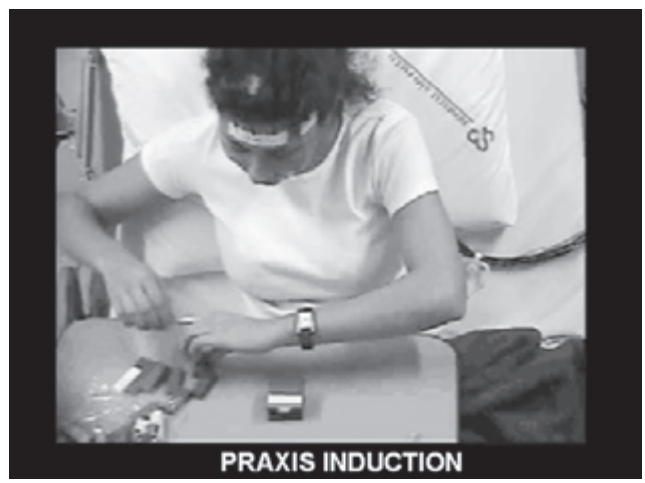


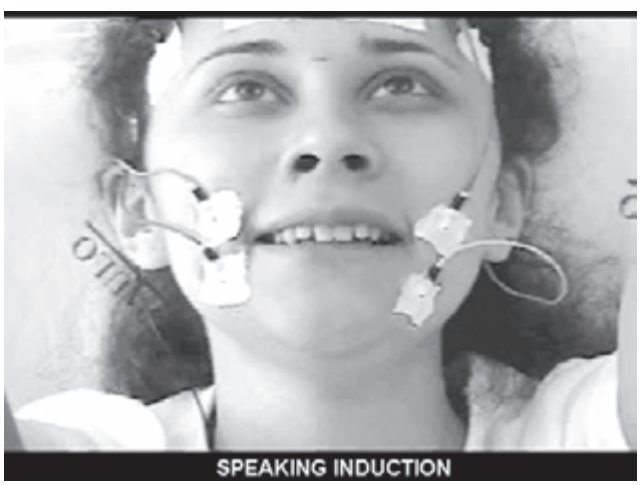


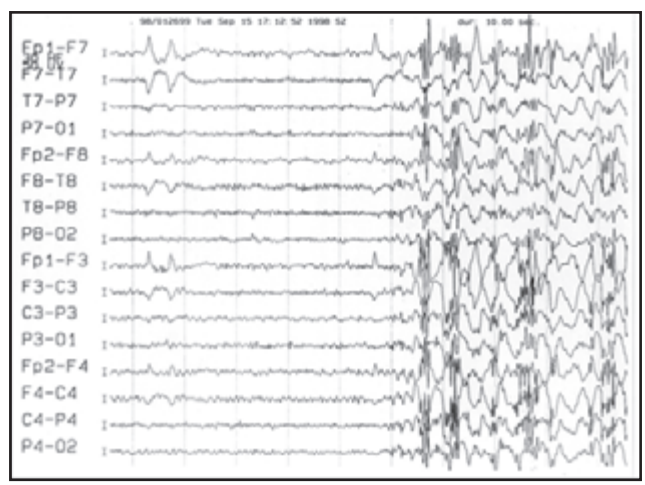
JUVENILE MYOCLONIC EPILEPSY (impulsive petit mal)

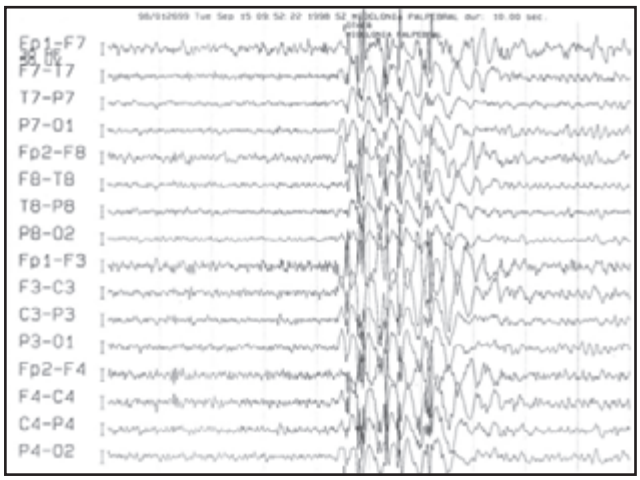
- Manifestations around puberty
- Sex distibution is equal
- Bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms
- Shortly after awakening and precipitated by sleep deprivation
- Association with GTCS
- Infrequent absences
- Frequent photosensitivity

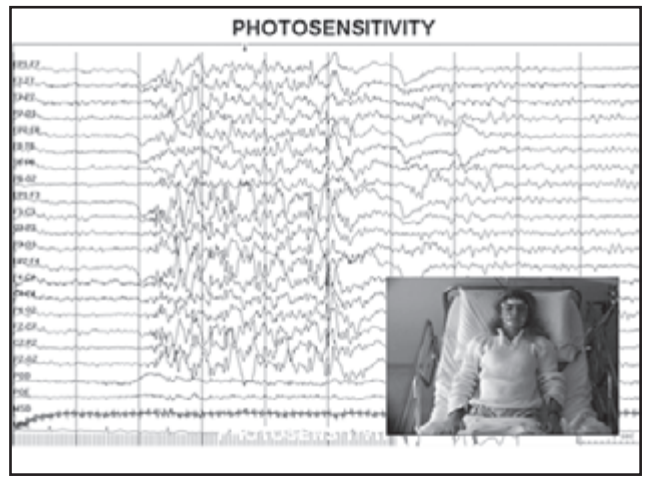



PRAXIS INDUCTION


SPEAKING INDUCTION







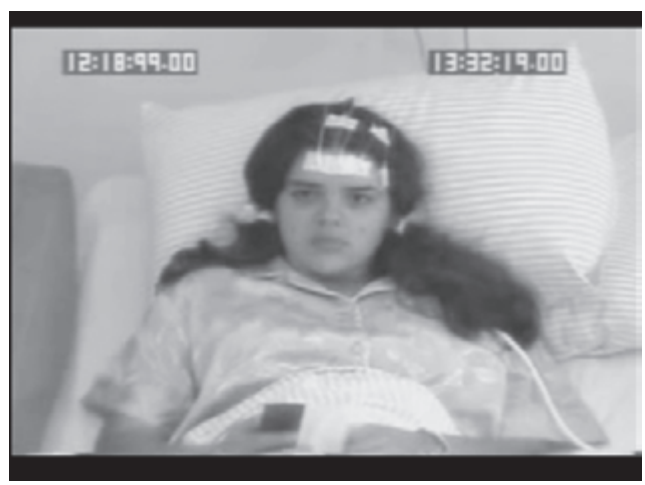
2. 1. Idiopathic (with age-related onset - listed in order of age)

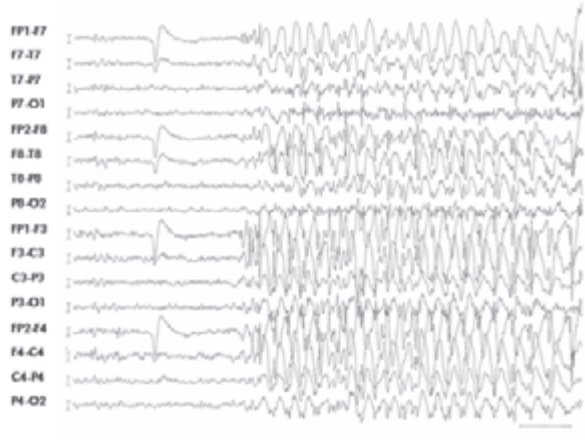
- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

Absence epilepsy with perioral myoclonia

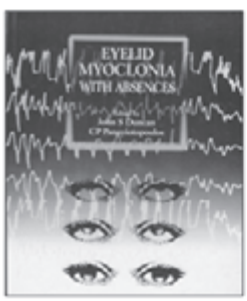
- Very frequent typical absences
- Localized rhythmic myoclonia on facial, perioral and masticatory muscles
- Brief absences (2-10 seconds)
- No photosensitivity. No eye closure sensitivity
- GTCS; frequent absence status

Panayiotopoulos et al. 1995



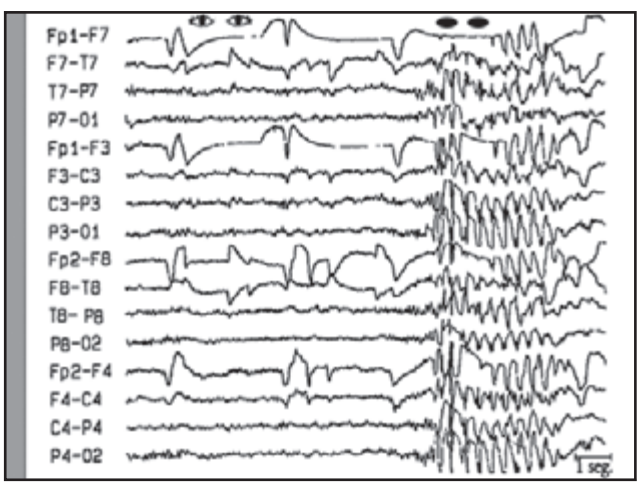


Eyelid Myoclonia with Absences



- Onset 2-5 years
- Absences and photosensitivity
- Eyelid myoclonia (marked jerking of the eyelids) with upward deviation of the eyes occurring on closure of the eyes

Jeavons, 1977

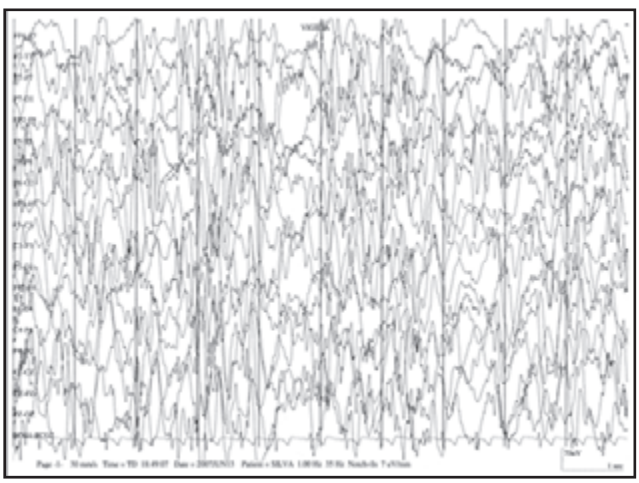


2. 2. Cryptogenic or symptomatic (in order of age)

- West syndrome
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures
- Epilepsy with myoclonic absences

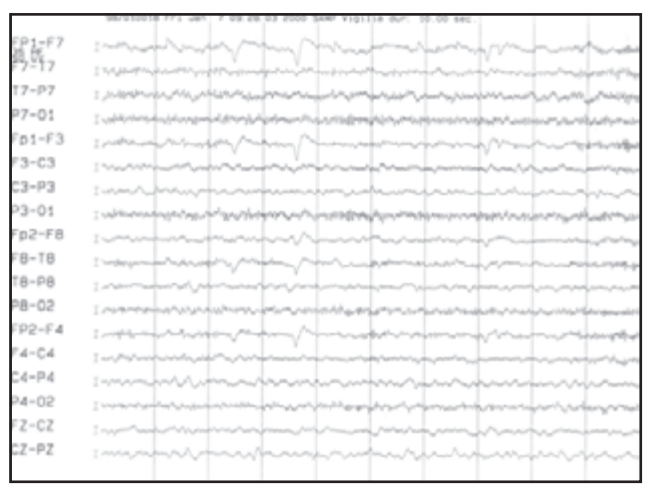
WEST SYNDROME

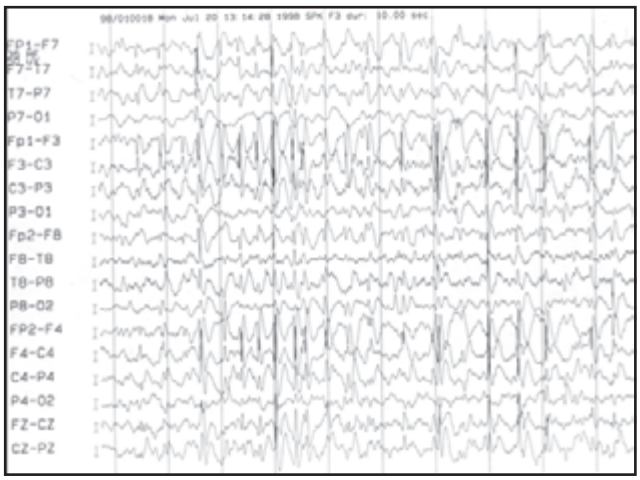
- A characteristic triad: infantile spasms, arrest of psychomotor development, and hypsarrhythmia, although one element may be missing
- Onset peaks 4-7 months
- Boys are more commonly affected
- Symptomatic group- previous existance of brain damage signs
- Cryptogenic and idiopathic (?) group

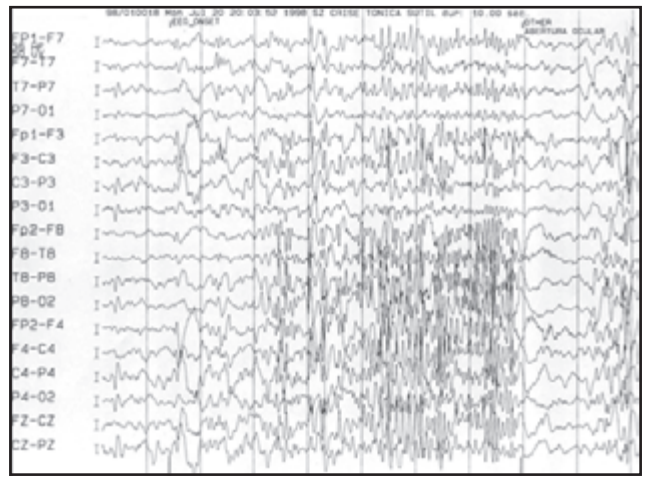


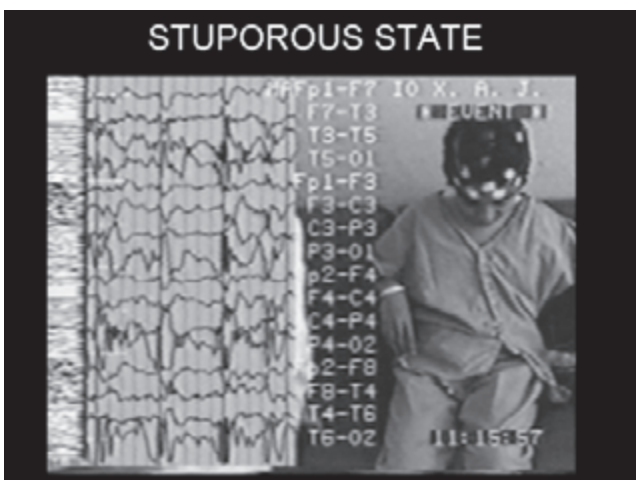
LENNOX-GASTAUT SYNDROME

- Manifests in children aged 1-8 years (mainly pre-school children)
- Tonic, atonic and absence seizures; myoclonic, GTCS and partial seizures
- Seizure frequency is high
- Status epilepticus is frequent
- Mental retardation
- Previous encephalopathy



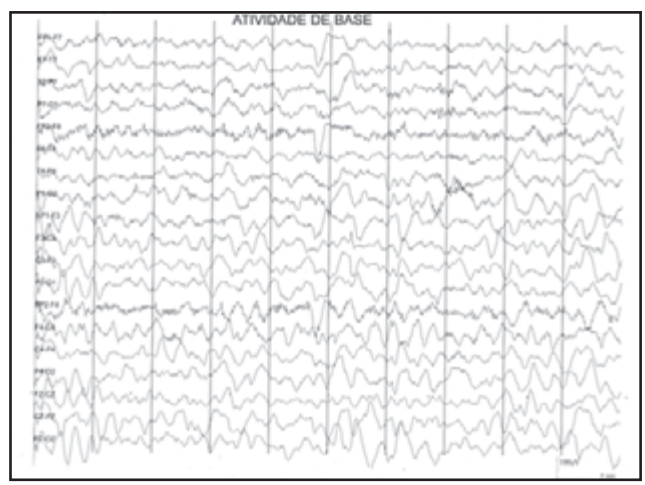


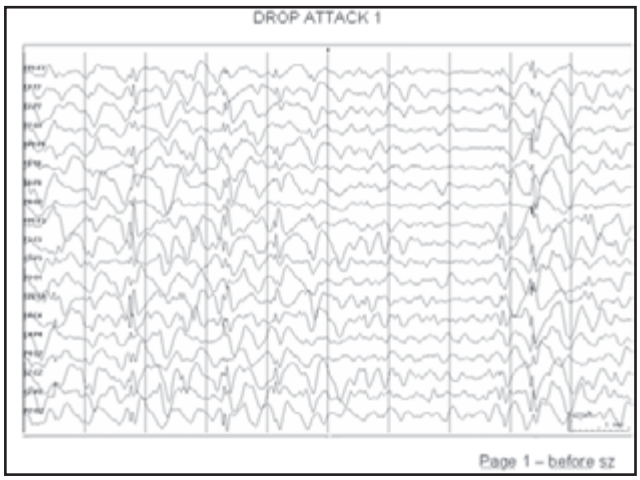




EPILEPSY WITH MYOCLONIC-ASTATIC SEIZURES

- Manifests in children aged 7 months-6 years (mainly 2-5 years)
- Twice as many boys affected
- Normal development
- Hereditary predisposition
- Myoclonic, astactic, myoclonic-astatic seizures, GTCS and absences
- Seizure frequency is high
- Status epilepticus is frequent





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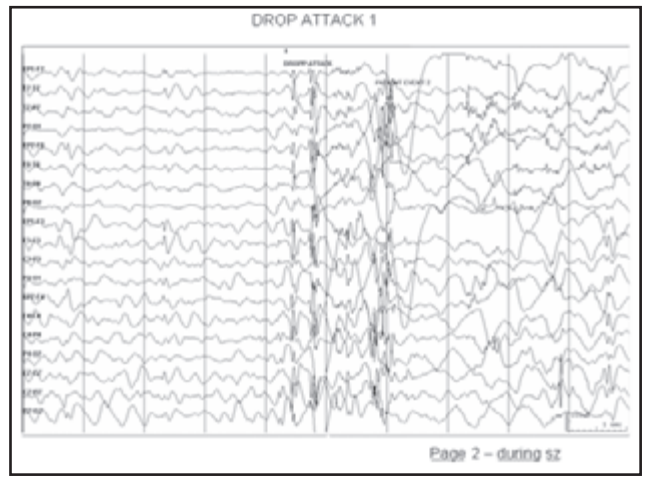

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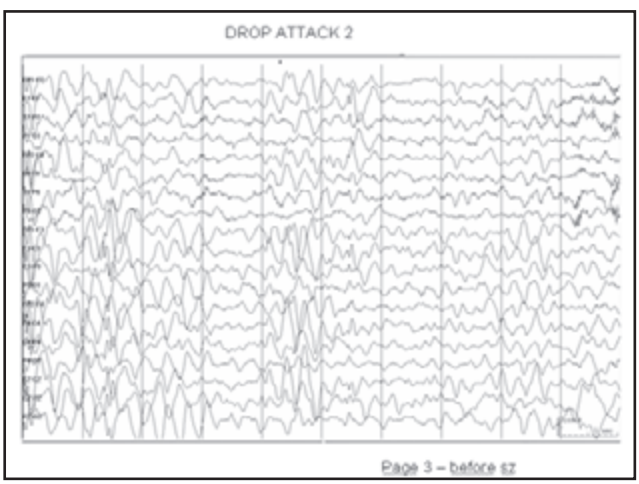

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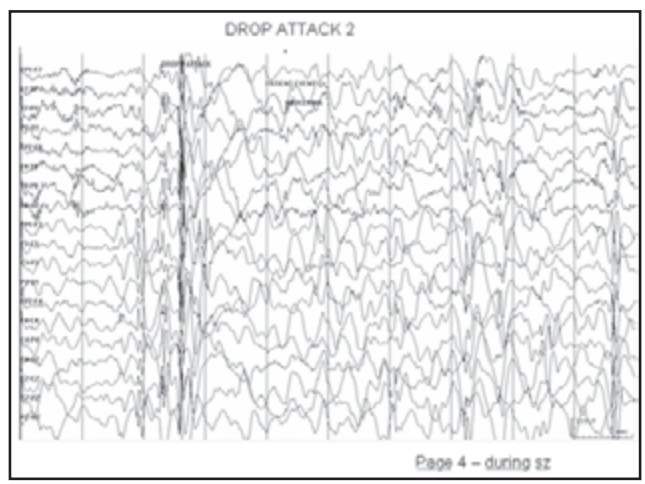

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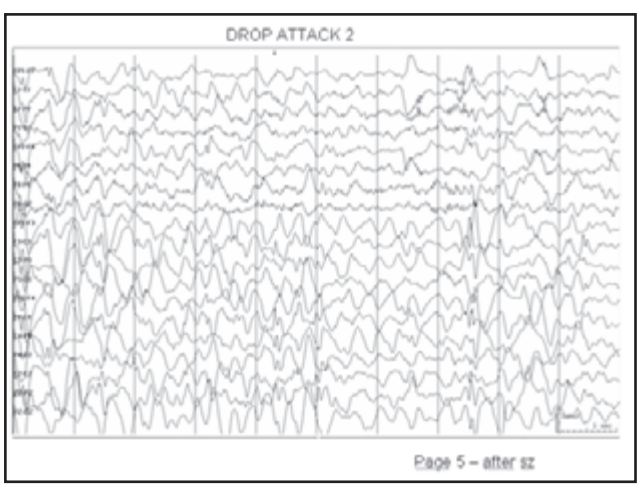

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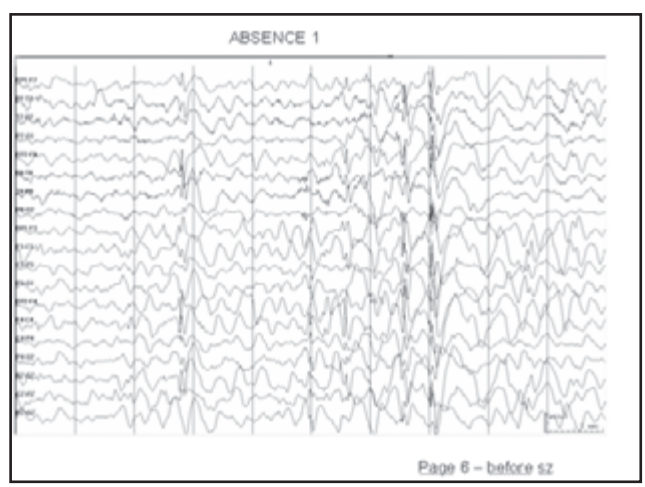

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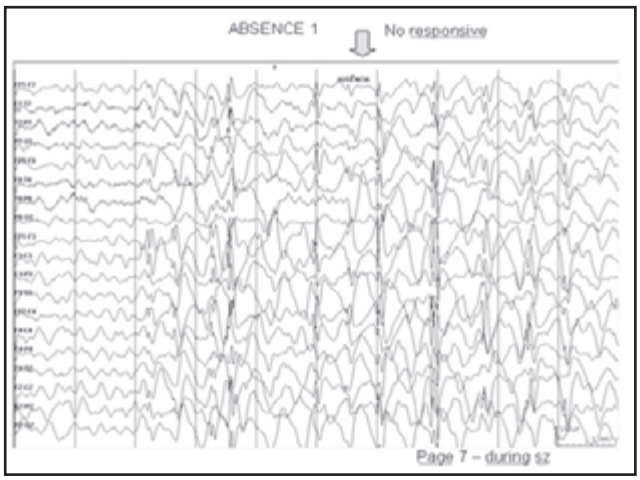
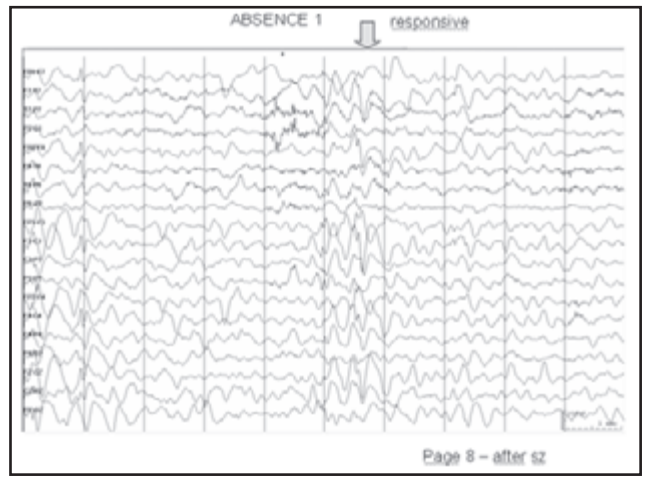
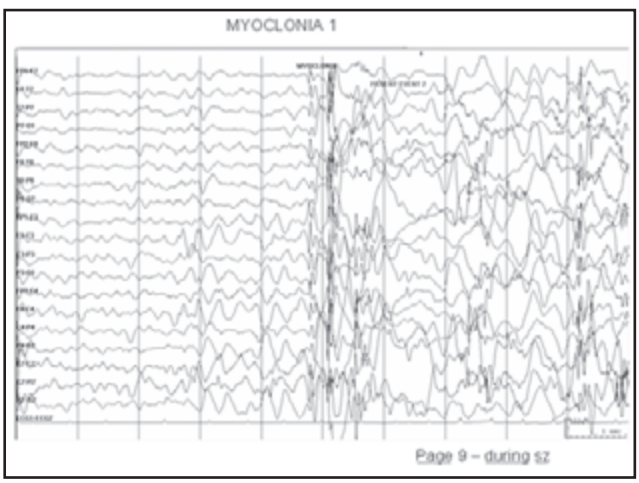
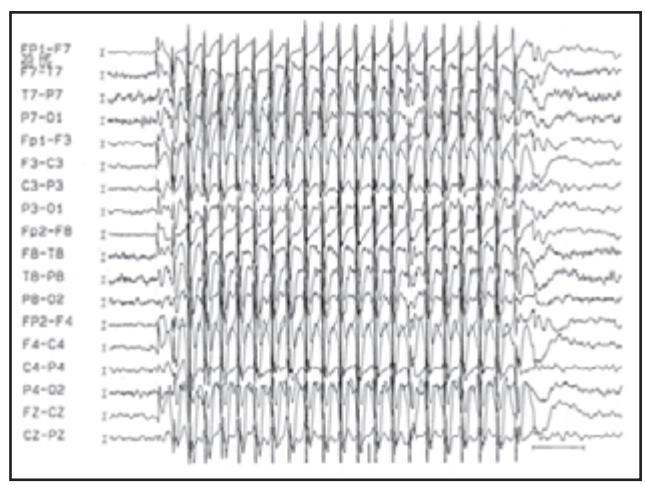






EPILEPSY WITH MYOCLONIC ABSENCES

- Absences with severe bilateral rhythmical clonic jerks, often associated with a tonic contraction
- Age of onset is around 7 years
- Many seizures a day
- Normal development
- Male preponderance
- Associated seizures are rare



2. 3. Symptomatic

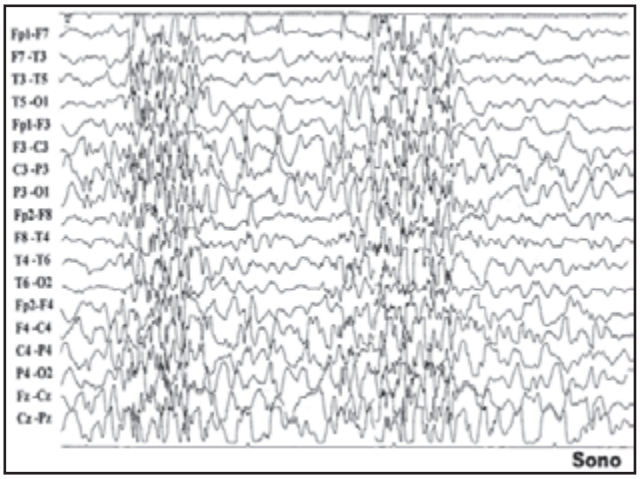
2.3.1 Non-specific etiology
Early myoclonic encephalopathy
Early infantile epileptic encephalopathy with supression burst (Ohtahara syndrome)
Other symptomatic generalized epilepsies not defined above

2.3.2 Specific syndromes
Epileptic seziures may complicate many disease states. Under this heading are included diseases in which seizures are a presenting or predominant feature

2.3.1 Non-specific etiology Neonatal period

Early myoclonic encephalopathy

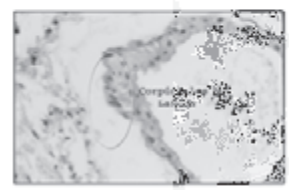
- **Erratic and massive myoclonia- non-ketotic hyperglycemia, metilmalonic/propionic acidemia, pyridoxine deficiency, Menkes disease or no metabolic inborn error is detected**
- **Normal MRI**
- **Familial history**



2.3.2 Specific etiology

LAFORA'S DISEASE- Progressive myoclonic epilepsy

- Autosomal recessive form of epilepsy
- Beginning in childhood: 6-19 years of age
- GTCS, myoclonic jerking
- Mental deterioration leading to dementia
- Lafora's bodies are present in the nervous system, retina, heart, muscle, liver, sudoriparous glands
- Average time of survival: six years



A Classificação das Síndromes Epilépticas (2001)

4. Epilepsias generalizadas idiopáticas

- **Epilepsia mioclônica benigna do lactente**
- Epilepsia com crises mioclono-astáticas
- Epilepsia ausência da infância
- Epilepsia com ausências mioclônicas
- Epilepsias generalizadas com fenótipos variáveis
  - ➢Epilepsia ausência juvenil
  - ➢Epilepsia mioclônica juvenil
  - ➢Epilepsia com crises tônico-clônicas generalizadas
- **Epilepsias generalizadas com crises febris plus ***

A Classificação das Síndromes Epilépticas (2001)

6. Encefalopatias epilépticas

- Encefalopatia mioclônica precoce
- **Síndrome de Ohtahara**
- Síndrome de West
- **Síndrome de Dravet (epilepsia mioclônica severa da infância)**
- **Status mioclônico em encefalopatias não progressivas ***
- Síndrome de Lennox-Gastaut
- **Síndrome de Landau-Kleffner**
- **Epilepsia com ponta-onda contínua durante sono lento**

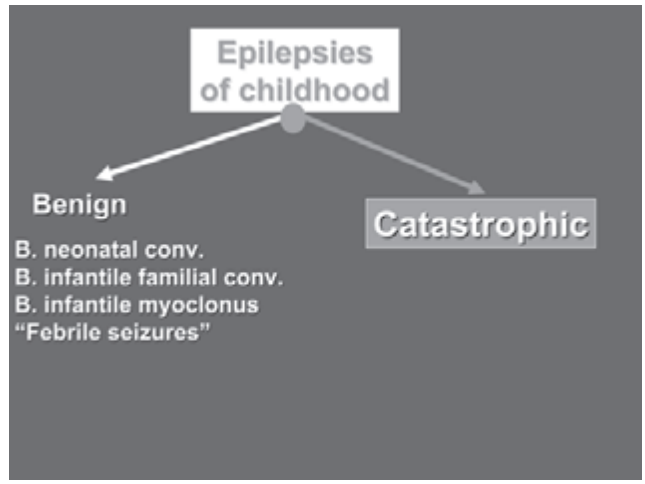
A Classificação das Síndromes Epilépticas (2001)

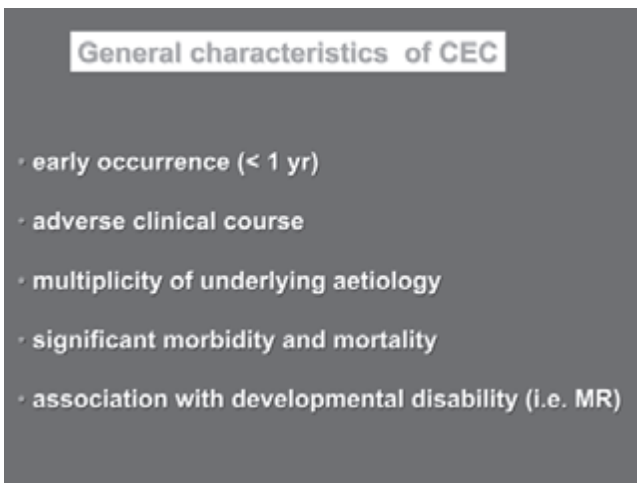
7. Epilepsias mioclônicas progressivas

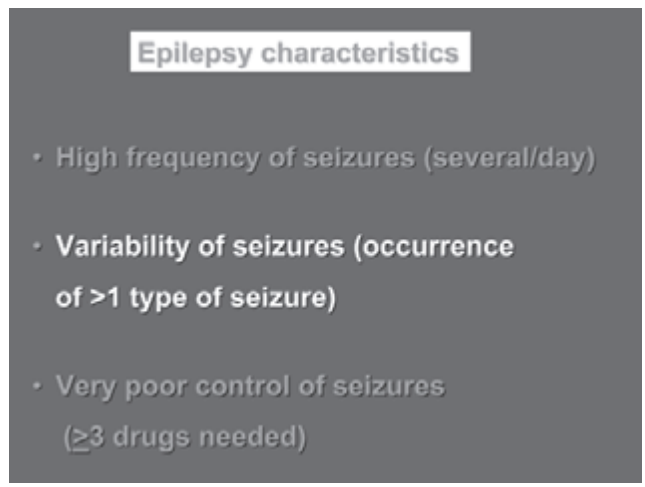
- **Doenças específicas: Doença de Lafora**

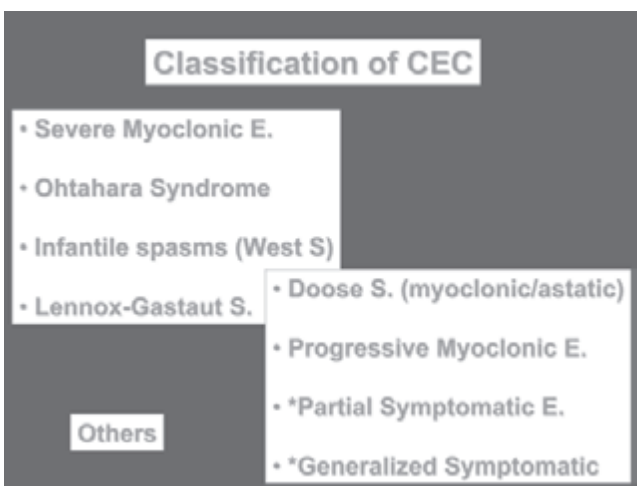
Catastrophic epilepsies in the childhood

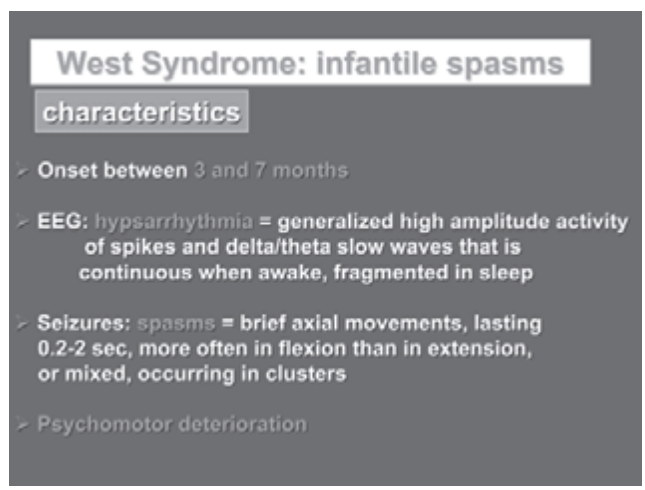
Maria Chiara Stefanini (Brazil)









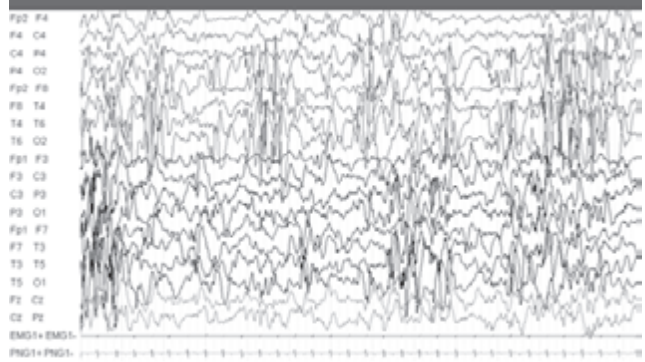


West Syndrome: infantile spasms

Differential diagnosis with

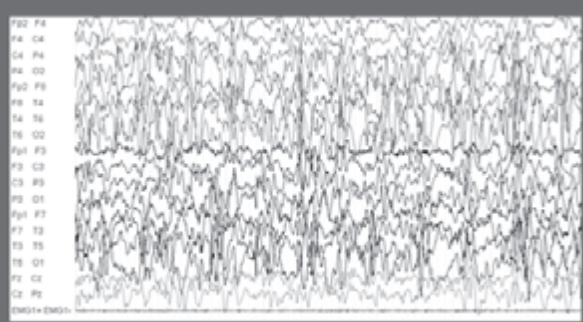
1. benign infantile familial convulsions
2. benign infantile myoclonus

West Syndrome (1)



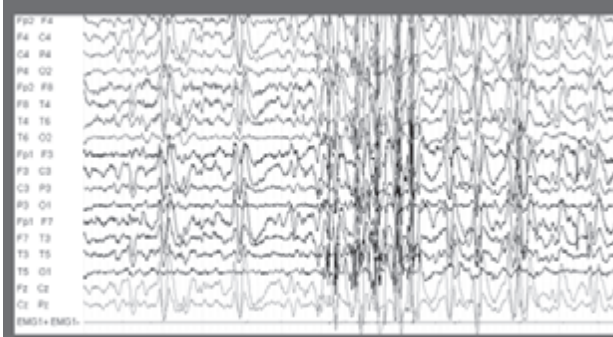
sleep

West Syndrome (1)



awake

West Syndrome (2)



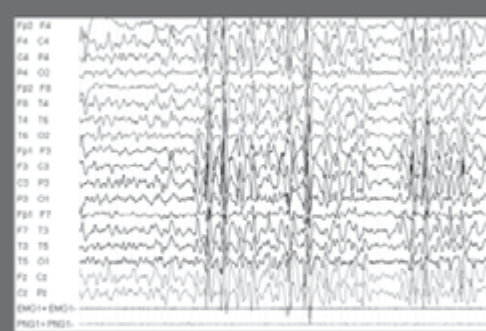
awake

Lennox Gastaut Syndrome

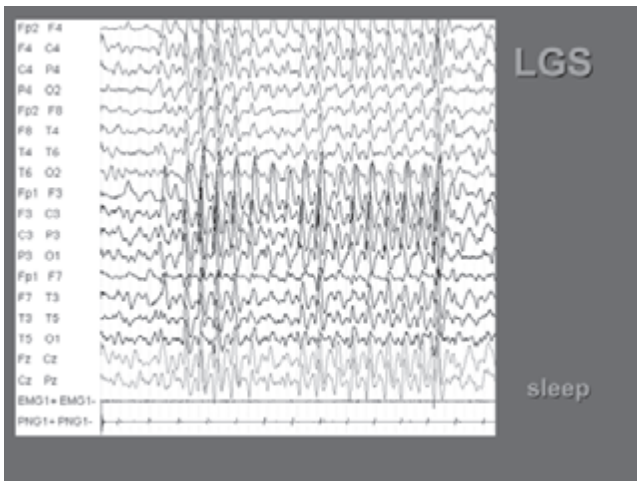
- 3-10% of all pediatric epilepsies
- defined by:

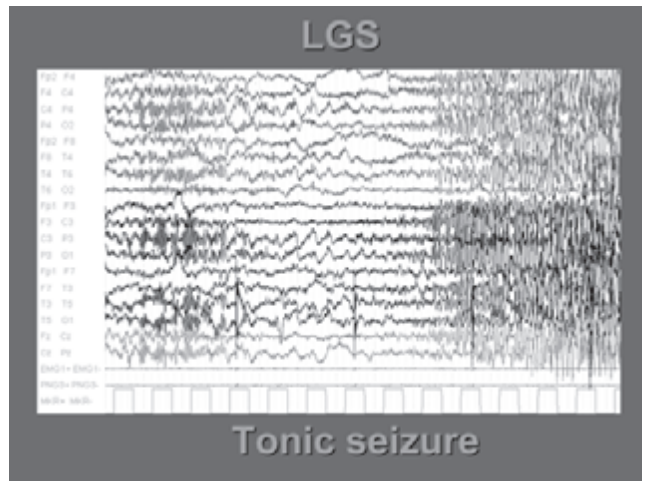
1. multiple seizure types: myoclonic jerks, atypical absences, head drops, falls, etc.
2. slow spike-and-wave EEG abnormalities
3. mental retardation

LGS



sleep





Progressive Myoclonic Epilepsies

A group of rare, genetic, catastrophic disorders:

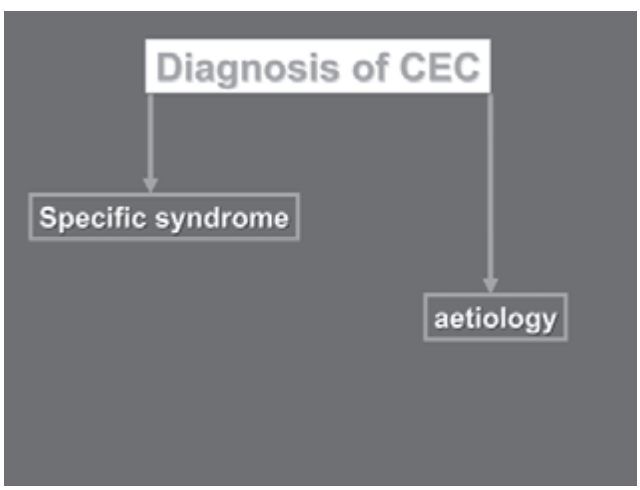
1. Unverricht-Lundborg Disease [AR]
2. Mitochondrial Encephalopathy with Ragged Red Fibres (MERRF)
3. Lafora Body Disease [AR]
4. Neuronal Ceroidolipofuscinosis (NCL) [AR]
5. Sialidosis (cherry red spot myoclonus disease) [AR]

Progressive Myoclonic Epilepsies

Characteristics shared by all PME

1. Myoclonus and tonic-clonic seizures

2. Progressive neurological disturbance:
   - ataxia
   - dementia



Pharmacologic treatment of CEC

challenge

complete seizure control
↓
near impossible

Pharmacologic treatment of CEC

WEST S ➔ ACTH, VGB, 'new drugs' (ZNS, TPM), nonAEDs (vitamins, cofactors, nutritional suppl)

LGS ➔ FBM, LTG, TPM, steroids.
Typically unresponsive

PME ➔ VPA, LEV, ZNS, LTG
Typically unresponsive

Nonpharmacologic treatment of CEC

- epilepsy surgery
- ketogenic diet
- vagus nerve stimulation

Our experience

- 155 cases of early onset epilepsy(< 1 year of life)
- 100 (65%) diagnosed as CEC:

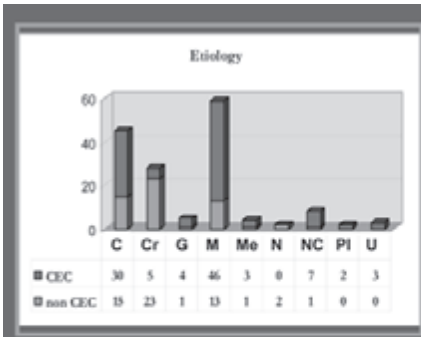
⇨ high frequency of seizures (several/day)
⇨ variability of seizures (>1 type of seizure)
⇨ very poor control of seizures (≥ 3 drugs needed)
⇨ progressive loss (or lack) of acquisition of cognitive skills.

Protocol

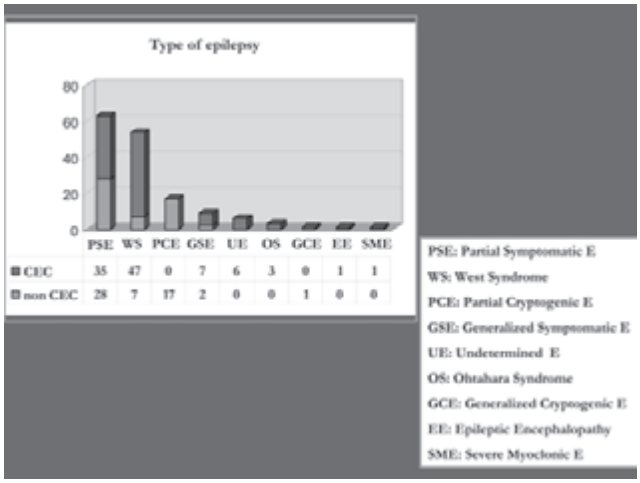
1. neuroimaging examination (CT scan and/or MRI)
2. follow up ≥ 1 year (mean follow-up 4 y and 4 m)
3. Periodic controls included: 1) Neurological examination, 2) Ictal and interictal EEG videorecording, 3) Griffith's Developmental Scale

Etiopathogenesis

1. Brain malformation, either focal or involving one hemisphere or all the brain
2. "Clastic" damages (related to hypoxic–ischemic or haemorrhagic pre, peri or postnatal insult)
3. Metabolic diseases
4. Post-infectious damages
5. Neurocutaneous syndromes
6. "Cryptogenic" (Unclear pathogenesis with normal MRI)



C: clastic
Cr: cryptogenic
G: genetic
M: malformations
Me: metabolic
N: neoplastic
NC: neurocutaneous
PI: post-infectious
U: undetermined



RESULTS AFTER SURGERY

aetiology	P	Mean age surgery (months)	Mean FU duration (months)	surgery	Cognitive outcome after surgery: Unchanged/Improved
Hemi megalo encephalopathy	12	22	85	hemispherect	8U 4I
Sturge Weber	3	20	148	hemispherect	1U 2I
Poroencephaly	4	61	75	3 emispherect. 1 corticectomy	1U 3I
Complex hemispheric malformations	1	15	68	Partial resection	1U
Plurilobar dysplasia	7	17	43	Plurilobar resection	5U 2I
TOTAL	27	26	78		16U 11I

In our series:

- ➔ "Clastic" damages and brain malformations are the largely most frequent cause of CEC (77/100)
- ➔ West syndrome (47%) and partial symptomatic epilepsy (35%) are clearly the most represented type of epilepsy
- ➔ When the surgical treatment was performed, the cognitive outcome improved in 41% of cases

EARLY CORRECT DIAGNOSIS
CAN HELP TO IMPROVE THE COURSE OF CEC

Treatment must be aimed to, as for all epilepsies,

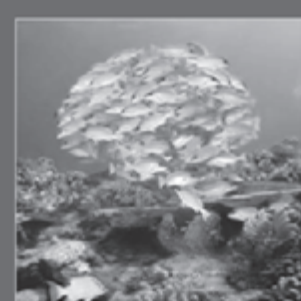
- ➔ MAXIMIZE SEIZURE CONTROL
- ➔ MINIMIZE ADVERSE EFFECTS
- ➔ THE BEST POSSIBLE QOL

UNDERSTANDING OF THE PATHOGENESIS OF CEC
CAN HELP IN DEVELOPING NEW TREATMENT TOOLS

IN CONCLUSION

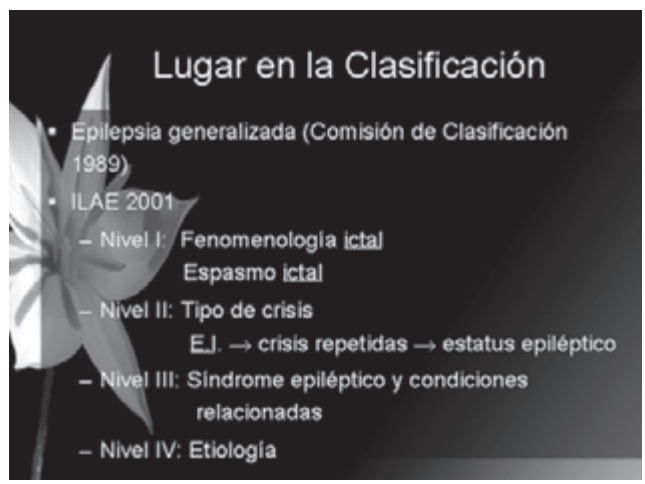
CEC PRESENTS MANY CHALLENGES TO BOTH CLINICIANS AND PATIENTS

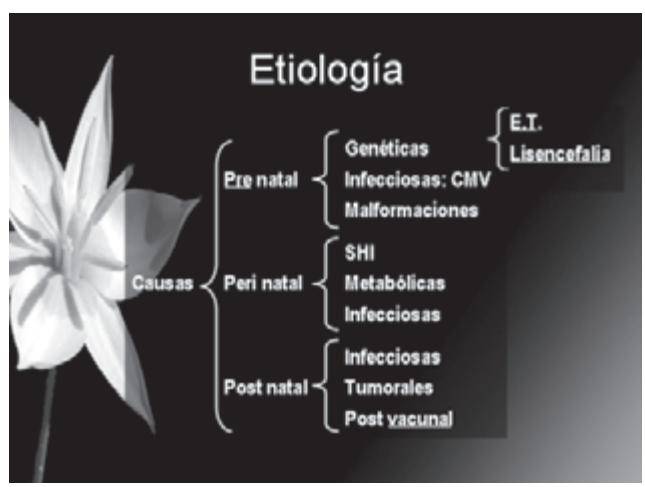
ONLY THE BETTER UNDERSTANDING OF PATHOGENESIS AND UNDERLYING MECHANISMS CAN HELP



West Syndrome

Patricia Campos Olezabal (Peru)





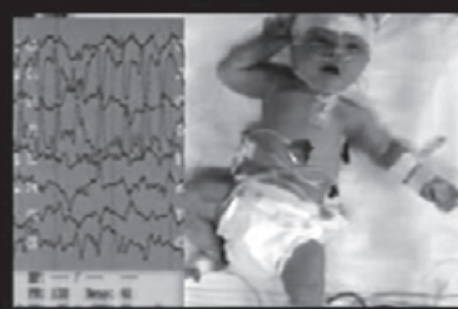
Etiología

- Muchas WS se asocian a lesiones corticales no progresivas
  Las WSC tienen hipsarritmia asimétrica hasta en 94% *(Donat y Rho 1994)*
- Características focales indican presencia de lesión hemisférica *(Yamamoto 1988)*

Transición entre Síndromes
Diagnóstico Diferencial entre Síndromes

	OH	WS	LGS
Edad	RN meses	Lactante	Niño
Diferentes crisis	±	+	++
Espasmos tónicos	+	±	±
Respuesta ACTH	Pobre	Buena	Pobre
EEG interictal	Burst - supression	Hipsarritmia	Difuso

Características Electroclínicas



Síndrome de Aicardi

- Descrito en 1969
- Pacientes sexo femenino
- Espasmos infantiles
- Agenesia de cuerpo calloso
- Retardo mental
- Corioretinopatía específica
- Anomalías vertebrales
- EEG Característico

Diagnóstico Diferencial

- Mioclonus benigno de la infancia *(Dravet 1986, Fejgrman- Caraballo 2002)*
- Epilepsia Mioclónica benigna
- Epilepsia Mioclónico – Astática
- Encefalopatía Mioclónica Precoz
- Reflejo de Moro
- Cólico abdominal
- Mioclonias del sueño
- Reacción de sobresalto
- Desviación tónica conjugada benigna de ojos para arriba *(Guerrini 1998)*
- Crisis tónicas del LGS

Genética

- Esclerosis tuberosa
- Aicardi
- Mutación Gen ARX
- Lisencefalia tipo I
- PEHO
- Familiar 4-5% *(Riikonen 1987, Dulac 1993)*
- Idiopático familiar *(Vivegano 1993)*

Pronóstico

En relación a etiología – imagen EEG

- MRI normal pronóstico bueno
- PET hipometabolismo multifocal o difuso con MRI normal pronóstico pobre *(Chugani 1996)*
- Hipsarritmia asimétrica o unilateral: pronóstico pobre
- ET – Tuber y pronóstico
- NF1 mejor pronóstico

- Actividad rápida ictal asimétrica es más frecuente en WSS *(Gaily 2001)*
- Cuando las lesiones son occipitales el cuadro clínico es de aparición más precoz que si las lesiones son frontales *(Chugani 1987, Dulac 1999)*

EEG Interictal

- Hipsarritmia con sincronización
- Hipsarritmia asimétrica
- Hipsarritmia con foco
- Hipsarritmia con burst supression
- Hipsarritmia con ondas lentas de alto voltaje
- Hipsarritmia con actividad rápida persistente

Desarrollo Psicomotor en WS

- Cognición
- Seguimiento en WSC
- E.I. de inicio tardío
- Recuperación espontánea

Tratamiento

- Médico
- Quirúrgico

Protocolos de Tratamiento en Espasmos Infantiles

Hrachowy 1983	ACTH / Prednisona
Baram 1996	ACTH / Prednisona
Hrachowy 1994	ACTH dosis alta / ACTH dosis baja
Yanagaki 1999	ACTH dosis alta / ACTH dosis baja
Chiron 1997	Vigabatrina / Hidrocortisona
Vigevano 1997	Vigabatrina / Hidrocortisona
Appleton 1999	Vigabatrina / Placebo
Elterman 2001	Dosis baja de VGB / Alta dosis de VGB
Lux 2004	Vigabatrina / Prednisona o ACTH
Dyken 1985	Valproatoe / Placebo
Hrachowy 1989	Metisergide / Alfa-metiparatirosina
Dreifuss 1986	ACTH / Nitrazepam
Debus 2004	Sulthiame / Placebo

Eficacia de Tratamientos para Espasmos Infantiles

Medicación usada para espasmos infantiles	Promedio de respuesta
ACTH, prednisone, u otros esteroides	-70% con 35-50% recaida
Piridoxina	11-25%
Vigabatrina	40-90%
Topiramato	45%
Lamotrigina	30%
Ácido valpróico	15-50%
Zonisamida	25%
Clonazepam	25-50%
Nitrazepam	15-50%
Felbamato	9-75%
Dieta cetogénica	40-60%

TratamientoS Recomendados en Convulsiones Sintomáticas NICE

Síndrome epiléptico	Drogas de primera línea	Drogas de segunda línea	Otras drogas	Drogas que deberán evitarse (puede empeorar convulsiones)
Espasmos infantiles	Esteroides Vigabatrina	Clobazam Clonazepam Valproato sódico Topiramato	Nitrazepam	Carbamazepina Oxcarbazepina
Epilepsia mioclónica severa de la infancia (SMEI)	Clobazam Clonazepam Valproato sódico Topiramato	Levetiracetam Stiripentol	Fenobarbital	Carbamazepina Lamotrigina Oxcarbazepina Vigabatrina
Síndrome Lennox-Gastaut	Lamotrigina Valproato sódico Topiramato	Clobazam Clonazepam Etosuximida Levetiracetam	Felbamato	Carbamazepina Oxcarbazepina
Síndrome Landau-Kleffner	Lamotrigina Valproato sódico Esteroides	Levetiracetam Topiramato	Sulthiame	Carbamazepina Oxcarbazepina
Ondas pico continuas o lentas durante el sueño (CSWS)	Clobazam Clonazepam Etosuximida Lamotrigina Valproato sódico Esteroides	Levetiracetam Topiramato		Carbamazepina Oxcarbazepina Vigabatrina
Epilepsia mioclónica astática (MAE)	Clobazam Clonazepam Valproato sódico Topiramato	Lamotrigina Levetiracetam		Carbamazepina Oxcarbazepina

TRATAMIENTO EN SW SINTOMÁTICO

- Etiologia Prenatal
  - Malformaciones:
    - Difusas: BZ
    - Hemimegalencefalia: VGB, Hemisferectomia
    - Focal Displasia: Tx para crisis focal, Corticotomia, Esteroides
- Sind. Neurocutáneos: ET VGB; NF ACTH; NSL semejante Hemimegalencefalia
- Fetopatías Virales: No esteroides; Valproato – BZ+ VGB
- Enf. Vasculares: Esteroides - VGB
- Anormalidades cromosómicas: Esteroides - valproato
- Etiologia peri y post natal
  - Metabolica: No Valproato; BZ
  - SHI e infecciones: ACTH; VGB – LMT+ Valp

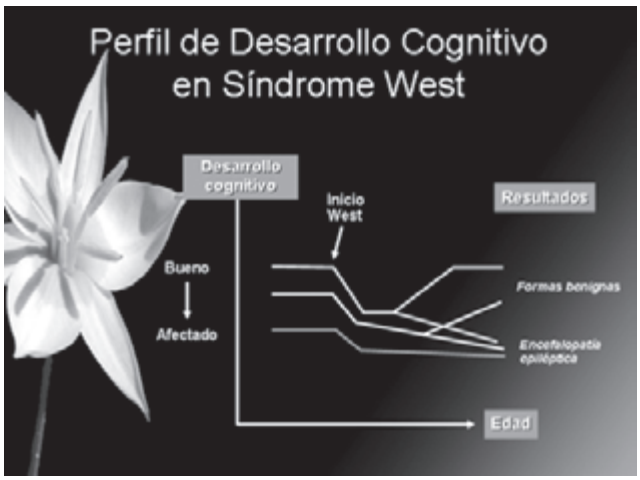
Secuencia Lógica de Tratamiento para Síndrome West

1. Identificar etiologia subyacente:
   - Sintomático
     - Con terapia especifica (ejem: TSC, displasia cortical, en errores congénitos de metabolismo)
     - Sin terapia especifica
     - Criptogénico / Idiopático
2. Terapias médicas iniciales
   - Dirigida hacia etiologia especifica, si es posible
   - Piridoxina 100-200 mg/dosis; corto tiempo de respuesta)
   - Vigabatrina (corto tiempo de tratamiento)
   - ACTH/prednisona (ser cuidadoso con niños sintomáticos y enfermedad sistémica, ejem: falla cardiaca/renal)

Secuencia Lógica de Tratamiento para Síndrome West

3. Si enfoque estándar falla, evaluar para posible intervención quirúrgica
4. Si el paciente no es candidato ó si la cirugía falla, entonces considerar:
   - Ácido valpróico
   - Topiramato
   - Lamotrigina
   - Levetiracetam
   - Zonisamida
   - Benzodiazepinas (clonazepam, nitracepam, clobazam)
   - Dieta cetogénica
   - Estimulación de nervio vago

(Shiekis 2002)


Perfil de Desarrollo Cognitivo en Síndrome West
Desarrollo cognitivo
Inicio West
Resultados
Bueno
Afectado
Formas benignas
Encefalopatía epiléptica
Edad


Mecanismo Cortical de Atención visual en Síndrome West
Rango de maduración de estructuras visuales corticales dependientes de la edad
Sensibilidad a descargas epilépticas
Localización posterior del foco epiléptico (EEG, SPECT)
Inatención visual


Mecanismos de Deterioro Cognitivo en el Síndrome West: Un Modelo Posible
Desorden epiléptico pervasivo de West (+ lesiones corticales)
Maduración del proceso de impulso central (período crítico)
Deterioro de las funciones neurosensoriales
Transitoria
Desorden epiléptico persistente o con recidivas
Buen pronóstico mental
Pobre pronóstico mental

Experimental Models/Basic mechanisms of the epilepsies

Giuliano Avanzini (Italy)/ Luiz Mello (Brazil)/ João Pereira Leite (Brazil)

Febrile status epilepticus: a translational approach

Solomon Moshé (USA)

Epilepsy-Neurotrasmitters-Neuroreceptors and comorbidities

Harry Stokes (Guatemala)

Cognitive deterioration in epilepsy

Salvador Gonzales Pal (Cuba)

Programa – 09.02.2008

Morning session – 9:00 – 13:00

- Pharmacodynamic- Receptors and pathways applied to AEDs - Regina P Markus (Brazil)

Afternoon session – 14:30-18:30

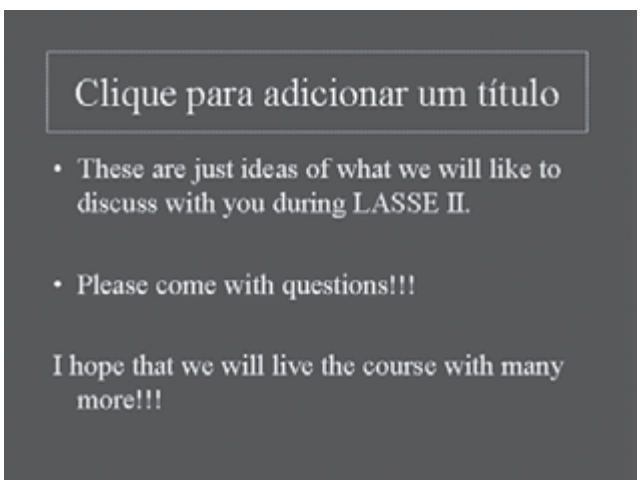
- Pharmacokynetic applied to AEDs - Teresa Della Costa (Brazil)

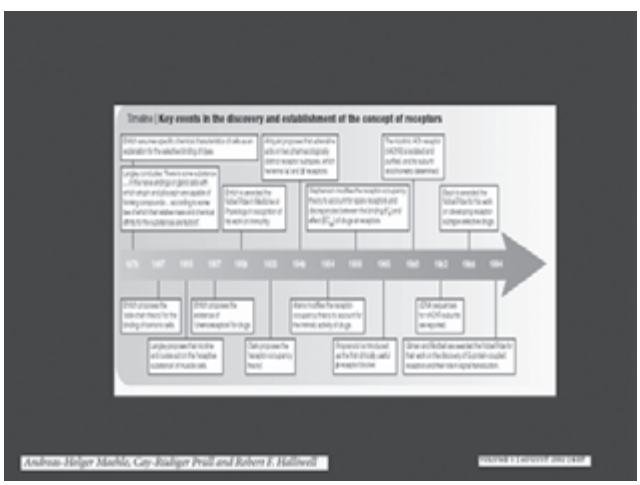
Evening Session

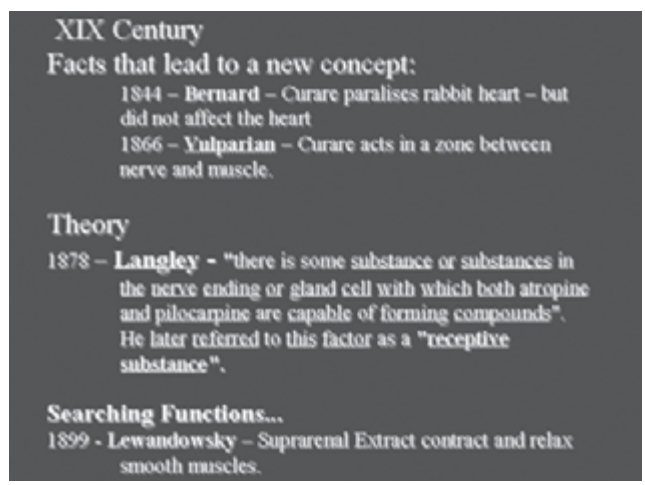
- Development of the cerebral cortex and neuronal migration – Marina Bentivoglio (Italy)
- Epilepsies related to cortical developmental malformations – Alejandro Scaramelli (Uruguay)

Pharmacodynamic – Receptors and pathways applied to AEDs

Regina P. Markus (Brazil)







1900 - 1920

1901 – John Newport Langley – Nicotine stimulates cells of the sympathetic ganglia.
1904 – Elliot – Adrenaline acts at the junction between nerves and smooth mucles.
1905 – Langley – Nicotine stimulates and curare blocks skeletal muscle neurotransmission
1906 – Langley - The 'receptive substance,' shown to provide the receptor for alkaloids such as nicotine and curare
Hunt and Taveau – synthesizes acetylcholine
1914 – Dale – disclose the similarity between acetylcholine and vagus stimulation of smooth and cardiac muscles.

1920 – 1930

1921 – Loewi - 'Vagusstoff' is released by the vagus and controls heart contractility.

1926 – Loewi and Navratil – Physostigmine potentiates the effect of acetylcholine on the heart.

1929 – Dale and Dudley – Vagustoff is Acetylcholine

1948 – Alquist – Define the alpha and beta adrenoceptors and the order of potency for the agonists.

1955 –Blake – first beta-adrenoceptor antagonist – propranolol.

1956 – Stephenson – Receptor Reserve – a huge theorectical step for understanding the complex regulation of receptors.

Paul Erlich

"Corpora non agunt nisi fixata

Ehrlich based his hypothesis upon his experiences in the treatment of infectious diseases with drugs derived from the German dye industry. He postulated that a drug could have a therapeutic effect only if it has the "right sort of affinity". Ehrlich specifically wrote "that combining group of the protoplasmic molecule to which the introduced group is anchored will hereafter be termed receptor". At this time Ehrlich visualised receptors as being part of side-chains in mammalian cells, today we realise that drug-binding sites may be part of any cellular constituent.

•The concept of drugs acting on receptors is generally credited to John Langley 1878. Langley while studying the antagonistic effects of atropine against pilocarpine induced salivation wrote "that there is some substance or substances in the nerve ending or gland cell with which both atropine and pilocarpine are capable of forming compounds". He later referred to this factor as a "receptive substance". Despite this observation, the word "receptor" was not introduced into the medical literature until the turn of the century by Paul Ehrlich.

Different Types of Membrane Receptors

We will focus on channels and seven-membrane GPCRs

NEXT

MEMBRANE PROTEINS

1 - Receptors GPCRs
Ligand-coupled ion channels
Enzymes – ex. Tyrosine quinases
Intracellular

2 – Ion channels
3 - Transporters
4 - Enzymes

Mode of Action

1 – direct - **agonist; competitive antagonist**
2 – alotropic – binds to the receptor molecule in a site different from the agonist

RPMarkus 2000

Receptor Theories

1. Occupation
2. Frequency of Interaction
3. Operational Models

constitutive activation of the receptor

Therefore

A drug may act:

1 - activating

2 - inhibiting

3 - modulating

the receptor

Drug Classification

Agonist direct full/partial
inverse full/partial

Antagonist competitive reversible
non-revers

non-competitive

Occupation Theory

Drug-Receptor interaction follows Law of Mass Action

At equilibrium → occupancy is a function of concentration

Maximal concentration is inversely related to affinity

The same rules apllies when one or more chemical substances compete for the same binding site

Classical

$$D + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} DR$$

(1-y) y

$V_1 = k_1 * [A] * (1-y)$ $V_2 = k_{-1} * y$

Equilibrium $\longrightarrow$ $V_1 = V_2$

$$y = \frac{[A]}{[A] + k_{-1}/k_1}$$

Equilibrium Constant

K_A

RPMarkus 2000

What does 50% of the effect indicate?

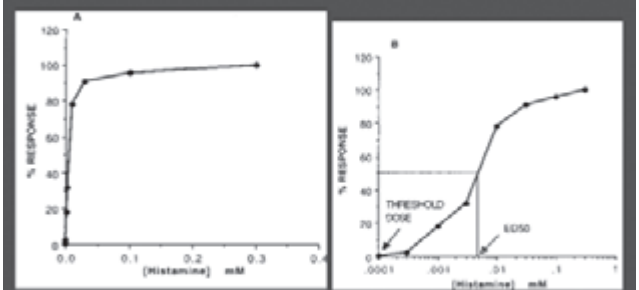
y proporcional to effect

$$y = 0{,}5 = \frac{[A]}{[A] + Keq}$$

$$2\,[A] = [A] * Keq$$

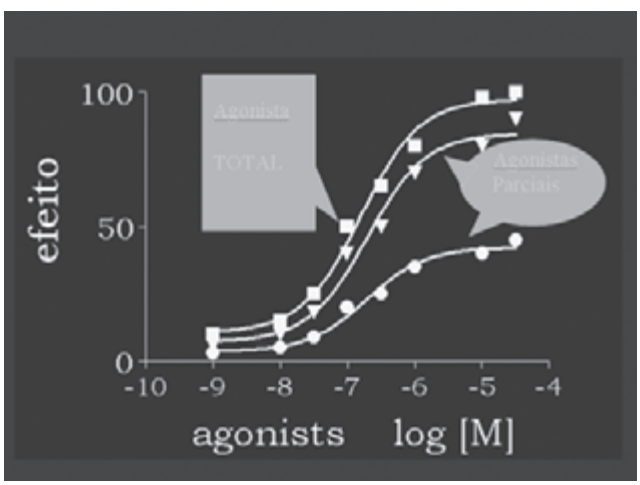
$Keq = [A] = EC_{50}$

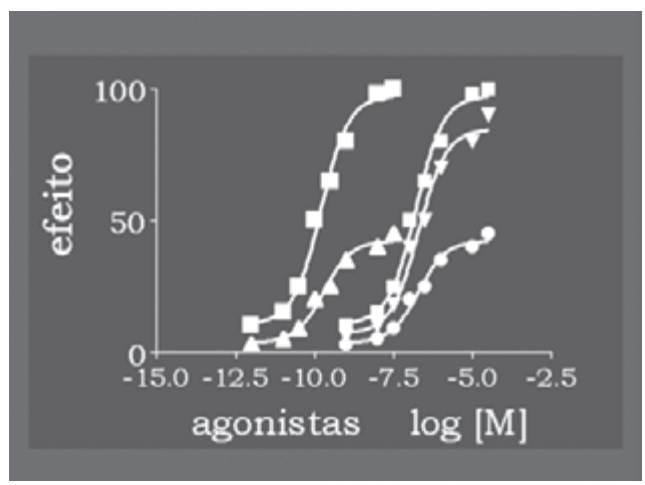
RPMarkus 2000



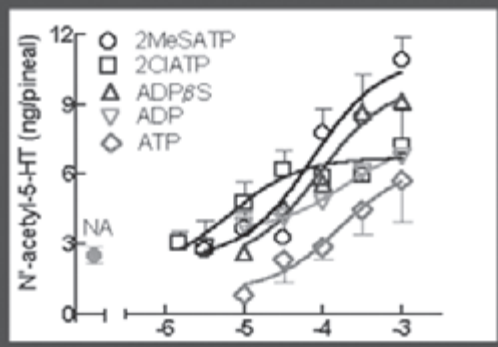
$$\text{Response} = f(S) = \frac{\varepsilon\,[A]}{[A] + Kd}$$

These classical concepts will be reviewed according to interaction with dimers of multimers, or due to the WEB of signaling pathways





P2 receptor agonists - Pineal gland



Ferreira et al., 2001

Antagonismo Competitivo

$$A + R \underset{k\text{-}1A}{\overset{k1A}{\rightleftharpoons}} DR$$

(1-y) y

$$B + R \underset{k\text{-}1B}{\overset{k1B}{\rightleftharpoons}} DR$$

(1-y) y

$$K = \frac{k_{-1}}{k_1}$$

Competitive Antagonism

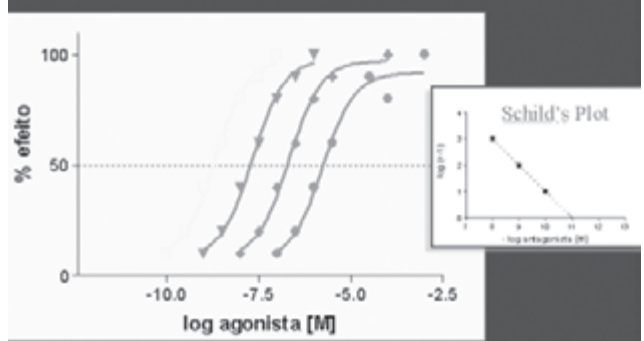
$$y = \frac{[A] / K_A}{[A]/ K_A + [B]/ (K_B + 1)}$$

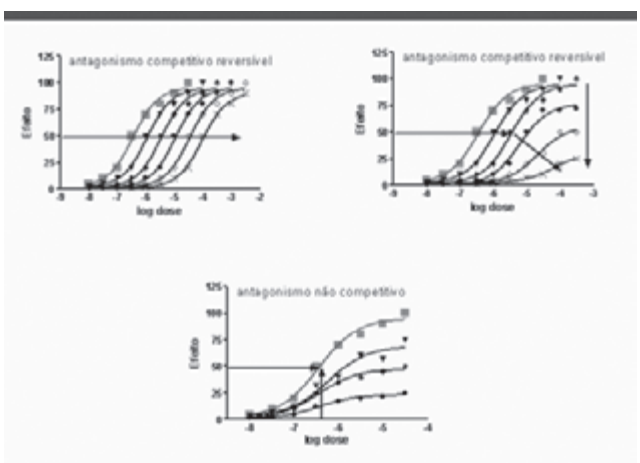
$$r = [A] / [\Delta o] \quad \text{ou} \quad r = ([B]/ K_B) + 1$$

$$\log (r-1) = \log [B] - \log K_B$$

Schild Equation

Competitive Antagonist





Efficacy and Receptor Reserve

This is a concept disclosed by Stephenson in 1956 and still now is being developed.

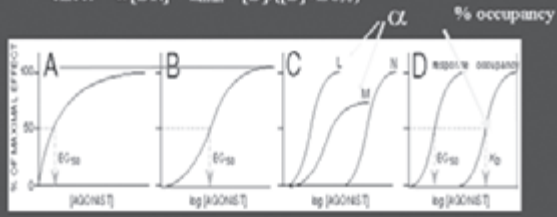
The theory of two states (Colquhoun, 1973) improves our comprehension of efficacy and receptor reserve.

In nowdays the greater understanding of the signaling pathway and their multiple regulation indicate that these theories need to be revised. We will discuss some cases.

Occupacy and Efficacy

$$effect = \alpha [DR] = E_{max} * [D]/([D]+EC_{50})$$

effect = α [DR] = Emax * [D]/([D]+EC50)



2004-2005

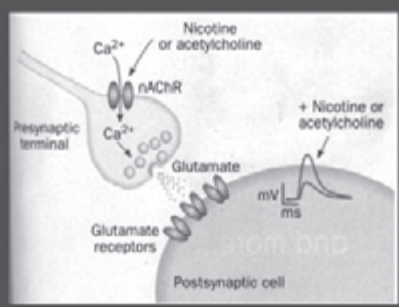
Concept: spare receptors

Specificity

The Interaction is specific

- Optical isomery
- There is no full specificity
- As a general rule: lower specificity means lower potency

Channel Receptors



For GPCRs a ternary complex is formed:

AGONIST-RECEPTOR-PROTEIN G

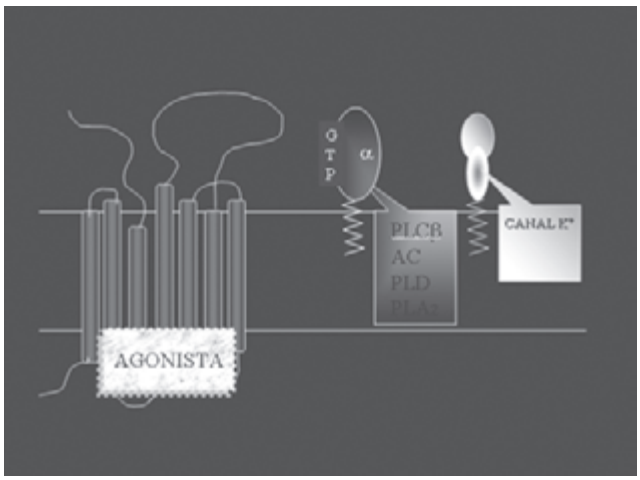
This ternary complex may add some complexity to the classical model, and this will be discussed

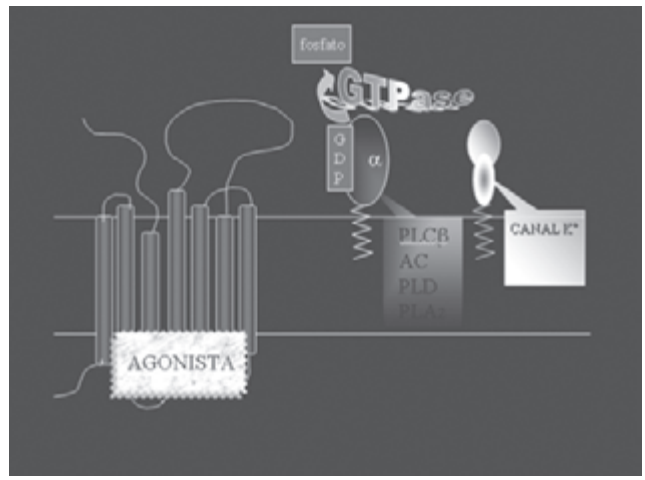
NEXT

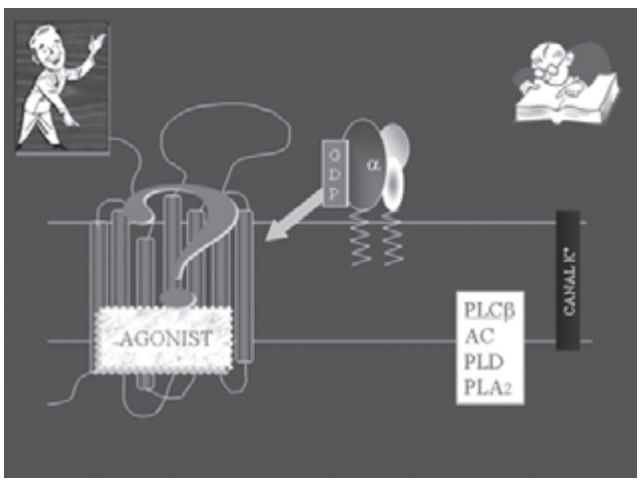
GPCRs

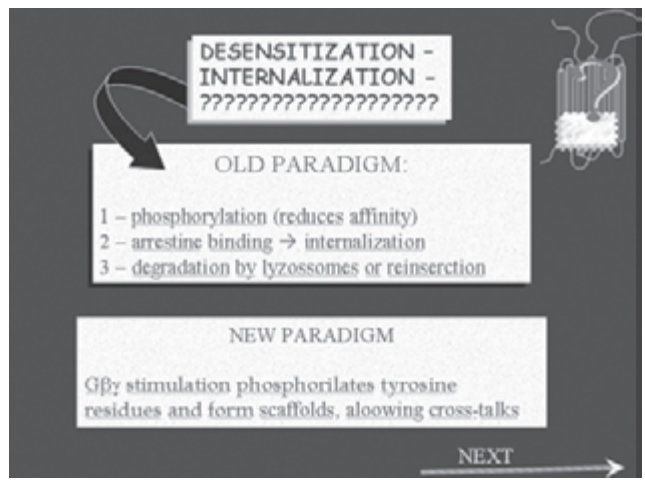
- SIGNAL PATHWAYS
  - Goal directed
  - Cross-talk
  - Transient, long-lasting and late responses

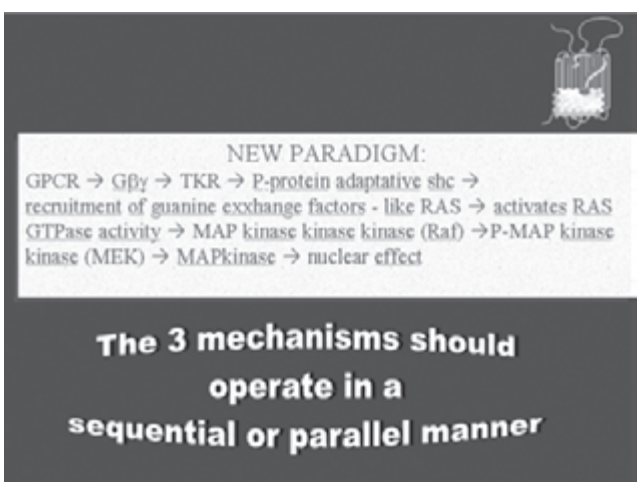
It will be discussed models and time-course of signaling

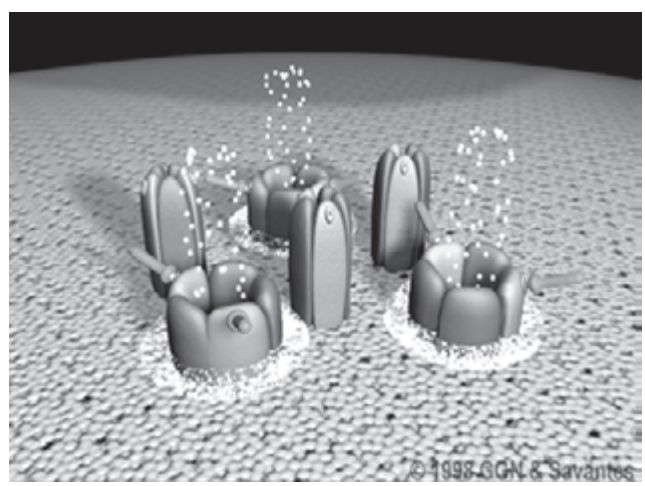

GTP
α
PLCβ
AC
PLD
PLA2
CANAL K+
AGONISTA

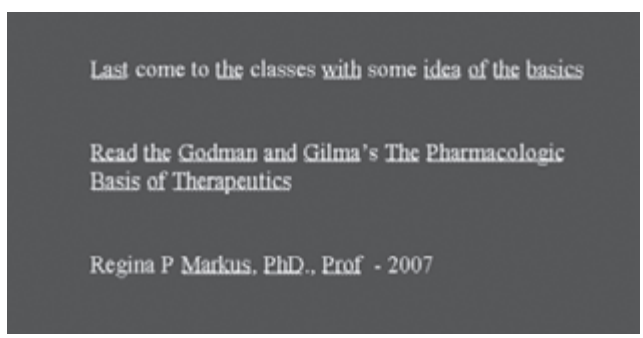

fosfato
GTPase
GDP
α
PLCβ
AC
PLD
PLA2
CANAL K+
AGONISTA


GDP
α
AGONIST
PLCβ
AC
PLD
PLA2
CANAL K+


DESENSITIZATION -
INTERNALIZATION -
??????????????????
OLD PARADIGM:
1 – phosphorylation (reduces affinity)
2 – arrestine binding → internalization
3 – degradation by lyzossomes or reinserction
NEW PARADIGM
Gβγ stimulation phosphorilates tyrosine residues and form scaffolds, aloowing cross-talks
NEXT


NEW PARADIGM:
GPCR → Gβγ → TKR → P-protein adaptative shc →
recruitment of guanine exxhange factors - like RAS → activates RAS
GTPase activity → MAP kinase kinase kinase (Raf) →P-MAP kinase
kinase (MEK) → MAPkinase → nuclear effect
The 3 mechanisms should
operate in a
sequential or parallel manner


© 1998 GCN & Savantes


Last come to the classes with some idea of the basics
Read the Godman and Gilma's The Pharmacologic Basis of Therapeutics
Regina P Markus, PhD., Prof - 2007

Pharmacokynetic applied to AEDs

Teresa Della Costa (Brazil)

Basic Pharmacokinetics

Pharmacokinetic Processes and Parameters

Part 1

Profa. Dra. Teresa Dalla Costa
Programa de Pós-Graduação em Ciências Farmacêuticas
Universidade Federal do Rio Grande do Sul

Pharmacokinetics

Chronological study of the drug and its metabolites in the body

Pharmacokinetics aids drug therapy optimization

- Dose
- Dosing interval
- Dosage form

PK Goal

To produce adequate concentrations in the body by using the best dosing regimen and dosage form

Drug fate in the body

Liberation
Absorption
Distribution
Metabolism
Excretion

LADME system

LADMER System

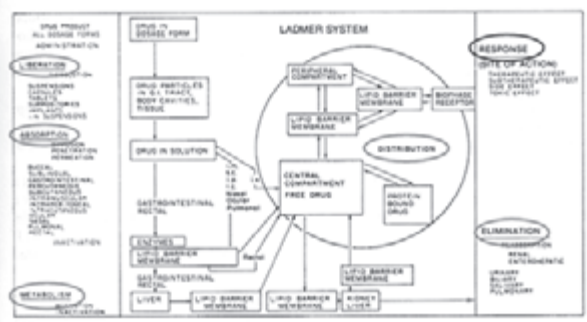


Figure 2-1. Diagram of LADMER System showing the complex interrelationships among drug, drug product, and body.

Ritschel and Kearns, 2004

Pharmacokinetic Parameters

Bioavailability (E_{abs})

Volume of distribution (Vd)

Clearance (CL)

Half-life (t½)

LIBERATION

DRUG + ADJUVANTS + TECHNOLOGY = DF

LIBERATION

SOLID DISPERTION OD THE DRUG

DISSOLUTION

MOLECULAR DISPERTION OF THE DRUG

ABSORPTION

BLOOD

MEMBRANE

BLOOD

ABSORPTION

Drug input into blood stream (systemic circulation) or lymph

- Drug must be dissolved (in general)
- Active or passive transport
- Absorption can be incomplete
- Bioavailable fraction (E_{abs}): fraction of the administered dose that reaches the systemic circulation after absorption in comparison to i.v. dosing.

Transport Process Across Membranes

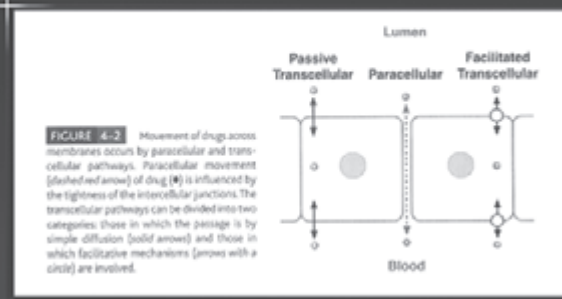


FIGURE 4–2 Movement of drugs across membranes occurs by paracellular and transcellular pathways. Paracellular movement (dashed red arrows) of drug (●) is influenced by the tightness of the intercellular junctions. The transcellular pathways can be divided into two categories: those in which the passage is by simple diffusion (solid arrows) and those in which facilitative mechanisms (arrows with a circle) are involved.

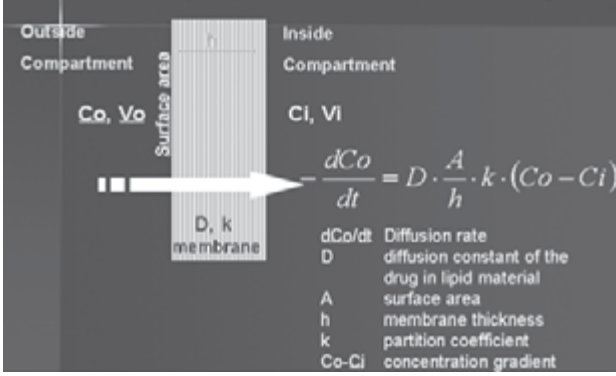
Tozer and Rowland, 2006

Mechanisms of Transport

- **Passive**
  - Diffusion (1)
  - Convection Transport (2)
  -
- **Active**
  - Active Transport (3)
  - Facilitated Transport (diffusion) (4)
  - Ion-Pair Transport (5)
  - Endocytosis-Pinocytosis (6)

Diffusion

natural tendency for molecules to move down a concentration gradient



Drug Properties Determining Permeability

- Charge (degree of ionization)
  - Only drug in the more lipossoluble state (nonionized) can cross the membrane
- Lipophilicity/Hydrophilicity Balance
  - Higher the lipophilicity = higher diffusion = higher absorption
  - However, the drug must present some hydrophilicity to be able to dissolve in water in order to be absorbed.
- Molecular size
  - Molecular size has a major impact on drugs movement through membranes

Degree of ionization and pH

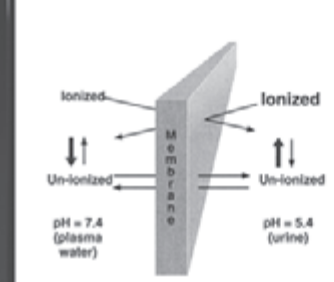


FIGURE 4–5 When a drug is a weak acid or weak base, its total concentration on one side of a lipophilic membrane may be very different from that on the other at equilibrium, if the pH values of the two aqueous phases are different. One mechanism producing this concentration difference is the pH partition hypothesis, which states that only the un-ionized form can cross the membrane and that the total concentration on each side at equilibrium depends on the degree of ionization. The side with greater ionization has the higher total concentration. For weak bases, in the example shown, the total concentration is greater on the side with the lower pH; the opposite applies to weak acids. The relative concentrations of un-ionized and ionized drug on both sides of the membrane are shown by the font sizes. The weak base has a pKa of 6.4.

Tozer and Rowland, 2006

Lipophilicity

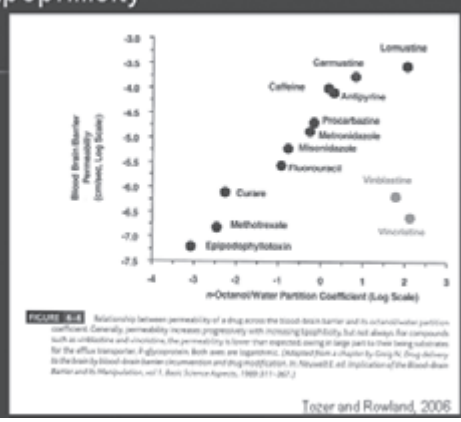
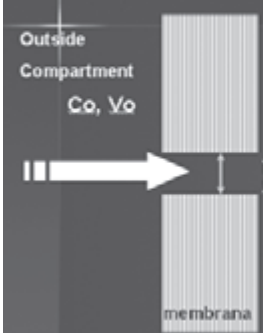


FIGURE 4–6 Relationship between permeability of a drug across the blood-brain barrier and its octanol/water partition coefficient. Generally, permeability increases progressively with increasing lipophilicity, but not always. For compounds such as vinblastine and vincristine, the permeability is lower than expected, owing in large part to their being substrates for the efflux transporter, P-glycoprotein. Both axes are logarithmic. (Adapted from a chapter by Greig NH: Drug delivery to the brain by blood-brain barrier circumvention and drug modification. In: Neuwelt EA, ed: Implication of the Blood-Brain Barrier and Its Manipulation, vol 1. Basic Science Aspects, 1989:211–267.)

Tozer and Rowland, 2006

Convective Transport



- Passage through the aqueous pores of the membrane
- Water: hydrostatic pressure
- Hydrosoluble molecules
- Small molecules
  - MW < 150 - spheric
  - MW < 400 – linear

Kinds of Active Transport

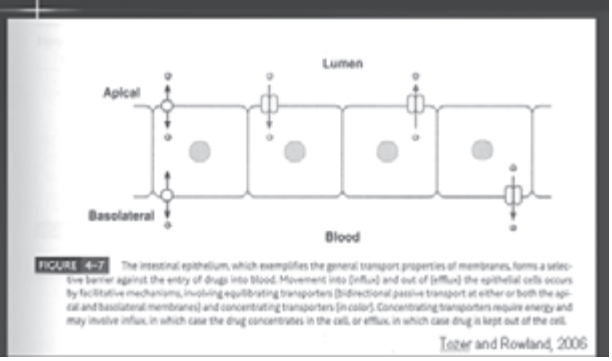
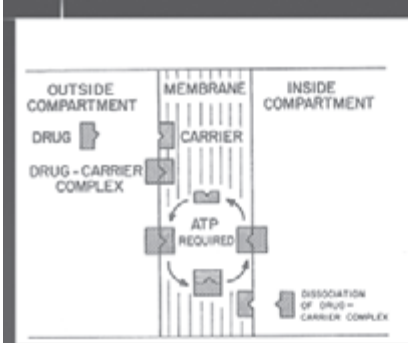


FIGURE 4–7 The intestinal epithelium, which exemplifies the general transport properties of membranes, forms a selective barrier against the entry of drugs into blood. Movement into (influx) and out of (efflux) the epithelial cells occurs by facilitative mechanisms, involving equilibrating transporters (bidirectional passive transport at either or both the apical and basolateral membranes) and concentrating transporters (in color). Concentrating transporters require energy and may involve influx, in which case the drug concentrates in the cell, or efflux, in which case drug is kept out of the cell.

Tozer and Rowland, 2006

Active Transport



- Carrier and (ATP)
- Against concentration gradient and electrochemical potential
- Saturation
- Specificity and competition
- Cardiac glycosides, pyrimidine bases, 5-fluorouracil

Active Transport *vs.* Diffusion

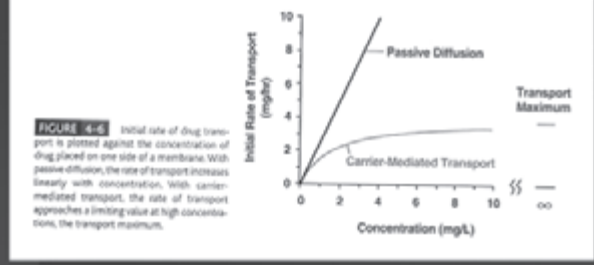
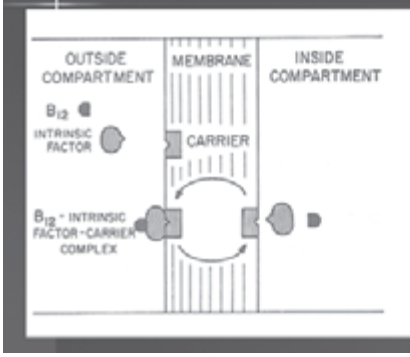


FIGURE 4-6 Initial rate of drug transport is plotted against the concentration of drug placed on one side of a membrane. With passive diffusion, the rate of transport increases linearly with concentration. With carrier-mediated transport, the rate of transport approaches a limiting value at high concentrations, the transport maximum.

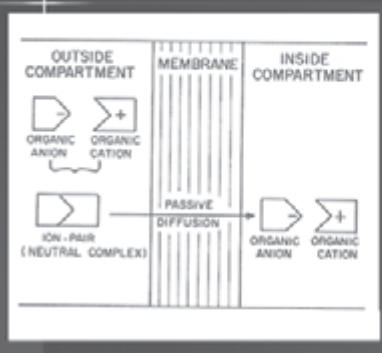
Tozer and Rowland, 2006

Facilitated Transport



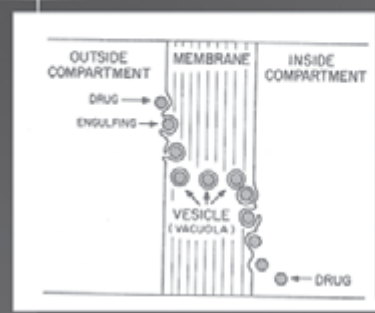
- Needs carrier
- With concentration gradient
- Specificity and competitive inhibition
- Saturation
- OATP: NSAD, statins, some fluoroquinolones
- OCT: antiarrhythmics, some antihistamines

Ion-Pair Transport



- Complex of organic ion of substances with counterion of the medium or membrane
- Transport of drugs ionized in physiological pH
- Neutral complex cross by diffusion
- Drugs (ions): ampicillin, atenolol, quinine HCl, bretylium bromide
- Conterions: mucin, cholate, taurocholate, hexylsacylate, alkylsulfate

Endocytosis-Pynocytosis



- Engulfing vesicles
- Passage of big molecules
- Drugs does not need to be in aqueous solution (small oil droplets and solid particles)
- Vit A, D, E, K; ferritin, insulin, glycoproteins, thyroid hormones, …

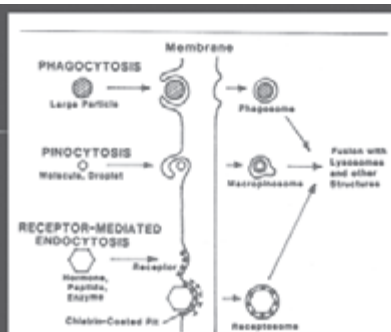
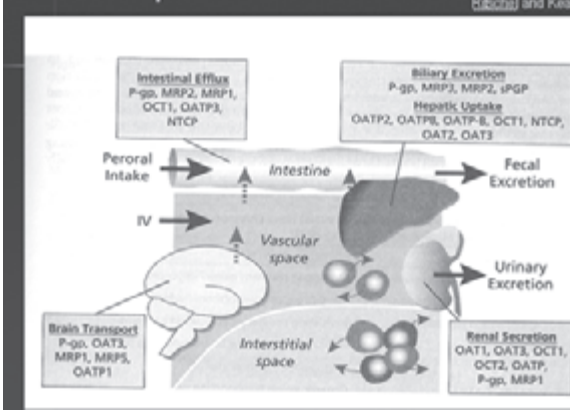


Figure 6-11. Schematic diagram of endocytosis by phagocytosis, forming a phagosome, pinocytosis, forming a macropinosome, and receptor-mediated endocytosis, forming a receptosome, all of which fuse intracellularly with structures, usually lysosomes.

Transport Proteins

Ritschel and Kearns, 2004



Human drug transporters that have pharmacokinetic significance

ABBREVIATION	FULL DESIGNATION
MDR1/P-gp	Multidrug resistant gene/P-glycoprotein
BSEP/SPGP	Bile salt export pump/sister P-glycoprotein
MRP1, MRP2, MRP3	Multidrug resistance associated proteins
NTCP	Sodium taurocholate co-transporting peptide
PEPT1, 2	Oligopeptide transporter 1
OATP1, OATP2	Organic anion transporting peptide
OCT1, OCT2	Organic cation transporter
OAT1, OAT2, OAT3	Organic anion transporter

Ribchel and Kearns, 2004

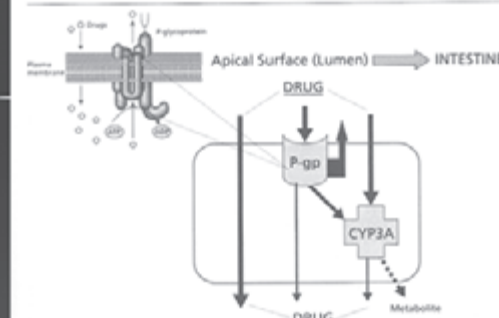


Figure 6-13. Schematic diagram of the action of P-glycoprotein (P-gp) in the small intestine. As illustrated, P-gp is colocated with cytochrome P450 3A (CYP3A) in the enterocyte and in a cooperative fashion can increase the first-pass effect (presystemic clearance) of drugs that are substrates for these proteins by extrusion of the drug back into the intestinal lumen (by the efflux transporter P-gp) and/or biotransformation in the enterocyte by CYP3A.

Examples of P-gp interactions with drugs and natural products

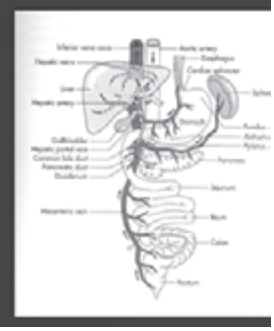
COMPOUND	INHIBITOR OR INDUCER	REPORTED INTERACTIONS
Atorvastatin	Inhibitor	Digoxin (↑ AUC by 15%)
Cyclosporine	Inhibitor	Docetaxel, Paclitaxel (↑ bioavailability 8–11-fold)
Erythromycin	Inhibitor	Atorvastatin, Cyclosporine, Fexofenadine, Saquinavir (↑ Cmax and AUC by 32–115%)
Grapefruit juice	Inhibitor	Paclitaxel (↑ bioavailability by 7-fold)
Ketoconazole	Inhibitor	Fexofenadine, Saquinavir, Tacrolimus (↑ AUC by 1.6–2-fold)
Rifampin	Inducer	Digoxin, Fexofenadine, Saquinavir, Tacrolimus, Talinolol (↓ AUC by 37–70%)
Ritonavir	Inhibitor	Saquinavir (↑ AUC)
St. John's wort	Inducer	Digoxin (↓ AUC)
Verapamil	Inhibitor	Talinolol (↑ clearance by 29–56%)

Ribchel and Kearns, 2004

Oral Absorption

- **Small intestine**
  - Macrovilli and microvilli
  - High blood irrigation
  - pH approx. neutral
  - Contact time

Absorption window: drug uptake from a limited portion of GIT



First-Pass Effect

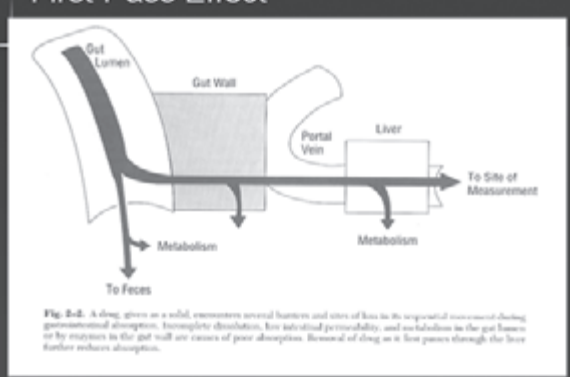
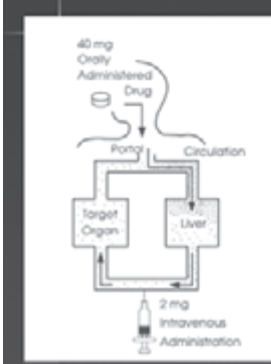


Fig. 8-2. A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement during gastrointestinal absorption. Incomplete dissolution, low intestinal permeability, and metabolism in the gut lumen or by enzymes in the gut wall are causes of poor absorption. Removal of drug as it first passes through the liver further reduces absorption.

First-Pass Effect



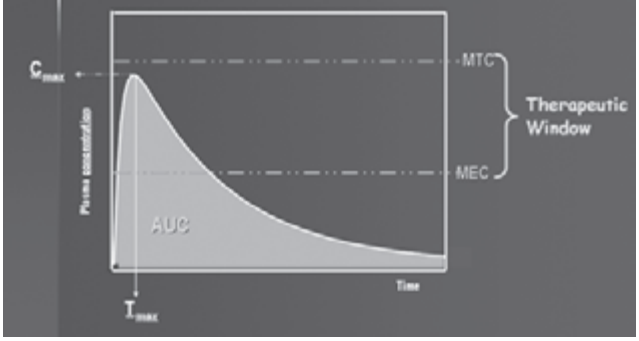
- Elimination of the drug due to metabolization before reaching systemic circulation. Other sources of drug loss also reduce absorption.
- May occur in the gut wall and in the liver following p.o. and deep rectal administration (50%). In these cases, can be avoided by sublingual and buccal routes.
- Pulmonary first pass cannot be avoided by i.v., buccal or sublingual routes
- Lead to the need of bigger oral doses comapared to i.v. doses. Ex.: nytroglicerin, salicilamide, propranolol
- Saturable: drug increase causes disproportional higher

Bioavailability

Defined as both the relative amount of drug from an administered dosage form which enters systemic circulation and the rate at which the drug appears in the bloodstream

- Extent of absorption
  - ✓ Area under the plasma concentration vs. time curve (AUC)
- Rate of absorption
  - ✓ Peak plasma level (C_{max})
  - ✓ Time to peak (T_{max})

Bioavailability

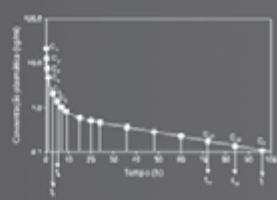


Trapezoidal Rule

$$ASC_{0-t} = \left(\frac{C_1 + C_0}{2}\right)\cdot(t_1) + \left(\frac{C_2 + C_1}{2}\right)\cdot(t_2 - t_1) + \ldots + \left(\frac{C_n + C_t}{2}\right)\cdot(t_t - t_n)$$

$$ASC_{extrap} = \frac{C_t}{k_e}$$

$$ASC_{0-\infty} = ASC_{0-t} + ASC_{0-extrap}$$

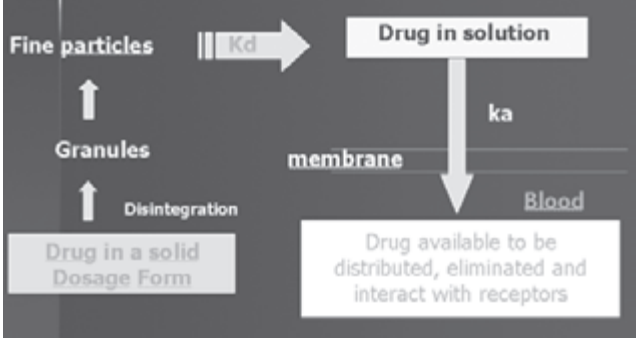


Absolute Bioavailability
Fraction bioavailable (E_{abs} or F)

- Fraction of the administered dose that reaches systemic circulation after oral or other route of administration in comparison to the i.v. dosing.

$$F = \frac{AUC_{0-\infty teste} \cdot D_{iv}}{AUC_{0-\infty iv} \cdot D_{oral}} \cdot 100$$

Factors Affecting Drug Absorption from GIT



Factors Affecting Drug Absorption from GIT

- Related to the drug physico-chemical properties
  - Solubility
  - Stability in the GIT
  - Chemical variation: type of salt or ester (acid/basic drugs)
  - Polymorphism
  - Anhydrous form, hydrates, and solvates
  - Amorphous and crystalline form and particle size
  - First-Pass effect
  - Drug interaction
    - Other drugs
    - Food
    - Beverages

Chemical Variation

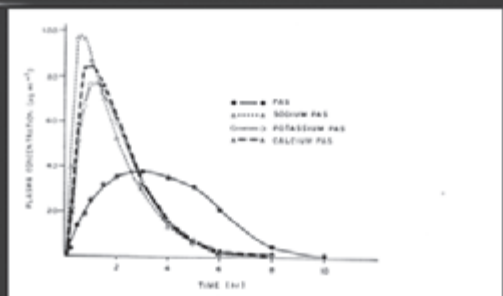


Figure 57 Mean plasma concentrations of unchanged drug from 12 subjects following administration of four different preparations of aminosalicylic acid (PAS). Data were corrected to 70-kg body weight. (From Ref. 267.)

Drug Particle Size

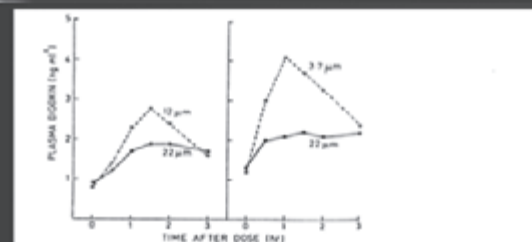


Figure 62 Mean plasma digoxin levels recorded in fasting patients on maintenance digoxin therapy before (•) and after (○) 0.5 mg of digoxin powder of mean particle size 22 μm (four patients) and 12 μm and 3.7 μm (four patients). (From Ref. 237.)

Drug-Food Interaction

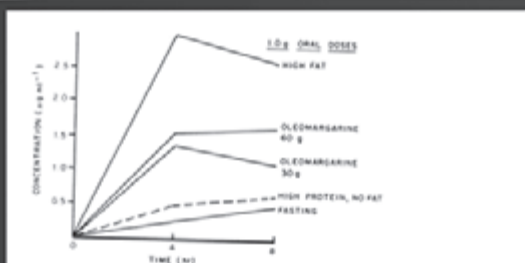
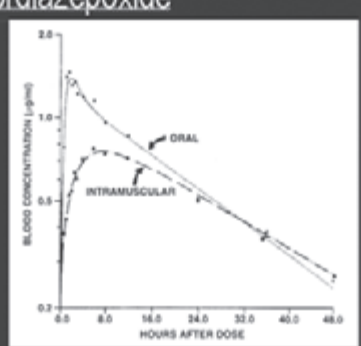


Figure 24 Effects of different types of food intake on the serum griseofulvin levels following a 1-g oral dose. (From Ref. 74.)

Factors Affecting Drug Absorption from GIT

- Related to the dosage form
  - Administration route
  - Dosage form
  - Excipients
    - Type and amount of excipient and used
    - Adsorption properties of the excipients
  - Technology used to prepare the dosage form
    - Type of process
    - Type of equipments used
    - Temperatures
    - Compression force used

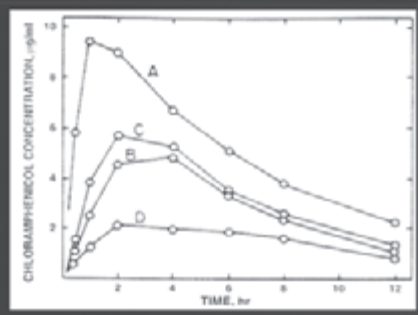
Administration route
Chlordiazepoxide



Factors Affecting Drug Absorption from GIT

- Related to the Patient
  - Viscosity of gastrointestinal content
  - GIT motility
  - GIT pH
  - GIT blood flow
  - Gastric empty time
  - Physical activities
  - Type of diet (meat, barbecue, vegetarian)
  - Patients lifestyle (use of drugs, alcohol , cigarettes)
  - Diseases: hepatic and renal diseases, cirrhosis

Variable bioavailability among formulations of the same drug



500 mg de chloramphenicol p.o. - 4 brand names (EUA)

Bioequivalence

- Two product are considered bioequivalents when they extent and rate of absorption are not statistically different when administered at the same molar dose in the same conditions
- Bioequivalence study
  - One product is the reference medicine
  - The other product is the test medicine
- For bioequivalent medicines the difference in rate and extent of absorption can not be bigger than 20%

Relative bioavailability (f_{rel})

Ratio between absolute bioavailabilities of test and reference medicines at the same route of administration

$$f_{rel} = \frac{AUC_{0-\infty test}}{ASC_{0-\infty reference}}$$

Bioavailability *vs.* Bioequivalence

Bioavailability

- Rate and extent of absorption of a drug product administered to a non-systemic route in comparison to the i.v. route which, by definition, presents 100% or absolute bioavailability
  - Reference route = i.v.
  - Test route = other administration route (p.o, i.m., ...)
  - Absolute bioavilability is determined

Bioequivalence

- Comparison of bioavailabilities of two drug formulations in the same route of administration
  - Test product x reference product
  - Relative bioavailability is determined

Basic Pharmacokinetics

Pharmacokinetic Processes and Parameters
Part 2

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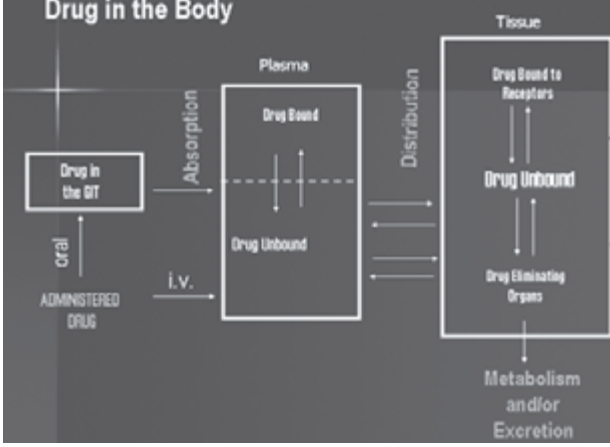
Programa de Pós-Graduação em Ciências Farmacêuticas
Universidade Federal do Rio Grande do Sul

Drug in the Body



Distribution
reversible drug transport from and to the blood

- Free (unbound) fraction of the drug is in equilibrium with the fraction bound to plasma proteins, tissues, bones, erythrocytes, ...
- **Distribution depends**
  - Blood perfusion to the tissue
  - Plasma protein binding
  - Membranes permeability

Extent of Distribution

- Drug hydrophilicity /lipophilicity
- Drug plasma protein binding
- Drug binding to tissues

- Drug physico-chemical properties are important
  - O/A partition coefficient
  - Size
  - Charge

Unbound (free) Fraction

- Can cross membranes and be distributed
- Can bind to receptors to produce pharmacological action
- Can be eliminated from the body (biding increases half-life)
- Bound fraction = active depot
- Plasma proteins
  - Albumin : weak acids
  - α_1-acid glycoproteins: weak bases
  - Transcortin: cortisol
  - γ-globulins: antigens

Drug-Protein Binding
reversible complex

- Saturable
- Competitive (amount *vs.* affinity)
- Drug interactions
- Amount of blood proteins (albumin) can be altered by diseases: hepatic cirrhosis, renal impairment, desnutrition

Which drug will suffer a bigger impact due to displacement from protein binding by competition?
High or low protein binding drug?

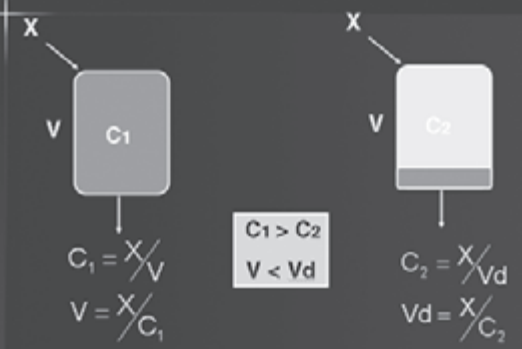
Free Fraction of Drugs in Plasma

Percent unbound (%)	Drug
100	Ethosuximide/gabapentin
> 90	Levetiracetam
60	Oxcarbamazepine
50	Phenobarbital
10-60	Carbamazepine
50-60	Lamotrigine
5-10	Valproic acid/phenytoin
0.2	Naproxen

Apparent Volume of Distribution (Vd)

- The hypothetical volume of body fluid that would be required to dissolve the total amount of drug at the same concentration as that found in the blood.
- Its no a real volume but an apparent one
- The higher the Vv, the bigger is the drug distribution in the body

Apparent Volume of Distribution



Volume of Distribution

$$Vd = \frac{X}{C} = \frac{D}{Cp}$$

Proportionality constant relating the amount of drug in the body to the measured concentration in biological fluid (blood, plasma or serum)

Volume of Distribution

$$Vd = Vp + Vt \cdot \frac{fu}{fu_t}$$

Apparent Vd = volume of plasma + apparent volume of tissue

Vp = volume of plasma

Vt = volume outside the plasma

fu = unbound fraction of drug in plasma

fu_t = unboud fraction of drug in tissues

What is the bigger Vd of a drug in the body?

What is the lowest Vd possible?

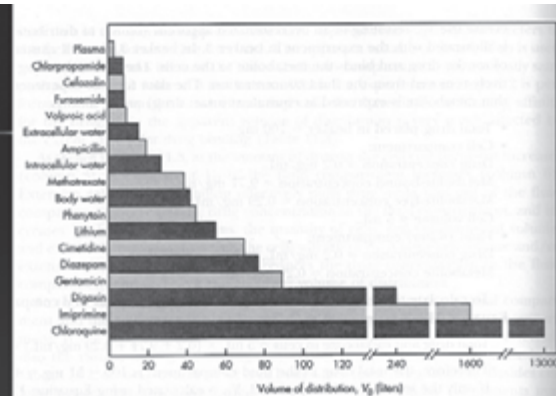


Figure 11-10. Lists of steady-state volumes of distribution of 10 common drugs in ascending order showing various factors affect V_D. Drugs with high V_D generally has high tissue affinity or low binding to serum albumin. Polar or hydrophilic drugs tend to have V_D similar to the volume of extracellular water.

Drug Elimination

- Comprehends the metabolization and excretion processes
- Takes place in tissues such as liver, kidney, lungs, plasma, gut wall

✓ **Metabolism:** aim to transform the drug in a more hydrophilic moiety viewing to easy its excretion as well as to reduce its activity (bio-inactivation)

✓ **Excretion**: elimination of the drug unaltered (intact) or its metabolites mainly by the kidney

Metabolism

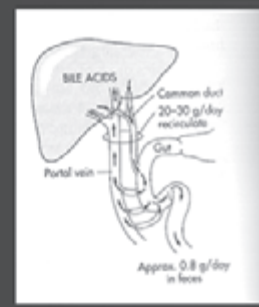
- Phase I: chemical alteration in drug moiety
  - Oxidation, reduction, hydrolysis
  - Cytochrome P-450 (CYP) (isozymymes)
- Phase II: conjugation
  - Glucuronidation, peptide conjugation
  - Acetylation, methylation
- Drug can suffer reaction of phase I or II or both

TABLE 13.3 Some Common Drug Biotransformation Reactions

PHASE I REACTIONS	PHASE II REACTIONS
Oxidation	Glucuronide conjugation
Aromatic hydroxylation	Ether glucuronide
Side chain hydroxylation	Ester glucuronide
N-, O-, and S-dealkylation	Amide glucuronide
Deamination	
Sulfoxidation, N-oxidation	Peptide conjugation
N-hydroxylation	
Reduction	Glycine conjugation (hippurate)
Azoreduction	
Nitroreduction	Methylation
Alcohol dehydrogenase	N-methylation
Hydrolysis	O-methylation
Ester hydrolysis	
Amide hydrolysis	Acetylation
	Sulfate conjugation
	Mercapturic acid synthesis

Types of Excretion

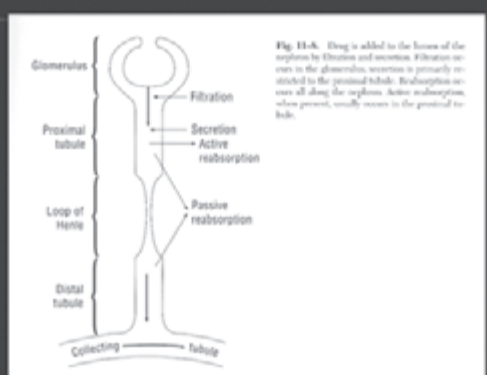
- Renal
- Biliary
- Pulmonary
- Salivary
- Intestinal
- Skin
- Maternal milk
- Hair



Enterohepatic Cycle

Kidney

Elimination of intact drug and metabolites



Process of Drug Excretion by the Kidney

Any combination

- Glomerular Filtration
- Active Tubular Secretion
- Tubular Reabsorption

Glomerular Filtration (GF)

- Unidirectional process that occur for most small molecules (MW<500), including ionized and unionized drugs
- Only free plasma fraction is filtered
- Driving force: hydrostatic pressure within the glomerular capillary
- Glomerular filtration rate (GFR) measured by drug that are only eliminated by filtration (neither reabsorbed nor secreted): inulin and creatinine
- Clearance of creatinine = GFR: 125 -130 mL/min

Active Tubular Secretion

- Carrier-mediated active transport process, requires energy because the drug is carried against a concentration gradient
- Carrier systems are capacity limited and can be saturated
- Drugs can compete for the same carrier (affinity and amount)
- Excretion of free and protein bound drug in the plasma

Two systems

- Weak acids: probenecid/penicillin
- Weak bases: ranitidine

Active Tubular Secretion

- Active tubular secretion rate depend on renal plasma flow. Drugs used to measure it are *p*-amino-hippuric acid (PAH) and iodopyracet (Diostrat). These drugs are filtered and secreted in a single pass by the kideny.
- *Clearance* of these drugs reflect *effective renal plasma flow* (ERPF) - 425 a 650 mL/min

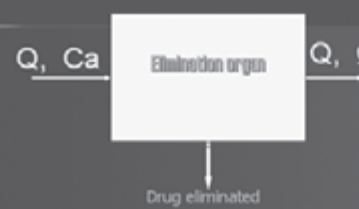
Tubular Reabsorption

- Occur after the drug is filtered through the glomerulus and ca be active or passive
- If a drug is completely reabsorbed (glucose), its clearance is approx. zero
- For drugs that are partially reabsorbed, clearance values will be < 125-130 mL/min
- Absorption of weak bases and weak acids are influenced by urine pH and drugs pka
- Drug in the unionized form is reabsorbed
- Urine pH varies (4.5 to 8) and is depended on diet, pathophysiology and drug intake
- Intravenous infusion of solutions of bicarbonate and ammonium chloride are used to change urine pH
  - To increase clearance of weak base, acidify the urine
  - To increase the clearance of a weak acid, basify the urine

Clearance (CL, CL_{tot})

- Term used to describe drug elimination from the body without identifying the mechanics of the process
- Volume of fluids clear of drug per time unit (volume/time)
- Volume of fluid (volume of distribution) clear of drug per unit of time
- Relates drug elimination rate with plasma levels

Elimination Organ Model



$$CL = \frac{Q \cdot (Ca - Cv)}{Ca} = Q \cdot E$$

Q = Blood Flow
Ca = Arterial Conc. (input)
Cv = Venous Conc. (output)
E = Extraction ratio

Renal Clearance

$$CL_R = \frac{GFR + ASR - RE}{C_{plasma}}$$

$$CL_R = \frac{\Delta E / \Delta t}{C_{average}}$$

GFR	Glomerular filtration rate
ASR	Active secretion Rate
RE	Reabsorption rate
$\Delta E/\Delta t$	Amount excreted in a time interval
$C_{average}$	Average plasma concentration in the interval

Hepatic Clearance

$$CL_{hep} = \frac{Q \cdot fu \cdot CL_{int}}{Q + (fu \cdot CL_{int})}$$

Q	Hepatic blood flow
CL_{int}	Intrinsic Clearance
fu	Unbound fraction of drug in plasma

Hepatic Clearance

- High extraction drug (E > 0.7)

$$CL_{hep} = Q$$

- Low extraction drug (E < 0.3)

$$CL_{hep} = fu \cdot CL_{int}$$

Classification of Drugs Eliminated Primarily by CL_{hep}

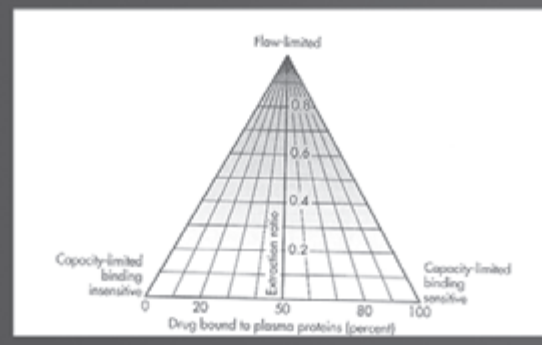


TABLE 13.10 *Pharmacokinetic Classification of Drugs Eliminated Primarily by Hepatic Metabolism*

DRUG CLASS	EXTRACTION RATIO (APPROX.)	PERCENT BOUND
Flow-Limited		
Lidocaine	0.83	45–80*
Propranolol	0.6–0.8	93
Pethidine (meperidine)	0.60–0.95	60
Pentazocine	0.8	—
Propoxyphene	0.95	—
Nortriptyline	0.5	95
Morphine	0.5–0.75	35
Capacity-Limited, Binding-Sensitive		
Phenytoin	0.03	90
Diazepam	0.03	98
Tolbutamide	0.02	98
Warfarin	0.003	99
Chlorpromazine	0.22	95–99
Clindamycin	0.23	94
Quinidine	0.27	82
Digitoxin	0.005	97
Capacity-Limited, Binding-Insensitive		
Theophylline	0.09	59
Hexobarbital	0.16	—
Amobarbital	0.03	61
Antipyrine	0.07	10
Chloramphenicol	0.28	60–80
Thiopental	0.28	77
Acetaminophen	0.43	5*

*Concentration dependent in part.

From Boschke (1977), with permission.

TABLE 13.11 *Hepatic and Renal Extraction Ratios of Representative Drugs*

EXTRACTION RATIOS		
LOW (<0.3)	INTERMEDIATE (0.3–0.7)	HIGH (>0.7)
HEPATIC EXTRACTION*		
Amobarbital	Aspirin	Arabinosyl-cytosine
Antipyrine	Quinidine	Encainide
Chloramphenicol	Desipramine	Isoproterenol
Chlordiazepoxide	Nortriptyline	Meperidine
Diazepam		Morphine
Digitoxin		Nitroglycerin
Erythromycin		Pentazocine
Isoniazid		Propoxyphene
Phenobarbital		Propranolol
Phenylbutazone		Salicylamide
Phenytoin		Tocainide
Procainamide		Verapamil
Salicylic acid		
Theophylline		
Tolbutamide		
Warfarin		

CL_{hep} *vs.* Bioavailability

- A drug given orally must pass through the liver to reach general circulation
- The fraction escaping fist-pass effect by the liver (F_H) is the upper limit of the oral bioavailability

$$F_{abs} = 1 - E_{hep}$$

Fabs	Bioavailability
Ehep	Hepatic extraction ratio

Total Clearance

$$CL_{tot} = \frac{f \cdot D}{ASC_{0-\infty}}$$

Additive properties: CLtot is the somation of the clearances in each of the elimination organs

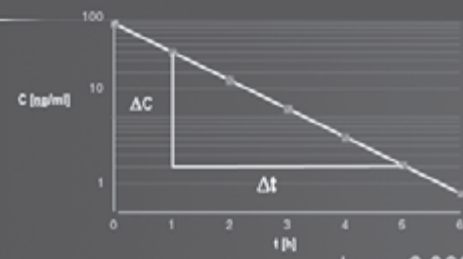
$$CL_{tot} = CL_{hep} + CL_R + CL_{other\ pathways}$$

$$CL_{tot} = CL_R + CL_{non-R}$$

Half-life (t½)

- Chronological concept
- Time needed for the drug to reduce its concentration by half, independent of the initial concentration (Linear PK)
- Drug elimination rate constant is determined by the slope of the elimination phase of concentration vs time plot

t½ Determination



$$k_e = -2.303 \cdot \text{slope}$$

$$\text{slope} = \frac{\log C_1 - \log C_2}{t_1 - t_2}$$

$$t_{1/2} = \frac{0.693}{k_e}$$

Pharmacokinetic Parameters

- Absolute Bioavailability (%)
  $E_{abs} = (ASC_{oral} / ASC_{iv})*100$
- Volume of distribution (L or L/kg)
  $Vd = D / C_0$
- Clearance (mL/min or L/h or mL/min/Kg or L/h/kg))
  $CL = (\Delta E / \Delta t) / C_{average}$
  $CL = D / ASC_{iv} = f.\ D / ASC_{oral}$
  $CL = ke\ .\ Vd$
- Half-life (min or h)
  $t½ = 0.693 / ke$

t½ dependence on CL and Vd

$$k_e = \frac{CL}{Vd}$$

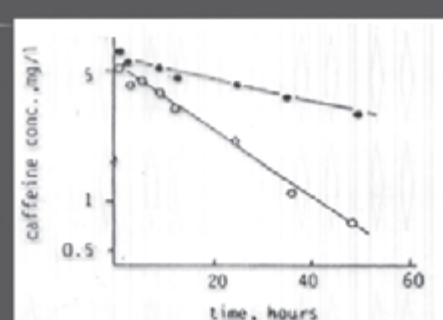
$$t_{1/2} = \frac{0.693}{k_e} = \frac{0.693 \cdot Vd}{CL}$$

k_e (t½) depends on clearance and volume of distribution, two independent variables

Sources of PK Inter-individual variability

- Age
- Weight
- Disease
  - Renal impairment
  - Hepatic impairment
- Pregnancy
- Lifestyle and diet
- Genetic variability
- Drug/drug, food/drug, herbal plant/drug interactions

Age



● 1.5 m old - $t_{1/2}$ 41 h ❍ 2.5 m old - $t_{1/2}$ 16 h

Obesity

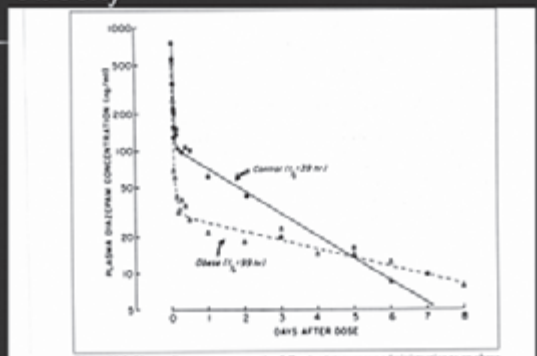


Figure 11-2. Plasma diazepam concentration following intravenous administration to an obese and normal-weight subject (reproduced with permission from J Clin Pharmacol. 1983;23:388–76).

Renal Impairment

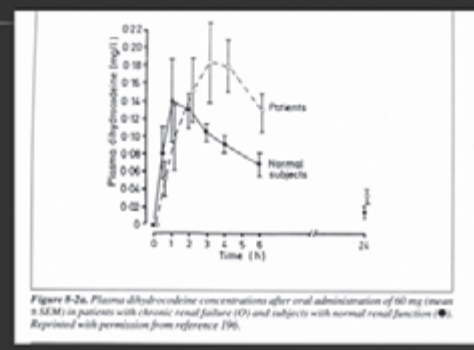
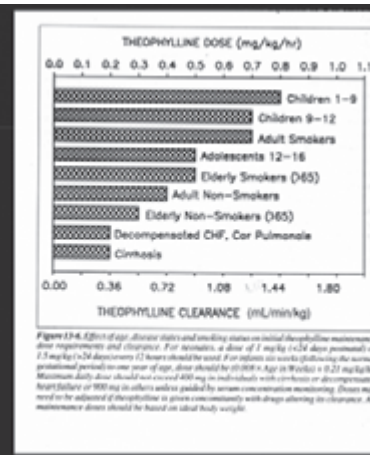


Figure 8-2a. Plasma dihydrocodeine concentrations after oral administration of 60 mg (mean ± SEM) in patients with chronic renal failure (○) and subjects with normal renal function (●). Reprinted with permission from reference 196.

60 mg de Dihydrocodein p.o.

Volume of distribution *vs.* Renal Impairment

Volume Aumentado	Volume Diminuído	Volume Inalterado
Amicacina	Cloranfenicol	Diazepam
Eritromicina	Digoxina	Lidocaína
Furosemida	Etambutol	Procainamida
Minoxidil	Pindolol	Quinidina



Genetic Variability

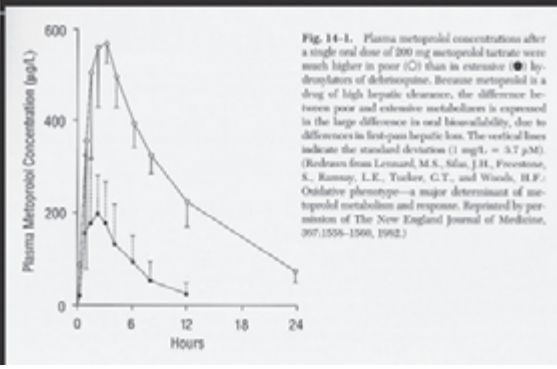


Fig. 14-1. Plasma metoprolol concentrations after a single oral dose of 200 mg metoprolol tartrate were much higher in poor (○) than in extensive (●) hydroxylators of debrisoquine. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers is expressed in the large difference in oral bioavailability, due to differences in first-pass hepatic loss. The vertical lines indicate the standard deviation (1 mg/L = 3.7 µM). (Redrawn from Leonard, M.S., Silas, J.H., Freestone, S., Ramsay, L.E., Tucker, G.T., and Woods, H.F.: Oxidative phenotype—a major determinant of metoprolol metabolism and response. Reprinted by permission of The New England Journal of Medicine, 307:1558–1560, 1982.)

Basic Pharmacokinetics

Compartmental Analysis
Part 3

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Basic Mathematics

C increase

C decrease

$$\pm \frac{dC}{dt} = k \cdot C^n$$

n = 0 (zero order)

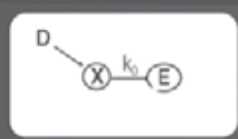
n = 1 (first order)

k = *rate constant*

n = kinetic order

Zero Order Kinetics (n = 0)

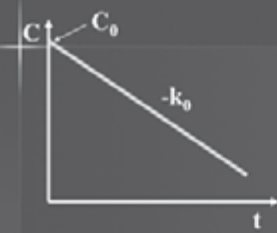
$$-\frac{dC}{dt} = k_0$$



$$C = C_0 - k_0 \cdot t$$

$$k = \text{conc./time}$$

Half-life:



$$C = C_0 - k \cdot t$$

$$t = t_{1/2} \rightarrow C = \frac{C_0}{2}$$

$$\frac{C_0}{2} = C_0 - k \cdot t_{1/2}$$

$$t_{1/2} = \frac{C_0}{2 \cdot k}$$

Zero order elimination $t_{1/2}$ is not constant

$t_{1/2}$ depends on initial concentrations (dose)

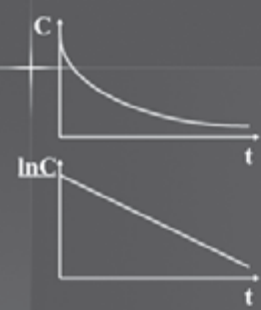
1st order kinetics (n = 1)

$$-\frac{dC}{dt} = k_e \cdot C$$

$$C = C_0 \cdot e^{k_e \cdot t}$$

$$k = \text{time}^{-1}$$

Half-life:



$$C = C_0 \cdot e^{k_e \cdot t}$$

$$t = t_{1/2} \rightarrow C = \frac{C_0}{2}$$

$$\frac{C_0}{2} = C_0 \cdot e^{-k_e \cdot t}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{k_e}$$

First order elimination $t_{1/2}$ is constant

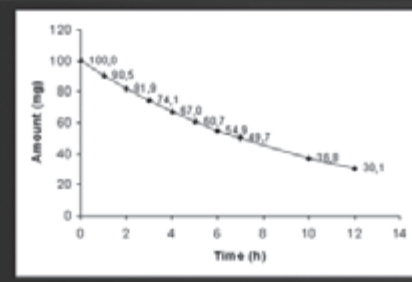
$t_{1/2}$ **do not depend** on concentration (dose)

First Order Elimination $A = D \cdot e^{k_e \cdot t}$

Time interval (h)	Amount Lost During Interval (mg)	Amount Remaining in the Body (mg)
0	--	100
0-1	9.5	90.5
1-2	8.6	81.9
2-3	7.8	74.1
3-4	7.0	67.0
6-7	5.2	49.7

D = 100 mg, k_e = 0.1 h^{-1}

First Order Elimination $A = D \cdot e^{k_e \cdot t}$



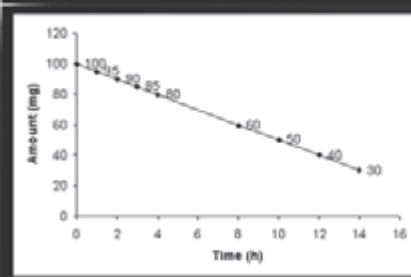
D = 100 mg, k_e = 0.1 h^{-1}, $t_{1/2}$ = 6.9 h

Zero Order Elimination $A = D - k_0 \cdot t$

Time interval (h)	Amount Lost During Interval (mg)	Amount Remaining in the Body (mg)
0	5	100
0-1	5	95
1-2	5	90
2-3	5	85
3-8	25	60
8-10	10	50
10-12	10	40
12-14	10	30

D = 100 mg, k_0 = 5 mg/h

Zero Order Elimination $A = D - k_0 \cdot t$



D = 100 mg, k_0 = 5 mg/h

$t_{1/2}$, 100-50 = 10 h

$t_{1/2}$, 80-40 = 8 h

$t_{1/2}$, 60-30 = 6 h

Compartment Models

- Models are used to describe and interpret a set of data obtained experimentally
- In PK, a model is a hypothetical structure which can be used to characterize with reproducibility the behavior or "fate" of a drug in biological systems when given by a certain route of administration and in a particular dosage form

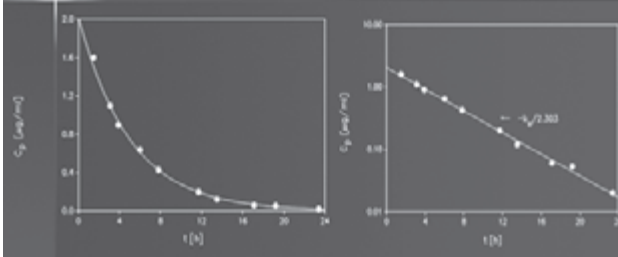
Compartment Models

- The humans body is a multimillion compartment model considering drug concentration in different organelles, cells or tissues
- In living body one have access to only two types of body fluids: blood (plasma or serum) and urine
- Therefore, the compartment PK analysis is used to fit experimental data from blood levels *vs.* time curves or cumulative excretion *vs.* time curves to models

Compartment Models

- A compartment in PK is an entity that can be described by a definite volume and a concentration (of drug contained in the volume)
- Behavior of drug in biological systems
  - One-comparment model
  - Two-comparment model

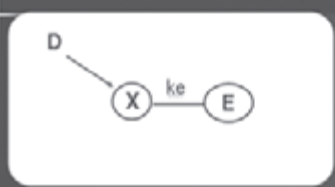
1 compartment model following i.v. dosing



Cartesian plot

Semilogarithmic plot

1 compartment model without absorption



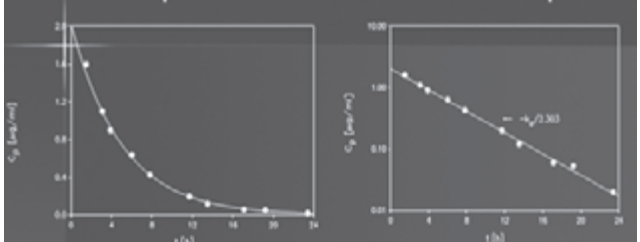
$$\frac{dX}{dt} = -k_e \cdot X$$

D	Dose
X	Amount of drug in the body
E	Amount of drug eliminated
k_e	First order elimination rate constat

Assumptions

- Distribution is instantaneous (no possible to see distribution phase in the plots)
- Organs do not have the same total concentration of the drug
- Unbound concentrations in tissue are in equilibrium with unbound concentrations in plasma

1 compartment model without absorption



Cartesian plot

Semilogarithmic plot

$$C = \frac{D}{Vd} \cdot e^{-k \cdot t}$$

$$\log C = \log \frac{D}{vd} - \frac{ke}{2{,}303} \cdot t$$

1 compartment model without absorption

Plasma levels

$$C = \frac{D}{Vd} \cdot e^{-k_e \cdot t}$$

Volume of distribution

$$Vd = \frac{D}{C_0}$$

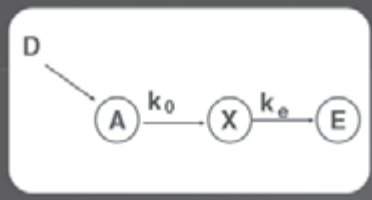
Clearance

$$CL = k_e \cdot Vd = \frac{D}{AUC}$$

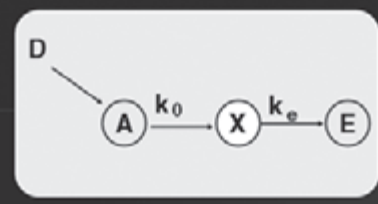
Half-life

$$t_{1/2} = \frac{0.693}{k_e}$$

1 compartment model - constant infusion



D	Dose
A	Amount of drug in the local of absorption
X	Amount of drug in the body
E	Amount of drug eliminated
k_0	Zero order infusion rate constant
k_e	First order elimination rate constant



During infusion

$$-\frac{dA}{dt} = k_0$$

$$\frac{dX}{dt} = k_0 - k_e \cdot X$$

After infusion

$$-\frac{dA}{dt} = 0$$

$$\frac{dX}{dt} = -k_e \cdot X$$

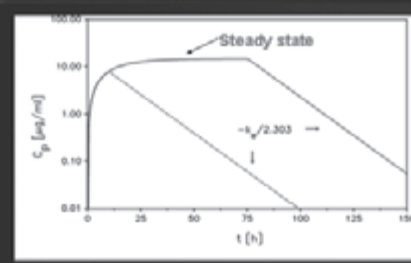
1 compartment model - constant infusion

- T = infusion time
- t = real time

- During infusion t = T
- After end of infusion T = cte, t > T

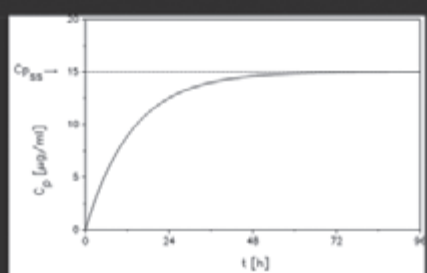
Total Dose administered $D = k_0 \cdot T$

Drug Plasma Levels During and After End of Infusion



$$Cp = \frac{k_0}{k_e \cdot Vd} \cdot \left(e^{k_e \cdot T} - 1\right) \cdot e^{-k_e \cdot (t-T)}$$

Drug Plasma Levels at SS



$$Cp_{ss} = \frac{k_0}{CL_{tot}}$$

1 compartment model – constant infusion

Volume of distribution $Vd = \frac{k_0}{k_e \cdot Cp_{ss}}$

Clearance $CL_{tot} = \frac{k_0}{Cp_{ss}} = k_e \cdot Vd$

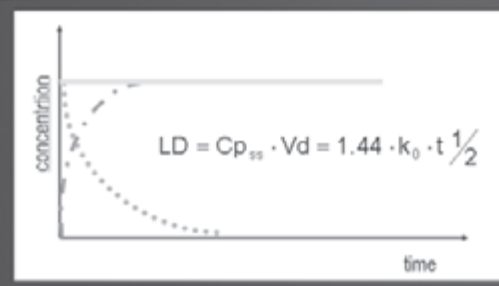
Half-life $t_{1/2} = \frac{0{,}693}{k_e}$

Time to reach SS

$$f = \frac{Cp}{Cp_{ss}} \cdot 100 = \left(1 - e^{-k_e \cdot t}\right) \cdot 100$$

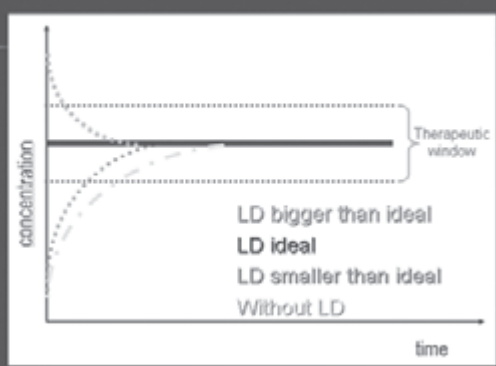
Time	% of *Steady state*
1 t1/2	**50**
2 t1/2	**75**
3 t1/2	**87,5**
3.3 t1/2	**90**
4 t1/2	**95**
6.6 t1/2	**99**

Loading Dose + Maintenance Dose

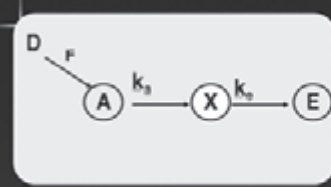


$$MD = k_0 = Cp_{ss} \cdot CL_{tot}$$

Inadequate LD



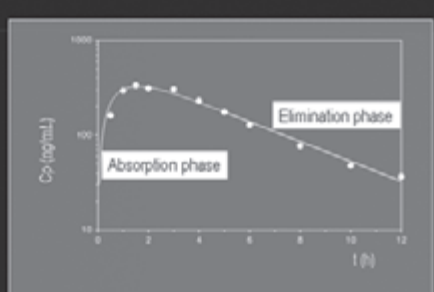
1 compartment with first order absorption



$$\frac{dX}{dt} = k_a \cdot A - k_e \cdot X$$

D	Dose
A	Amount of drug at administration site
X	Amount of drug in the body
E	Amount of drug eliminated

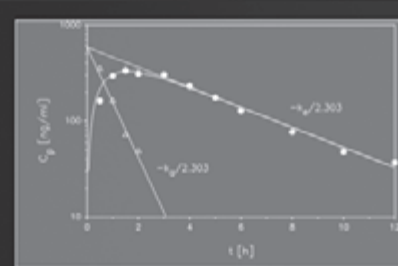
1 compartment with first order absorption



$$C = \frac{f \cdot D \cdot ka}{Vd \cdot (ka - ke)} \cdot \left(e^{-ke \cdot t} - e^{-ka \cdot t}\right)$$

1 compartment with first order absorption

Feathering or stripping



$$C_0' = \frac{F \cdot D \cdot ka}{Vd \cdot (ka - ke)}$$

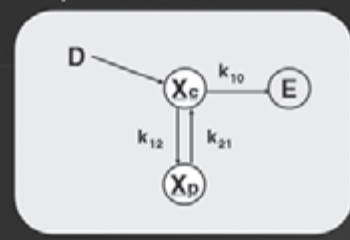
1 compartment with first order absorption

Volume of distribution $Vd = \frac{F \cdot D \cdot ka}{Cp_0' \cdot (k_a - k_e)}$

Clearance $CL_{tot} = \frac{f \cdot D}{AUC_{0-\infty}} = k_e \cdot Vd$

Half-life $t_{1/2} = \frac{0.693}{k_e}$

2 compartment i.v. *bolus* dosing

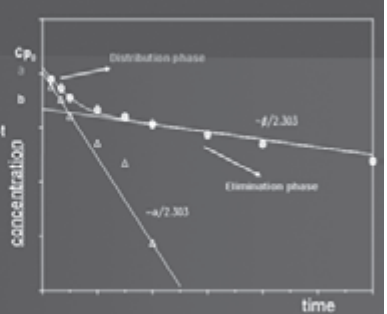


D	Dose
Xc	Amount of drug in the central compartment
Xp	Amount of drug in the peripheral compartment
E	Amount of drug eliminated
k_{12}, k_{21}, k_{10}	micro-constants of distribution and elimination

2 compartment i.v. *bolus* dosing

$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta t}$

$\alpha >> \beta$



A, B, α e β hybrid constants estimated from k_{12}, k_{21} e k_{10}
a e b - intercepts of distribution and elimination phases, respectively
α e β – distribution and elimination rate constants, respectively

Volumes of Distribution

Volume of distribution of the central compartment (Vc)

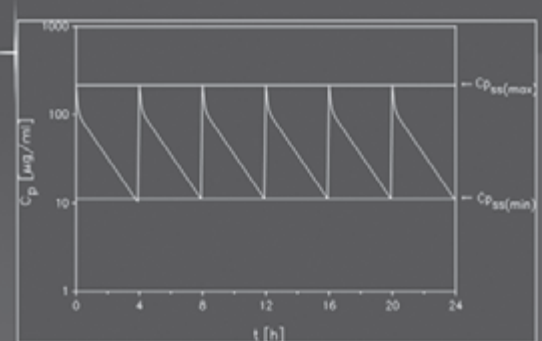
$Vc = \frac{D}{a+b}$ $\quad CL_{tot} = k_{10} \cdot Vc$

Volume de distributions at steady state (Vd_{ss})

$Vd_{ss} = \frac{\left(a \cdot \beta^2 + b \cdot \alpha^2\right)}{(a \cdot \beta + b \cdot \alpha)^2} \cdot D$ $\quad ke = \frac{K_{10} \cdot Vc}{Vd_{ss}}$ $\quad CL_{tot} = ke \cdot Vd_{ss}$

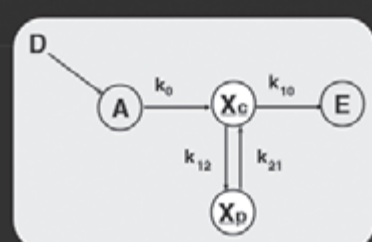
Elimination half-life $t_{1/2}\beta = \frac{0.693}{\beta}$

2 compartment i.v. *bolus* multiple dosing



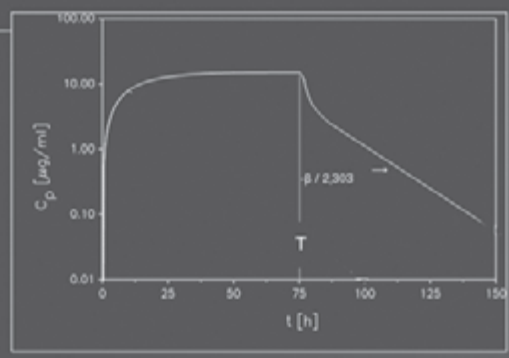
Monitor as 1 compartment if 5 x $t_{1/2}$ α < 20-30 min

2 compartment model - constant infusion



D	Dose
A	Amount of drug in the administration site
Xc	Amount of drun in the central compartment
Xp	Amount of drug in the peripheral compartment
E	Amount of drug eliminated

2 compartment model - constant infusion



2 compartment model - constant infusion

Plasma levels

$$C = \frac{k_0}{V_c} \cdot \left(\frac{\left(1 - e^{\alpha T}\right) \cdot (k_{21} - \alpha)}{\alpha \cdot (\alpha - \beta)} \cdot e^{-\alpha t} + \frac{\left(1 - e^{\beta T}\right) \cdot (k_{21} - \beta)}{\beta \cdot (\beta - \alpha)} \cdot e^{-\beta t} \right)$$

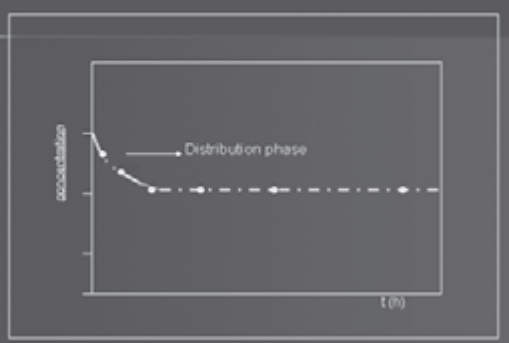
Loading Dose (LD)

$$LD = C_{ss} \cdot Vd_{ss}$$

Infusion rate (k_0)

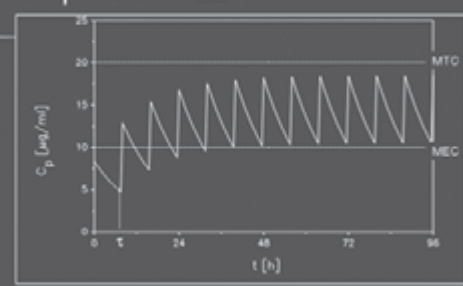
$$k_0 = \frac{C_{ss}}{1 - e^{-\beta \cdot T}}$$

2 compartment - constant infusion with LD



$$LD = C_{ss} \cdot Vd_{ss}$$

Multiple Dose i.v. *bolus*



MEC Minimum effective concentration
MTC Minimum Toxic concentration
τ Dosing interval

Multiple Dose i.v. *bolus*

Accumulation factor (r)

$$r = \frac{1 - e^{-n \cdot ke \cdot \tau}}{1 - e^{-ke \cdot \tau}}$$

r = accumulation factor
n = number of doses

C_{max} e C_{min} after *n* doses

$$C_{n\,max} = \frac{D}{Vd} \cdot r \qquad C_{n\,min} = \frac{D}{Vd} \cdot r \cdot e^{-ke \cdot \tau}$$

Multiple Dose i.v. *bolus*

Accumulation factor at SS (r_∞)

$$r_\infty = \frac{1}{1 - e^{-ke \cdot \tau}}$$

Fluctuation (F)

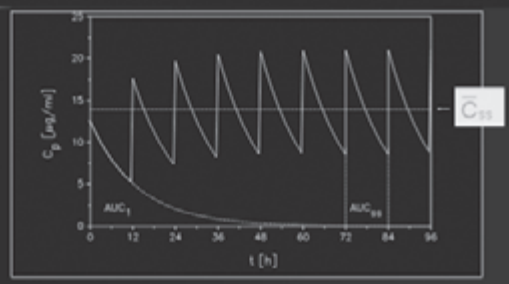
$$F = \frac{Css_{max}}{Css_{min}}$$

Css_{max} and Css_{min}

$$Css_{max} = \frac{D}{Vd \cdot \left(1 - e^{-ke \cdot \tau}\right)}$$

$$Css_{min} = \frac{D \cdot e^{-ke \cdot \tau}}{Vd \cdot \left(1 - e^{-ke \cdot \tau}\right)}$$

Multiple Dose i.v. *bolus*

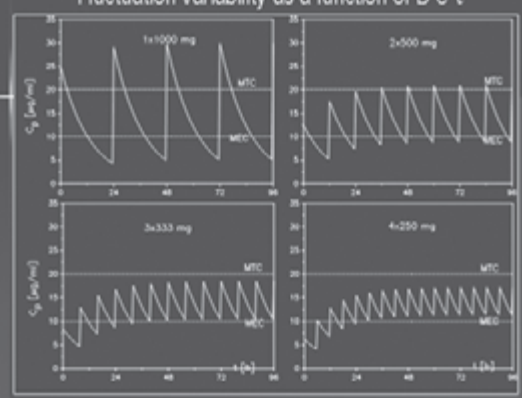


$$\overline{C_{ss}} = \frac{AUC}{\tau} = \frac{D}{CL_{tot} \cdot \tau}$$

Average Steady State Concentration

- It is not the average between Css_{max} and Css_{min}
- Concentration that would be obtained if the dose were given by infusion at steady state
- Gives no idea of fluctuation
- Same $\overline{C_{ss}}$ for different D e t with different fluctuations
- If :
  - CL_{tot} = 1L/h
  - D = 500 mg q6h
  - D = 250 mg q3h
  - Same $\overline{C_{ss}}$ fluctuation in the second regimen is half of the flutuation in the first regimen

Fluctuation variability as a function of D e τ



The bigger the number of doses administered daily, for the same total daily dose, the smaller the fluctuation

Dosing Regimen Determination

Dosing interval (τ)

$$\tau = \frac{\ln F}{ke}$$

$\tau = t_{1/2}$ ——— $F = 2$

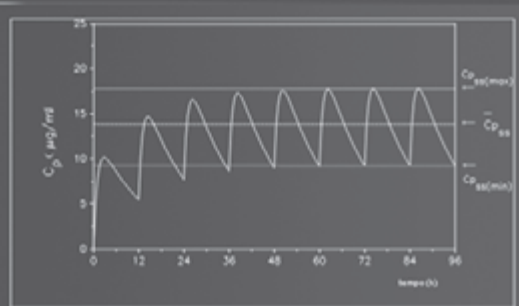
$\tau < t_{1/2}$ ——— $F < 2$

$\tau > t_{1/2}$ ——— $F > 2$

Choose τ smaller than calculated to fit q4h, q6h, q8h, q12h, q24h

Loading Dose (LD)	Maintenance Dose (MD)
$LD = Css_{max} \cdot Vd$	$MD = \overline{C_{ss}} \cdot CL_{tot} \cdot \tau$

Multiple Dose Oral Administration



Multiple Dose Oral Administration

$$C_n = \frac{f \cdot D \cdot ka}{Vd \cdot (ka - ke)} \cdot \left(re \cdot e^{-ke \cdot t} - ra \cdot e^{-ka \cdot t}\right)$$

Elimination Accumulation Factor (re)

$$re = \frac{1 - e^{-n\,ke\,t}}{1 - e^{-ke \cdot \tau}}$$

Absorption Accumulation Factor (ra)

$$ra = \frac{1 - e^{-n\,ke\,\tau}}{1 - e^{-ka\,t}}$$

Multiple Dose Oral Administration

Plasma levels at steady state (C_{ss})

$$C_{ss} = \frac{f \cdot D \cdot ka}{Vd \cdot (ka - ke)} \cdot \left(\frac{e^{-ke \cdot t}}{1 - e^{-ke \cdot \tau}} - \frac{e^{-ka \cdot t}}{1 - e^{-ka \cdot \tau}} \right)$$

Average plasma level at steady state $\overline{C_{ss}}$

$$\overline{C_{ss}} = \frac{f \cdot D}{CL_{tot} \cdot \tau}$$

Dosing Regimen Determination

Dosing interval (τ)

$$\tau = \frac{\ln F}{ke}$$

Maintenance Dose (MD)

$$MD = \frac{\overline{C_{ss}} \cdot CL_{tot} \cdot \tau}{f}$$

Loading Dose (LD)

$$LD = \frac{MD}{\left(1 - e^{-ke \cdot \tau}\right) \cdot \left(1 - e^{-ka \cdot \tau}\right)}$$

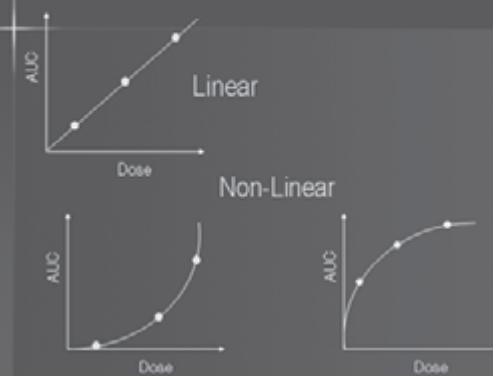
Time to Steady State

% SS	Tempo
90	3.3 t1/2
95	4.3 t1/2
99	6.6 t1/2

Number of doses to reach *steady state* (n_{ss})

$$n_{ss} = \frac{6.6 \cdot t1/2}{\tau}$$

Non-Linear Pharmacokinetics



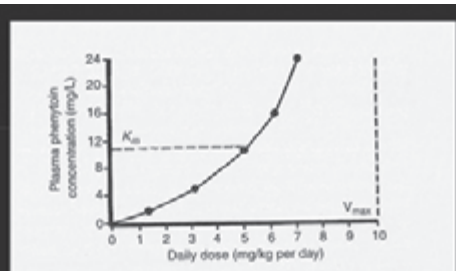


Figure 20-3 In an individual patient, the plasma phenytoin concentration at steady state increases disproportionately with an increase in the rate of administration. Note that the concentration required to achieve a steady-state concentration of 20 mg/L in this subject is not much greater than that required to achieve 10 mg/L. Most patients obtain the therapeutic response without undue adverse events when their plasma concentration is within this window. (Adapted from data from Martin E, Tozer TN, Sheiner LB, Riegelman S. The clinical pharmacokinetics of phenytoin. J Pharmacokinet Biopharm 1977;5:579–596.)

Plasma Concentrations

LINEAR PK

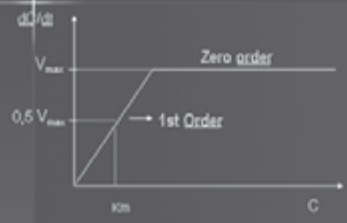
NON-LINEAR PK

$$-\frac{dC}{dt} = k \cdot C$$

APPARENT ELIMINATION RATE

$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{(K_m + C)}$$

Michaelis-Menten Plot



$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{(K_m + C)}$$

V_{max} = maximum elimination rate (concentration/time = µg/mL/h)

Km = *Michaelis* constant (concentration = µg/mL)

Linear *vs.* Non-Linear PK

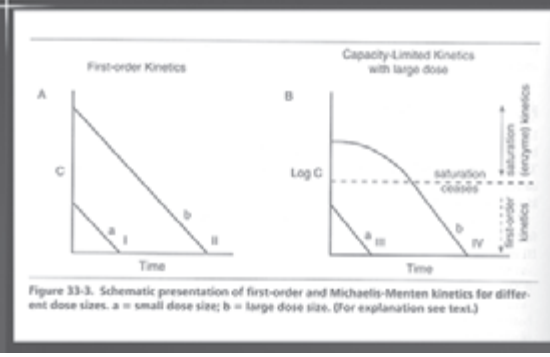


Figure 33-3. Schematic presentation of first-order and Michaelis-Menten kinetics for different dose sizes. a = small dose size; b = large dose size. (For explanation see text.)

Non-Linear Pharmacokinetics
Total Clearance

$$CL_{tot} = \frac{V_{max} \cdot Vd}{(K_m + C)}$$

Low concentrations	High concentrations
Km >> Cp	Km << Cp
$CL_{tot} = \frac{V_{max} \cdot Vd}{K_m}$	$CL_{tot} = \frac{V_{max} \cdot Vd}{C}$

Non-Linear Pharmacokinetics
Half-life

$$t_{1/2} = \frac{0.693 \cdot (Km + C)}{V_{max}}$$

Low concentrations	High concentrations
Km >> Cp	Km << Cp
$t_{1/2} = \frac{0.693 \cdot K_m}{V_{max}}$	$t_{1/2} = \frac{0.693 \cdot C}{V_{max}}$

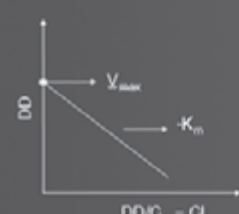
Non-Linear Pharmacokinetics
AUC

$$AUC_{\infty} = \frac{D}{V_{max} \cdot Vd} \cdot \left(K_m + \frac{D}{2Vd}\right)$$

Low concentrations	High concentrations
Km >> D/2Vd	Km << D/2Vd
$ASC_{\infty} = \frac{D \cdot K_m}{V_{max} \cdot Vd}$	$ASC_{\infty} = \frac{D^2}{V_{max} \cdot 2 \cdot Vd^2}$

Non-Linear Pharmacokinetics
Daily Dose (DD)

Steady state ⟹ **Input rate = output rate**

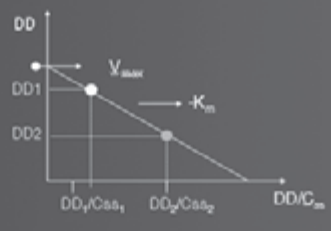


$$DD \rightarrow -\frac{dC}{dt} = \frac{V_{max} \cdot C_{ss}}{(K_m + C_{ss})}$$

$$DD = -k_m \cdot \left(\frac{DD}{C_{ss}}\right) + V_{max}$$

Non-Linear Pharmacokinetics
Dose Adjustment by Daily Dose (DD)

Patient Titration $\begin{cases} DD_1 \rightarrow C_{ss}1 \\ DD_2 \rightarrow C_{ss}2 \end{cases}$



Linear *vs.* Non-Linear PK

- **Linear**
  - Parameters are constant: CL, Vd, k_e, t½ and dose independent
  - Doubling dose, doubles: plasma concentration (C, C_{ss}) and AUC
- **Non-Linear**
  - Parameters are dose dependent (CL, t½, Vd)
  - Zero order elimination constant is constant
  - Doubling dose produces a disproportional increase in plasma concentrations (C, C_{ss}) and AUC

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- ROWLAND, M; TOZER, TN. Clinical Pharmacokinetics – Concepts and Applications 3.ed. Philadelphia: Lippincott William & Wilkins, 1995
- BURTON, ME; SHAW, LM; SCHENTAG, JJ; EVANS, WE. Applied Pharmacokinetics & Pharmacodynamics. Principles of Therapeutic drug Monitoring. 4.ed. Philadelphia: Lippincott William & Wilkins, 2006

Thank you!

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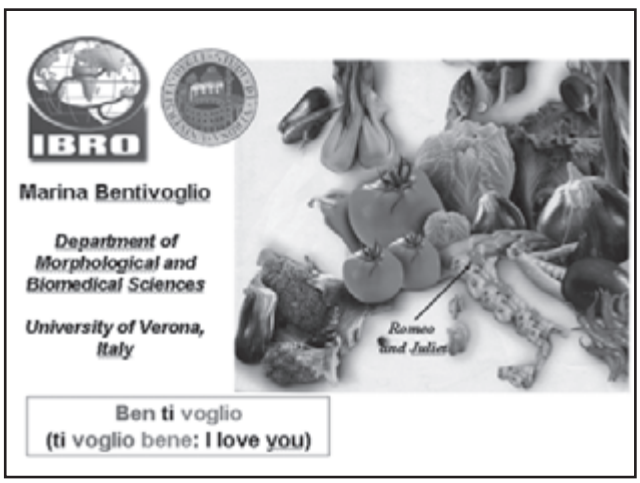
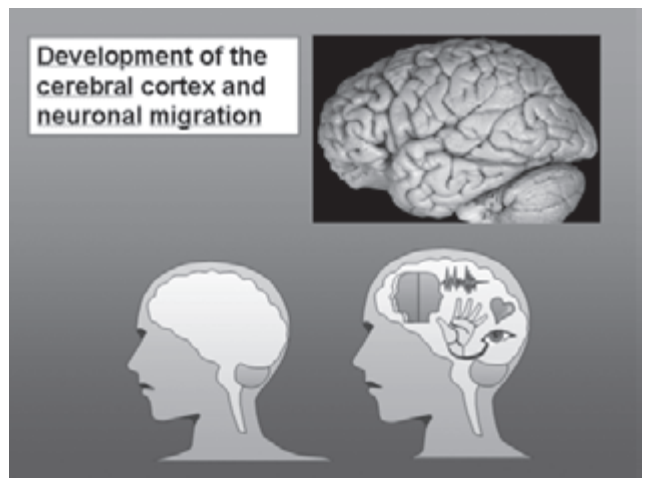
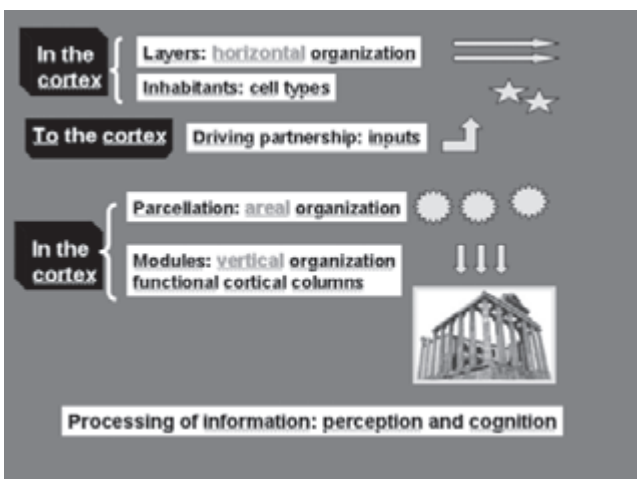
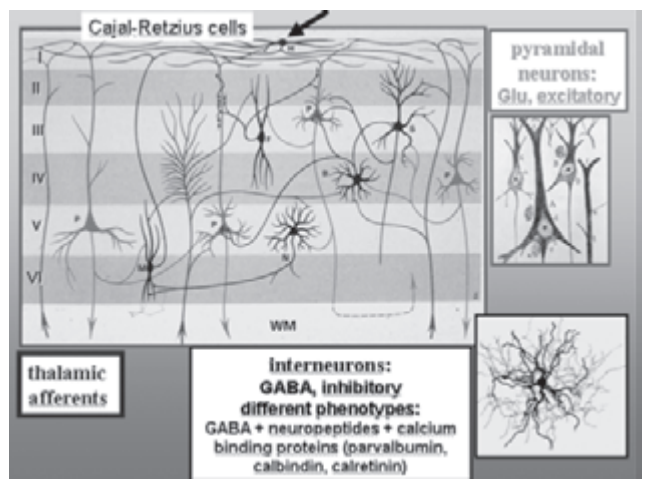
Development of the cerebral cortex and neural migration

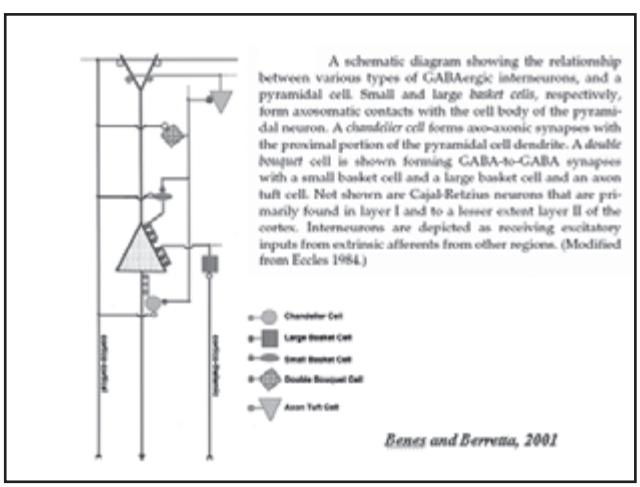
Marina Bentivoglio (Italy)

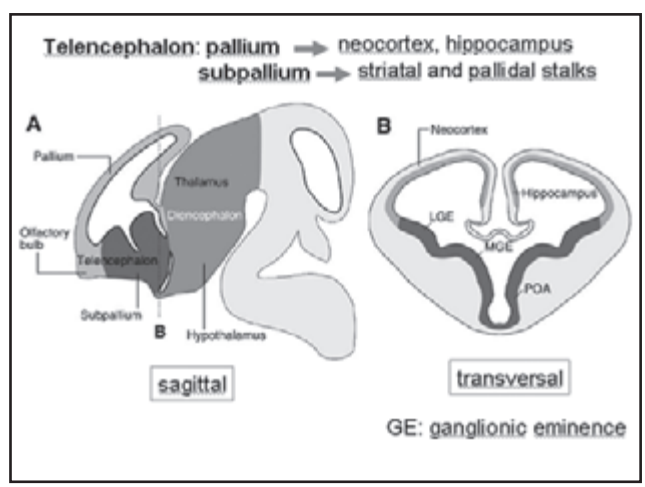












Corticogenesis

Three major, sequential but partially overlapping, processes:

3) Cell differentiation

2) Migration of neuroblasts

1) Proliferation of undifferentiated cells in the neuroepithelium

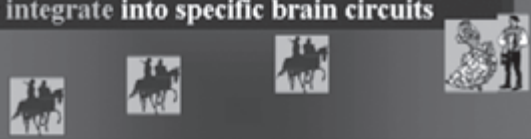
- Perturbation of any of these processes, as a result of a genetic defect or noxious environmental influence, can result in malformations of cortical development (MCD)
- MCD are associated with neurological deficits, cognitive impairment and epilepsy

- 8-12% of cases of intractable epilepsy are associated with MCD
- 14-26% of surgically treated cases of paediatric epilepsy have MCD

All neurons of the CNS are gipsies for some time of their career

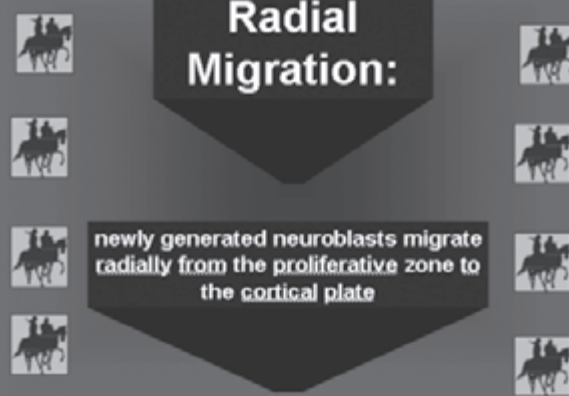
G. Edelman

Most neurons migrate from the site of their last mitotic division, near the ventricle, towards the outer surface of the CNS, where they integrate into specific brain circuits



Cell migration is a fundamental process in CNS development because both neuronal and non-neuronal cells are generated in sites that differ from those in which they eventually reside

Radial Migration:

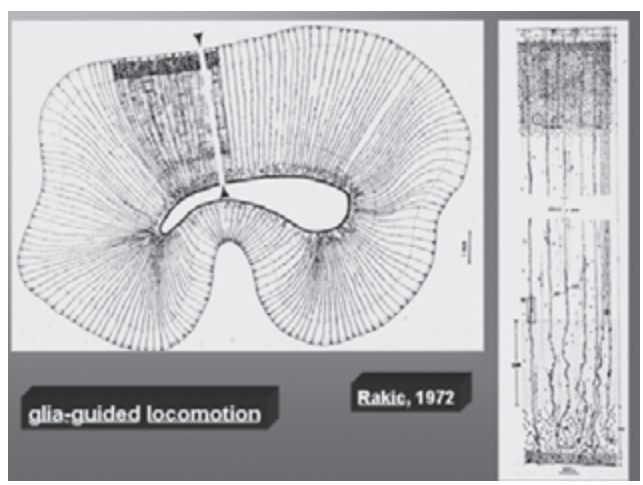


newly generated neuroblasts migrate radially from the proliferative zone to the cortical plate

Radial soma translocation

Cells with a long process terminating at the pial surface and a short trailing process

- During early stages of corticogenesis
- Direction predetermined by the pia connected process
- Migratory behavior distinct from glia-guided locomotion (movement relatively continuous)

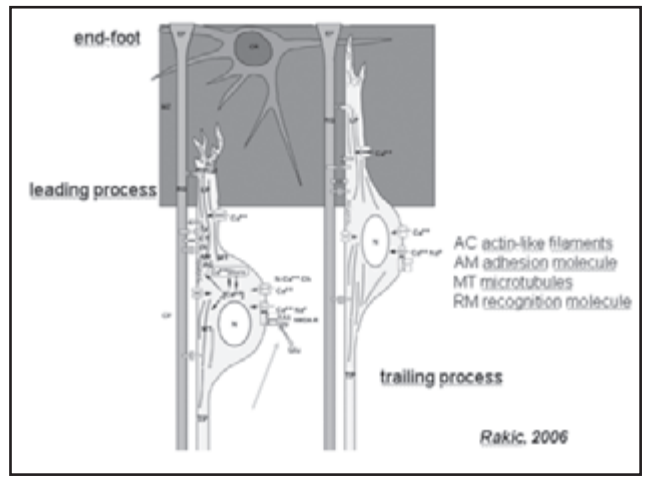


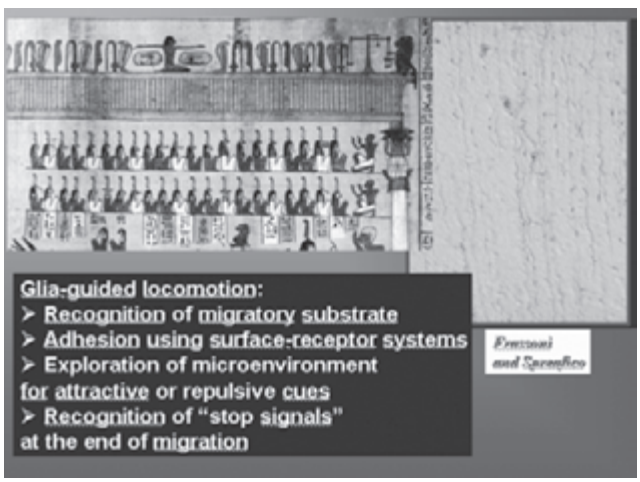
glia-guided locomotion

Rakic, 1972

In the telencephalon, radial migration is recognized as the primary mechanism by which developing neurons reach their final position

As the cortex thickens, radial migration is largely dependent on the interactions of migrating neurons with radial glial fibers



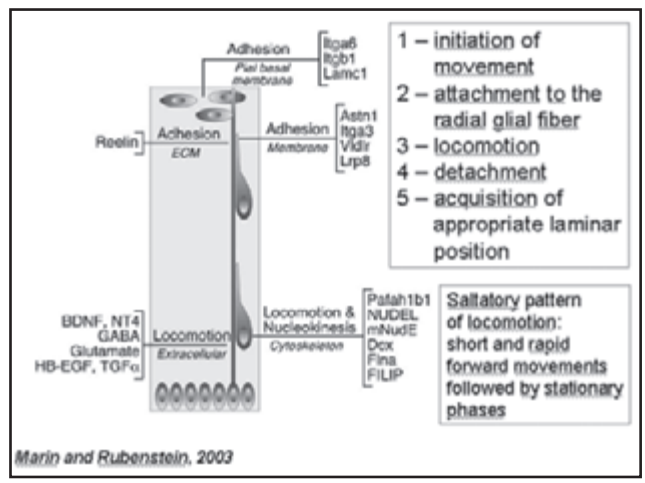


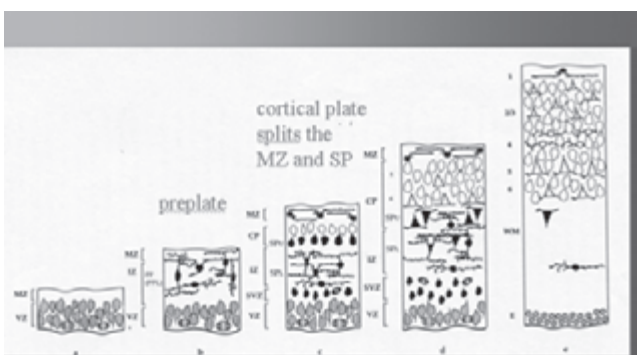
Glia-guided locomotion:
- Recognition of migratory substrate
- Adhesion using surface-receptor systems
- Exploration of microenvironment

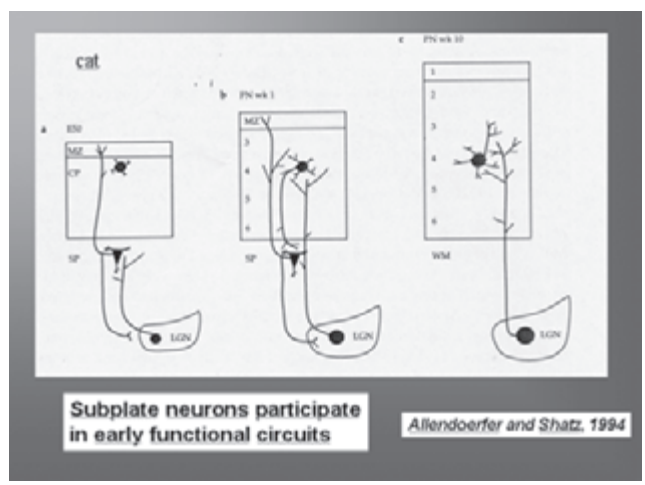
for attractive or repulsive cues
- Recognition of "stop signals"

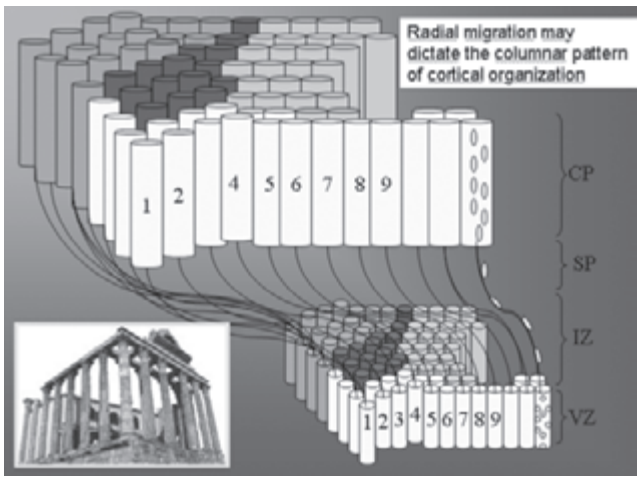
at the end of migration

Ferrari and Spreafico



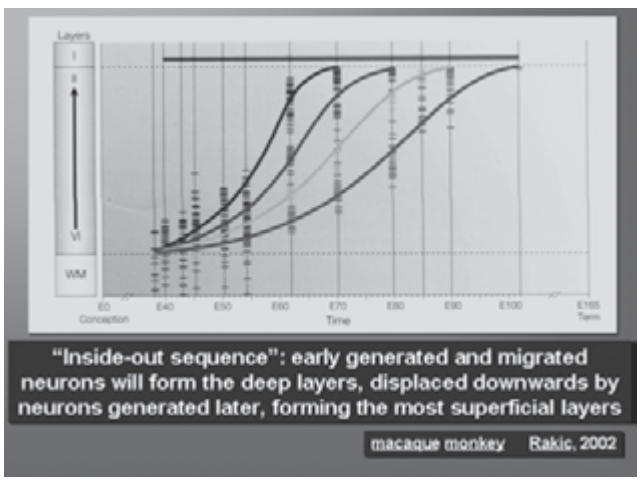






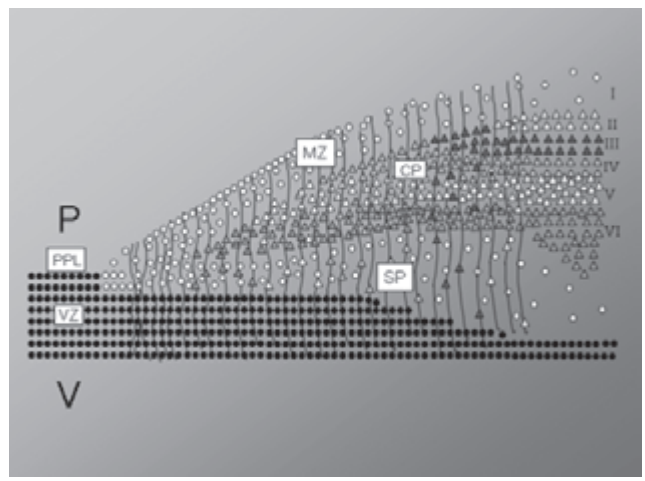
There is a progressive restriction of cell fate in the precursor population:

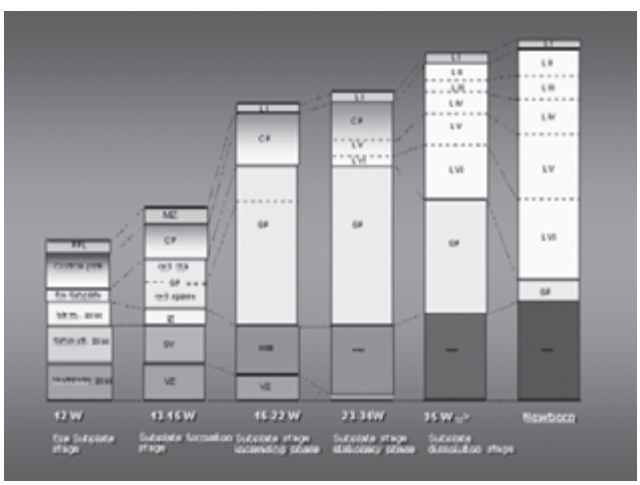
- early progenitors are pluripotent and might give rise to neurons that come to reside in any cortical layer
- later progenitors give rise only to neurons of more superficial layers

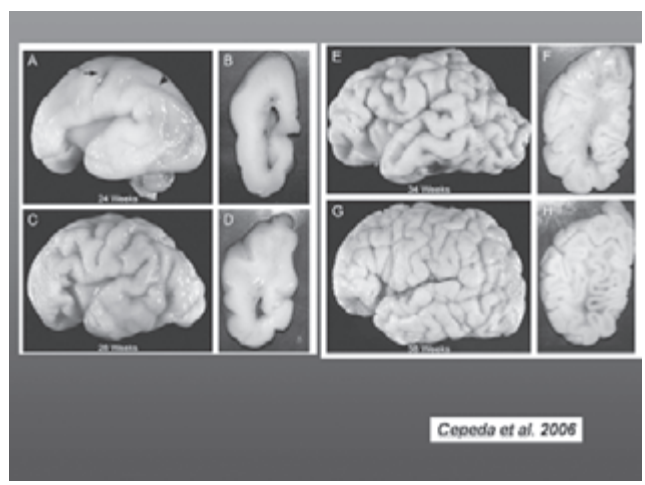


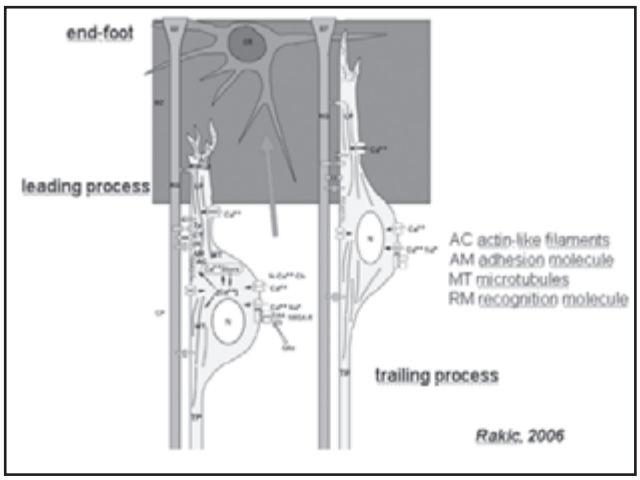
"Inside-out sequence": early generated and migrated neurons will form the deep layers, displaced downwards by neurons generated later, forming the most superficial layers

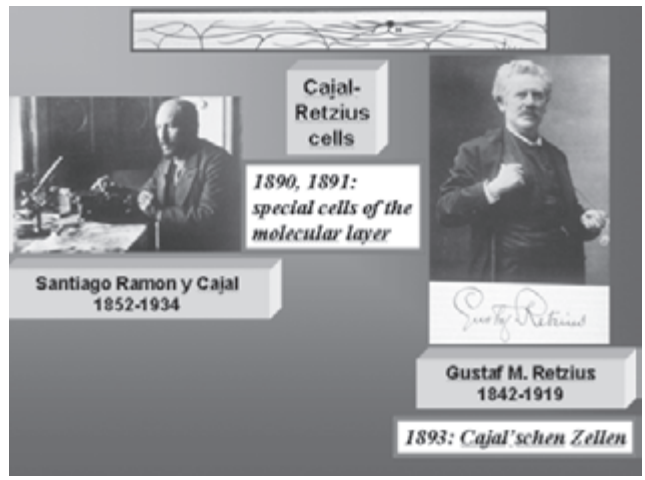
macaque monkey Rakic, 2002

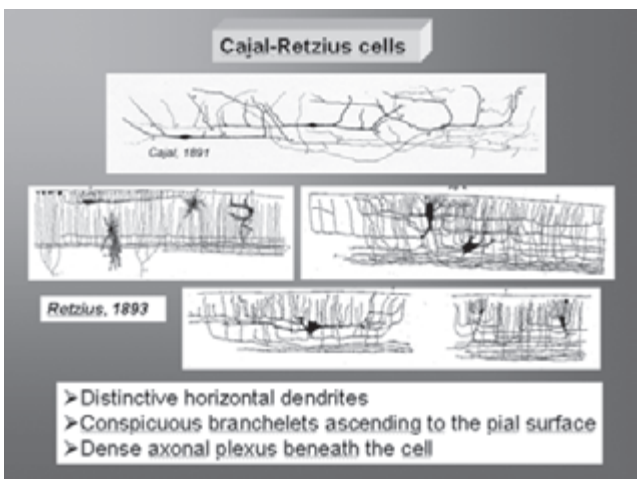


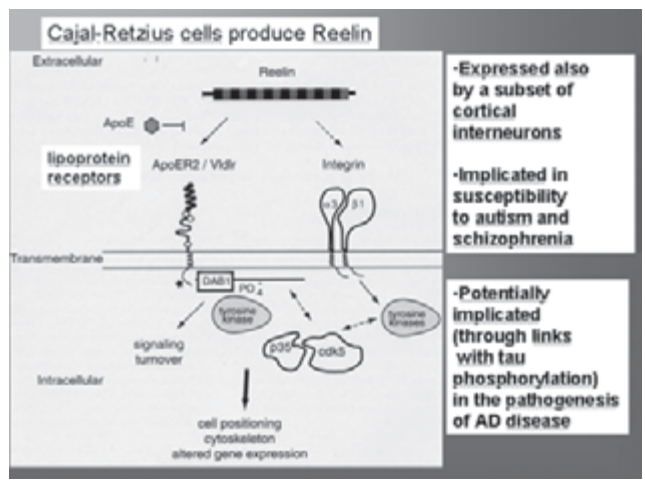


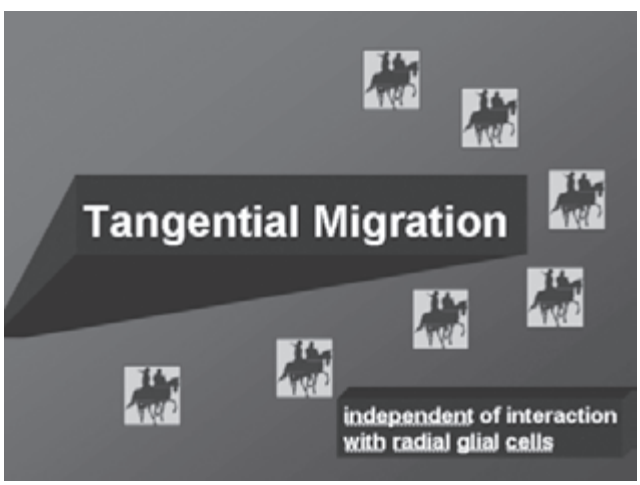


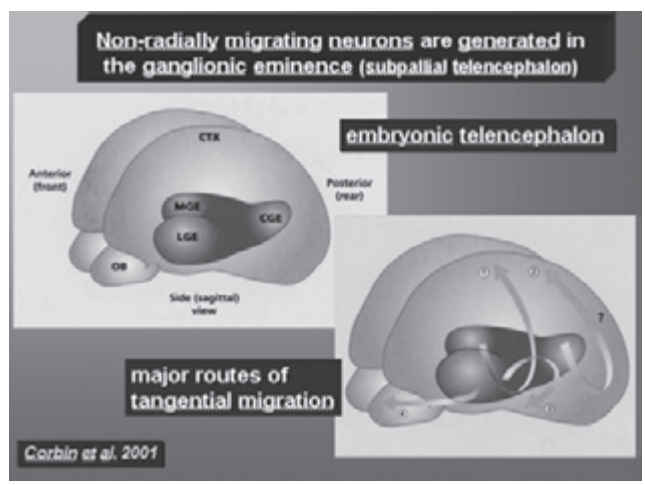

end-foot
leading process
AC actin-like filaments
AM adhesion molecule
MT microtubules
RM recognition molecule
trailing process
Rakic, 2006

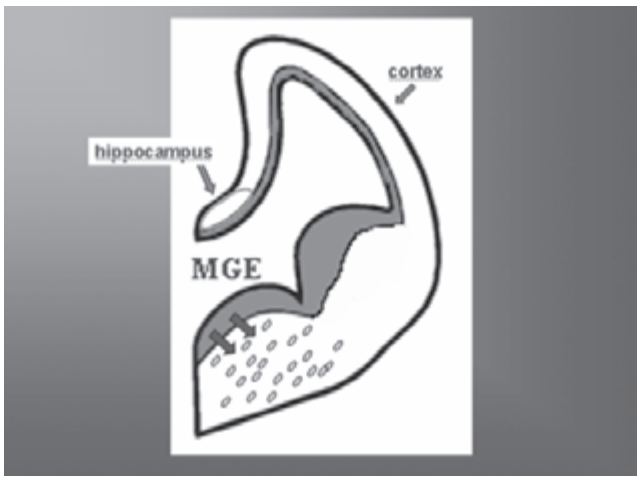

Cajal-Retzius cells
1890, 1891: special cells of the molecular layer
Santiago Ramon y Cajal
1852-1934
Gustaf M. Retzius
1842-1919
1893: Cajal'schen Zellen

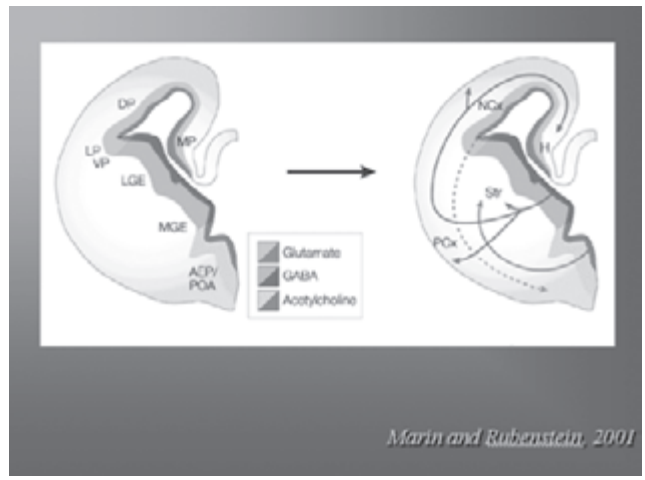

Cajal-Retzius cells
Cajal, 1891
Retzius, 1893
➢Distinctive horizontal dendrites
➢Conspicuous branchelets ascending to the pial surface
➢Dense axonal plexus beneath the cell

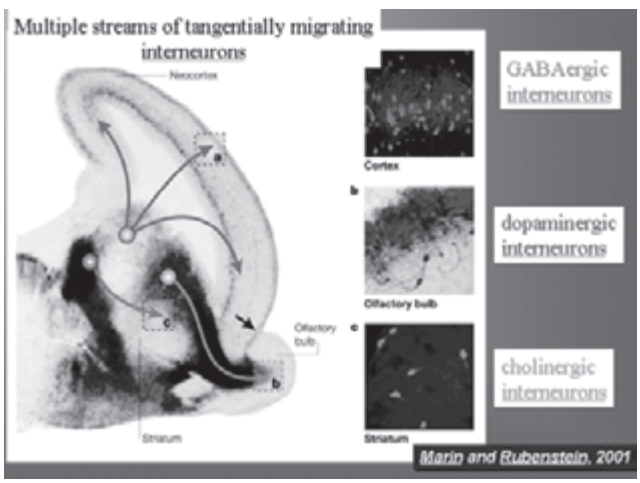

Cajal-Retzius cells produce Reelin
Extracellular
Reelin
ApoE
lipoprotein receptors
ApoER2 / VldlR
Integrin
Transmembrane
DAB1
signaling turnover
p35
cdk5
Intracellular
cell positioning
cytoskeleton
altered gene expression
·Expressed also by a subset of cortical interneurons
·Implicated in susceptibility to autism and schizophrenia
·Potentially implicated (through links with tau phosphorylation) in the pathogenesis of AD disease

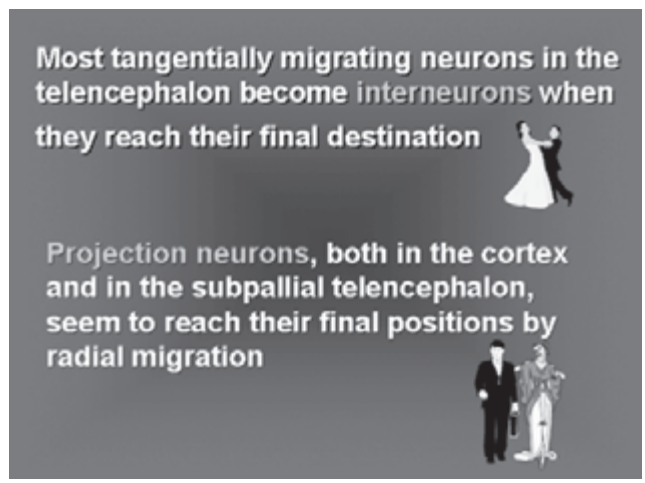

Tangential Migration
independent of interaction with radial glial cells

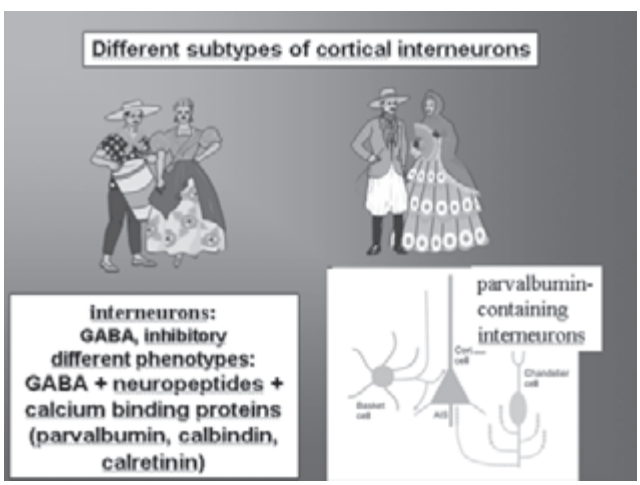

Non-radially migrating neurons are generated in the ganglionic eminence (subpallial telencephalon)
embryonic telencephalon
CTX
MGE
CGE
LGE
OB
Anterior (front)
Posterior (rear)
Side (sagittal) view
major routes of tangential migration
Corbin et al. 2001

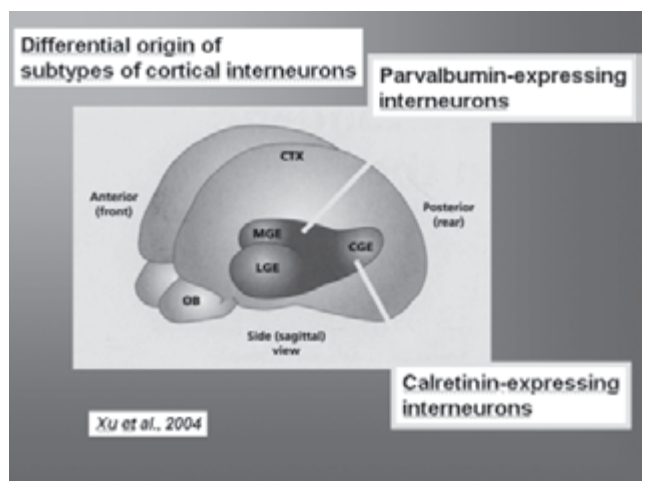

cortex
hippocampus
MGE

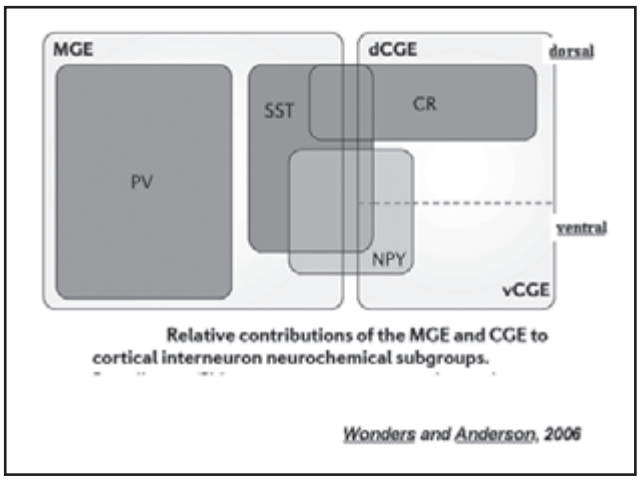

Dp
LP
VP
MP
LGE
MGE
ADP
POA
Glutamate
GABA
Acetylcholine
NCx
H
Str
PCx
Marin and Rubenstein, 2001


Multiple streams of tangentially migrating interneurons
Neocortex
Olfactory bulb
Striatum
Cortex
Olfactory bulb
Striatum
GABAergic interneurons
dopaminergic interneurons
cholinergic interneurons
Marin and Rubenstein, 2001


Most tangentially migrating neurons in the telencephalon become interneurons when they reach their final destination
Projection neurons, both in the cortex and in the subpallial telencephalon, seem to reach their final positions by radial migration

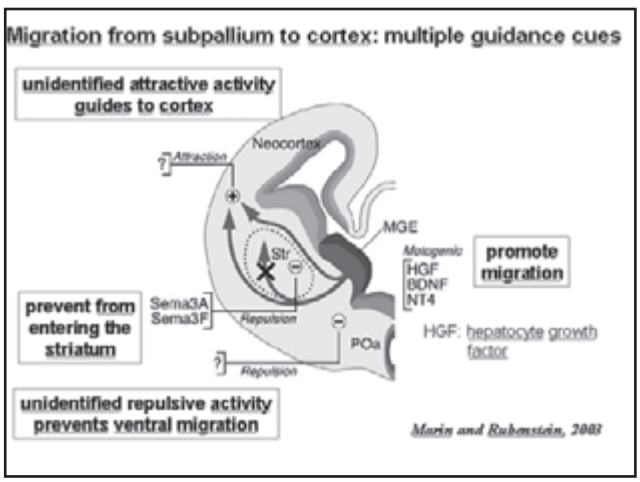

Different subtypes of cortical interneurons
interneurons:
GABA, inhibitory
different phenotypes:
GABA + neuropeptides +
calcium binding proteins
(parvalbumin, calbindin,
calretinin)
parvalbumin-containing interneurons

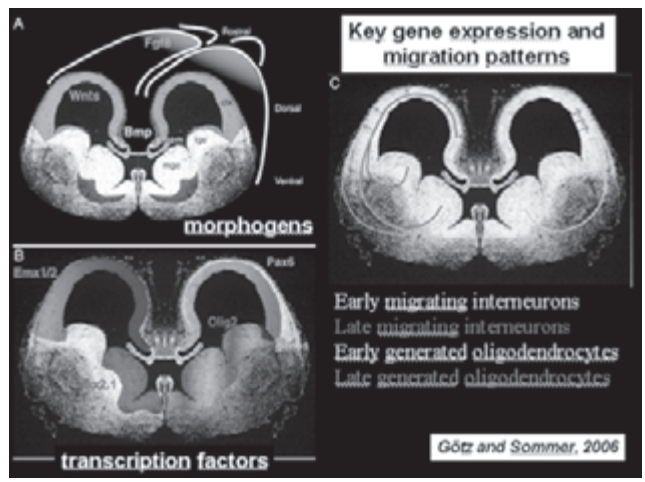

Differential origin of subtypes of cortical interneurons
Parvalbumin-expressing interneurons
CTX
Anterior (front)
Posterior (rear)
MGE
CGE
LGE
OB
Side (sagittal) view
Calretinin-expressing interneurons
Xu et al., 2004

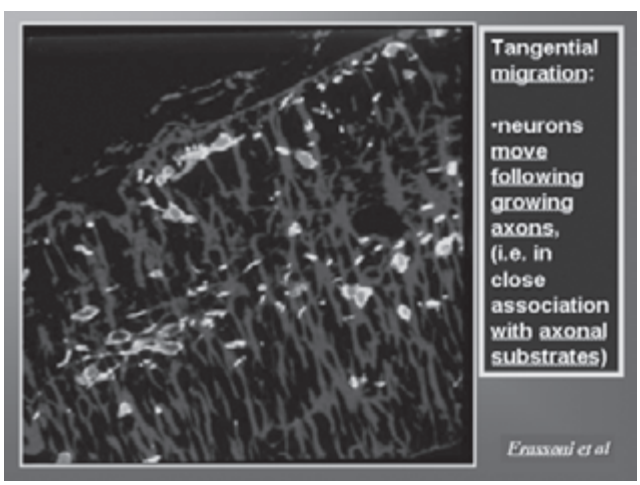


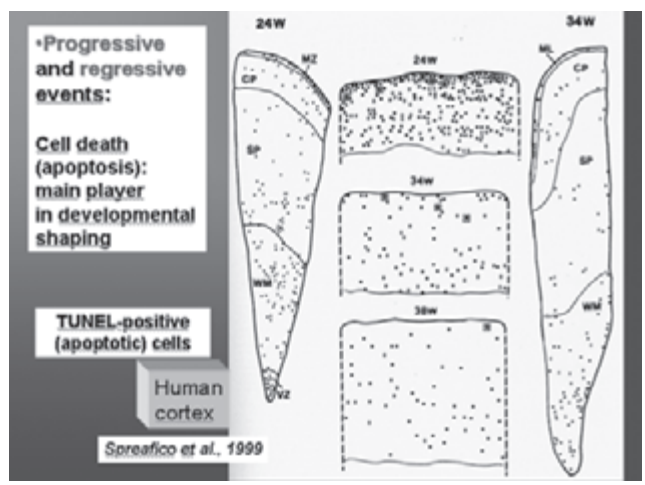
A variety of guidance systems is needed to direct the diverse migrations. Once a cell has been specified to take a tangential migratory course, at least three types of factors can regulate this process:

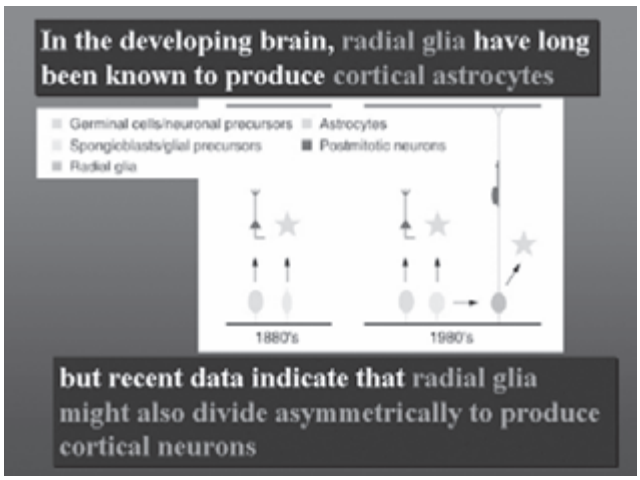
1) Motogenic factors (that stimulate the cell movement)
2) Extracellular substrates for migration
3) Guidance factors (guiding different migratory streams through appropriate pathways towards their targets)

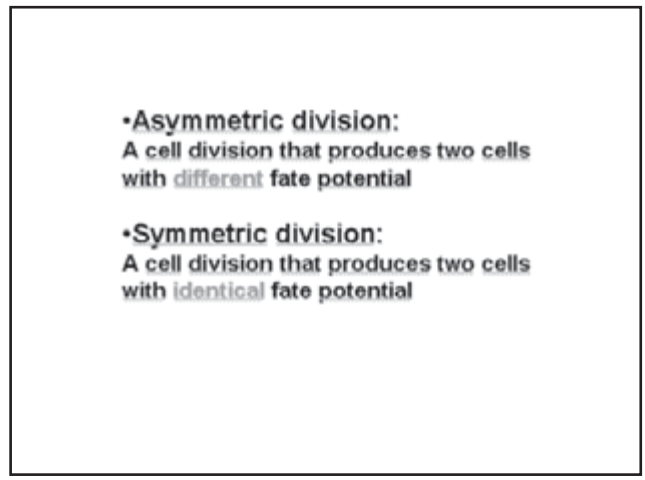


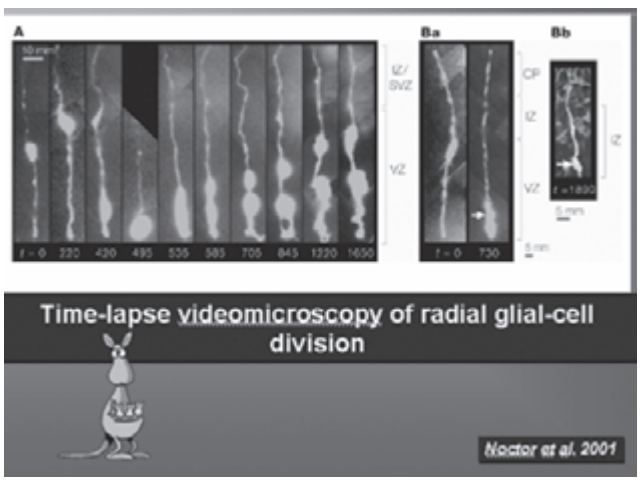


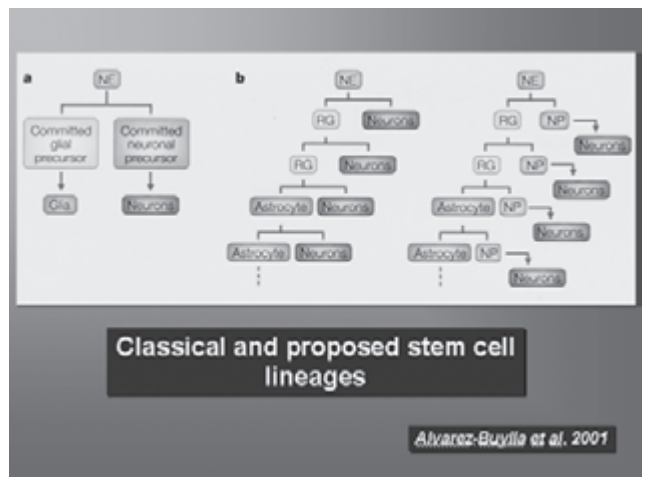


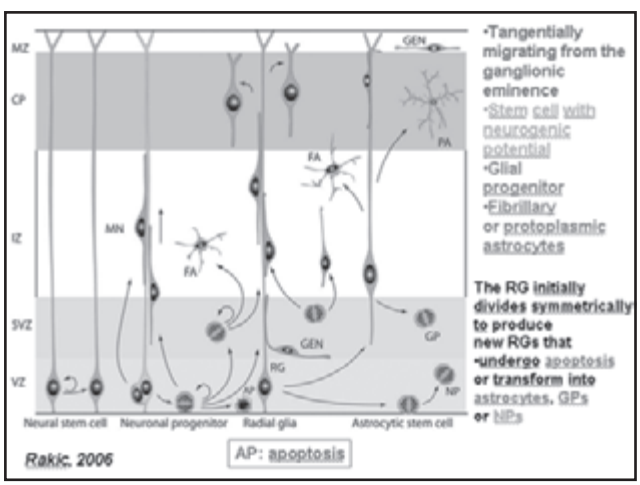


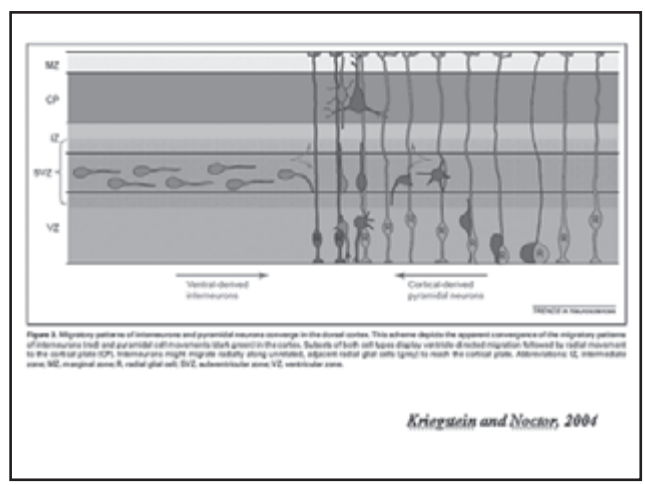

In the developing brain, radial glia have long been known to produce cortical astrocytes
Germinal cells/neuronal precursors
Spongioblasts/glial precursors
Radial glia
Astrocytes
Postmitotic neurons
1880's
1980's
but recent data indicate that radial glia might also divide asymmetrically to produce cortical neurons

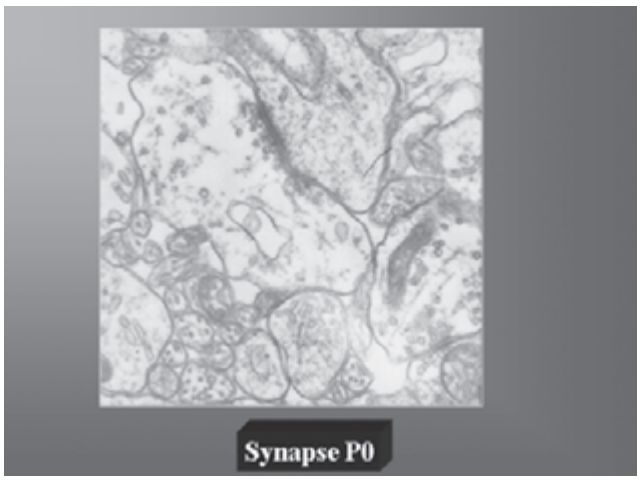

•Asymmetric division:
A cell division that produces two cells with different fate potential
•Symmetric division:
A cell division that produces two cells with identical fate potential

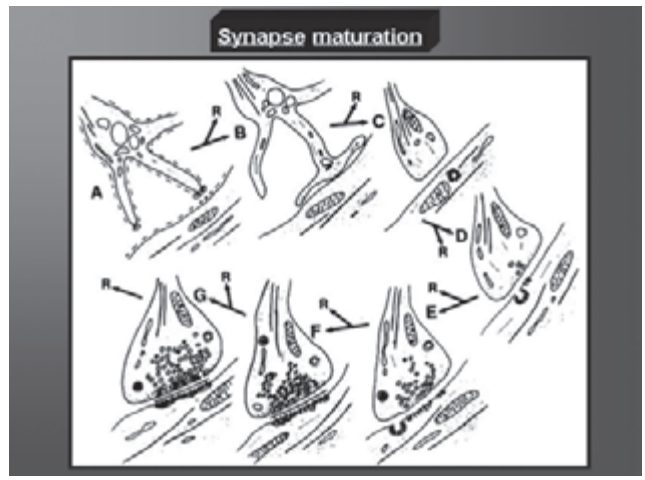

A
Ba
Bb
IZ/SVZ
VZ
CP
IZ
VZ
Time-lapse videomicroscopy of radial glial-cell division
Noctor et al. 2001

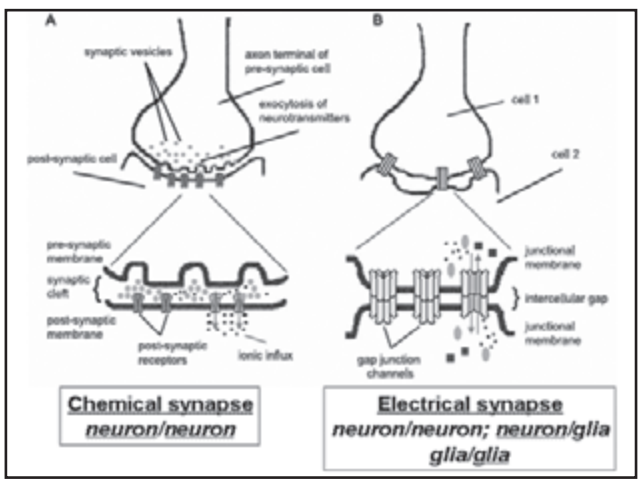

a
b
NE
Committed glial precursor
Committed neuronal precursor
Glia
Neurons
RG
NP
Astrocyte
Classical and proposed stem cell lineages
Alvarez-Buylla et al. 2001

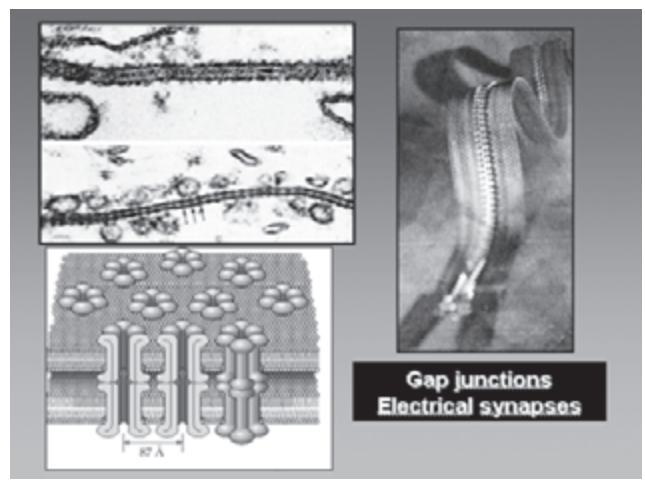

MZ
CP
IZ
SVZ
VZ
GEN
PA
FA
MN
GP
RG
NP
Neural stem cell
Neuronal progenitor
Radial glia
Astrocytic stem cell
Rakic, 2006
AP: apoptosis
•Tangentially migrating from the ganglionic eminence
•Stem cell with neurogenic potential
•Glial progenitor
•Fibrillary or protoplasmic astrocytes
The RG initially divides symmetrically to produce new RGs that
•undergo apoptosis or transform into astrocytes, GPs or NPs

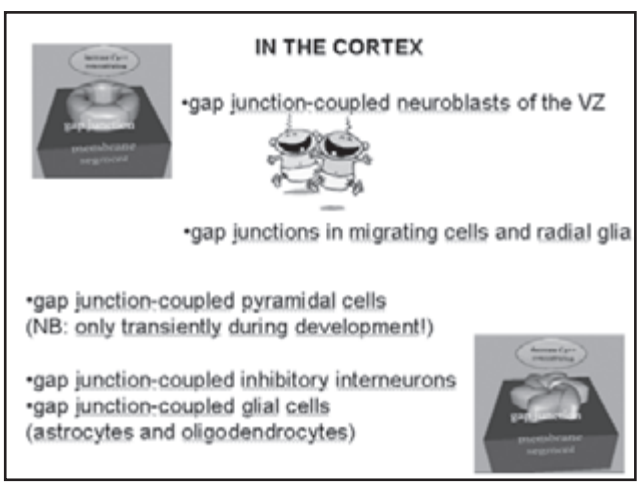

MZ
CP
IZ
SVZ
VZ
Ventral-derived interneurons
Cortical-derived pyramidal neurons
Kriegstein and Noctor, 2004

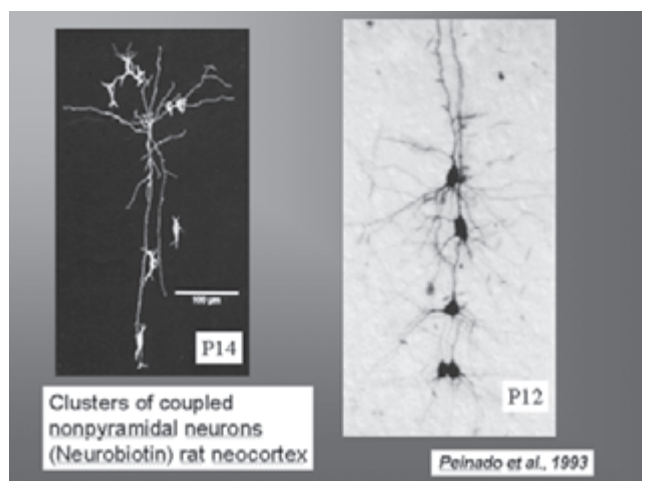

Synapse P0

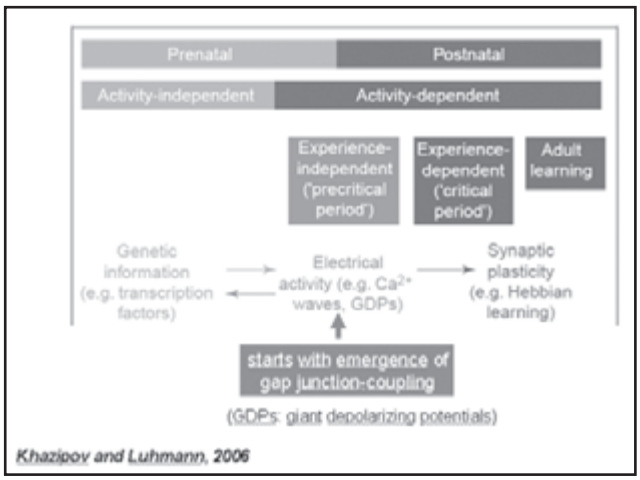

Synapse maturation
A
B
C
D
E
F
G
R

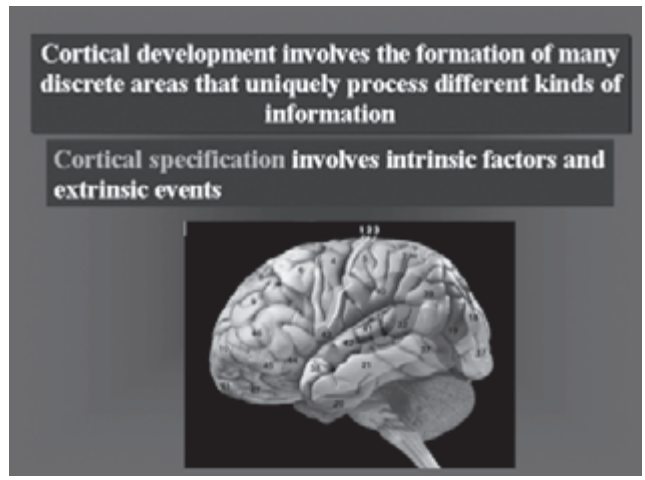

A
B
synaptic vesicles
axon terminal of pre-synaptic cell
exocytosis of neurotransmitters
post-synaptic cell
cell 1
cell 2
pre-synaptic membrane
synaptic cleft
post-synaptic membrane
post-synaptic receptors
ionic influx
junctional membrane
intercellular gap
junctional membrane
gap junction channels
Chemical synapse
neuron/neuron
Electrical synapse
neuron/neuron; neuron/glia
glia/glia

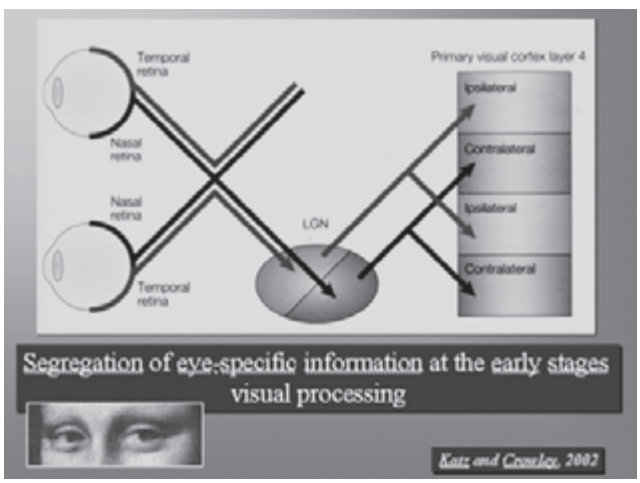

Gap junctions
Electrical synapses

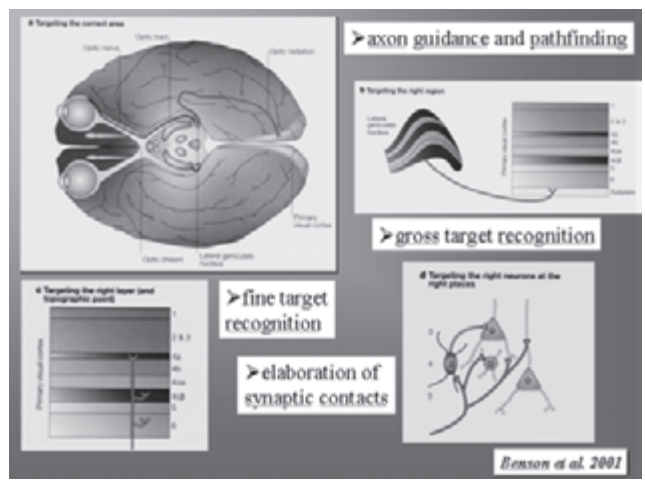

IN THE CORTEX
•gap junction-coupled neuroblasts of the VZ
•gap junctions in migrating cells and radial glia
•gap junction-coupled pyramidal cells
(NB: only transiently during development!)
•gap junction-coupled inhibitory interneurons
•gap junction-coupled glial cells
(astrocytes and oligodendrocytes)

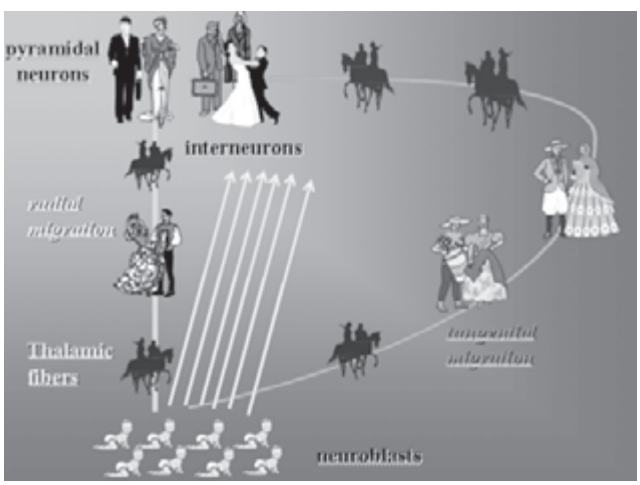

P14
P12
Clusters of coupled
nonpyramidal neurons
(Neurobiotin) rat neocortex
Peinado et al., 1993

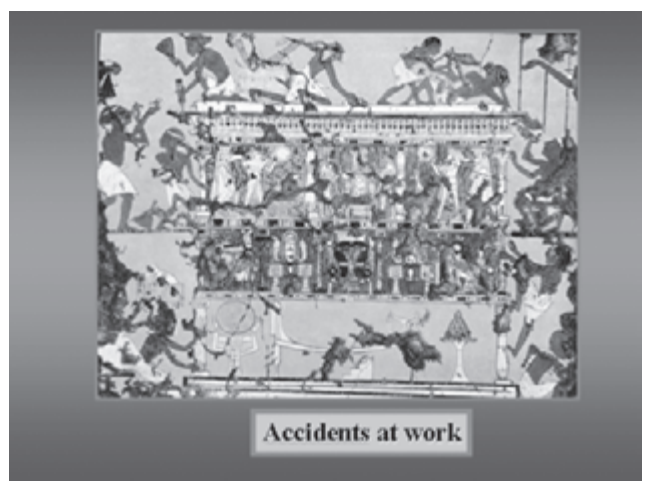

Prenatal
Postnatal
Activity-independent
Activity-dependent
Experience-independent ("precritical period")
Experience-dependent ("critical period")
Adult learning
Genetic information (e.g. transcription factors)
Electrical activity (e.g. Ca^{2+} waves, GDPs)
Synaptic plasticity (e.g. Hebbian learning)
starts with emergence of gap junction-coupling
(GDPs: giant depolarizing potentials)
Khazipov and Luhmann, 2006

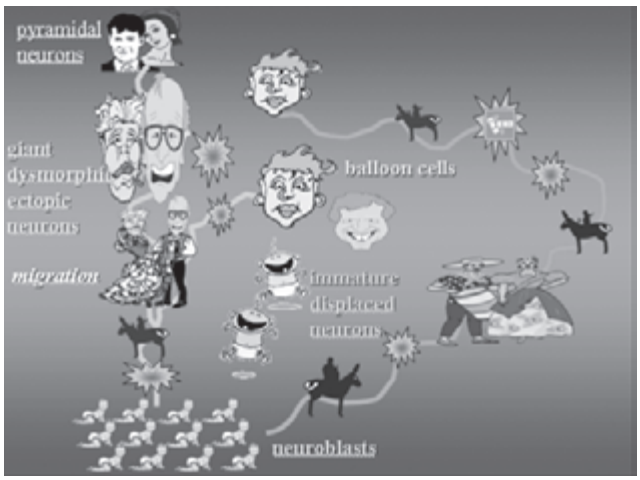

Cortical development involves the formation of many discrete areas that uniquely process different kinds of information
Cortical specification involves intrinsic factors and extrinsic events


Temporal retina
Nasal retina
Nasal retina
Temporal retina
LGN
Primary visual cortex layer 4
Ipsilateral
Contralateral
Ipsilateral
Contralateral
Segregation of eye-specific information at the early stages visual processing
Katz and Crowley, 2002


➢axon guidance and pathfinding
➢gross target recognition
➢fine target recognition
➢elaboration of synaptic contacts
Benson et al. 2001


pyramidal neurons
interneurons
radial migration
Thalamic fibers
tangential migration
neuroblasts


Accidents at work


pyramidal
neurons
giant
dysmorphic
ectopic
neurons
balloon cells
migration
immature
displaced
neurons
neuroblasts


Obrigada!!!
Grazie!!!
Thank you!!!

Epilepsies related to cortical developmental malformations

Alejandro Scaramelli (Uruguay)

Programa – 10.02.2008

Morning session – 9:00 – 13:00

- Mechanism of actions of AEDs - G. Avanzini (Italy)
- Pharmacokinetics of AEDs - M. Bialer (Israel)
- Drug interactions in epilepsy - E Perucca (Italy)

Afternoon session – 14:30-18:30

- Clinical drug development - E. Perucca (Italy)
- Evidence-based therapy? Clinical trials vs clinical practice -T. Tomson (Sweden)
- Journal club - G. Avanzini/E Perucca/T Tomson/ M. Bialer

Mechanism of actions of AEDs

G. Avanzini (Italy)

Pharmacokinetics of AEDs

Meir Bialer (Israel)

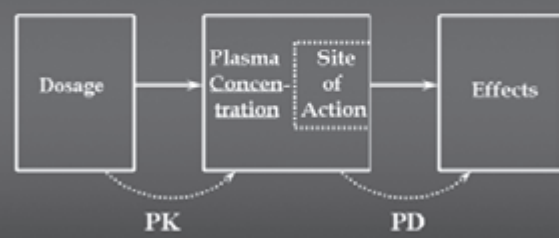
Pharmacokinetics (PK) of Antiepileptic Drugs (AEDs)

Prof. Meir Bialer
Hebrew University
Jerusalem, Israel

Latin-American Summer School on Epilepsy (LASSE II)
February 7-16, 2008, Sao Paulo, Brazil

1

Pharmacokinetics (PK) & Pharmacodynamics (PD)



Rowland & Tozer, *Clinical Pharmacokinetics*, 1995

2

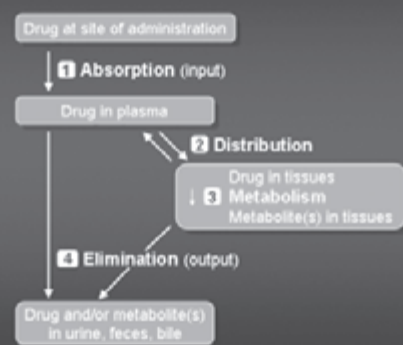
Time Course of Drugs in the Body (ADME)

Absorption
Distribution
Metabolism
Excretion

Rowland & Tozer, *Clinical Pharmacokinetics*, 1995

3

Distribution vs Elimination



4

Oral vs Intravenous

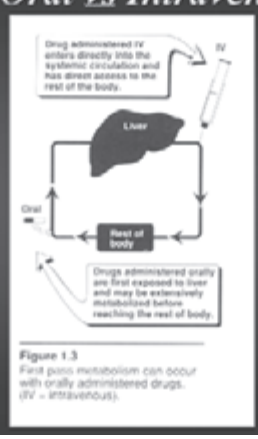


Figure 1.3
First pass metabolism can occur with orally administered drugs. (IV = intravenous).

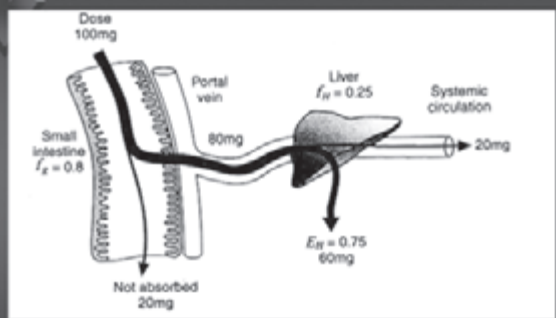
5

PK Parameters of Drug Disposition & Absorption

- Disposition (Distribution + Elimination)
  - Clearance (CL)
  - Volume of distribution (V)
  - CL and V are primary PK parameters
  - Half life ($t_{1/2}$)
  - Fraction excreted unchanged in urine (fe)
  - Fraction metabolized (fm)
- Absorption
  - Absorption rate constant (ka)
  - Absolute bioavailability or oral availability (F)
  - ka & F depend not only on the drug but also on the formulation (drug product)

6

Factors Affecting Bioavailability

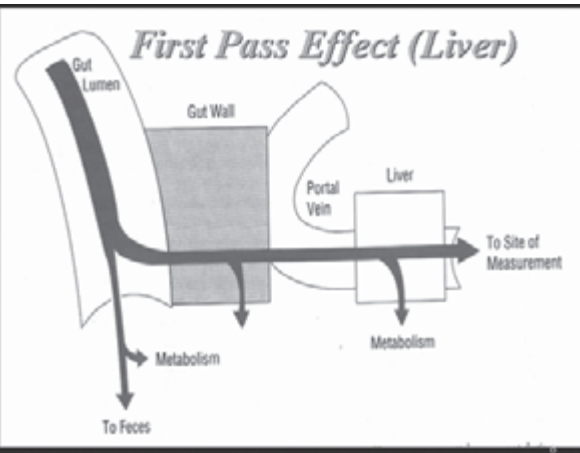


The bioavailability is: $F=f_g*f_H = 0.8*0.25=0.2=20\%$

$E_H+f_H = 1$

7

First Pass Effect (Liver)



Rowland & Tozer, *Clinical Pharmacokinetics*, 1995

Clinical Implications of PK Parameters

- CL determines steady state plasma concentration (Css)
- V determines the dose (D)
- $t_{1/2}$ determines the dosing interval (τ), the shorter the $t_{1/2}$ the more frequent the dosing intervals (τ)
- F determines the oral dose

$$\overline{Css} = \frac{FD}{CL\tau}$$

$$D = V\,\overline{Css}$$

Elimination & Metabolism of Drugs (AEDs)

Elimination:

Metabolism:

Williams et al, *Drug Metab Disposit*, 2004

10

Isozymes Involved in Drug Metabolism

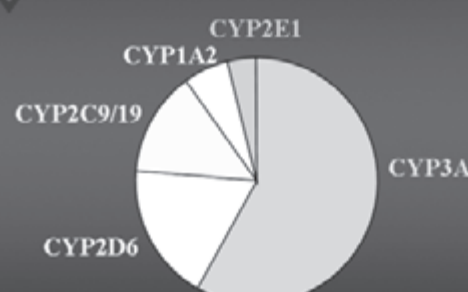
CYPs:

UGTs:

Williams et al, *Drug Metab Disposit*, 2004

11

The Proportion of Drugs Metabolized by P450 Isozymes



CYPs 2D6, 2C19 & 2C9 are susceptible to genetic polymorphism

Benet et al, in: *Goodman and Gilman's* 1996; Wilkinson, *ibid*, 2001

12

Effect of Drugs & Plasma Levels:PK-PD Correlation

Drug (AED) effect is related to the plasma levels which a patient is exposed to after single or multiple dosing, as reflected by the exposure (AUC) or average plasma steady-state concentration ($\overline{C}ss$)

Changes in AUC and/or $\overline{C}ss$ may reduce efficacy or cause side effects

13

Free Drug Hypothesis

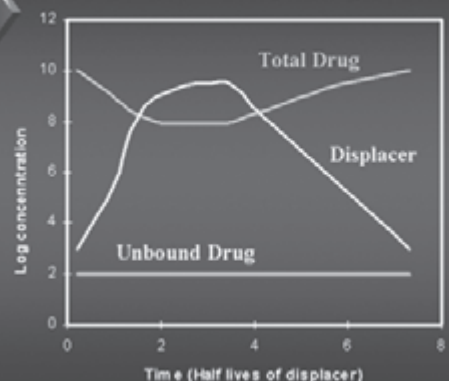
Only a free drug can cause a pharmacological effect

$$C = \frac{Cu}{fu}$$

Total concentration (C) is a function of the free concentration (Cu) and the plasma free fraction (fu)

14

Protein Binding Displacement



Rowland & Tozer, *Clinical Pharmacokinetics*, 1995

15

Protein Binding and Enzyme Induction

$$\overline{C}_{ss}\uparrow\downarrow = \frac{FD}{CL\tau} = \frac{FD}{fu\uparrow CLint\downarrow \tau}$$

$$\overline{Cu}_{ss} = fu\ \overline{C}_{ss}$$

$$\overline{Cu}_{ss}\uparrow = \frac{\cancel{fu}FD}{\cancel{fu}CLint\downarrow \tau}$$

↑ Protein Binding
↓ Inhibition

16

Total (AUC_{po}) & Unbound (AUC_{po}^{u}) & Exposure

$$F_{oral} = F_{abs} F_G F_H$$

For drugs (AEDs) eliminated primarily by the liver (po):

$$\uparrow\downarrow AUC_{po} = \frac{F_{abs} F_G D}{\uparrow fu\ CLint\downarrow}$$

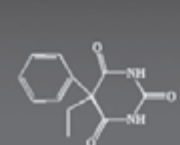
$$\uparrow AUC_{po}^{u} = fuAUC_{po} = \frac{\cancel{fu}\ F_{abs} F_G D}{\cancel{fu}\ CLint\downarrow}$$

Unlike changes in fu, changes in CLint will affect the unbound exposure AUC_{po}^{u} & consequently, drug effect

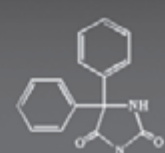
Benet & Hoener, *Clin Pharmacol Ther*, 2002

17

Established Antiepileptic Drugs (AEDs)

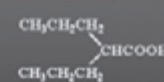


Phenobarbital (PB)



Phenytoin (PHT)

Carbamazepine (CBZ)

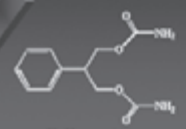


Valproic acid (VPA)

PB, PHT, CBZ & VPA per se are water-insoluble drugs

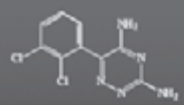
18

New Marketed AEDs

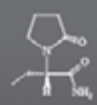


Felbamate

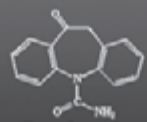
Gabapentin



Lamotrigine



Levetiracetam



Oxcarbazepine

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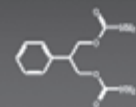
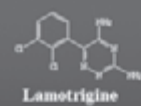
New Marketed AEDs



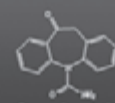
Felbamate

Gabapentin



Lamotrigine

Levetiracetam



Oxcarbazepine

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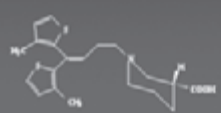
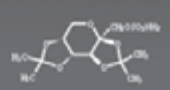
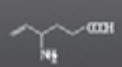
New Marketed AEDs (cont.)



Tiagabine



Topiramate



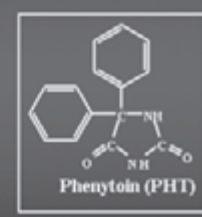
Vigabatrin

Zonisamide

21

Phenytoin (PHT)

- F = 90 ± 3%
- CL = Concentration-dependent PK
- Vmax = 413 ± 84 mg/day
- Km = 5.7 ± 2.9 mg/L
- V = 0.64 ± 0.04 L/Kg
- t1/2 = 6 - 24 hr
- fe = 2 ± 8%
- Effective Conc. = 10 - 20 mg/L

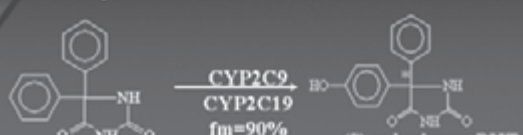


Phenytoin (PHT)

Eldon et al, 1993; Tozer & Winter, 1993; Browne & LeDuc, in: *AED V*, 2002

22

Phenytoin (PHT) Metabolism by CYPs 2C9 & 2C19



Phenytoin (PHT)
A prochiral drug

(S)-p-hydroxy-PHT
((S)-HPHT)
A chiral metabolite

CYP2C9 —95%→ (S)-HPHT

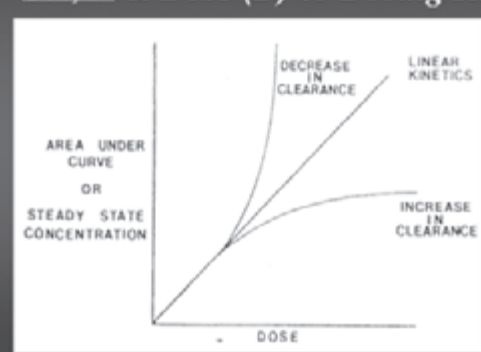
CYP2C19 —5%→ (R)-HPHT

Phenotyping using the (S)-HPHT to PHT ratio

Caraco et al, *Pharmacogenetics*, 2001

23

Relationship Between AUC or Css,av & Dose (D) or Dosing Rate



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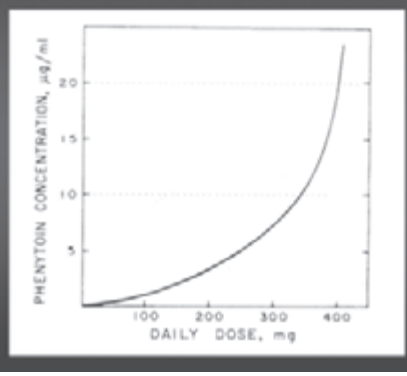
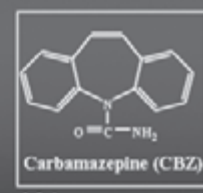
Relationship Between PHT Average Steady-State Levels & Daily Dose



25

Carbamazepine (CBZ)

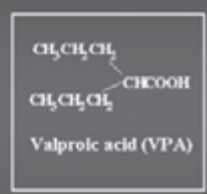
- F = > 70%
- CL (time-dependent PK) = 91 ± 35 mL/min
- V = 1.4 ± 0.4 L/Kg
- t1/2 = 15 ± 5 hr
- fe < 1%
- Effective Conc. = 4 -10 mg/L
- (an active metabolite- CBZ-epoxide)



Bertilsson & Tomson, *CPK*, 1986; Spina, in: *AED V*, 2002 26

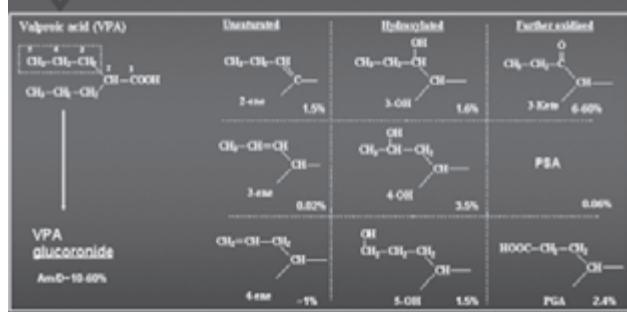
Valproic Acid (VPA)

- F = 100 ± 10%
- CL = 7.7 ± 1.4 mL/min
- V = 0.22 ± 0.07 L/Kg
- t1/2 = 14 ± 3 hr
- fe = 1.8 ± 1.4 %
- Effective Conc. = 40-100 mg/L
- Inhibitor of CYPs 2C9, 2C19, 3A4 & UGTs



Zaccara et al, *CPK*, 1988; Levy et al, in: *AED V*, 2002 27

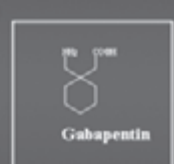
VPA- Major Metabolites



Levy et al, *Clin Pharmacol Ther*, 1990; Levy et al, in: *AED V*, 2002 28

Gabapentin (GBP)

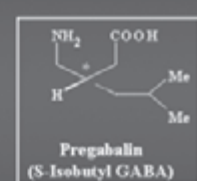
- F = 60% (active absorption)
- CL = 120 - 130 mL/min
- V = 0.7 L/Kg
- t1/2 = 5 - 7 hr
- fe = 64 - 68%



Vajda, in: *AED V*, 2002 29

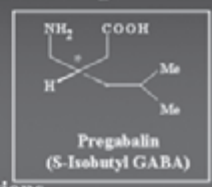
Pregabalin - PK

- F = 90%
- fe = 98%
- $t_{1/2}$ = 6h
- Linear PK
- No drug interactions
- Possible active absorption?



Beb-Menahem & Kugler, in: *AED V*, 2002 30

Pregabalin (PGB) vs Gabapentin



Pregabalin
(S-Isobutyl GABA)

- In the future PGB will have to compete with :
- Generic GBP, CR GBP formulations
- XP13512 (Xenoport & GSK)
- A transported GBP prodrug designed to utilize endobiotic GI (food) transporters & thus resulting in superior PK and therapeutic utility

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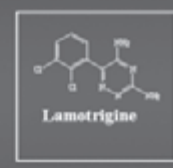
Lamotrigine (LTG)

- F = 95 ± 5 %
- CL = 27 - 43 mL/min
- V = 0.9 - 1.2 L/Kg
- t1/2 = 24 - 35 hr
- fe = 10 %


Lamotrigine

Chen et al, *Pharmacotherapy* 1999; Dickins & Chen, in: *AED V*, 2002

Lamotrigine (LTG)

- Increases its own clearance by 36% after 3 weeks of administration (induction of glucuronidation)
- LTG metabolism is induced by CBZ, PHT & OC and is inhibited by VPA

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Levetiracetam (LEV)

- F = 100%
- CL/F = 0.6 mL/min/kg
- V/F = 0.5 - 0.7 L/Kg
- t1/2 = 7 - 10 hr
- fe = 67%


Levetiracetam

Patsalos, in: *AED V*, 2002

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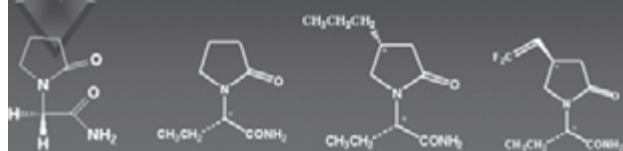
Levetiracetam (LEV)

- fe = 65%
- Major metabolite: ucb LO57 (fm = 24%)
- Low potential for metabolic drug interactions
- Drugs excreted by tubular secretion inhibit the urinary excretion of the major acidic metabolite ucb LO57 but not of LEV

Patsalos, *Pharmacol Ther*, 2000; Browne et al, *Epilepsia*, 1998

LEV & its 2nd Generation AEDs



	Piracetam	Levetiracetam (LEV)	Brivaracetam (ucb 34714)	Seletracetam (ucb 44212)
		ED_{50} (mg/kg)	ED_{50} (mg/kg)	
Kindled rat		7.3	1.2	
Frings mice		30	2.4	

- Levetiracetam (LEV) is a second generation of piracetam, ucb 34714 & 44212 are second generation of LEV
- ucb 34717 has been granted orphan drug status for PME

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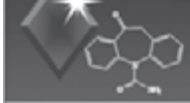
Matagne et al, in: EILAT VII, 2004; Bialer, Expert Opin Investig Drug, 2006

Oxcarbazepine (OXC)



	OXC	MHD	
		(R)-MHD	(S)-MHD
F	Presystemic first pass effect	89%	
CL/F	162 ±76 (Single Dose) 109 ±32 (Multiple Dose)	4.2±0.9	3 ±0.7
V/F(L)	525 ±599	55	46
t1/2 (hr)	3.774 (Single Dose)	9.0 ±1.5	10.6±2.6
fe (%)	0.6	2.7 ±1.7 (oxc po)	16 ±3 (oxc po)
CLf (L/h)		0.35 ±0.2 (oxc po)	0.48 ±0.2 (oxc po)

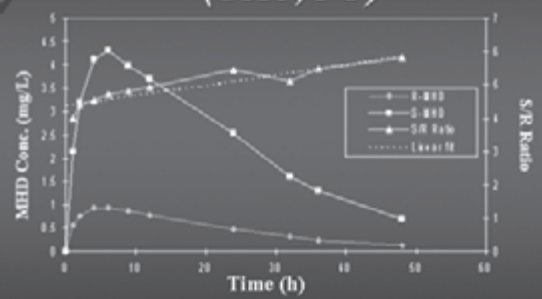
Volosov et al, *CPT*, 1999; Bialer, in: *AED V*, 2002; Flesch et al, *EJPS*, 1999; Dikinsöö et al, *EJCP*, 1989

Oxcarbazepine (OXC)

- OXC is a prodrug to MHD (active entity)
- Minor CYP metabolism with no autoinduction
- OXC/MHD has little enzyme inducing capacity
- MHD reduces OC levels and efficacy
- Other AEDs do not modify the PK of OXC and MHD

Bialer, in: *AED V*, 2002; Albani et al, in: *AED V*, 2002 38

S- and R-MHD - Humans (OXC, PO)



Volosov et al, *Clin Pharmacol Ther*, 1999 39

Stereoselective PK Of MHD

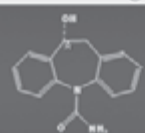
	MHD (250 mg-iv)		OXC (300 mg-po)	
	R-MHD	S-MHD	R-MHD	S-MHD
AUC (µmol/L*h)	120	167	64	241
CL (L/h)	4.1	2.9	-	-
CLr (L/h)	0.9	0.9	1.0	1.1
fe (%)	12	16	4.9	22
t1/2 (h)	9	11	16	11

A randomized two-way crossover study (n=12;% CV~25%)

Flesch et al., *Eur J Pharm Sci*, 1999 40

Licarbazepine (MHD) & Eslicarbazepine Acetate (BIA 2-093)

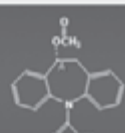
PK-based design



Licarzepine (MHD)

OXC is a prodrug to MHD
OXC ⟶ MHD is stereoselective

PD-based design



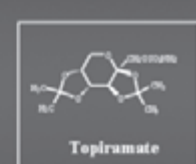
Eslicarzepine acetate (BIA 2-093)

t1/2 20 - 24 h
Only 5% chiral inversion
F' of S-MHD is 16% greater than that of OXC

Bialer, *AED V*, 2002; Soares-da-Silva in: *EILAT VII*, 2004, Benes et al., *J Med Chem*, 1999; Elger et al., Epilepsia, 2007

Topiramate (TPM)

- F = 83 - 91%
- CL/F = 22 - 36 mL/min
- CL increases with inducing AEDs
- V/F = 0.6 - 0.8 L/Kg
- t1/2 = 20 - 40 hr
- fe = 55 - 67%



Topiramate

Doose et al, 1995; Wu & McKown, 2000; Sachdeo et al, 2002 42

Topiramate (TPM)

- fe = 40-60%, fm increases in polytherapy
- PHT, CBZ and PB decrease TPM plasma levels by 50%
- TPM does not affect CBZ , PB, LTG, VPA plasma levels, but induces OC (EE) at high doses (>200 mg/day)

Doose et al, *Epilepsia*, 2003; Bialer et al, *Clin Pharmacokinet*, 2004; Britzi et al, & Mimrod et al, *Epilepsia*, 2005

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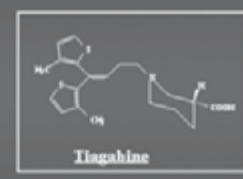
Tiagabine (TGB)

- F = 90 ± 10%
- CL = 109 ± 25 mL/min
- V = 1.1 - 1.3 L/Kg
- $t_{1/2}$ = 4 - 13 hr
- fu = 4%
- fe < 1%



Tiagabine

Sommerville & Collins, in: *AED V*, 2002

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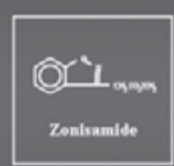
Zonisamide (ZNS)

- F ~ 90%
- CL/F = 18 - 22mL/min
- V/F = 1 - 1.5L/Kg
- $t_{1/2}$ = 50 - 60hr
- fu = 40 - 60%
- fe < 1%

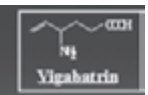


Zonisamide

Shah et al, in: *AED V*, 2002

45

Vigabatrin (VGB)



Vigabatrin

	S(+) ENANTIOMER	R(-)ENANTIOMER
F	Complete Absorption	
CL (mL/min)	89 ± 22	90 ± 20
V (L/Kg)	1.23	0.86
t1/2 (hr)	7.5 ± 2.2	8.1 ± 1.3
fe (%)	49 ± 6	65 ± 6

Undefined Effect. Conc. due to a lack of PK-PD correlation

Rey et al, *CPK*, 1992; Bialer, *CPK*, 1993

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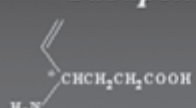
The GABA Analogs: Vigabatrin, Gabapentin & Pregabalin

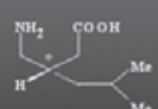


Vigabatrin-VGB (1989, Europe)
(racemate, only S-VGB is active)

Gabapentin (1994)

Chiral Switches
Racemate ⟶ Pure active enantiomer
(drug, metabolite, derivative)

Chiral drugs should not be developed as a racamate!



Pregabalin (2004)
(S-Isobutyl GABA)

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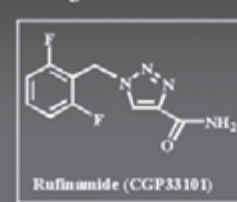
Rufinamide



Rufinamide (CGP33101)

- Linear PK at 40-1600 mg/day; nonlinear > 1600 mg
- V=50-60L; $t_{1/2}$=6-10h
- Major metabolite: the corresponding acid (fm=85%)
- F=60% increases by 40% with food
- Approved by EMEA for LG

Rosenfeld & Karolchyk, in EILAT V Summary, Epilepsy Res, 2001; Jain, EXOIT, 2000; Arzimanglou, in EILAT VIII Summary, Epilepsy Res, 2007

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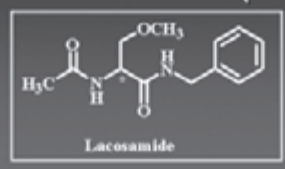
Lacosamide (LCS)



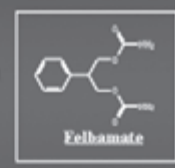
Lacosamide

- Linear PK (100-800 mg/day); fe=40%; $t_{1/2}$=13h
- Complete oral absorption
- Major metabolite: O-desmethyl-LCS (inactive)
- A Second Phase III epilepsy trial showed that add-on LCS (400 & 600 mg/day) significantly reduced seizure frequency in refractory patients

Doty et et al., in EILAT V III Summary, Epilepsy Res, 2004; Doty & Whitesides, in EILAT VIII Summary, Epilepsy Res, 2007

Felbamate (FBM)

- F > 80%
- CL = 35 ± 9 mL/min
- V = 0.8 ± 0.1 L/Kg
- t1/2 = 21 ± 2 hr
- fe = 40 - 50%


Felbamate

Bialer, *CPK*, 1993; Pellock et al, in: *AED V*, 2002

50

Felbamate (FBM)

- fe = 50% ; fm-glucuronidation = 20% ; fm-CYP3A4/2E1 = 15%
- An inhibitor of CYP2C19 (PB & PHT) & β-oxidation
- An inducer of CYP3A4 (CBZ & OC)
- FBM metabolism is induced by PB, PHT & CBZ

Glue et al, *CPT*, 1997; Anderson, *Annal Pharmacother*, 1998

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AEDs and Genetic Polymorphism

AED	CYP (%)	Isozymes involved	UGT	Renal CL (%)
Carbamazepine	65	Major: CYP3A4 Minor: CYP2C9, 1A2	15	<1
Phenobarbital	20	CYP2C9	no	25
Phenytoin	90	Major: CYP2C9 Minor: CYP2C19	no	<5
Valproic acid	10	CYP2C9, 2C19, 2A6	40	<5
Topiramate	>15	Not identified	?	60
Tiagabine	>30	CYP3A4		

Anderson, *Ann Pharmacother*, 1998 & *Neurology*, 2004

52

Drug-Drug Interactions (DDI)

- Most DDI are pharmacokinetic (PK)
- The incidence of clinically significant adverse-DDI=1-10 in 1000 patients (Jankel & Fitterman, 1993)
- PK=ADME; Absorption, Distribution, Metabolism, Excretion
- Most DDI are metabolic. Therefore, enzyme induction or inhibition (and not protein binding) is the most important factor in clinically-relevant DDI

New AEDs & their Fraction Excreted Unchanged (fe)

- Felbamate - 50%
- Gabapentin – 64 - 68%
- Lamotrigine - 8%
- Levetiracetam - 65%
- Oxcarbazepine - <1%
- Pregabalin->90%
- Tiagabine - <1%
- Topiramate – 60 - 65%
- Vigabatrin - 49% S(+); 65% R(-)
- Zonisamide - <1%

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New AEDs in which Metabolism is Induced by PB, PHT or CBZ

- Lamotrigine (fm=85%) - $t_{1/2}$ 25h --> 15h
- Tiagabine (fm=99%) - $t_{1/2}$ 8h --> 3h
- Topiramate (fm=30%) - $t_{1/2}$ 25h --> 15h
- Zonisamide (fm=99%) - $t_{1/2}$ 55h --> 30h

AEDs with fm<30% will be less involved in DDI and only in induction-based DDI (topiramate)

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Conclusions

- **Compared to older AEDs the new AEDs: GBP,VGB, LEV, OXC & TPM have more favorable PK due to:**
  - **Higher fe**
  - **Less drug interactions due to enzyme induction or inhibition**
  - **Less variable PK**

Nevertheless about 30% of the epileptic patients are still not seizure-free

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Drug interactions in epilepsy
Emilio Perucca (Italy)

Drug Interactions In Epilepsy

Emilio Perucca

Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE Course, 10 February 2008

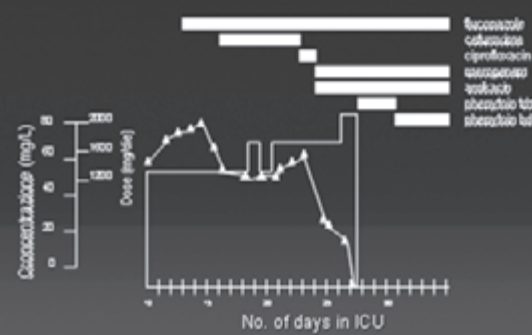
AED Interactions

- Use of AED combinations remains highly prevalent in refractory epilepsies
- Concurrent use of other drugs for unrelated conditions is common
- Over 500 interactions with AEDs have been described, and clinical relevance is claimed almost invariably
- How can really important adverse interactions be predicted, prevented and managed?

Factors Influencing Clinical Relevance of Adverse Drug Interaction

- Frequency of occurrence, predictability and monitoring tools
- Magnitude of interaction
- Time course
- Therapeutic index of the affected drug and consequence of an increase/decrease in pharmacological response

Changes in Serum VPA Levels in a Patient given Meropenen (+ Amikacin)

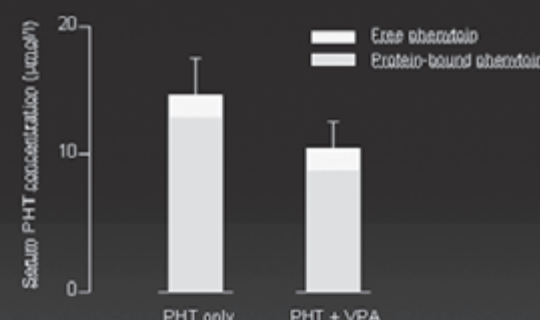


J. Antimicrob Chemother. 42,563-4,1998

Mechanisms of Interactions Involving AEDs

- Alterations in drug absorption → rarely significant
- Plasma protein binding interactions → clinically NOT important
- Induction or inhibition of metabolizing enzymes → common, clinically important
- Other mechanisms
  - Changes in renal excretion → rarely significant
  - Pharmacodynamic interactions → can be important

Effect of Valproic Acid on Free and Total Serum Phenytoin Levels (n=6)



Perucca et al, Clin Pharmacol Ther. 1980;28:779-89

Metabolic Drug Interactions A Changing Scenery

The past:
- Poor predictability
- Discovery by change / accident
- "Telephone directory" approach

The present:
- Excellent predictability
- Rational discovery / prevention
- Easy handling based on simple concepts

How To Predict Metabolic Drug Interactions?

- Most rate-limiting metabolic pathways involve cytochrome P450 (CYP) isozymes
- The isozymes responsible for the metabolism of any given drug are mostly known
- Effects of other drugs on these isozymes (and the effect of that drug on other isozymes) are also known - or can be easily determined in vitro

PREDICTING METABOLIC DRUG INTERACTIONS
The example of carbamazepine

- CBZ is metabolized primarily by the inducible enzyme CYP3A4. Predictably, its plasma levels are reduced by phenytoin and phenobarbital
- Some macrolides are known CYP3A4 inhibitors. Predictably, they cause CBZ intoxication
- Carbamazepine is a CYP3A4 inducer. Predictably, it lowers the levels of oral contraceptives, statins and risperidone…

AEDs as Enzyme Inducers and Inhibitors

Enzyme inducers

Broad spectrum inducers:	Phenytoin Carbamazepine Phenobarbital Primidone
CYP3A4 inducers:	Oxcarbazepine Felbamate Topiramate (high doses)
Glucuronosyl transferase inducer:	Lamotrigine (?)

Enzyme inhibitors

Valproic acid (UGT, CYP2C9, epoxide-hydrolase), oxcarbazepine (CYP2C19), felbamate (CYP2C19, epoxide-hydrolase)

Interactions Caused by Enzyme Inhibition

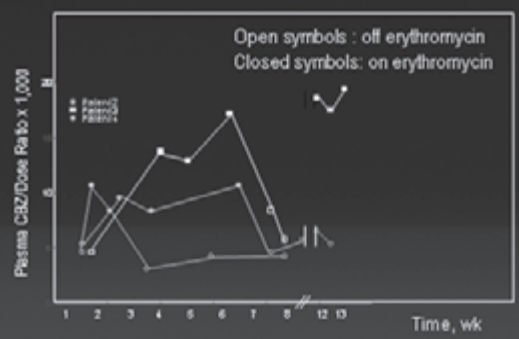
- Usually predictable, based on in vitro data
- Often result in clinical intoxication
- Usually occur rapidly after addition of the interacting drug - precise time course depends on half-lives of the drugs involved
- Most common examples in AED therapy: increase in PB and LTG levels by VPA
- May be caused by other comedications (e.g., inhibition of CBZ metabolism by erythromycin, diltiazem, verapamil, etc)

Examples of Important Drug Interactions mediated by Metabolic Inhibition

Interacting drug	Affected drug
Erythromycin	Carbamazepine
Isoniazid	Phenytoin
Fluoxetine	Phenytoin
Propoxyphene	Carbamazepine
Valproic acid	Lamotrigine Phenobarbital

Patsalos & Perucca, Lancet Neurology 2003;2:473-81

Effect of Erythromycin on the Plasma Levels of Carbamazepine in 3 Patients



Wroblewski et al, JAMA 255, 1165-7, 1987

Interactions of Macrolide Antibiotics with Carbamazepine

Potent CYP3A4 inhibitors (2-4-fold ↑ of CBZ levels)

- Erythromycin
- Troleandomicin

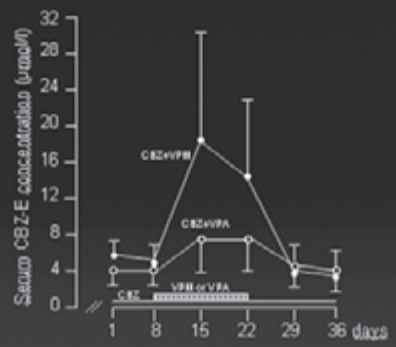
Moderate CYP3A4 inhibitors (modest ↑ of CBZ levels)

- Clarythromicin
- Elurythromicin
- Josamicin
- Midecamicin
- Myocamycin
- Roxythromycin

Macrolides not causing significant CYP3A4 inhibition

- Azythromycin
- Dirythromycin
- Rokytamycin
- Spiramycin

Effect of Valproate and Valpromide on Serum Carbamazepine-10,11-Epoxide Concentration (n=6)



Pisani et al, Epilepsia 1986;27:548-52

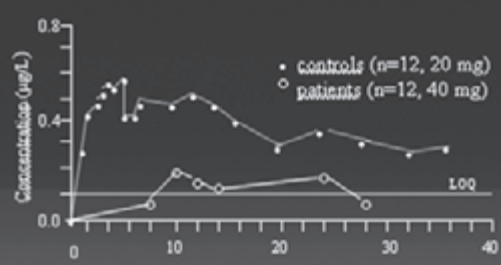
Interactions Caused by Enzyme Induction

- Most commonly caused by carbamazepine, phenytoin and barbiturates
- Often result in loss of clinical effect of the affected drug
- Danger of rebound effects when interacting drug is removed
- Occur after a delay, related to synthesis of new enzyme and half-lives of the drugs involved

Examples of Drugs whose Efficacy is Impaired by Enzyme Inducing AEDs

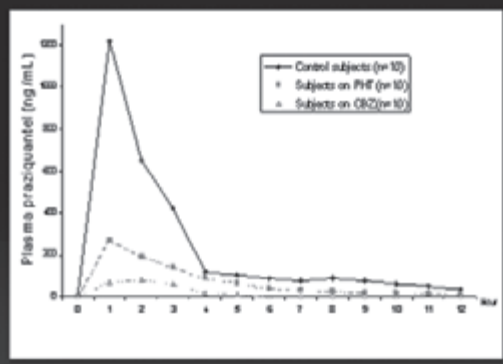
- Many psychotropic drugs
- Many anticancer agents
- Most calcium antagonists
- Steroids
- Many antidysrhythmics
- Statins
- Cyclosporine A
- Oral anticoagulants
- Many antimicrobials

Effect of Enzyme Inducing AEDs on Plasma Nisoldipine Levels after a Single Nisoldipine Dose



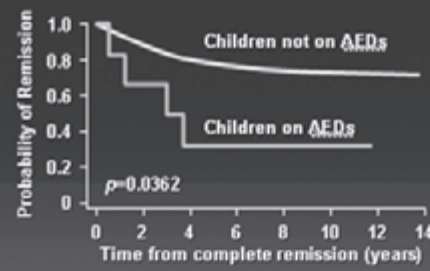
Michelucci et al, Epilepsia 1996; 37:1107-10

Effect of Phenytoin and Carbamazepine on the Blood Levels of Praziquantel (25 mg/kg)



Neurology 1992, 42:492-6

Effect of Enzyme Inducing AEDs on Event -free Survival in Children with Leukaemia

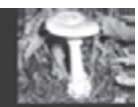


Relling et al., *Lancet* 2000; 356:285-90

Effect of Enzyme Inducing AEDs on Teniposide Clearance in Children with Leukaemia

Relling et al., *Lancet* 2000;356:285-90

Annals of Pharmacotherapy 2000 April, Volume 34, 465-70

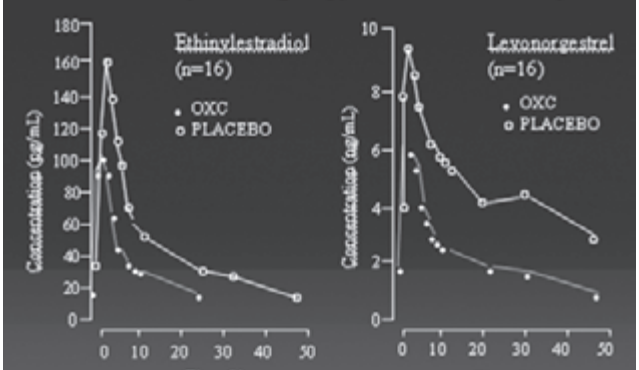


Carbamazepine-Indinavir Interaction Causes Antiretroviral Therapy Failure

Patricia WH Hugen, David M Burger, Kees Brinkman, Hadewych JM ter Hofstede, Rob Schuurman, Peter P Koopmans and Yechiel A. Hekster

Department of Clinical Pharmacy, University Hospital Nijmegen, Nijmegen, the Netherlands

Effect of OXC (1200 mg/day) on Oral Contraceptives



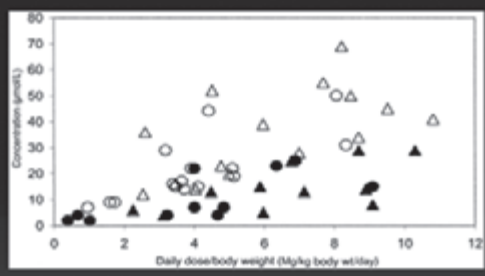
Fattore et al, Epilepsia, 1999

Interactions of AEDs with Oral Contraceptives (OCs)

Reduced OCs levels	Reduced levels of both OCs and AED	Reduced AED levels	No interaction described
Carbamazepine	Lamotrigine	Valproate	Levetiracetam
Phenobarbital			Gabapentin
Primidone			Tiagabine
Phenytoin			Pregabalin
Oxcarbazepine			Benzos
Topiramate (≥200mg/d)			Vigabatrin
Felbamate			

Perucca, Brit J clin Pharmacol 2006; 61:246-255

Oral Contraceptives Decrease Markedly Serum Lamotrigine Concentrations



Filled symbols: On oral contraceptives
Open symbols: Not on oral contraceptives

Sabers et al. *Neurology* 2003

Clinical Reports of Adverse Pharmacodynamic Interactions with AEDs

Drug combination	Level of evidence*	Reference
Oxcarbazepine + Carbamazepine	+++	Barcs, 2001
Lamotrigine + Carbamazepine	+++	Besag, 1998
Lamotrigine + Phenytoin	++	Brodie, 1997
Topiramate + Carbamazepine (?)	+	Privitera, 2001
Levetiracetam + Carbamazepine (?)	+	Kelly, 2004
Levetiracetam + Lamotrigine (?)	+	Kelly, 2004

* +++ Controlled trials ++ Case series studies + Anedoctical (case reports)

Findings from Clinical Studies: Positive Pharmacodynamic Interactions

Drug combination	Level of evidence*	Reference
Valproate + Lamotrigine	+++	Pisani, 1999
Valproate + Ethosuximide	++	Rowan, 1983
Valproate + Carbamazepine	++	Brodie, 1999
Carbamazepine + Vigabatrin	++	Brodie, 1999
Lamotrigine + Tiagabine (?)	+	Schapel, 1996
Tiagabine + Vigabatrin (?)	+	Leach, 1994
Topiramate + Lamotrigine (?)	+	Stephens, 1996
Gabapentin + Lamotrigine (?)	+	Pisani, 2000

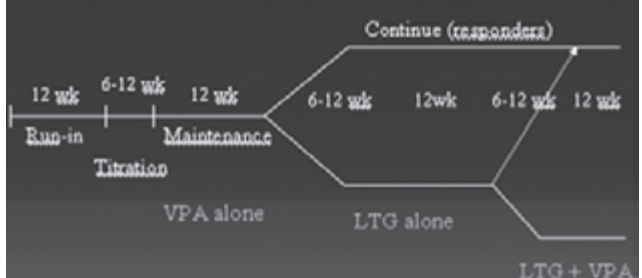
* +++ Controlled trials ++ Case series studies + Anedoctical (case reports)

Covariate Analysis of Outcome Predictors in 1050 Patients given Add-on Lamotrigine

- Patients comedicated with CBZ were 3 times less likely to become seizure-free than those not on CBZ ($p<0.02$)
- Patients on VPA were twice as likely to stay on long-term LTG than those not on VPA ($p<0.001$)
- The positive effect of VPA was also significant for the subgroups with partial and generalised epilepsy

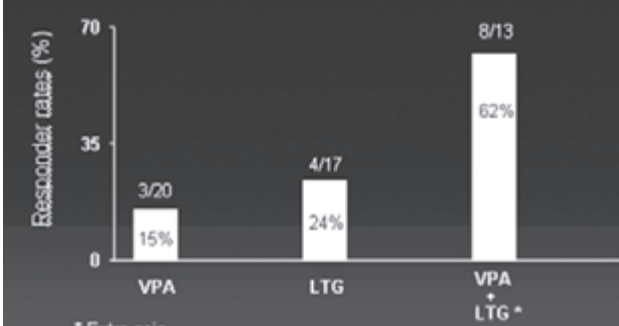
Wong et al, Epilepsia 42, 1354-8, 2001

Sequential Trial of Valproate, Lamotrigine and their Combination in Partial Epilepsy



Pisani et al, Epilepsia 1999; 40:1141-6

Valproate, Lamotrigine and their Combination: 50% Responder Rates



Pisani et al, Epilepsia 1999; 40: 1141-6

Prevention and Management of Adverse AED interactions

- Use multiple drug therapy only when necessary
- Avoid combination of drugs with similar adverse effects (e.g. PB and BZD)
- Be aware of main mechanisms of drug interaction
- Be aware of most important adverse drug interactions
- Within drug classes, choose agent with lowest interaction potential
- Monitor carefully clinical response and, if appropriate, serum drug levels. Adjust dosage if necessary

Clinical drug development
Emilio Perucca (Italy)

Clinical Development of Antiepileptic Drugs

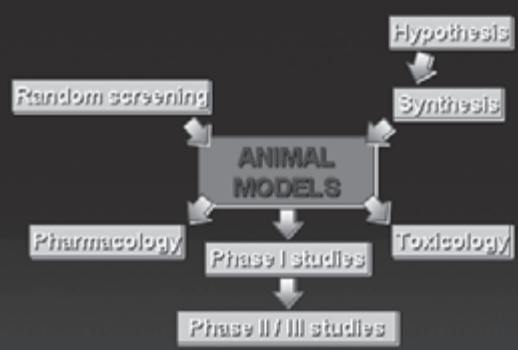
Emilio Perucca
Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE Course, 10 February 2008

Shortcomings of Existing AEDs

- Suboptimal pharmacokinetics (e.g., non linearity, short half life)
- High interaction potential (enzyme induction, enzyme inhibition)
- Adequate efficacy in no more than 70% of patients
- Considerable potential for toxicity (narrow therapeutic index)

Antiepileptic Drug Development



Sills, ECE, 2004

Use of Preclinical Models

- To investigate mechanisms of epileptogenesis, seizure generation and seizure propagation
- To identify candidate AEDs for clinical development
- To obtain a rough estimate of efficacious blood levels prior to first use in man
- To obtain preliminary evidence of therapeutic index
- Characterize ADME and predict PK and interaction profile in humans

Decision to Enter Phase I: Desirable Preclinical Data

- Conventional screening tests (including threshold tests)
- Kindling and kindled seizures
- One absence seizure model (lh/lh mouse, GAERS)
- Refractory seizure models (?)
- Tox data - Protective indexes
- ADME data and interference with CYPs/UGTs
- Models for non-epilepsy indications
- Mechanisms of action

Requirements vary depending on specific contexts (e.g development of analogues)

Ideal Preclinical Features for a Potential AED

- High potency
- Broad spectrum (partial + generalized seizure models – other indications)
- Low neurotoxicity
- No teratogenicity
- High bioavailability
- Renal elimination
- No interference with CYPs and UGTs

Developing a New AED: Phase I Objectives

- PK assessment (healthy subjects/patients)
- Highest tolerated dose (healthy subjects/patients)
- Most common side effects
- Tolerability as a function of titration rate/dosing schedule
- Interactions with concomitant AEDs (healthy subjects and patients)

Methodology for Phase I Tolerability Studies

- Single dose, ascending
- Multiple dose, ascending
- Randomized, double-blind, placebo-controlled
- Parallel-group or cross-over

Developing a New AED: Ideal Phase I Profile

- Good tolerability at expected anticonvulsant blood levels
- Favourable kinetics
- No interactions
- No enzyme induction

Entering Phase II: Usefulness of Initial Open-label Exploratory Add-on Studies

- To confirm Phase I tolerability over a longer treatment period and in an add-on setting
- To better characterize interaction potential
- To better assess highest tolerated dose, using different dose escalation schemes
- To obtain an impression of "efficacious" doses

Entering Phase II: Usefulness of Initial Open-label Exploratory Add-on Studies

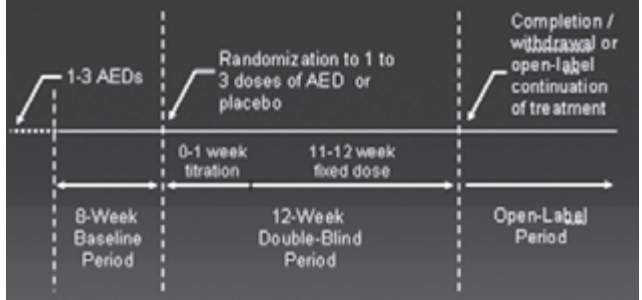
- To confirm Phase I tolerability over a longer treatment period and in an add-on setting
- To better characterize interaction potential
- To better assess highest tolerated dose, using different dose escalation schemes
- To obtain an impression of "efficacious" doses

Impression of efficacy from these studies can be very misleading!

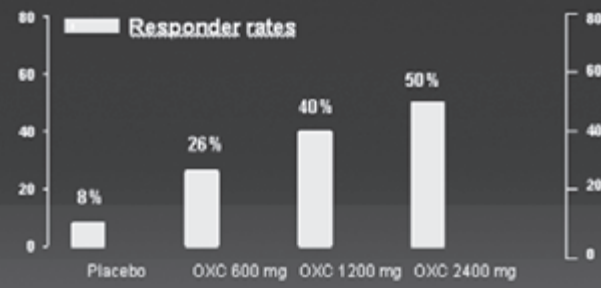
Developing a New AED: Early Proof of Efficacy

- Add-on placebo-controlled efficacy studies
  - ✓ Parallel group, high dosage
  - ✓ Parallel group, multiple-dose
  - ✓ Cross-over designs
  - ✓ Enrichment designs
- Acute models
  - ✓ Photoparoxismal response
  - ✓ Interictal epileptiform EEG discharges
  - ✓ Response to TMS stimulation

A Typical Design for an Add-on Placebo-Controlled AED Trial



RCT Adjunctive-Therapy Trial of Oxcarbazepine vs Placebo in Refractory Partial Seizures



* All OXC dosages: p<0.001 vs placebo

Difficulties in Extrapolating Results of Add-on Trials to Monotherapy Use

- Efficacy during add-on use may be influenced by drug interactions
- Tolerability may differ substantially during add-on use compared with monotherapy
- Dosage requirements during monotherapy may also differ, due to avoidance of drug interactions and differences in patient's characteristics
- Adequate trials necessary to fully assess the potential of a new AED as monotherapy

Challenges in Obtaining Regulatory Approval for Monotherapy

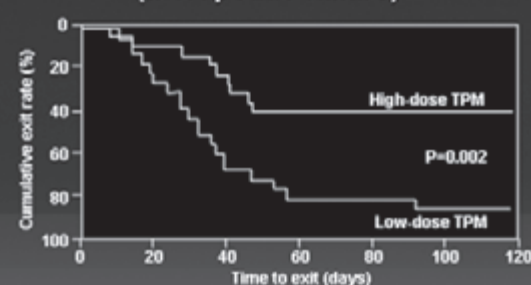
- Use of placebo monotherapy in a control group is not ethically acceptable
- Aiming at superiority over an optimized dose of an established reference AED is unrealistic
- Equivalence (or non inferiority) to an active control at optimized doses is not accepted as proof of efficacy by the FDA
- To circumvent this problem, short term monotherapy trials have been used where a high dose of the test drug is compared to a suboptimal dose (pseudoplacebo)

Short-Term Monotherapy Trials

- Conversion to monotherapy, presurgical, time-to exit trials (refractory patients or newly diagnosed)
- Designed to show superiority over some kind of control (FDA-driven approach)
- Control is either placebo or a suboptimal dose - a violation of the Helsinki Declaration
- Assess seizure deterioration (or lack of seizure control) rather than improvement – exit criteria are set to prevent excessive deterioration
- Time scale and clinical setting irrelevant from a therapeutic viewpoint. Inference of applicability questionable from regulatory viewpoint

Topiramate monotherapy in chronic refractory partial epilepsy

Time to exit due to seizures (therapeutic failure)



All patients reached target dose
Sachdeo RC et al. Epilepsia 38:294–300, 1997

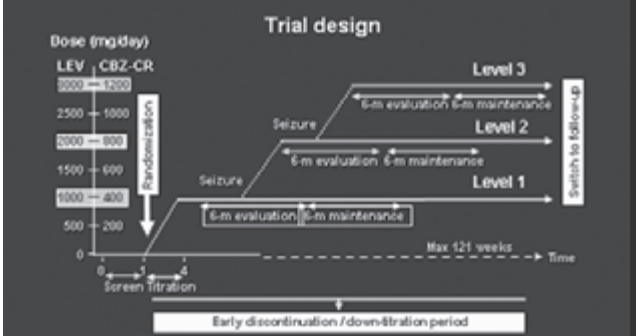
Conversion to Monotherapy Trials Some Concerns

- To what extent can results be extrapolated to populations in everyday clinical practice?
- How can results be extrapolated to different dose schedules, titration rates, duration of therapy?
- Range of effective/tolerated dosages unlikely to apply to monotherapy in newly diagnosed patients

Longer-Term Active Monotherapy Trials

- Non inferiority trials (accepted by EMEA guidelines)
- Especially suitable for newly diagnosed patients – usually no major ethical concerns
- Seizure freedom rates and tolerability evaluable in a clinically meaningful setting
- Optimization of dosing schedule, duration of follow-up and sample size most critical factors
- Many trials of new AEDs had low power and used suboptimal comparators, leading to potentially biased results

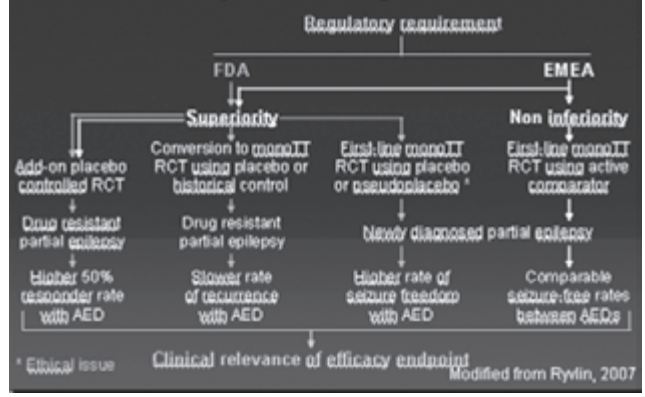
Randomized Controlled Trial of Levetiracetam vs CBZ-CR in Newly Diagnosed Partial Epilepsy



Brodie et al. Neurology 2007; 68: 402-8.

The Flow of AEDs development

and its impact on efficacy assessment



Modified from Rylvin, 2007

Regulatory Randomized Controlled Trials

Advantages	Disadvantages
Usually double-blind	Often "artificial" setting
Often placebo-controlled	Patients, dosing, and trial duration may not reflect optimal clinical use
Standardized methodology	
High scientific standards	Question addressed differs from clinician's needs

Important Aspects which Can Only be Addressed by Observational Studies (mostly investigated during Phase IV)

- Chronic or delayed adverse effects
- Second-generation effects (including teratogenicity)
- Rare adverse effects
- Certain drug interactions

Beware, however, uncontrolled postmarketing "efficacy" trials

Seeding Trials

Post-marketing studies of little or no scientific value whose aim is to:

- Familiarize physicians with the use of a given drug
- Increase prescription through through recruitment in the study
- Produce misleading estimates og high efficacy
- At times, extend utilization of the drug to non-approved indications

Developing a New AED
Common Errors from Past Experience

- Underestimation of importance of drug interactions
- Inadequate exploration of dose ranges
- Inadequate exploration of titration rates
- Inadequate exploration of efficacy spectrum
- Use of suboptimal formulations

Optimizing Development of a New AED
What should be done

- Syndrome-oriented studies
- Better characterization of recruited patients (pharmaco-resistance)
- Early pediatric studies (after proof of efficacy in adults)
- Explore efficacy spectrum and seizure aggravation
- Test concentration response-relationships
- Flexible dosage studies
- Good studies on cognitive effects
- Long-term follow-up (>2 yrs) and assessment of tolerance

Evidence-based therapy? Clinical trials vs clinical practice

Torbjörn Tomson (Sweden)

Evidence-based therapy
Clinical trials vs. Clinical practice

LASSE II

Torbjörn Tomson

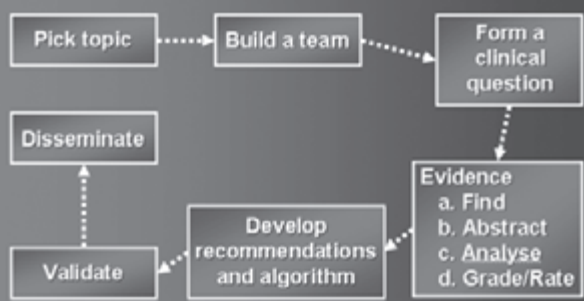
Evidence-based therapy

Clinical guidelines

- Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances
  - Should be comprehensive
  - Should prioritise evidence coming from best level of scientific evidence (preferably RCTs)
  - Should integrate evidence with clinical experience
  - Should be up to date and widely disseminated

Institute of Medicine of the National Academies

Guideline Development: Overview of Activities



Rating Evidence & Recommendations

Level of Evidence	Grading of Recommendation
Ia Systematic review or meta-analysis of RCTs	A. Based directly on level I evidence
Ib At least one RCT	B. Based directly on level II evidence
IIa At least one well-designed non-randomised controlled study	C. Based directly on level III evidence
IIb At least one well-designed quasi-experimental (cohort) study	D. Based directly on level IV evidence
III Well-designed descriptive studies, case-control studies, case series	
IV Expert committee reports	

National Institute of Clinical Excellence (NICE)

Clinical Trials vs Clinical Practice

RCTs

- Least biased and thus most reliable evidence
- Could be difficult to generalize from because of
- Highly selected populations
- Artificial study design
- Endpoints of limited clinical relevance

Clinical practice

- Real life
- Range of patients with their individual needs and circumstances
- No exclusions
- Flexible management tailored to the individual patient
- Subject to bias

Clinical Trials vs Clinical Practice

RCTs

- Primary objective often to gain marketing license
- Aim at demonstrating a difference (sometimes equivalence)
- The clinical relevance of endpoint often not prioritised

Clinical practice

- Primary aim to provide best possible treatment for each individual patient

Examples of clinical treatment issues addressed in RCTs

- When to start AED treatment (FIRST;MESS studies)
- Selection of AEDs for intitial treatment (Numerous RCTs including SANAD)
- Strategy when 1st monotherapy fails (BASE study)
- Efficacy of AEDs as add-on in refractory epilepsy (Numerous placebo controlled RCTs)
- Withdrawal of AEDs in seizure free patients (MRC)

Examples of treatment issues that cannot be addressed in RCTs

- The teratogenic effects of AEDs
- Rare idiosyncratic adverse effects
- Late adverse effects and long-term safety
- Pharmacokinetics and drug interactions

Examples of treatment issues that are rarely addressed in RCTs

- Dose optimisation including
  - -dose (concentration) effect relationship
  - -dosing regimens
  - -titration schedules
- Efficacy of specific AED combinations
- Efficacy beyound most common seiure/epilepsy types and patient groups
- Interaction with comorbidity
- Efficacy beyond epilepsy

Do we always provide all our epilepsy patients with the best possible management?

Why we Need Evidence-based Guidelines

If Not, is There an Implementation Gap?

- Because we don't know what is the best management
- There are numerous options
  - Drug selection
  - Treatment strategies
- Massive information flow
  - Patients
  - Practitioners

Numerous Treatment Choices

- Barbexaclone
- Carbamazepine
- Clobazam
- Clonazepam
- Ethosuximide
- Felbamate
- Gabapentin
- Lamotrigine
- Levetiracetam
- Mephenytoin
- Mephenobarbital
- Methsuximide
- Nitrazepam
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- Suthiame
- Tiagabine
- Topiramate
- Valproic acid
- Vigabatrin
- Zonisamide

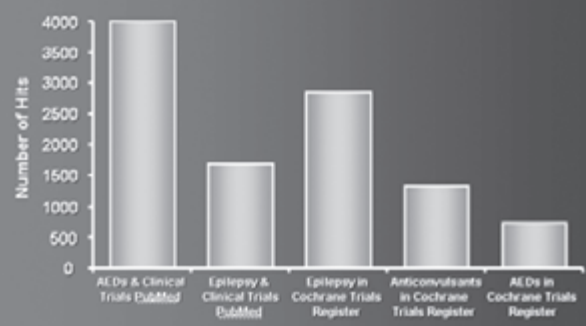
24 options as monotherapy

552 options as duotherapy

?? options as triple therapy

Licensed uses vary by country

Massive Information Flow



Why we Need Guidelines to Interpret the Evidence:

- Majority of trials un-controlled and non-randomised
- Many RCTs are of poor quality, flawed design and irrelevant for every-day practice
- Results may be difficult to interpret
- Prescribers targeted by promotional activities presenting manufacturers' interpretation
- Approved indications may vary between countries

Stakeholders and their Potential Benefits from Guidelines

- Patients
  - Empowerment
  - Promote consistency in care
  - Improve quality of care
- Practitioners
  - Provide evidence-based recommendations
- Clinical researchers
  - Highlight gaps in evidence / areas for research
- Health care systems / providers
  - Improve efficiency and optimise value for money
- Industry
  - Promote marketing
  - Identify areas of interest for investments

Evidence-based Guidelines in Epilepsy: Examples

- National Institute for Health and Clinical Excellence (NICE)
  - *Newer drugs for epilepsy in adults. www.nice.org.uk*
- American Academy of Neurology (AAN)
  - *Efficacy and tolerability of the new antiepileptic drugs I, II, Neurology 2004;62:1252–73*
- International League Against Epilepsy (ILAE)
  - *Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094–1120*

NICE

Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care

Guidance on:

- Coping with epilepsy
- Information
- Following a first seizure
- Diagnosis
- Investigations
- Classification
- Management
- Prolonged or repeated seizures in the community
- Treatment of status epilepticus
- Women with epilepsy
- Older people with epilepsy

NICE
Newer Drugs for Epilepsy in Children

TA79 Epilepsy (children) - newer drugs: Guidance

The newer antiepileptic drugs gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin (as an adjunctive therapy for partial seizures), within their licensed indications, are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable

NICE
Newer Drugs for Epilepsy in Adults

- Evidence does not suggest differences in effectiveness in seizure control between newer and older AEDs in monotherapy
- Evidence inadequate to support conclusion that newer AEDs are generally associated with improved quality of life
- Given the higher cost of newer AEDs, 1st line monotherapy should be an older AED, carbamazepine or valproate, unless unsuitable because of:
  - Contraindications
  - Potential for interactions
  - Woman of childbearing potential

NICE
Newer Drugs for Epilepsy in Adults

1 Guidance

1.1 The newer antiepileptic drugs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin, within their licensed indications, are recommended for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:

- there are contraindications to the drugs
- they could interact with other drugs the person is taking (notably oral contraceptives)
- they are already known to be poorly tolerated by the individual
- the person is a woman of childbearing potential (see Section 1.4 below).

NHS National Institute for Clinical Excellence

Technology Appraisal 76
March 2004

American Academy and AES Assessment of Efficacy & Tolerability of new AEDs
Evidence & Recommendations

- Class I D-B RCT with
  - Clearly defined primary outcome(s)
  - Clearly defined exclusion / inclusion criteria
  - Adequate accounting for drop-outs and crossovers
  - Baseline variables equivalent for treatment groups
- Class II RCT failing one class I criterion of non-randomised DB study
- Class III other controlled studies
- Class IV uncontrolled studies

A Recommendation
- At least one Class I or two consistent class II studies

B Recommendation
- At least one class II study or at least three consistent class III studies

C Recommendation
- At least two consistent class III studies

Neurology 2004;62:1252–60

AAN A or B Recommendations
Newer AEDs in Newly Diagnosed, Monotherapy

Drug	Partial / mixed	Absence
Gabapentin (GBP)	Yes*	No
Lamotrigine (LTG)	Yes*	Yes*
Topiramate (TPM)	Yes*	No
Tiagabine (TGB)	No	No
Oxcarbazepine (OXC)	Yes	No
Levetiracetam (LEV)	No	No
Zonisamide (ZNS)	No	No

* Not FDA approved for this indication
Neurology 2004; 62:1252–60

AAN A or B Recommendations
Newer AEDs in Refractory Epilepsy

AED	Partial adjuntive adult	Partial monother	Primary general.	Symptomatic general.	Pediatric partial
GBP	Yes	No	No	No	Yes
LTG	Yes	Yes	No	Yes	Yes
TPM	Yes	Yes*	Yes GTC	Yes	Yes
TGB	Yes	No	No	No	Yes
OXC	Yes	Yes	No	No	Yes
LEV	Yes	No	No	No	No
ZNS	Yes	No	No	No	No

* Not FDA approved for this indication
Neurology 2004; 62:1261–73

AAN *vs.* ILAE
Rating the Evidence

Class I (AAN)
- DB RCT with Clearly defined primary outcome(s)
- Clearly defined exclusion / inclusion criteria
- Adequate accounting for dropouts and crossovers
- Baseline variables for treatment groups

Class I (ILAE)
- Primary outcome: efficacy or effectiveness
- Treatment duration: ≥48 weeks (>24 wk seizure freedom data for efficacy or >48 wk retention data for effectiveness)
- Study design: double-blind
- Superiority demonstrated or actual sample sufficient to show non-inferiority no worse than a 20% relative difference to acceptable comparator
- Study exit: not forced by a predetermined number of treatment emergent seizures
- Appropriate statistics

ILAE Criteria for Class II–III

- Class II
  - An RCT or meta-analysis meeting all the Class I criteria except that:
  1. No superiority was demonstrated and the study's actual sample was sufficient only to show non-inferiority at a 21–30% relative difference in effectiveness / efficacy
     OR
  2. Treatment duration: ≥24 wks but ≤48 wks
- Class III
  - An RCT or meta-analysis not meeting the criteria for any Class I or Class II category
- Class IV

ILAE Methodology: From Evidence to Recommendations

- Recommendations – 6 Levels
  - Level A: ≥1 Class I RCTs or meta-analysis OR ≥2 Class II RCTs
  - Level B: 1 Class II RCTs or meta-analysis
  - Level C: ≥2 Class III double-blind or open-label studies
  - Level D: 1 Class III double-blind or open label
  - Level E: ≥1 class IV OR expert opinion
  - Level F: Positive evidence of lack of efficacy OR Significant risk of seizure aggravation based on Class I–IV evidence

A and B AED should be considered for initial monotherapy
C AED may be considered for initial monotherapy
D Weak efficacy or effectiveness data available to support the use of the AED for initial monotherapy

Summary of Evidence

Seizure / Epilepsy syndrome	Class I	Class II	Class III
Partial onset, adults	2	1	30
Partial onset, children	1	0	17
Partial onset, elderly	1	1	2
GTCS, adults	0	0	23
GTCS, children	0	0	14
Absence seizures, children	0	0	6
BECTS	0	0	2
Juvenile myoclonic epilepsy	0	0	0

Summary of Recommendations

Seizure / Epilepsy syndrome	Level A	Level B	Level C
Partial onset, adults	CBZ,PHT	VPA	GBP,LTG,OXC,PB,TPM,VGB
Partial onset, children	OXC	None	CBZ,PB,PHT,TPM,VPA
Partial onset, elderly	GBP,LTG	None	CBZ
GTCS, adults	None	None	CBZ,LTG,OXC,PB,PHT, TPM,VPA
GTCS, children	None	None	CBZ,PB,PHT,TPM,VPA
Absence seizures, children	None	None	ESM,LTG,VPA
BECTS	None	None	CBZ,VPA
JME	None	None	None

Issues with Evidence Based Guidelines

- How can evidence based guidelines come to different conclusions and recommendations?
- What is the half-life of the validity of a guideline?
- How relevant are evidence based guidelines for clinical practice?

Recommendations by different guidelines

Seizure	NICE	AAN*	ILAE
Partial onset	CBZ	GBP, LTG, TPM, OXC	CBZ, PHT
Generalized onset	VPA		None
Absence		LTG	None

*AAN assessed only newer generation

AAN vs. ILAE

Reference	AAN	ILAE	Downgrade motive
Chadwick 1998 GBP	I	III	Forced exit
Brodie 1995 LTG	I	III	DNIB >30%
Brodie 1999 LTG	I	II	Short duration
Steiner 1999 LTG	I	III	DNIB >30%
Gilliam 2003 TPM	I	III	Forced exit
Privitera 2003 TPM	I	III	DNIB >30%
Bill 1997 OXC	I	III	DNIB >30%
Christie 1997 OXC	I	III	DNIB >30%
Dam 1989 OXC	I	III	DNIB >30%
Guerreiro OXC	I	I	
Trudeau GBP	I	III	Short duration

Guidelines
Weaknesses & Limitations

- Includes in assessment only few of several variables of importance for drug selection
- Penalizes non-blinded randomized studies that could be of high relevance
- Compares AEDs with respect to level of evidence for efficacy/effectiveness not actual difference in efficacy/effectiveness
  -Lack of evidence for efficacy is not equal to evidence of lack of efficacy
  -Better evidence of efficacy is not equal to evidence of better efficacy
- Lack of evidence leaves the prescriber with poor support
- Assesses only some types of seizures/syndromes

Issues with Evidence based Guidelines

- How can evidence based guidelines come to different conclusions and recommendations?
- What is the half-life of the validity of a guideline?
- How relevant are evidence based guidelines for clinical practice

RCTs published after major guidelines

- LEV vs. CBZ-ER in newly diagnosed with partial onset Brodie et al. Neurology 2007; 68: 402-8
- LTG vs. CBZ-ER in elderly newly diagnosed Saetre et al Epilepsia 2007;48:1293
- CBZ vs. LTG, TPM, GBP, OXC in newly diagnosed with presumed partial onset SANAD A
- VPA vs. LTG, TPM in newly diagnosed with presumed generalized/unclassified onset SANAD B

Marson et al. The Lancet 2007;369;1000-15/1016-29

SANAD
Standard And New Antiepileptic Drugs

- The largest comparative RCT of AEDs in newly diagnosed epilepsy
- A Class III RCT according to ILAE Criteria but with the aim to mimic as much as possible clinical practice
- A compromise between the rigour of the RCT and the flexibility of clinical practice

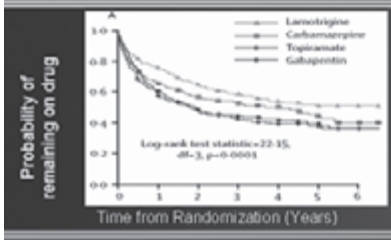
Marson et al. The Lancet 2007;369;1000-15/1016-29.

SANAD
Standard And New Antiepileptic Drugs

- "Objective: To assess the clinical effectiveness and cost effectiveness of new versus standard AEDs given as monotherapy in epilepsy"
- Prospective, randomized open study coparing old and newer AEDs (n=2437)
- Those considered suitable for CBZ randomized to CBZ, LTG, TPM, OXC or GBP SANAD A
- Those considered suitable for VPA randomized to VPA, LTG or TPM SANAD B
- Primary endpoint: Time to treatment failure

Marson et al. The Lancet 2007;369;1000-15/1016-29.

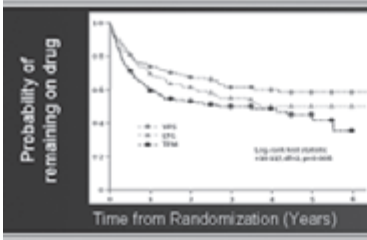
Results and Conclusions Arm A



Marson et al. The Lancet 2007;369;1000-15/1016-29

- Lamotrigine is significantly less likely to fail than CBZ, GBP, TPM
- Lamotrigine efficacy is similar to carbamazepine and approaches non-inferiority
- **Lamotrigine should be considered the first line AED for patients with partial onset seizures**

Results and Conclusions Arm B



Marson et al. The Lancet 2007;369;1000-15/1016-29

- Valproate is significantly more effective than lamotrigine
- Valproate is significantly better tolerated than topiramate
- **Valproate should remain first line treatment for generalised onset seizures or unclassified seizures**

SANAD
Concerns with design & interpretation

- Open design, likely to influence patients'/physicians' decisions (Class III according to ILAE criteria)
- SANAD-A: CBZ arm disadvantaged by
  - use of suboptimal formulation
  - unnecessarily high initial target dose (600mg)
  - inclusion of generalized/unclassified seizures
- SANAD-B: TPM arm disadvantaged by
  - inclusion of patients with absence siezures
- Randomization and intepretation based on physicians' drug preference rather than seizure type makes little biological sense and hampers generalisation of results

Issues with Evidence Based Guidelines

- How can evidence based guidelines come to different conclusions and recommendations?
- What is the half-life of the validity of a guideline?
- How relevant are evidence based guidelines for clinical practice?

Variables Affecting Initial AED Selection

AED-specific	Patient-specific	Nation-specific
• Seizure type or epilepsy syndrome specific efficacy or effectiveness	• Genetic background	• AED availability
• Dose-dependent adverse effects	• Age	• AED cost
• Idiosyncratic reactions	• Gender	• Insurance coverage
• Chronic toxicities	• Comedications	
• Teratogenicity	• Comorbidities	
• Carcinogenicity	• Insurance coverage	
• Pharmacokinetics	• Ability to swallow pills / tablets	
• Interaction potential		
• Formulations		

ILAE Treatment Guidelines: Evidence Based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes

Variables Affecting Initial AED Selection Assessed in Guidelines

AED-specific	Patient-specific	Nation-specific
• Seizure type or epilepsy syndrome specific efficacy or effectiveness	• Genetic background	• AED availability
• Dose-dependent adverse effects	• Age	• AED cost
• Idiosyncratic reactions	• Gender	• Insurance coverage
• Chronic toxicities	• Comedications	
• Teratogenicity	• Comorbidities	
• Carcinogenicity	• Insurance coverage	
• Pharmacokinetics	• Ability to swallow pills / tablets	
• Interaction potential		
• Formulations		

ILAE Treatment Guidelines: Evidence Based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes

Clinical Trials vs Clinical Practice
Which drug for Epilepsy X?

Evidence-based guideline

- May provide information on which AED(s) have the best level of evidence for efficacy/effectiveness
- Does not necessarily mean evidence of best efficacy

Clinical practice

- We need to know which AED would be the best choice for patient Y with Epilepsy X
  - gender
  - age
  - socio-economics
  - co-morbidity
  - concurrent medication

Clinical Trials vs Clinical Practice
How shall I use the drug?

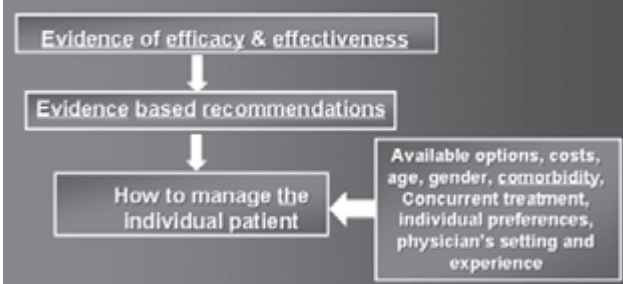
Evidence-based guideline

- ?

Clinical practice

- Likely to provide information on suitable titration rates, target doses etc.

Guidelines & Management of the Individual Patient (Clinical Practice)



Integrating evidence from RCTs and experience from clinical practice

1. Identify patient's type of seizures/epilepsy
2. Check guidelines to find the AEDs with acceptable level of evidence
3. Choose the AED which best matches the relevant individual patient characteristics
   - -age
   - -gender
   - -comorbidity
   - -concurrent medication
   - -etc..

General recommendations 1st line monotherapy adults

Seizure	NICE	AAN*	ILAE	SANAD
Partial onset	CBZ	GBP, LTG, TPM, OXC	CBZ, PHT	LTG
Generalized onset	VPA		None	VPA
Absence		LTG	None	

*AAN assessed only newer generation

Recommendations special populations

- Women of childbearing potential
  - VPA if possible avoided
  - Selection in IGE: LTG? LEV? CBZ??
- The elderly
  - Low dose CBZ-ER after all?
- Polulations prone to drug-drug interactions
  - Some interactions best avoided (with warfarin, anti-AIDS, anti-neoplastics, OCs??)
- Co-morbidities of relevance for AED selection
  - hepatic and renal failure
  - psychiatric conditions, obesity, osteoporosis

Journal club
G. Avanzini/E Perucca/T Tomson/ M. Bialer

Programa – 11.02.2008

Morning session – 9:00 – 13:00

- Spectrum of efficacy of AEDs - G. Avanzini (Italy)
- Adverse effects of AEDs E. Perucca (Italy)
- When to start treatment and how? -T. Tomson (Sweden)

Afternoon session – 14:30-18:30

- Dose optimization and therapeutic drug monitoring - T. Tomson (Sweden)
- Seizure aggravation - E. Perucca (Italy)
- Interactive case discussions - G. Avanzini/E Perucca/T Tomson

Spectrum of efficacy of AEDs

G. Avanzini (Italy)

Adverse effects of AEDs
Emilio Perucca (Italy)

Adverse Effects of Antiepileptic Drugs

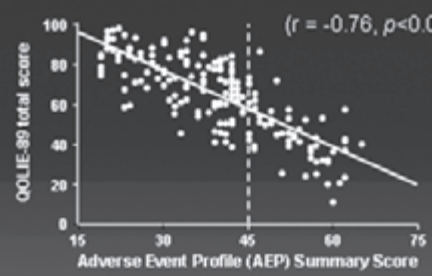
Emilio Perucca
Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE Course, 11 February 2008

Adverse Effects of AEDs

- A major cause of treatment failure (up to 40% of patients) - some potentially life threatening
- Highly prevalent (up to 60% or more in a typical epilepsy clinic population)
- Differ greatly from drug to drug
- The most important consideration for AED selection in individual patients

Adverse Effects of AEDs: Impact on Quality of Life



Gilliam FG *et al. Neurology* 2004; 62:23-27

Tools for the Detection of Adverse Effects

- Randomized controlled trials (RCTs)
- Uncontrolled studies
- Pharmacosurveillance studies: cohort, case control, PEM
- Spontaneous reports

Randomized Controlled Trials as Tools for the Detection of Adverse Effects

Strengths	Weaknesses
• Assessment of background noise (placebo)	• "Artificial" populations
• Denominator known (reliable incidence and prevalence)	• Inflexible dosing schemes
• Ideal to assess relation with dose	• Short follow-up
• Minimization of bias	• Unsuitable to pick-up rare or delayed AEs
• Sensitivity dependent on methodology	

Advantages and Limitations of a Check-List vs Spontaneous Reporting

Advantages	Weaknesses
• Minimizes risk of missing adverse experience	• Leads to overestimation of real incidence
• Excludes that failure of reporting is due to overlooking	• Biased towards those effects that are already known
• Allows detailed and quantitative investigation of specific adverse effects	

VPA and CBZ in Adults with Newly Diagnosed Epilepsy: Most Common Adverse Effects

	Mattson et al 1992		Richens et al 1994	
	VPA, % (N=240)	CBZ, % (N=231)	VPA, % (N=140)	CBZ, % (N=141)
Tremor	45	22*	6	2
Sedation, fatigue	42	41	19	26
GI symptoms	33	28	9	11
Weight gain	20	8*	15	1*
Hair loss	12	6	4	1
Nystagmus	26	30	0	0
Dizziness	23	29	4	8
Ataxia	23	25	0	3
Mood changes	25	24	3	3
Skin rashes	1	11*	2	1

Mattson et al. N Engl J Med 1992;327:765; Richens et al J Neurol Neurosurg Psych 1994;57:682..

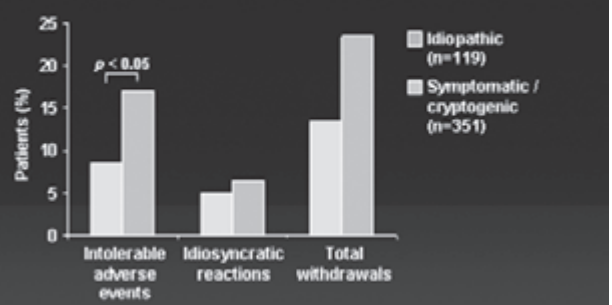
Elusive Adverse Effects

- Rare adverse effects (incidence <0.1%)
- Effects which are bizarre of unexpected based on kown drug properties (e.g., shoulder-hand syndrome with barbiturates)
- Effects which overlap with underlying pathology (e.g., psychiatric disorders, seizure aggravation)
- Effects requiring special testing for detection (e.g., visual field loss)
- Effects with delayed onset (e.g., osteomalacia)

Classification of Adverse Drug Effects

- Type A Related to the primary or ancillary drug's mechanisms of action – common, usually dose dependent and reversible
- Type B Idiosyncratic, related to individual vulnerability (immunologic, genetic or other mechanisms)
- Type C Long- term (chronic) or delayed effects
- Type D Teratogenic and cancerogenic effects
- Type E Adverse drug interactions

Withdrawal due to Adverse Events in New-onset Epilepsy



Kwan, Brodie. *Epilepsia* 2001;42:1255-60

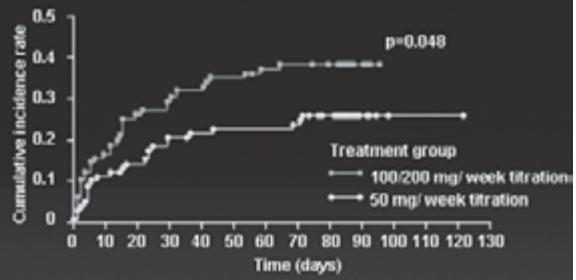
Dose-Related Type A Adverse Effects (AEs)

- Can affect any system, most commonly the CNS
- Frequent AEs include somnolence, other sleep disturbances, headache, dizziness, ataxia, and changes in cognition, mood or behavior
- Related to serum drug concentration, but also to titration rate

Titration Side Effects

- Occur when the drug is titrated up too fast (often a consequence of suboptimal regulatory trials) – also applicable to idiosyncratic reactions
- Aggravated by drug promotion (fast titration being wrongly perceived as a major advantage)
- A concern with all AEDs – some more than others
- Minimized by the "start low – go slow" principle

Cumulative Incidence of Adverse Events Leading to TPM Dose Reduction or Discontinuation (adjunctive therapy, epilepsy)



Biton et al, Ann Pharmacother 2001;35:173-9

Dose-Related Type A Adverse Effects: Risk Factors beyond Titration

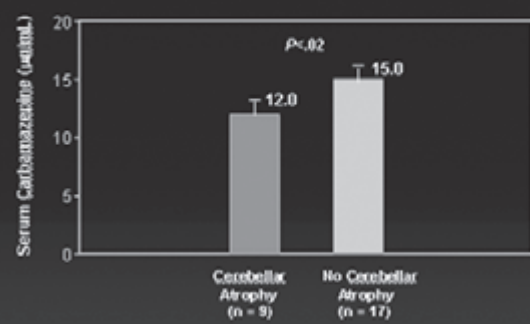
- Genetic factors (e.g., genotypes affecting AED clearance)
- Epilepsy syndrome (risk for seizure aggravation)
- Co-morbidities
- Age (particularly old age!)
- Comedication

CYP2C9 and 2C19 Genotype and Severe Phenytoin Intoxication

- A 31-year-old woman was started on phenytoin 300 mg/d
- After 9 days → dysarthria, nystagmus, dysmetria, hemifacial dyskynesias and altered mental status
- Phenytoin level >100 μg/mL – Phenytoin half-life 103 h !
- Genotype: CYP2C9*3/*3 and CYP2C19*1/*2

Brandolese et al, Clin Pharmacol Ther 2001;70:391-4

Threshold Serum Carbamazepine Concentrations Causing Ataxia



Specht et al. *Arch Neurol* 1997; 54:427-31.

Increased Pharmacodynamic Sensitivity in Old Age?

VA Cooperative Studies #118 & #264

Mean Plasma Concentration in Patients With Adverse Effects (μg/mL)

Age	CBZ	VPA
<40	7.4	79.5
40-64	5.9	83.7
≥65	3.6	66.3

Ramsay et al. *Epilepsia*. 1994;35(suppl 8):91A.

Influence of Comedication on TPM Tolerability: Most Common AEs in TPM Double-Blind Trials

	% Patients		
	Monotherapy TPM 200/500 mg (N=71)	Adjunctive Therapy Placebo (N=291)	Adjunctive Therapy TPM 200-400mg (N=183)
Somnolence	13	12	29
Dizziness	13	15	25
Ataxia	6	7	16
Nervousness	6	6	16
Abnormal vision	3	2	13
Psychomotor slowing	6	2	13
Speech disorders	1	2	13
Memory difficulty	8	3	12
Confusion	6	5	11
Paresthesia	35	4	11

*Incidence ≥10% and ≥5% difference in incidence vs placebo
Monotherapy 16 wks; adjunctive therapy 12-16 wks

Rate 1998; Arroyo, 2003

Minimizing Type A Adverse Effects

- Chose AED least likely to cause AEs in the individual – strive for syndromic diagnosis, consider contraindications
- Unless situation dictates otherwise, start low and go slow – inform patient about possible AEs
- Optimize formulation, dosing schedule and target dose - monitor response carefully
- Identify individuals at special risk

Avoid overtreatment !!!

Using Serum Drug Levels to Minimize Toxicity

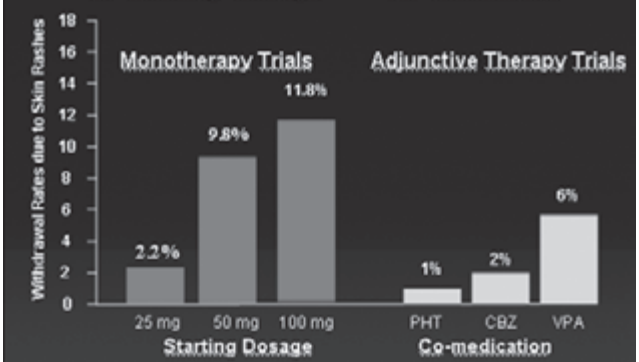
- May be used to prevent exposure to very high levels, likely to cause toxicity
- Allow to prevent toxicity from pharmacokinetic drug interactions
- Aid in the diagnosis of toxicity in special cases (e.g., patients with inability to communicate)
- For phenytoin, invaluable to decide on magnitude of dose increments

Diagnosis of toxicity is clinical, not biochemical!

Idiosyncratic Adverse Reactions

- Unrelated to the known mechanisms of action of the drug
- Occur in a minority of susceptible individuals, irrespective of dosage
- Etiology multifactorial – from genetic metabolic defects to immune-mediated hypersensitivity
- Usually occur within days or months - may related to dose and titration rate
- Poorly predictable, but risk factors may be known

Lamotrigine: Withdrawal Rates due to Skin Rash vs Starting Dosage and Co-Medication



Gubermann et al., Epilepsia 1999;40:985-91; Messenheimer et al, Drug Safety 1998;18:281-6

Predicting Idiosyncratic Drug Reactions Special Risk Groups

Reaction	Incidence	
LTG-induced Stevens-Johnson syndrome	Adults Children	1 : 1000 1 : 200 (?)
Fatal VPA hepatotoxicity	Infants Adults	1 : 700 1 : 50,000
PHT-induced skin reactions	Overall Previous rash on CBZ	6-10 % 60%

Hanley's Rule of Three

To have a 95% probability of encountering an adverse reaction, it is necessary to treat a number of patients three times as large as the actual frequency of that reaction in the population

Latent Period for Discovery of Rare or Unusual Adverse Effects

		Incidence	Latent Period	
PB	Shoulder-hand s.	5-12%	1912	1934
PHT	Ostemalacia	up to 5%	1938	1967
FBM	Aplastic anemia	1:3,000	1993	1994
VPA	Hepatotoxicity	1 : 50.000 (1:1000 below 2 years)	1967	1977
VGB	Visual field defects	33%	1989	1997

Some Chronic Adverse Effects of AED Therapy

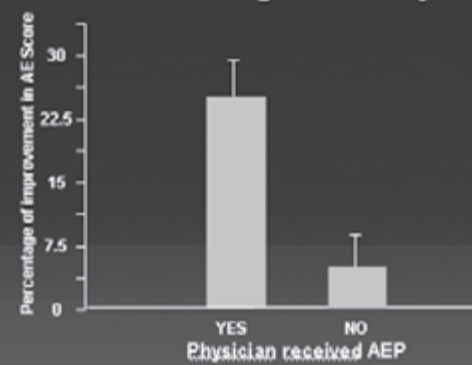
- Visual field defects (vigabatrin)
- Cerebellar atrophy (phenytoin)
- Metabolic and endocrine disorders (including weight changes and sexual dysfunction)
- Bone disorders
- Cosmetic effects

Usefulness of Systematic Screening for Adverse Effects: A Randomized Study

- Prospective study of 200 consecutive patients in an adult epilepsy clinic in St Louis
- The 65 patients with an Adverse Effect Profile (AEP) score ≥45 were randomized to two groups
- In the intervention group, the AEP questionnaire was made available to the clinician. In the control group, the AEP was not made available

Gilliam et al, Neurology 2004; 62:23-27

Usefulness of Systematic Screening for Adverse Effects: Change in Toxicity Scores



Gilliam et al, Neurology 2004; 62:23-27

Minimizing Adverse Effects (AEs) The Seven Commandments

1) Consider individual characteristics and risk factors when chosing an AED
2) Unless otherwise indicated, start low and go slow
3) Inform patient of possible AEs and heralding signs
4) Be aware of adverse drug interactions
5) Monitor response regularly and individualize therapy with appropriate tools (including drug monitoring)
6) Comply with drug surveillance regulations
7) Do not seek seizure control at all costs!

When to start treatment and how?
Torbjörn Tomson (Sweden)

When to start treatment and how

LASSE II
Sao Paulo 2008
Torbjorn Tomson

When?

When the benefits of treatment outweigh the risks and drawbacks

When?

Etiological insult
↓ ←
First seizure
↓ ←
Seizure recurrence
↓ ←
Chronic epilepsy

Factors to consider

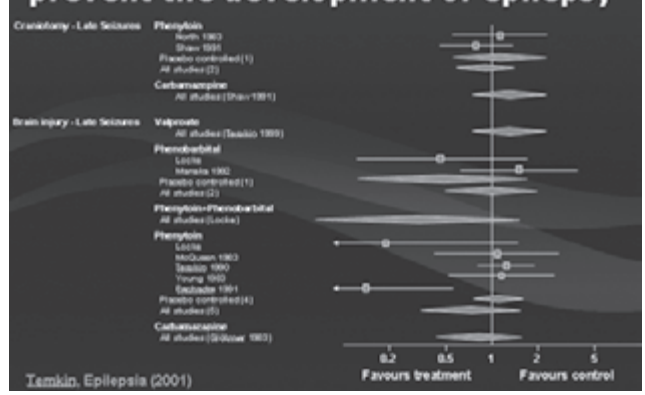
1. Which are the risks with withheld treatment?
   -what is the natural course?
   -which are the risks if seizures occur?
2. What are the possibilities with treatment?
3. What are the risks and drawbacks with treatment?

- Should result in an individual risk/benefit analysis of all available options

When?

Etiological insult
↓ ←
First seizure
↓
Seizure recurrence
↓
Chronic epilepsy

Prophylactic use of AEDs does not prevent the development of epilepsy



Temkin, Epilepsia (2001)

When?

Etiological insult

↓

First seizure

↓ ←

Seizure recurrence

↓

Chronic epilepsy

1. Prognosis without treatment

- Risk of recurrence
  - -after a first seizure
  - -after several seizures
- Risk factors
  - -provoked vs. unprovoked seizure
  - -other risk factors

1. Prognosis without treatment

- Risk of recurrence
  - -after a first seizure
  - -after several seizures
- Risk factors
  - -provoked vs. unprovoked seizure
  - -other risk factors

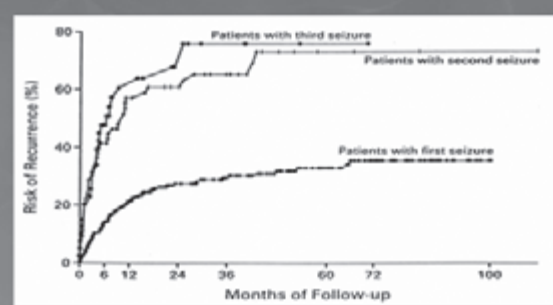
Provoked vs. unprovoked Acute symptomatic seizures

- Within a week after a stroke
- Within a week after a brain trauma
- In the acute phase of a CNS-infection
- In relation to intra-cranial surgery
- Toxic provocations (drugs, alcohol)
- Abstinence
- Metabolic disturbances
- Other…

1. Prognosis without treatment

- Risk of recurrence –unprovoked seizures
  - -after a first seizure
  - -after several seizures
- Risk factors
  - -provoked vs. unprovoked seizure
  - -other risk factors

Recurrence risk after 1st, 2nd, and 3rd unprovoked seizure



Hauser et al, New Eng J Med 1998; 338:429

Recurrence after a first unprovoked seizure, Meta-Analysis

- Recurrence
  - *Mean 51%*
  - *Range 23-71%*
- Risk factors
  - *Known etiology*
  - *Epileptiform activity on EEG*
  - *Seizures during sleep*
  - *Partial seizures*

Berg & Shinnar Neurology (1991)

1. Prognosis without treatment

- Recurrence risk
  - 40-50% after 1st unprovoked seizure
  - higher if underlying etiology, partial, EEG abnormalities
  - 60-80% after 2nd and 3rd seizure

Factors to consider

1. Which are the risks with withheld treatment?
   - what is the natural course?
   - which are the risks if seizures occur?
2. What are the possibilities with treatment?
3. What are the risks and drawbacks with treatment?

- Should result in an individual risk/benefit analysis of all available options

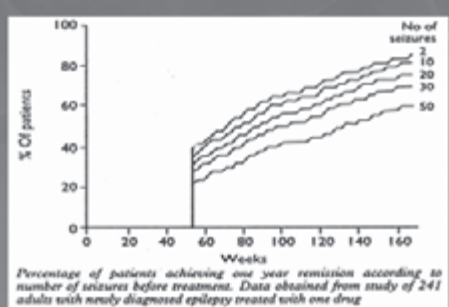
Do seizures beget seizures?

Interval between successive seizures, median (SD) weeks

1st-2nd seizure	12 (4-28)
2nd-3rd seizure	8 (4-16)
3rd-4th seizure	4 (2-23)
4th-5th seizure	3 (2-4)

Elwes et al 1988

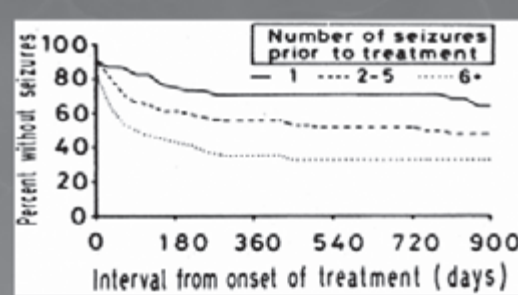
Do untreated repeated seizures affect long term prognosis?



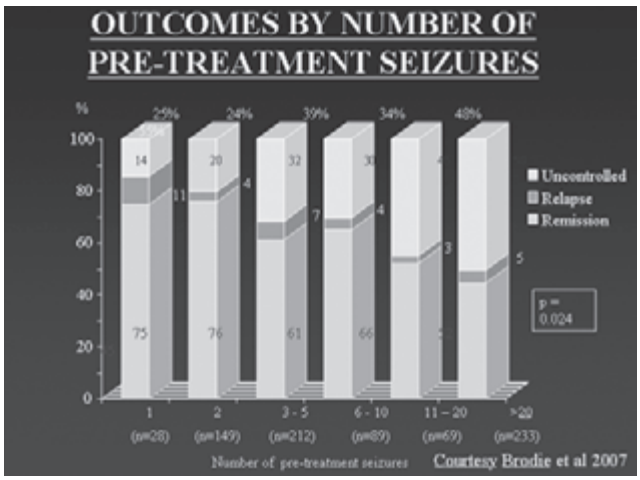
Percentage of patients achieving one year remission according to number of seizures before treatment. Data obtained from study of 241 adults with newly diagnosed epilepsy treated with one drug

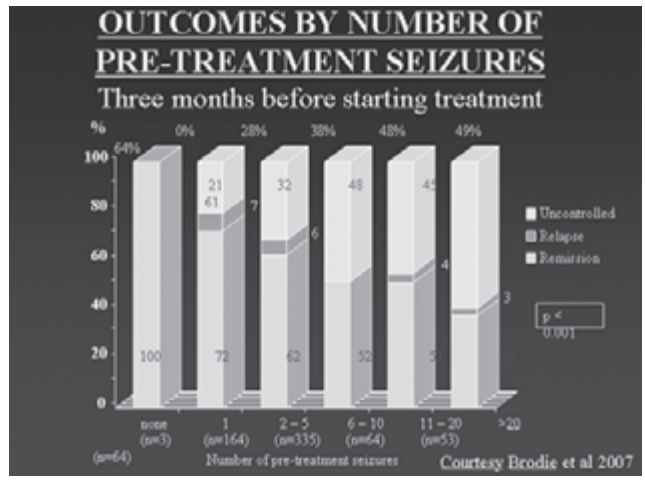
Reynolds EH

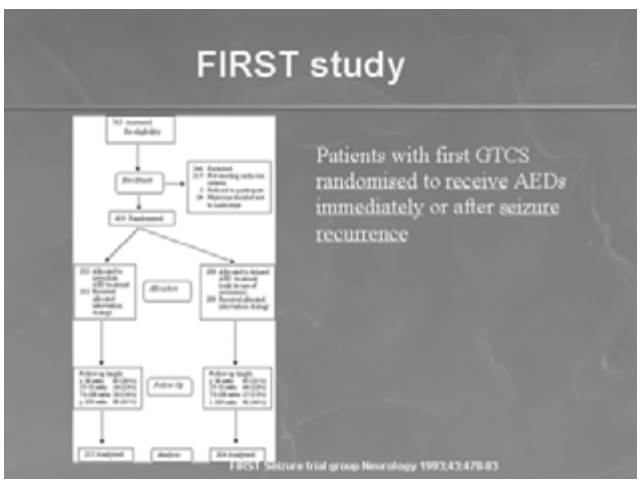
Risk of relapse as a function on number of seizures before treatment

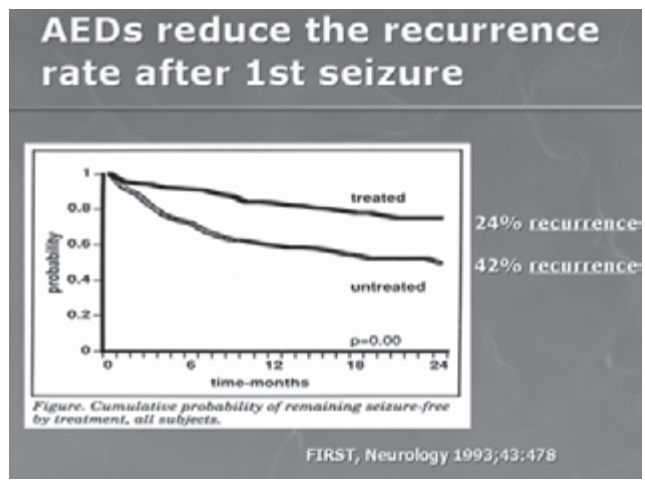


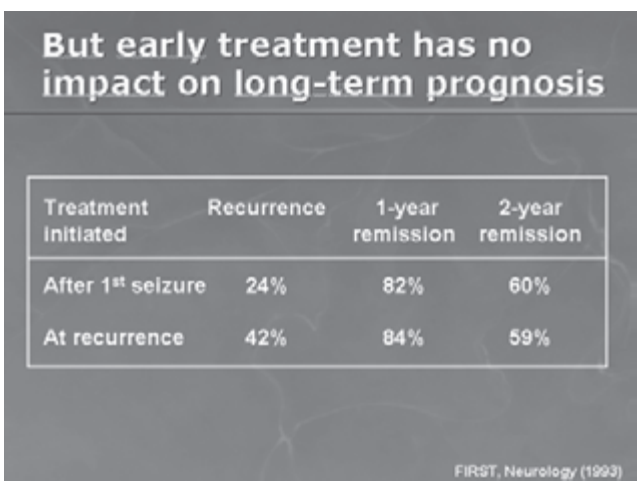
Beghi & Tognoni Epilepsia 1988

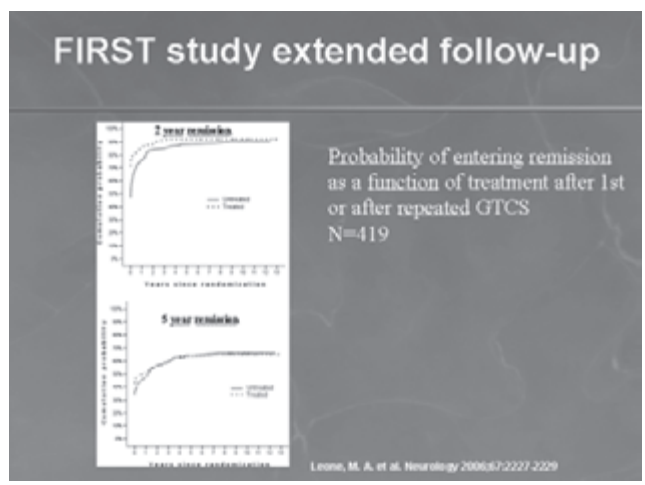

OUTCOMES BY NUMBER OF PRE-TREATMENT SEIZURES
%
25%
24%
39%
34%
48%
100
80
60
40
20
0
14
11
20
4
32
7
4
3
5
75
76
61
66
Uncontrolled
Relapse
Remission
p = 0.024
1 (n=28)
2 (n=149)
3 - 5 (n=212)
6 - 10 (n=89)
11 – 20 (n=69)
>20 (n=233)
Number of pre-treatment seizures
Courtesy Brodie et al 2007


OUTCOMES BY NUMBER OF PRE-TREATMENT SEIZURES
Three months before starting treatment
%
64%
0%
28%
38%
48%
49%
100
80
60
40
20
0
21
61
7
32
6
48
4
3
100
72
62
Uncontrolled
Relapse
Remission
p < 0.001
none (n=3)
1 (n=164)
2 – 5 (n=335)
6 – 10 (n=64)
11 – 20 (n=53)
>20 (n=64)
Number of pre-treatment seizures
Courtesy Brodie et al 2007

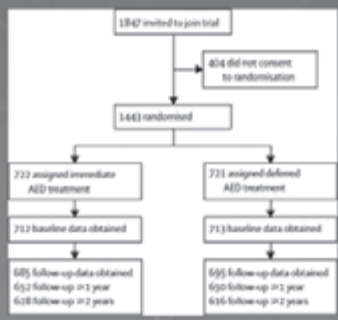

FIRST study
Patients with first GTCS randomised to receive AEDs immediately or after seizure recurrence
FIRST Seizure trial group Neurology 1993;43:478-83


AEDs reduce the recurrence rate after 1st seizure
probability
1
0.8
0.6
0.4
0.2
0
treated
untreated
p=0.00
0
6
12
18
24
time-months
Figure. Cumulative probability of remaining seizure-free by treatment, all subjects.
24% recurrence
42% recurrence
FIRST, Neurology 1993;43:478


But early treatment has no impact on long-term prognosis
Treatment initiated
Recurrence
1-year remission
2-year remission
After 1st seizure
24%
82%
60%
At recurrence
42%
84%
59%
FIRST, Neurology (1993)

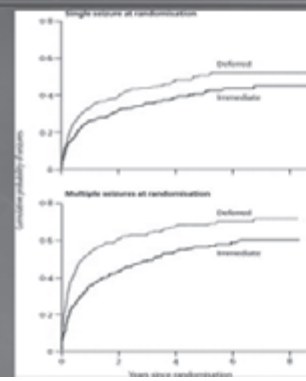

FIRST study extended follow-up
2 year remission
5 year remission
Probability of entering remission as a function of treatment after 1st or after repeated GTCS
N=419
Leone, M. A. et al. Neurology 2006;67:2227-2229

Immediate vs. deferred treatment The MESS study



Marson et al, Lancet 2005;365 2007-2013

Cumulative proportion of patients with first seizure after randomisation



Seizure during follow-up:
43% in immediate group
53% in deferred group

Seizure free at 3-5 years:
76% in immediate group
77% in deferred group

Prediction of risk of recurrence after a single seizure and early epilepsy

Starting value		
One seizure prior to presentation		0
Two or three seizures prior to presentation		1
Four or more seizures prior to presentation		2
Add if present		
Neurological disorder or deficit, learning disability, or developmental delay		1
Abnormal EEG		1
Risk classification group for seizure recurrence†		**Final score**
Low risk		0
Medium risk		1
High risk		2–4

	Treatment allocation	Probability of seizure by 1 year	Probability of seizure by 3 years	Probability of seizure by 5 years
Low risk	Start	0·26	0·35	0·39
	Delay	0·19	0·28	0·30
Medium risk	Start	0·24	0·35	0·39
	Delay	0·35	0·50	0·56
High risk	Start	0·36	0·46	0·50
	Delay	0·59	0·67	0·73

RCTs on effect of AEDs on seizure recurrence after new onset seizures

(with/without AED,%)

Study	N	1 year	2 years	5 years
Chandra 1992	228		4%/56%*	
Camfield 1989	31	14%/53%		
FIRST 1993	397		25%/51%	
Gilad 1996	87	13%/59%	20%/68%	
Das 2000	76		11%/45%**	
Marson 2005	812		32%/39%	42%/51%

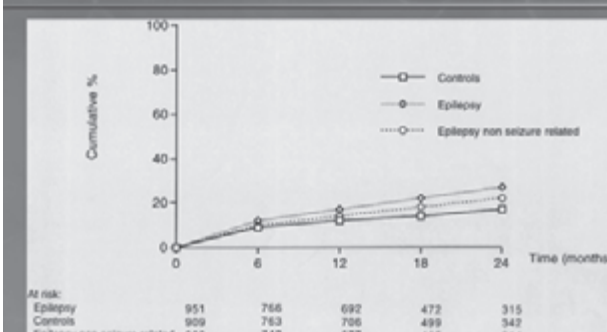
*Follow-up 9 months to 5 years
**Follow-up between 1 and 2 years

After Ryvlin Curr Opin Neurol 2006;19:154-156

1. Risks with uncontrolled seizures

- Worse long-term prognosis
- Loss of control and secondary psycho-social consequences
- Physical injuries
- Mortality

Risk for accidents and injuries



Beghi & Cornaggia, Epilepsia 2002; 43:1076

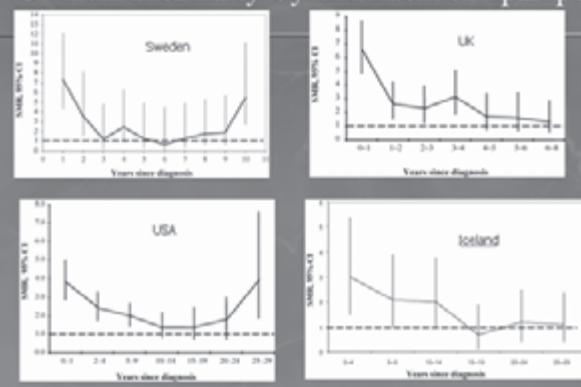
Mortality after a first unprovoked seizure

Hauser et al. 1980 **SMR 2,3 (1,5-3,3)**

Musicco et al. 1997 **SMR 3,4 (1,5-6,4)***

*Only patients with GTCS

Overall mortality by duration of epilepsy



Cause specific mortality

- **Causes of death:**
  - *not related to epilepsy*
  - *related to the underlying cause of epilepsy*
  - *related to the treatment of epilepsy*
  - *related to epilepsy and seizures*
    - Status epilepticus
    - Accidents
    - SUDEP

SUDEP rare among patients with new onset epilepsy

- **792 newly diagnosed patients followed up to 14 years, total 11,400 person-years**
- **1 SUDEP**
- **0.09/1,000 person-year**

NGPSE Lhatoo et al Ann Neurol 2001

Injuries and mortality as reason for early treatment

- **Seizure related injuries uncommon and risk of accidents marginally increased early in the course of epilepsy**
- **Excess mortality mainly related to the cause of epilepsy**
- **SUDEP and seizure related death rare in newly diagnosed epilepsy**

Immediate vs. deferred treatment The MESS study

"The two policies did not differ with respect to quality of life outcomes or serious complications"

Marson et al. Lancet 2005;365:2007-2013

Factors to consider

1. Which are the risks with withheld treatment?
   - -what is the natural course?
   - -which are the risks if seizures occur?
2. What are the possibilities with treatment?
3. What are the risks and drawbacks with treatment?

- Should result in an individual risk/benefit analysis of all available options

2. Efficacy of treatment

- AEDs do not prevent the development of epilepsy in high risk patients
- Early treatment does not seem to modify long-term prognosis
- Treatment is in general symptomatic
- AEDs reduce by up to 50% recurrence risk after first unprovoked seizure
- At least 50% of patients with newly diagnosed epilepsy respond to the first AED tried (e.g. Kwan & Brodie 2000)

3. Risks and drawbacks with treatment

- Costs
- Require regular intake
- Regular check-ups needed
- Adverse effects
  - -acute dose-dependent
  - -chronic
  - -idiosyncratic
  - -teratogenic

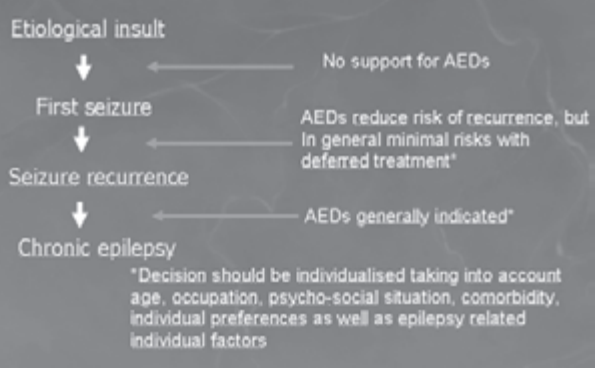
How many discontinue treatment due to AE?

Reaction to first tried AED

Unbearable AE	69	15%
Idiosyncratic AE	29	6%
Withdraw for other reasons	37	8%
Poor efficacy	113	24%
Continued treatment	222	47%
TOTAL	470	100%

Kwan & Brodie NEJM 2000

To treat or not to treat



*Decision should be individualised taking into account age, occupation, psycho-social situation, comorbidity, individual preferences as well as epilepsy related individual factors

How?

Objective of treatment

To find the lowest effective dose that controls seizures completely without causing adverse effects

How to do it
The common treatment strategy

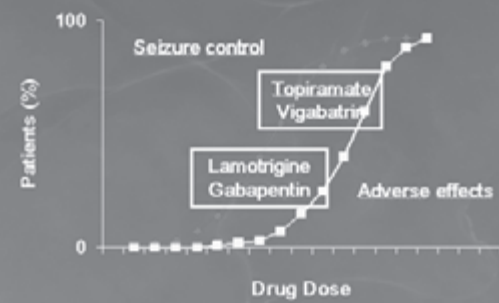
- Start low
- Go slow

1. Selection of titration rate to initial target dosage
2. Selection of initial target dosage
3. Gradual increase of maintenance dosage until seizure control or dose-related adverse effects

Time for titration

After Perucca et al CNS Drugs 2001

Which dose?
Dose-effect relationship

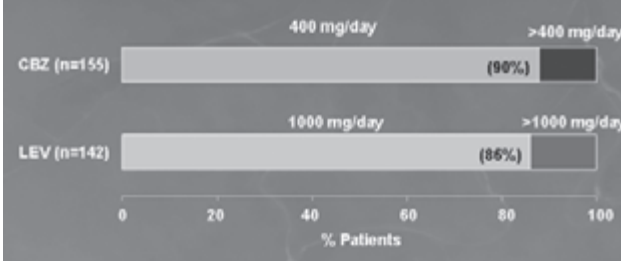


Which target dosage?

After Perucca et al CNS Drugs2001

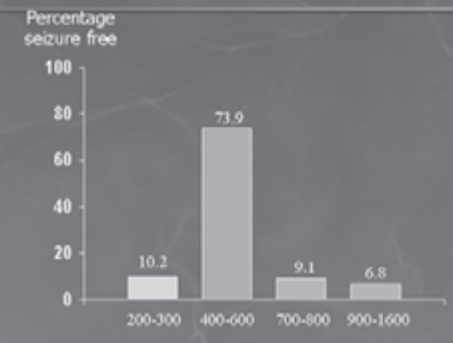
	Initial target mg/day	Usual maintenance mg/day	Max dosage mg/dag
Phenobarbital	50-100	50-200	?
Phenytoin	200-300	200-400	?
Carbamazepine	400-600	400-1600	?
Valproate	500-1000	500-2500	?
Oxcarbazepine	600-900	600-3000	?
Lamotrigine	50-100	50-200	?
Gabapentin	900-1800	900-3600	?
Topiramate	100	100-400	?
Tiagabine	15-30	15-50	?
Levetiracetam	1000-2000	1000-3000	?
Zonisamide	200	200-500	?
Felbamate	1800-2400	1800-3600	?

Newly Diagnosed Epilepsy: Distribution of Dosages in Patients Achieving 1-Year Remission



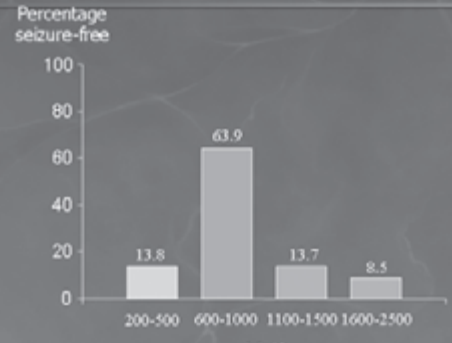
Brodie et al. Neurology 2007; 68: 402-8

CARBAMAZEPINE DOSE IN SEIZURE FREE PATIENTS



Kwan P and Brodie MJ, Epilepsia 2001; 42: 1255-60

VALPROATE DOSE IN SEIZURE FREE PATIENTS



Kwan P and Brodie MJ, Epilepsia 2001; 42: 1255-60

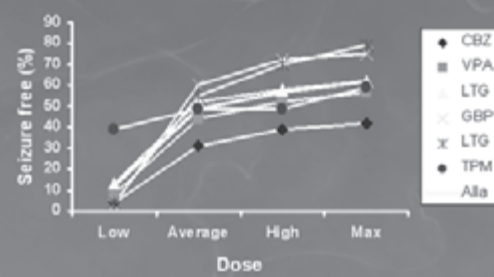
Incremental benefit of increasing maintenance dosage in new onset epilepsy (mg/day)

AED	Low	Average	High	Maximum
CBZ1	200-300	**400-600**	700-800	900-1600
VPA1	200-500	**600-1000**	1100-1500	1600-2500
LTG1,2	50-100	**125-200**	200-300	300-600
GBP2	1200	**1800**	2400	3600
TPM3	50	**50-100**	100-200	200-500

1. Kwan & Brodie 2001; 2. Brodie et al 2002; 3. Chadwick et al 1999

After Deckers et al Epilepsy Res 2003

Incremental benefit of pushing the dosage



After Deckers et al 2003

Incremental benefit of pushing the dosage

- Up to 80% of those who become seizure free on a drug do so at low-average dosage
- 10% of those who continue to have seizures on high dosage would become seizure free on maximum tolerated dosage

Strategy for selection of target dosage

- Is it reasonable to aim at a low initial target dosage?
- Is it reasonable to push the dosage to maximum tolerated in initial non-responders?

Strategy 1
Start low and increase if seizures

PRO

- Avoid unnecessary reversible dose-related adverse effects
- Reduce risks of idiosyncratic adverse effects?
- Reduce risks of chronic adverse effects?
- Increase overall tolerability?

CON

- Exposure to unnecessary seizures in about 20%

Strategy 2
Higher target dosage, decrease if adverse effects

PRO

- 20% more will be controlled from onset
- Reduced risk of adverse effects of seizures
  - drivers licence
  - injuries
  - confidence

CON

- Temporary exposure to unnecessarily high drug dosage
- Increased risk of
  - Reversible AE
  - Idiosyncratic effects?
  - Chronic AE?

Conclusions

- Dosing needs to be tailored to the individual
- Whenever possible, titration to first target dosage should be slow to enhance tolerability
- Target dosage should be defined based on individual pharmacokinetic and dynamic factors and above all on patient preferences
- Low, average or high target dose?
- Maintenance dose adjusted based on clinical response

Dose optimization and therapeutic drug monitoring

Torbjörn Tomson (Sweden)

Dose Optimisation and Therapeutic Drug Monitoring

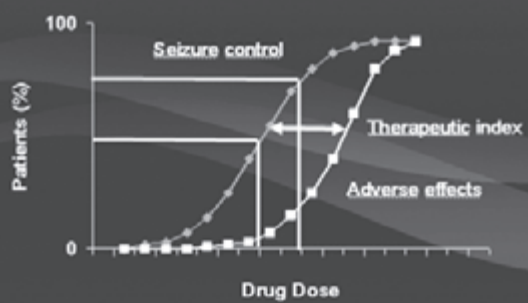
Torbjörn Tomson
Department of Clinical Neuroscience
Karolinska Institute
Stockholm, Sweden

LASSE II 2008

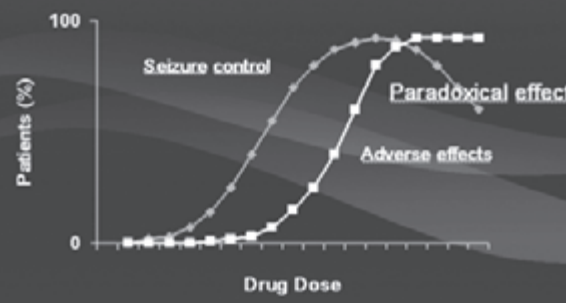
General dosing strategies

- Standard dose, same to all
- Dosing individualised according to clinical response
- Dosing adjusted according to intermediate surrogate markers of effects
- Dosing guided by drug concentrations

Which dose? Dose-effect relationship



Which dose? Dose-effect relationship



Dosing AEDs

- Pronounced inter-individual differences in dose-requirements of AEDs
- Most AEDs have a narrow therapeutic index
- High doses may even have paradoxical effects
- AED dose needs to be tailored to the individual patient

Reasons for individual variability in drug response

- Pharmacokinetic variability
  - Genetic factors
  - Environmental and physiological factors
- Pharmacodynamic variability
  - Genetic, environmental and physiological
    - Type of seizures and epilepsy
    - Etiology
    - Seizure severity
    - Age, comorbidity, concomitant treatment

Genetic Variability in Drug Response

- Metabolic polymorphism
  - Poor metabolisers
  - Extensive metabolisers
  - Hyperextensive metabolisers
- Transporter polymorphism
- Receptor level

Polymorphism of drug metabolism

Enzyme	Drug	Effect	Proportion slow metabolisers
CYP2C9	Warfarin Tolbutamide Phenytoin	Haemorrhage Hypoglycemia Toxicity	1-3 among Caucasians
CYP2C19	Omeprazole Diazepam Mephenytoin Mephenobarbital	Ulcer cure rate Prolonged sedation Toxicity Toxicity	3-5 among Caucasians 15-20 among Asians

Genetic predictors of maximum doses of CBZ and PHT

- Association between max doses in regular use of of CBZ (n=425) and PHT (n=281) and polymorphisms in CYP2C9, PGP, and alfa-subunit of sodium channel studied
- Association found with functional polymorphism in CYP2C9 and PHT max dose and between polymorphism in SCN1A gene and max dose CBZ as well as PHT

Tate, Sarah K. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 5507-5512

Environmental and physiological factors and kinetic variability

- Concomitant medication causing interactions
- Dietary factors
- Concurrent disorders, e.g. hepatic or renal dysfunction
- Age
- Pregnancy

Reasons for individual variability in drug response

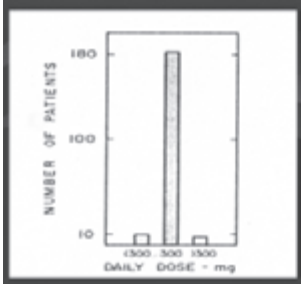
- Pharmacokinetic variability
  - Genetic factors
  - Environmental and physiological factors
- Pharmacodynamic variability
  - Type of seizures and epilepsy
  - Etiology
  - Seizure severity
  - Age, comorbidity, concomitant treatment

Dosing strategies

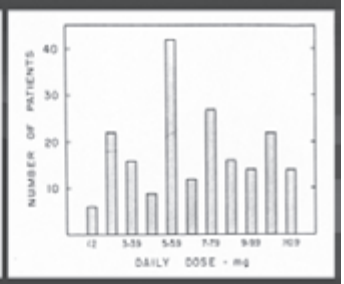
- Standard dose, same to all
- Dosing individualised according to clinical response
- Dosing adjusted according to intermediate surrogate markers of effects
- Dosing guided by drug concentrations

Dosing according to clinical effect or adjusted to intermediate markers

Phenytoin



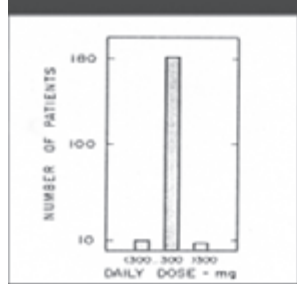
Warfarin

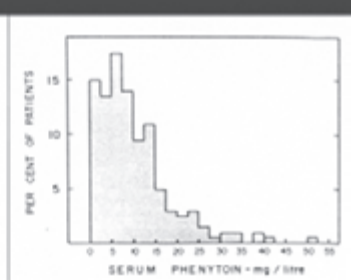


Koch Wagner 1981

Dosing according to clinical effect

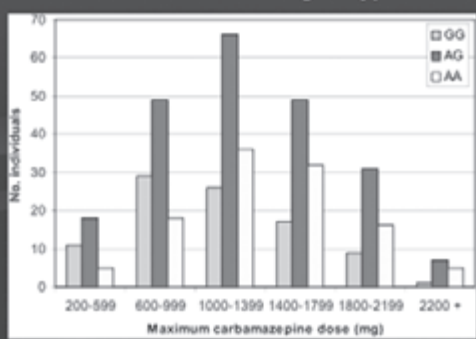
Phenytoin





Koch Wagner 1981

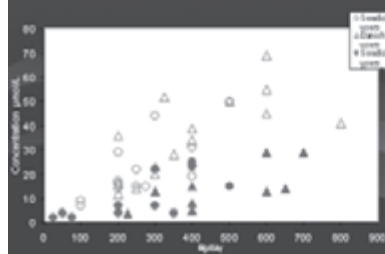
Distribution of maximum carbamazepine doses for each SCN1A IVS5-91 G>A genotype



Tate, Sarah K. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 5507-5512

PNAS

Are we doing better with individualisation?



	Conc. µmol/L	Dose Mg/day
+OC	13	349
-OC	28	327

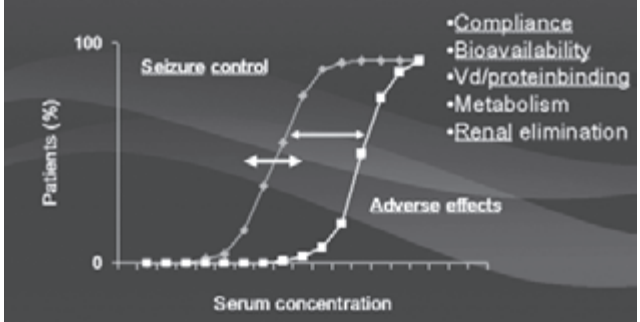
Sabers et al Neurology 2003

Which dose? Dose-effect relationship

Dosing strategies

- Standard dose, same to all
- Dosing individualised according to clinical effect
- Dosing adjusted according to intermediate surrogate markers of effects
- **Dosing guided by drug concentrations**

Which dose? Controlling Kinetic Variability



Therapeutic Drug Monitoring The Concept

- To optimise a patient's clinical outcome by managing their medication regimen with the assistance of measured drug concentrations
- Rests on the assumption that drug levels correlate better with clinical effects than the dose

Antiepileptic Drugs – Best Practice Guidelines for Therapeutic Drug Monitoring: A Position Paper by the Sub-commission on Therapeutic Drug Monitoring, ILAE Commission on Therapeutic Strategies

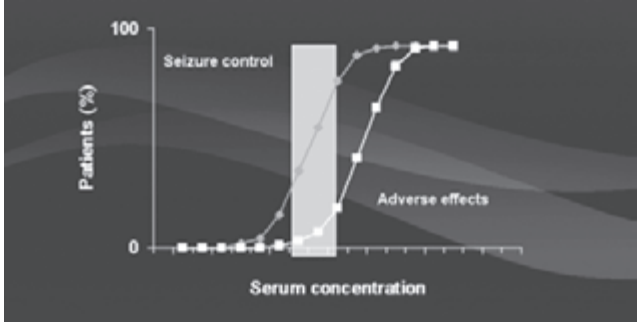
Philip N. Patsalos [1], David J. Berry [2], Blaise F. D. Bourgeois [3], James C. Cloyd [4], Tracy A. Glauser [5], Svein I. Johannessen [6], Ilo E. Leppik [7], Torbjörn Tomson [8], Emilio Perucca [9]

1 - Institute of Neurology/The National Hospital for Neurology and Neurosurgery London and The Chalfont Centre for Epilepsy, Chalfont St Peter, UK
2 - Medical Toxicology Unit, Guys and St Thomas' Hospital, London, UK
3 - Harvard Medical School, Children's Hospital Boston, USA
4 - Center for Orphan Drug Research, College of Pharmacy, University of Minnesota, Minneapolis, USA
5 - Children's Hospital Medical Center, Department of Neurology, Cincinnati, Ohio, USA
6 - The National Center for Epilepsy, Sandvika, Division of Clinical Neuroscience, Rikshospitalet University Hospital, Oslo, Norway
7 - University of Minnesota, Minneapolis, USA
8 - Karolinska University Hospital, Stockholm, Sweden
9 - Institute of Neurology, IRCCS C. Mondino Foundation and Clinical Pharmacology Unit University of Pavia, Pavia, Italy

Reference/target ranges

- The "reference range" is a range of concentrations for a particular drug that is quoted by a laboratory
  - Assumed to be the range of plasma concentrations at which most patients are expected to exhibit an optimal clinical response
  - Often poorly documented
  - The "reference range" is not a "therapeutic range" - the latter can only be determined for the individual patient
  - Concentrations lying within the reference range are not "normal" because the "normal" concentration of an AED is zero.

Reference plasma level range



Reference ranges

- Statistical
- Patients differ
  - type of seizures
  - severity of seizures
  - sensitivity to different blood levels
- Below - if seizures adequately controlled
- Above - if seizures inadequately controlled and if clinical symptoms of toxicity are absent

Reference ranges without lower limits

Richens and Perucca, in: Richens A, Marks V, eds, Therapeutic Drug Monitoring, Churchill-Livingstone, Edinburgh, 1980: 320-348

Phenytoin	Up to 20 μg/mL
Phenobarbital	Up to 40 μg/mL
Carbamazepine	Up to 12 μg/mL
Valproic acid	Up to 100 μg/mL

Reference ranges: Established AEDs

AED	μmol/L
CBZ	up to 51
ETS	up to 708
PB	up to 172
PHT	up to 79
VPA	up to 693

Refefence ranges: New AEDs

AED	mmol/L
FBM	up to 252
GBP	up to 117
LTG	up to 58
LEV	up to 270
TGB	up to 532 (nmol/L)
TPM	up to 59
VGB	up to 279
ZNS	up to 188

Reference range vs. Individual therapeutic range

The steady-state plasma concentration of the drug at which the MAJORITY of patients are assumed to have an optimal clinical response

But

Every patient has his/her own therapeutic concentration

Individual therapeutic ranges/concentrations

- Individualized therapeutic concentration
  - Defined as the concentration that has been measured in an individual patient after that patient had been stabilized on a dosage that produced the best response (complete seizure control; optimum seizure control/minimal adverse effects)
  - Sampling should occur at 3-6 months post optimum AED administration and 2-3 levels determined

Indications for AED TDM

- When drug therapy is initiated and after dosage adjustments
  - sampling at trough concentrations and at steady-state
- When a person has attained the desired clinical outcome
  - To establish an individual therapeutic concentration which can be used subsequently to assess potential causes of change in response (↓ seizure control or ↑ adverse effects)
    - sampling at trough concentrations and at steady-state

Indications for AED TDM

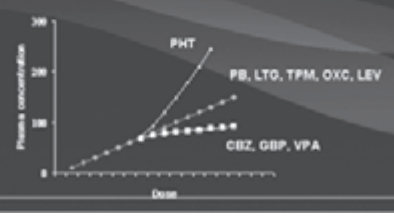
- Uncontrolled seizures - Persistence of seizures despite an "adequate" AED dosage
  - Potential causes of therapeutic failure:
    - Poor compliance – characterised by highly variable serum levels which increase following supervised drug intake
    - Low serum levels due to poor absorption, fast metabolism or drug interactions
    - Paradoxical worsening of seizures due to excessive drug load
      - sampling at trough concentrations and at steady-state

Indications for AED TDM

- Suspected toxicity
  - In patients in whom toxic symptoms are suspected:
    - AEDs levels can aid in confirming diagnosis of AED toxicity
    - Low AED levels do not necessarily exclude such a diagnosis
    - AED levels below the upper limit of TR does not allow the exclusion of intoxication – particularly in patients receiving complex polytherapies
      - sampling at peak concentrations or when symptoms are present if signs of toxicity are intermittent

Indications for AED TDM

- To guide dose adjustment for AEDs with dose-dependent PK (e.g. PHT, CBZ, VPA, GBP)



Indications for AED TDM

- To guide dosage adjustment in patients where potentially important PK changes are anticipated – Pregnancy
  - Pregnancy can affect drug absorption, binding to serum proteins and distribution, metabolism and renal elimination
  - PK changes vary between individuals - Insignificant in some and pronounced in others requiring dosage adjustment

Indications for AED TDM

- To guide dosage adjustment in patients where potentially important PK changes are anticipated – Pregnancy
  - TDM recommendations :
    - When pregnancy is planned, take two serum level values before pregnancy for future comparison
    - Sampling once each trimester sufficient in most women with stable seizure control
    - More frequent sampling – patients with complicated epilepsy or those previously known to be sensitive to modest changes in dose/levels
    - Highly protein bound AEDs (VPA and PHT) free levels
    - Post-partum monitoring will depend whether or not dosage changes were made during pregnancy

Indications for AED TDM

- To guide dosage adjustment in patients where potentially important PK changes are anticipated – AED polytherapy
  - Clinically relevant AED/AED interactions
  - AED/non-AED interactions – many hundreds!!!
  - Prescribed polytherapy with interacting drugs
  - When interacting drugs are withdrawn!
    - sampling at trough concentrations and at steady-state

Indications for AED TDM

- Special risk groups where drug PK is altered – Children
  - Several features that differentiate children from adults with regards to AED TDM
  - AED PK are age-dependent: infants/children have shorter T1/2 and faster Cl values; require dosage 2-3 times greater to get equivalent blood level
  - Cl decreases gradually throughout childhood but precise time-course not known and is characterised by pronounced inter-individual variability
  - Thus for children dosage requirements are less predictable than for adults and consequently TDM is more relevant for optimum management

Indications for AED TDM

- Special risk groups where drug PK is altered – Elderly
  - Greater morbidity
  - Sub-optimal compliance is common (under-dosing, over-dosing, missed dosing or make-up doses)
  - Greater risk of drug interactions – mean co-medicants 6.7
  - Variable age-dependent changes in PK (GI function, body mass composition, serum proteins, hepatic/renal function) – with substantial inter- and intra-individual variability
  - Decline in serum albumin – important for PHT and VPA
  - Renal/hepatic clearance declines by ~1%/year after age of 40
  - Variable age-dependent changes in PD – elderly are more sensitive and reference ranges may be misleading!

Free level monitoring for highly bound AEDs where albumin levels are low

Indications for AED TDM

- Special risk groups where drug PK is altered – Renal and hepatic disease
  - Patients with renal disease (PRM, LEV, PGB, GBP, VGB)
  - Patients with hepatic disease (PHT, CBZ, LTG, VPA, TPM, OXC, ZNS)
  - Renal disease – binding is substantially reduced
  - Hepatic disease – liver is the source of albumin formation therefore concentrations are reduced

Free level monitoring for highly bound AEDs where albumin levels are low

Indications for AED TDM

- Special risk groups where drug PK is altered – Pathological states
  - Pathological states
    - Stroke, burns, cardiac failure, febrile illnesses
    - Surgery, head trauma, malnutrition

~~Free level monitoring for highly bound AEDs where albumin levels are low~~

Indications for AED TDM

- The emergency situation
  - suspected overdose
  - status epilepticus
  - sampling at time patient presents at casualty
    - 2-3 samples during first 24 hours will allow prediction of elimination rate and maintenance dose respectively (population PK)

Sampling procedure

- Knowledge of sampling time and a meticulous dosage history is imperative if TDM is to be used to maximum utility
- Sampling should generally be undertaken at steady-state
  - 5 half-lives after starting treatment or a dose change
  - Long half-life drugs (e.g. ETS, PB and ZNS) fluctuations in blood levels is negligible – samples collected at any time
  - Short half-life drugs (e.g. CBZ, VPA, GBP, LEV, PGB, TGB, VGB, LTG and TPM) fluctuations in blood levels are substantial – important to standardize sampling time in relation to dose

Sampling procedure

- Ideal sampling time for all AEDs is immediately before the next oral dose (trough)
  - In an out-patient setting – note sampling time and time of drug ingestion
  - Transient concentration-related toxicity – sample at time of appearance of toxicity
  - During overdose – sample as soon as patient presence at casualty

What to measure

- Plasma/serum
  - Total levels
    - Only non-protein bound component pharmacologically active
    - Normally the degree of binding is constant
  - Free levels (AEDs > 90% bound e.g. PHT, VPA, TGB)
    - Altered protein binding

What to measure

- Saliva
  - Saliva reflects free levels
    - CBZ, PHT, PB, GBP, LTG, TPM, LEV, 10-OH-OXC, ZNS
  - Saliva does not reflect free levels
    - VPA
  - Saliva correlation uncertain
    - ETS, FBM, PRM, TGB, VGB

Saliva monitoring

Many advantages:

- Collection of saliva is simple and non-invasive
- Procedure may be cheaper than blood drawing
- Does not require expertise of drawing blood
- Preferred by children and their parents (many children fear blood sampling!)
- Measured concentrations reflect the free (pharmacologically relevant) concentration in blood

Comprehensive TDM epilepsy service

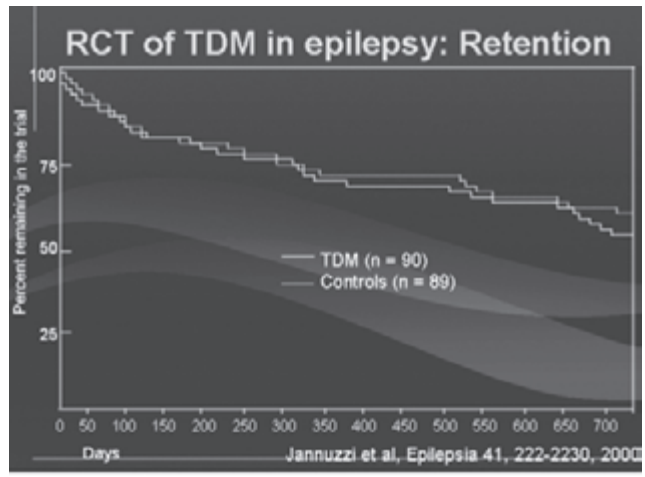
- Quality service
  - Accredited laboratory
  - State of the art instrumentation
  - Assay of all licensed AEDs + metabolites
  - Rapid turnaround times (preferably during patient consultation but not >24 h)
  - Interpretation available (based on PK)

Conclusions

- TDM:
  - well established surrogate marker
  - allows individualisation of AED therapy (maximum efficacy, minimal side effects)
  - requires considerable interpretative skills
- A "reference range" is a population range
- Every patient has his/her own "therapeutic range"

Conclusions

- A blood level is but a single piece of information
- Used in conjunction with the knowledge of the patient, the disease and the properties of the drug



Seizure aggravation
Emilio Perucca (Italy)

Seizure Aggravation

Emilio Perucca

Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE Course, 11 February 2008

Aggravation of Seizures: Definitions

- Re-appearance of seizures in previously controlled patients
- Increase in frequency or severity of pre-existing seizure types
- Emergence of new seizure types or status epilepticus

Aggravation of Seizures

- A common phenomenon in everyday practice
- Frequent cause for consultation/referral
- Adverse affectly affect QoL and costs of the disease
- → Understanding causes and mechanisms essential for prevention and management

Aggravation of Seizures: Causes

- Spontaneous ("random") fluctuation in seizures
- Progression of epileptogenesis
- Intercurrent medical conditions affecting seizure threshold
- Conditions leading to changes in drug response
- Drugs that aggravate seizures (including AEDs)

Some Conditions which may Cause Seizure Exacerbation

- Electrolyte disturbances (hypocalcemia, hyponatremia), hypoglycemia, uremia
- Hormonal changes (including pregnancy)
- Stress
- Voluctuary substances (alcohol, caffeine, bethel nuts, amphetamines, cocaine, ecstasy)
- Sleep deprivation
- Poor compliance with prescribed treatment

Seizure Breakthrough: How Often is it due to Poor Compliance?

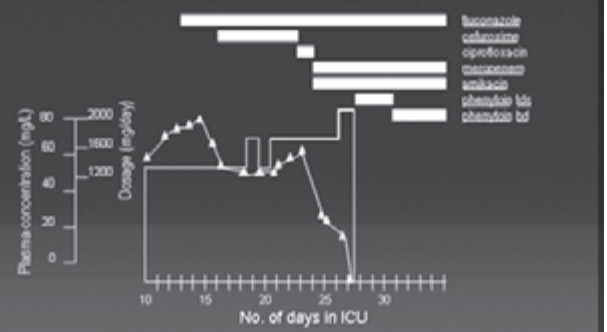
- Prospective study of 61 breakthrough seizures in 52 patients
- Blood samples for AED levels obtained within 12 h of a seizure
- In 44% of the seizures, AED level was <50% of the reference level obtained in the same patient on the same dose

Epilepsy and Behavior 2003;4:487-95

Changes in AED Response

- "Honey moon" effects and tolerance
- Changes in AED pharmacokinetics due to physiological or pathological factors
- Drug interactions

Dramatic Fall in Serum VPA Levels after Starting Meropenem in a 65-year-old Woman



J. Antimicrob Chemother 42,563-4,1998

Drugs Which May Exacerbate Seizures

- Antibiotics (e.g, penicillin, cephalosporins)
- Anticholinergics
- Antidepressants
- Antimalarials (mefloquine)
- Antipsychotics
- Baclofen
- ChE inhibitors (e.g., donepezil)
- Cyclosporin
- Isoniazid
- Ketamine
- Lidocaine
- Lithium
- Opioids
- Oral contraceptives
- Vincristine

Seizures Induced by Antibiotics

- β-lactam antibiotics and quinolones entail a less than 1.5% risk
- Predisposing factors important, especially renal impairment
- Aminoglycosides, tetracyclines and macrolides generally safe
- Seizures common in isoniazid overdose, rare at therapeutic dosages

Stimmel and Dopheide, CNS Drugs 5:37, 1996

Seizures Induced by Antipsychotic Drugs

- Always dose-related; mechanism poorly understood, partly related to D-receptor blockade
- Highest risk with clozapine (1-10%)
- Among phenothiazines, highest risk with chlorpromazine (5-9% at 1 g/day vs 0.5% at lower doses)
- Very rare with haloperidol

Stimmel and Dopheide, CNS Drugs 5:37, 1996

Seizures Induced by Antidepressants

- With TCAs, incidence varies with dose and predisposing factors (0.1% to 4%)
- Highest risk with maprotiline (up to 15% incidence, 77% in overdose cases) and bupropion
- SSRIs carry relatively low risk (≤0.2 %).

Stimmel and Dopheide, CNS Drugs 5:37, 1996

Epilepsia, 39(1):5 17, 1998
Lippincott Raven Publishers, Philadelphia
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Antiepileptic Drugs as a Cause of Worsening Seizures

E. Perucca, *L. Gram, †G. Avanzini, and ‡O. Dulac

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Seizure Aggravation by AEDs: Classification

Type A Increase in seizure frequency as a manifestation of excessive drug load (paradoxical intoxication)

Type B Patient- or disease-selective phenomenon in which certain seizures are aggravated as a consequence of a drug's mode of action (selective aggravation)

Perucca E. et al *Epilepsia*, 1998.39:5-17

Paradoxical Intoxication

- Best documented with PHT. Reports with VGB, TGB, LTG, TPM, LEV. Not uncommon with polypharmacy
- Unpredictable; may occur without other signs of toxicity; abates upon dosage reduction
- Convulsions seen after massive overdosage with most AEDs, even in non-epileptic subjects
- Mechanisms likely to be multifactorial (blockade of inhibitory pathways, aminergic effects, sedation, hyponatremia, etc)

Perucca E. *Neurologia*. 2001; 16 (suppl 2) 43-51.

Clinical Manifestations of AED Intoxication in 81 Patients

	n (%)
Incoordination / dysarthria	34 (42%)
Drowsiness / obtundity	31 (38%)
Flapping tremor	28 (35%)
Altered mood / behavior	21 (26%)
Paradoxical seizure exacerbation	20 (25%)
Nystagmus	13 (16%)
Confusion / hallucination	6 (7%)
Dyskinesias	5 (6%)

Laidlaw and Perucca, 1980

Selective Seizure Aggravation

- Absence and myoclonic seizures more commonly affected
- Somewhat predictable and syndrome-specific (more common in idiopathic generalized epilepsies)
- Caused mainly by drugs with a narrow efficacy spectrum (CBZ, PHT, OXC, VGB, TGB, GBP)

CBZ = carbamazepine; PHT = phenytoin; OXC = oxcarbazepine; VGB = vigabatrin; TGB = tiagabine; GBP = gabapentin

Seizures and Syndromes Most Commonly Subject to Selective Aggravation

AEDs	Seizures Aggravated
Barbiturates	Absence, tonic
Benzodiazepines	Tonic (i.v. use, Lennox-Gastaut syndrome and West syndrome)
Carbamazepine, oxcarbazepine, phenytoin	Absence, myoclonic, atonic, tonic
Vigabatrin, tiagabine	Absence, myoclonic
Gabapentin, pregabalin	Myoclonic
Lamotrigine	Many seizure types in SMEI, myoclonic jerks in many syndromes

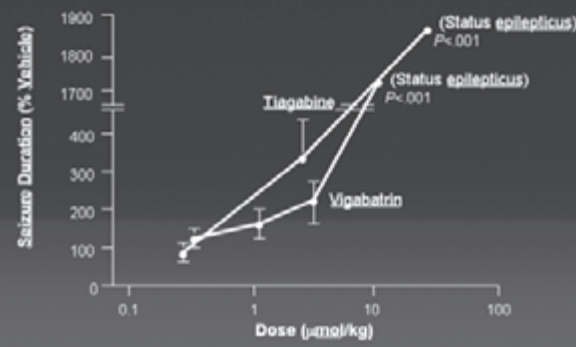
SMEI = severe myoclonic epilepsy of infancy; JME = juvenile myoclonic epilepsy

Mechanisms Underlying Selective Seizure Aggravation

- Reproducible in animal models, but mechanisms are not completely understood
- For GABAergic drugs, synchronization of neuronal firing in thalamo-cortical circuitries probably involved. Evidence for an activation of $GABA_B$ receptors
- Suppression of inhibitory pathways may be involved with other drugs. Sodium channel "alignment" could explain precipitation of absence seizures by CBZ and PHT

CBZ = carbamazepine; PHT = phenytoin

Pro-absence Effect of GABAergic Drugs in the Lethargic Mouse



Hosford DA, et al. *Epilepsia* 1997; 38:408-14

How Common Is Seizure Aggravation by CBZ? Relevance of Syndromic Classification

- Survey of 28 consecutive patients with juvenile myoclonic epilepsy (JME) who received CBZ:
  - 19 (68%) showed aggravation of seizures, especially myoclonic jerks
  - 2 developed myoclonic status
- Survey of 40 consecutive patients with benign epilepsy with centrotemporal spikes (BECT) who received CBZ:
  - Only 1 (2.5%) showed aggravation of seizures

CBZ = carbamazepine

Genton P, et al. *Neurology* 2000;55:1106-9
Genton P. *Epilepsia* 2001; 42:754-9

Aggravation of Severe Myoclonic Epilepsy (SMEI) by Lamotrigine

- Twenty-one SMEI patients (age 2-18 years)
- Convulsive seizures increased by >50% in 8 of 20 pts, myoclonic seizures worsened in 6 of 18 pts.
- Lamotrigine was withdrawn in 19 pts, with consequent improvement in 18

R. Guerrini et al. *Epilepsia* 1998;39, 508-12

Seizure Outcome and EEG Changes in Children Treated with Carbamazepine

	Unchanged/ Improved EEG (N=33)	EEG Deteriorated (Spike-and-Wave)* (N=26)
Successful treatment; CBZ withdrawn	39%	4%
Continuing		
On monotherapy	36%	12%
On polytherapy	6%	38%
Discontinued due to seizure exacerbation	0%	42%

*8/26 patients presumed to have cryptogenic partial epilepsy later shown to have myoclonic-astatic epilepsy (N=2); infantile myoclonic epilepsy (3), infantile spasms (3)

Tolvar et al. *Epilepsia* 35:1154-60, 1994

Aggravation of Tonic Seizures by CBZ A Case Report

- 13-year-old boy with mental retardation, spastic tetraplegia. Initially diagnosed with West syndrome
- After 2 years of age, frequent tonic seizures. Over past 6 years, average of 50 tonic seizures per month while taking CBZ and PMD
- After stopping CBZ, seizures decreased to no more than 3 per month. Long periods seizure-free
- Seizure-triggering effect of CBZ confirmed on rechallenge with telemetric recordings

BZD = benzodiazepines; PB = phenobarbital; CBZ = carbamazepine; PMD = primidone

Kramer G, et al. *Epilepsia* 1998.

CBZ and PHT as Causes of Refractory Absence Status in Patients With Idiopathic Generalized Epilepsy (IGE)

	Refractory Status* (n = 8)	Non-refractory Status (n = 10)
Patients on CBZ or PHT	8	0
Seizures worsened by drugs	8	0
Remitted after drug withdrawal	8	0
Syndromic form		
Childhood absence epilepsy	6	8
Juvenile myoclonic epilepsy	2	2

*Except for older age in the refractory group (39 versus 25 years), other clinical features were comparable in the 2 groups.

CBZ = carbamazepine; PHT = phenytoin

Osorio et al. *Epilepsia* 2000; 41:887-94

Seizure Aggravation by AEDs: Conclusions

- Common and clinically important
- Mostly related to over-aggressive treatment practices, or to inappropriate drug selection (misdiagnosis)
- Consider dose reduction or drug discontinuation whenever seizures deteriorate following an increase in drug load

Overall Conclusions

- Exacerbation of seizures has many causes
- Identification of cause is essential for proper management
- Education of patient is key factor for prevention
- Increasing drug dose or adding another drug is not always the best practice – and any drug change needs NOT to be long-term!

INTERACTIVE CASE DISCUSSIONS
G. AVANZINI/E PERUCCA/T TOMSON

Programa – 12.02.2008

Morning session – 9:00 – 13:00

- Infants and children - E. Perucca (Italy)
- Gender issues - T. Tomson (Sweden)
- The elderly - E. Perucca (Italy)

Afternoon session – 14:30-18:30

- The neurobiological bases of AED resistance - Alberto Lazarowski (Argentina)
- Clinical management of refractory epilepsies -T. Tomson (Sweden)
- Acute repetive seizures and status epilepticus - T. Tomson (Sweden)
- Interactive case discussions - G. Avanzini/E Perucca/T Tomson/ M. Bialer

Evening session

- Reflex epileptic seizures and ictogenesis – Peter Wolf (Denmark)

Infants and children
Emilio Perucca (Italy)

Children – Treatment Issues

Emilio Perucca
Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE Course, 12 February 2008

Issues with Antiepileptic Drug Treatment in Children

Children with epilepsy are not "small adults"

- The disease is different (many childhood epilepsies are not found in adults)
- Pharmacokinetics differ from those in adults
- Pharmacodynamic sensitivity to drugs may differ

Antiepileptic Drugs in children (1)

The "disease gap":

- Some syndromes are confined mostly to pediatric age and their treatment cannot be studied in adults:
  - West syndrome
  - Idiopathic partial epilepsies
  - Childhood absence epilepsy
  - Lennox-Gastaut syndrome
  - Some age-related encephalopathies
- Changes in syndromic from occur during development
  - e.g., West syndrome → Lennox-Gastaut → Syntomatic frontal lobe epilepsies

Antiepileptic Drugs in Children (2)

Pharmacokinetics change markedly during development:

- Absorption, protein binding, distribution and renal elimination may be altered, especially in the newborn
- Most drugs are metabolized at a slow rate in newborns, especially when premature
- Prenatal drug exposure may affect metabolizing capacity

Antiepileptic Drugs in Children (3)

Pharmacokinetics change markedly during development:

- During development metabolizing capacity usually exceeds the adult rate, but the time course of enzyme maturation changes from drug to drug
- Dosage requirements may be greatly affected, both with respect to total dose and dosing frequency

Antiepileptic Drugs in Children (4)

Pharmacodynamic response varies during development:

- Therapeutic response may change over time due to modification of the underlying disorder
- Drug-induced seizure exacerbation is not uncommon
- Some adverse drug reactions are age-dependent:
  - PHT: coarse facies, acne, hirsutism
  - VPA: hepatotoxicity
  - PB, BZD,and others: behavioural problems
  - LTG: Stevens-Johnson syndrome

Factors Affecting Decision To Start Anticonvulsant Treatment in Children

- Correct diagnosis of epilepsy
- Presence of avoidable triggering factors
- Definition of risk of seizure recurrence
- Definition of the impact of treatment on that risk
- Psychological / medical / social implications of seizure recurrence
- Risk : benefit ratio of treatment

Situations where Treatment is (usually) not Indicated

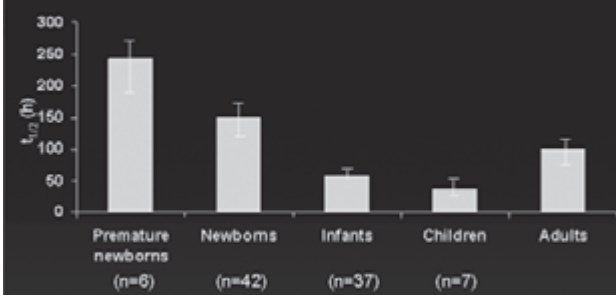
- Febrile seizures
- Some idiopathic partial epilepsies, particularly rolandic epilepsy
- Rare seizures, particularly when nocturnal

Treating Epilepsy in Childhood

Evidences to be Considered

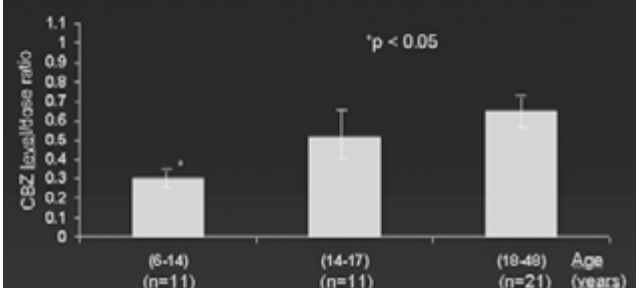
- Pharmacokinetic data
- Randomized controlled trials
- Other clinical studies
- Expert opinions /personal experience

Age-Dependent Changes in Phenobarbital Half-life



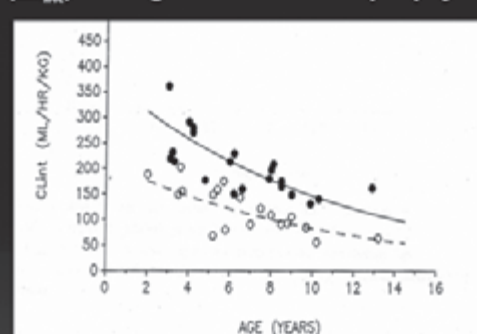
Data from different studies (reviewed by Morselli, 1977; Anderson, 2003)

Dose-Normalized Serum Carbamazepine Concentrations as a Function of Age



Morselli L, Drug Disposition during Development, Plenum Press, 1977

Relation between VPA Unbound Drug Clearance (Cl_{int}) and Age in Patients in Epilepsy



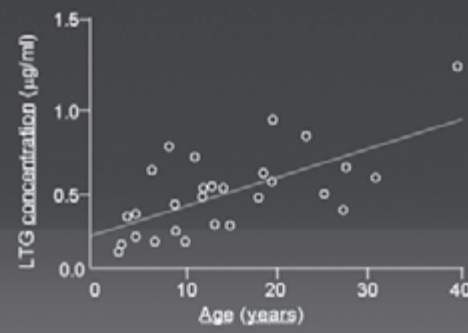
Cloyd et al, Clin Pharmacol Ther 1993; 53: 22-9

Increase in Clearance of New AEDs in Children Compared with adults

Felbamate	20 - 65%
Gabapentin	20 - 80%
Lamotrigine	35 - 125%
Levetiracetam	30 - 40%
Oxcarbazepine	30 - 160%
Pregabalin	no data
Tiagabine	35 - 120%
Topiramate	25 - 170%
S-Vigabatrin	30 - 45%
Zonisamide	20 - 100%

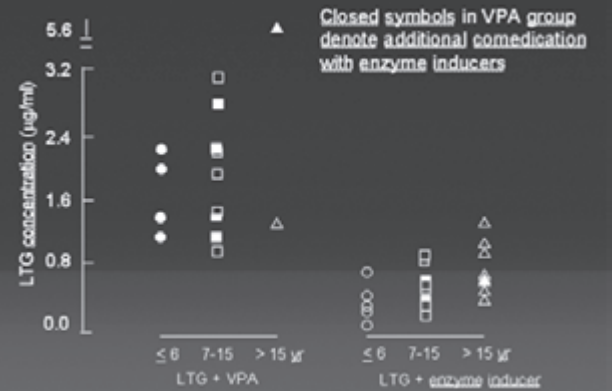
Perucca, Clin Pharmacokinet 2006;45:351-363

Dose-Normalized Plasma LTG Levels vs Age in 42 Patients comedicated with Enzyme-Inducers



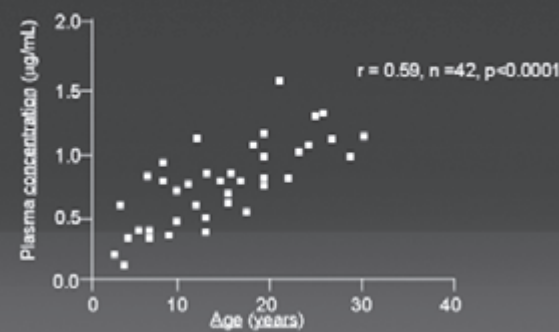
Bartoli et al, Ther Drug Monit 1997; 19:252-60

Dose-normalized Serum LTG Concentrations vs Age



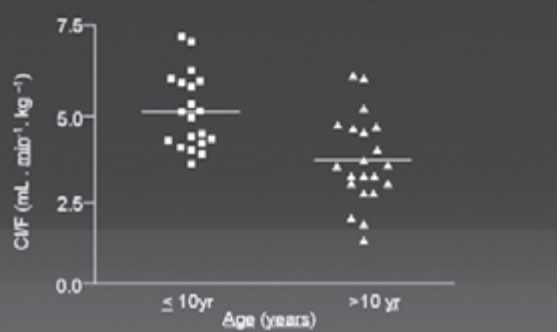
Bartoli et al, Ther Drug Monit 1997; 19: 252-60

Dose-Normalized Plasma TPM Levels vs Age in 42 Patients comedicated with Enzyme-Inducers



Ferrari et al., Ther Drug Monit 2003; 25: 700-8

Influence of Age on Gabapentin Clearance (CL/F) in Patients with Epilepsy



Gatti et al., Ther Drug Monit 2003; 25: 55-60

Latency in Evaluating AEDs in children

	First controlled trial in adults	First open study in children	First controlled trial in children	Year of registration
Clobazam	1981	1983	1990	1975
Vigabatrin	1983	1989	1995	1990
Oxcarbazepine	1989	1995	1997	1990
Lamotrigine	1986	1991	1997	1991
Felbamate	1991	1993	1993	1993

Major Determinants of the Clinical Usefulness of an AED

- Spectrum of activity (seizure types and syndromes)
- Efficacy
- Adverse effect profile
- Drug interactions
- Ease of use
- Cost

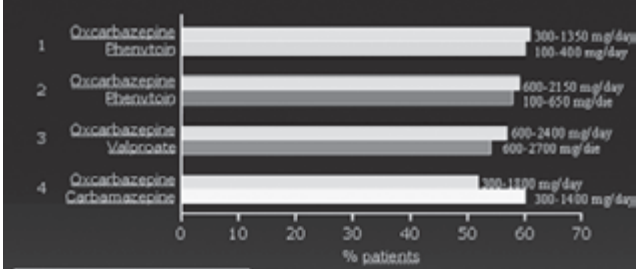
Efficacy Spectrum of Available AEDs

All seizures & syndromes	All seizures except absence	Partial and tonic-clonic	Absence only
Valproic acid	Phenobarbital	Carbamazepine*	Ethosuximide&
Benzodiazepines	Primidone	Phenytoin*	
Lamotrigine §		Oxcarbazepine*	
Levetiracetam §		Pregabalin*	
Topiramate§		Gabapentin*	
Zonisamide (?)		Tiagabine*	
Felbamate (?)		Vigabatrin*	

* May exacerbate myoclonic and absence seizures. Vigabatrin is also effective in infantile spasms.
§ Lamotrigine may aggravate severe myoclonic epilepsy of infancy Topiramate and levetiracetam efficacy in absence seizures is unclear
& Ethosuximide is a drug of choice in continuous spike-waves during slow sleep (CSWS)

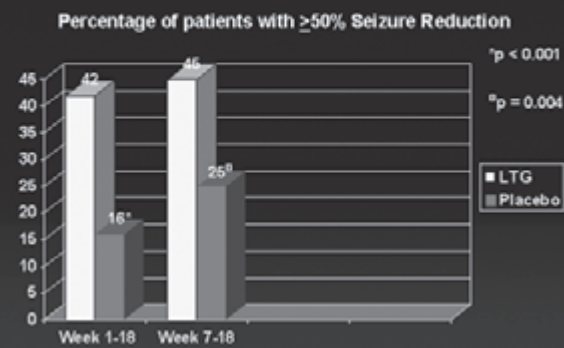
Perucca, 2005

Oxcarbazepine RCTs in New Onset Epilepsy: Seizure-freedom Rates

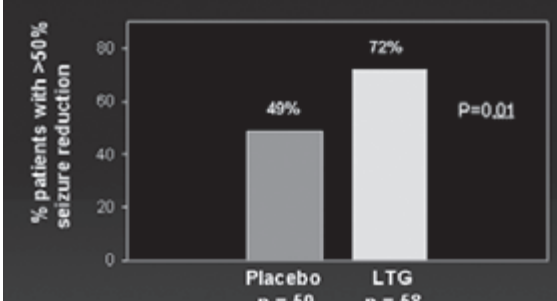


[1]Guerreiro et al, Epilepsy Res 1997
[2]Bill et al, Epilepsy Res 1997
[3]Christe et al, Epilepsy Res 1997
[4]Dam et al, Epilepsy Res 1989

Responder Rates to Lamotrigine in Refractory Partial Epilepsy in Children



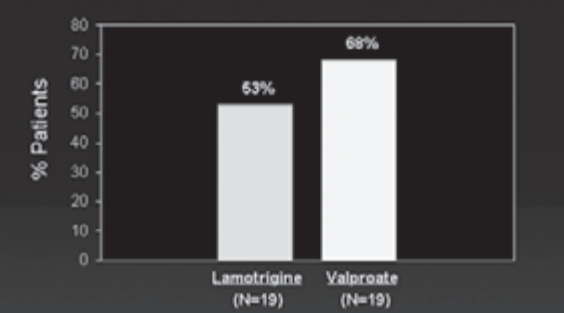
Responder Rate to Lamotrigine in a Placebo-Controlled RCT in Refractory Primary Generalized Tonic-Clonic Seizures (Adults and Children)



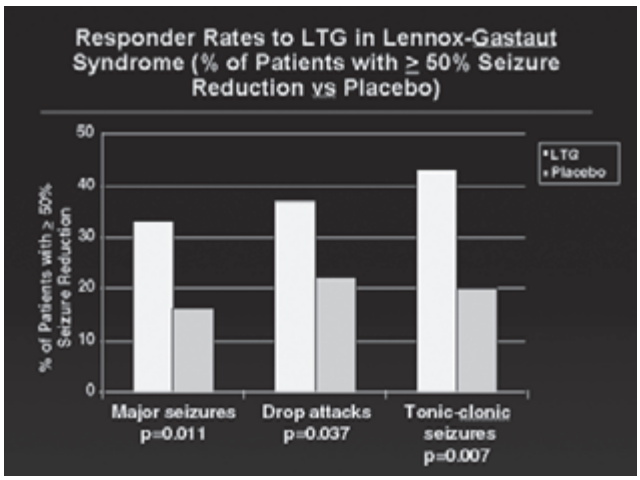
Biton et al, Neurology 2005; 65:1737-43

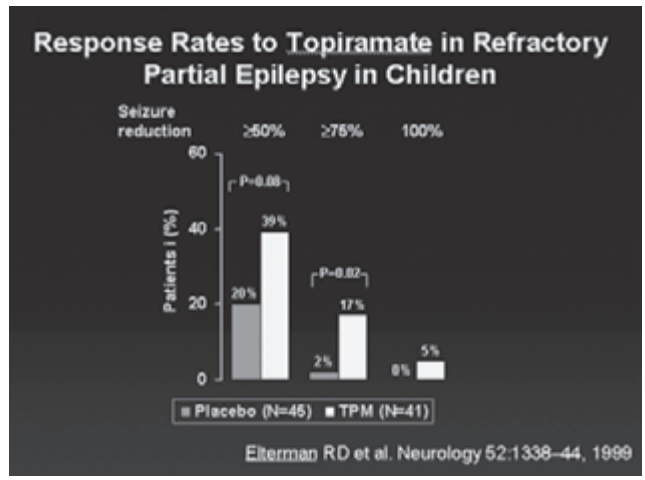
RCT of Lamotrigine vs Valproate in Children with Newly Diagnosed Absence Epilepsy

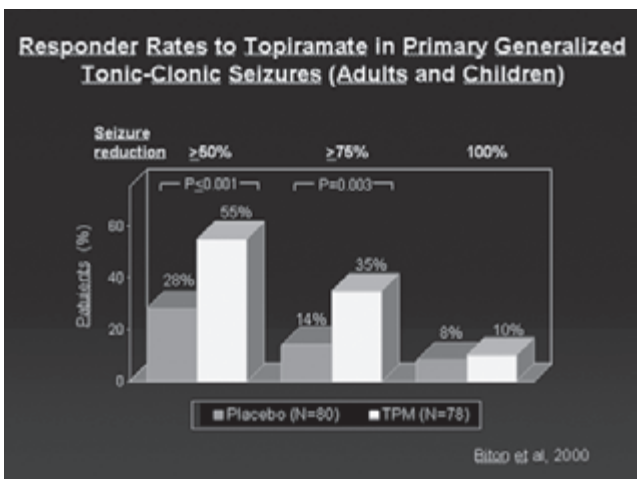
% Seizure-free at 1 Year

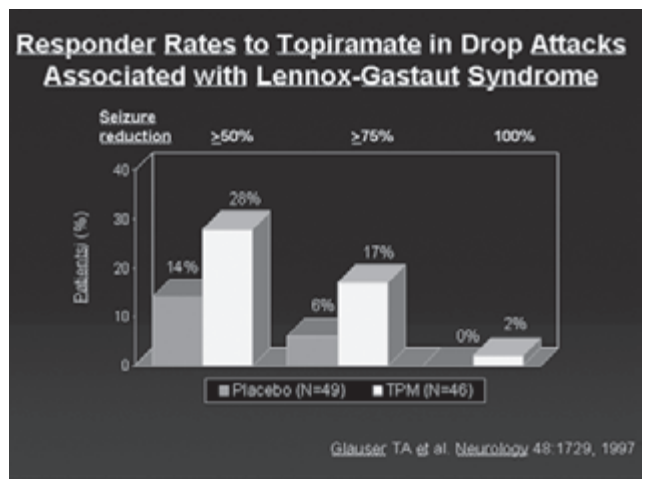


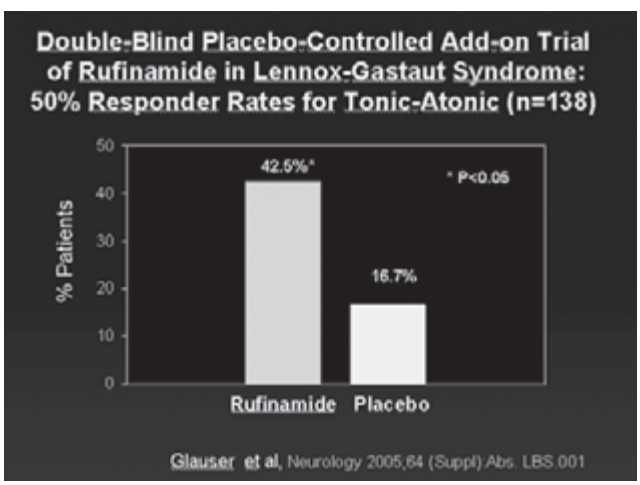
Coppola et al, Epilepsia 2004;45:1049-53

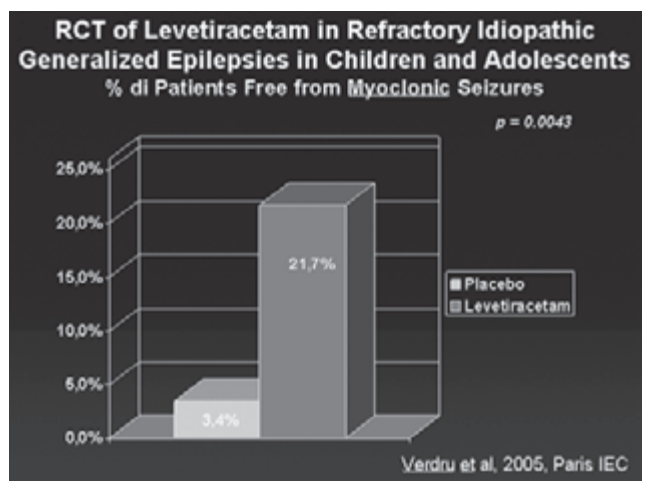

Responder Rates to LTG in Lennox-Gastaut Syndrome (% of Patients with ≥ 50% Seizure Reduction vs Placebo)
% of Patients with ≥ 50% Seizure Reduction
50
40
30
20
10
0
•LTG
•Placebo
Major seizures p=0.011
Drop attacks p=0.037
Tonic-clonic seizures p=0.007


Response Rates to Topiramate in Refractory Partial Epilepsy in Children
Seizure reduction
≥50%
≥75%
100%
Patients i (%)
60
40
20
0
P=0.08
P=0.02
20%
39%
2%
17%
0%
5%
Placebo (N=45)
TPM (N=41)
Elterman RD et al. Neurology 52:1338–44, 1999


Responder Rates to Topiramate in Primary Generalized Tonic-Clonic Seizures (Adults and Children)
Seizure reduction
≥50%
≥75%
100%
Patients (%)
P≤0.001
P=0.003
28%
55%
14%
35%
8%
10%
Placebo (N=80)
TPM (N=78)
Biton et al, 2000


Responder Rates to Topiramate in Drop Attacks Associated with Lennox-Gastaut Syndrome
Seizure reduction
≥50%
≥75%
100%
Patients (%)
14%
28%
6%
17%
0%
2%
Placebo (N=49)
TPM (N=46)
Glauser TA et al. Neurology 48:1729, 1997


Double-Blind Placebo-Controlled Add-on Trial of Rufinamide in Lennox-Gastaut Syndrome: 50% Responder Rates for Tonic-Atonic (n=138)
% Patients
42.5%*
* P<0.05
16.7%
Rufinamide
Placebo
Glauser et al, Neurology 2005;64 (Suppl) Abs. LBS.001


RCT of Levetiracetam in Refractory Idiopathic Generalized Epilepsies in Children and Adolescents
% di Patients Free from Myoclonic Seizures
p = 0.0043
25,0%
20,0%
15,0%
10,0%
5,0%
0,0%
21,7%
3,4%
Placebo
Levetiracetam
Verdru et al, 2005, Paris IEC

Controlled Trial of ACTH vs Vigabatrin in Infantile Spasms of Various Origin

39 patients, newly diagnosed (12 cryptogenetic, 27 symptomatic)

Randomization:	vigabatrin 100-150 mg/kg/day ACTH depot (0.1 ml/day)
Spasm-free rate:	9/21 (43%) on vigabatrin (3/3 with TS) 14/18 (78%) on ACTH (7/7 cryptogenic)
Severe side effects:	4/21 (19%) on vigabatrin 6/18 (33%) on ACTH

Vigevano and Cilio, 1997

Randomized Trial of Hydrocortisone vs VGB in Newly Diagnosed Infantile Spasms due to Tuberous Sclerosis

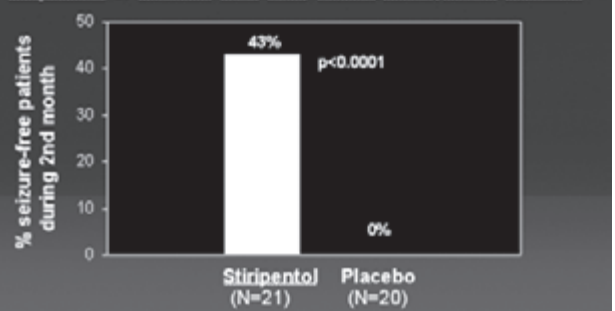
22 patients, newly diagnosed (all with tuberous sclerosis)

Randomization:	Vigabatrin 150 mg/kg/d (1 month) Hydrocortisone 15 mg/kg/d (1 month)
Spasm-free rate:	11/11 (100%) on vigabatrin 4/11 (26%) on hydrocortisone all 7 non responders to hydrocortisone responded later to vigabatrin
Side effects:	5/18 (28%) on vigabatrin 9/11 (82%) on hydrocortisone

Chiron et al, 1997

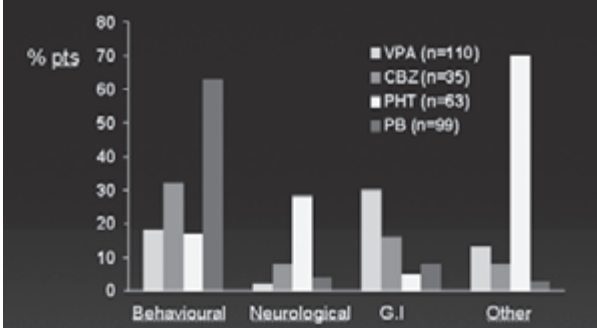
Double-Blind Placebo-Controlled Add-on Trial of Stiripentol in Severe Myoclonic Epilepsy in Infancy (Dravet's Syndrome)

Proportion of Patients Free from Clonic/Tonic-clonic Seizures



Chiron et al, Lancet 2000;356:1638-42

Proportion of Patients with AED-Induced Adverse Effects in a Pediatric Population



Herranz et al, Epilepsia 1988, 29:794-803

Some Drugs of Pediatric Relevance whose Clearance is Increased by Enzyme Inducing AEDs

- Anticancer drugs (some)
- Antidepressants (many)
- Antipsychotic drugs (many)
- Corticosteroids
- Cyclosporin
- Teophylline

Examples of Important Drug Interactions mediated by Metabolic Inhibition in Children

Interacting drug	Affected drug
Erythromycin	Carbamazepine
Isoniazid	Phenytoin
Fluoxetine	Phenytoin
Propoxyphene	Carbamazepine
Valproic acid	Lamotrigine Phenobarbital

Patsalos & Perucca, Lancet Neurology 2003;2:473-81

Factors Favoring Ease of Use

- Broad spectrum – no seizure aggravation
- High efficacy, good tolerability
- No contraindications
- No adverse drug interactions
- Friendly pharmacokinetics / once daily dosing
- Fast titration
- Availability of friendly pediatric formulation
- Availability of parenteral formulation

Which dose?

There is large interdividual variation in dosage requirements.

Factor to be considered:

- Age
- Body weight (body mass index)
- Type (number) of seizures and syndrome
- Associated diseases/drugs
- Need for slow dose titration?
- Choice of initial maintenance dosing schedule
- Serum drug level monitoring
- Implications of delay in seizure control

Treating Pediatric Epilepsies Special – Risk Groups

- Infants
- Epileptic enkephalopathies
- Catastrophic epilepsies
- Learning disability
- Multiple handicaps (e.g. brain damage)
- Other co-morbidities
- Cross-allergies

Needs for the Future

- Evidence for rational management strategies across all pediatric epilepsy syndromes
- Better prognostic tools to predict response to available drugs
- Drugs with fewer side effects for the newly diagnosed
- More effective drugs for refractory patients

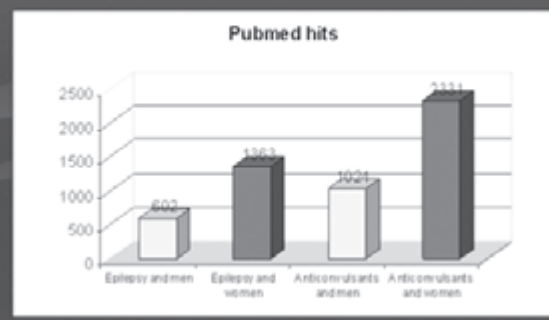
Gender issues
Torbjörn Tomson (Sweden)

Gender Issues in AED use

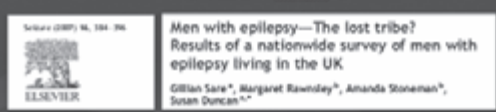
Torbjörn Tomson
Department of Clinical Neuroscience
Karolinska Institutet
Stockholm, Sweden

LASSE II
2008

Gender aspects on publications



What is special about gender and AED use?



- Treatment issues related to specific physiological functions of women
  - -Reproductive function
  - -Contraception
  - -Pregnancy
  - -Catamenial epilepsy
  - -Menopause

Treatment of epilepsy in women

- Reproductive function
- Contraception
- Pregnancy
- Catamenial epilepsy
- Menopause

Fertility may be decreased in women and men with epilepsy

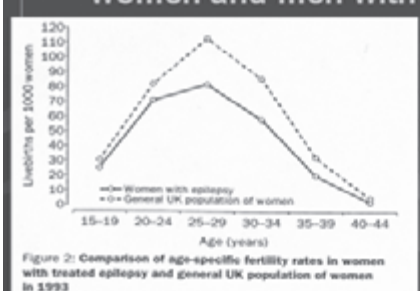


Figure 2: Comparison of age-specific fertility rates in women with treated epilepsy and general UK population of women in 1993

Potential explanations
- Social circumstances
- Comorbidity
- Genetic factors
- Factors related to the seizures
- Treatment with AEDs

Wallace et al Lancet 1998

AEDs and Sex Hormones

- Enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital)
  - -Decrease testosterone and estradiol
  - -Increase Sex Hormone Binding Globuline
- Enzyme-inhibitors (valproate)
  - -Increase androgens
- These effects possibly related to
  - Reduced libido
  - Menstrual disturbances
  - Polycystic ovary syndrome
  - Higher rates of infertility

Polycystic Ovary Syndrome (PCOS) NIH Criteria (1-3)

1. Menstrual disorders (amenorrhea, oligomenorrhea, or polymenorrhea)
2. Laboratory and clinical evidence of hyperandrogenism (hirsutism, acne, obesity, androgenic alopecia)
3. Exclusion of other endocrine disorders
4. More common among women with epilepsy
5. Conflicting results on association with valproic acid from cross-sectional studies
6. Randomized comparative studies lacking

Epilepsy & Reproductive Health a Consensus Statement

1. Reproductive endocrine disorders common among women with epilepsy and probably contribute to decreased fertility
2. Should be screened regularly for menstrual disorder, infertility, obesity, hirsutism and galactorrhea
3. May require further endocrine testing
4. Reproductive endocrine disorder should be considered in terms of etiology and potential contributory factors, including epilepsy and AEDs (in particular valproic acid)
5. Potential benefits of a change of AEDs must be balanced against seizure control and the side effects of alternative

Bauer et al J Neurol Neurosurg Psychiat 2002;73:121-125

Implications for treatment of young women with epilepsy

- Use most appropriate AED for seizure/syndrome type
- Provide information about risk of endocrine disorders
- Monitor clinical signs and symptoms

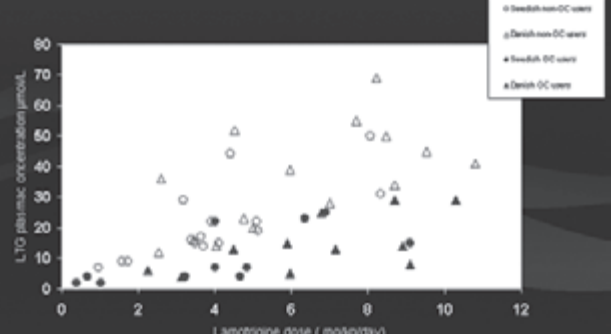
Treatment of epilepsy in women

- Reproductive function
- Contraception
- Pregnancy
- Catamenial epilepsy
- Menopause

Enzyme inducing AEDs reduce effectiveness of oral contraceptives

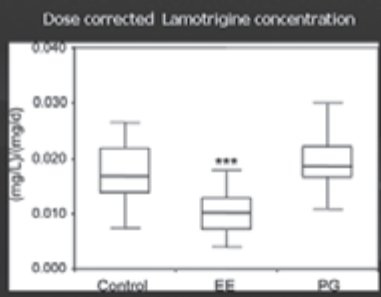
Reduce effects of OCs	Do not affect OCs
Carbamazepine	Vigabatrin
Phenobarbital	Benzodiazepines
Phenytoin	Valproic acid
Primidone	Gabapentin
Felbamate	Pregabaline
Oxcarbazepine	Levetiracetam
Topiramate (>200 mg/day)	Tiagabine
Lamotrigine?	

OCs reduce plasma concentrations of lamotrigine



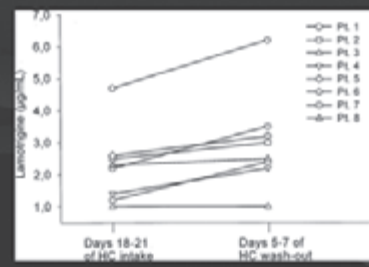
Sabers, Ohman and Tomson Neurology 2003

Estradiol containing OCs induce the metabolism of lamotrigine



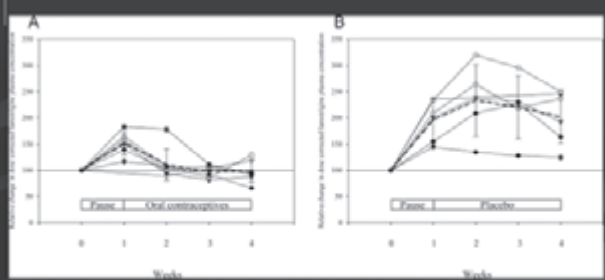
Reimers et al., Epilepsia 2005;46:1414-1417

LTG concentrations vary with the contraceptive cycle



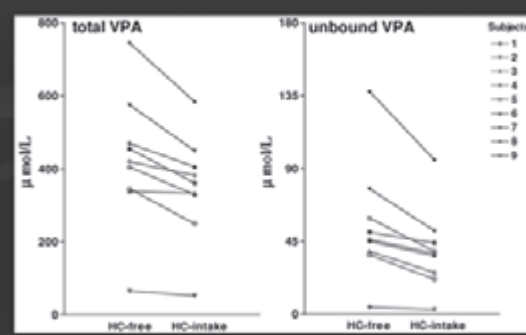
Contin et al Epilepsia 2006;1573-5

Effects of oral contraceptives on lamotrigine serum concentrations



Christensen et al Epilepsia 2007

Effects of hormonal contraceptives on VPA concentrations



Galimberti et al Epilepsia 2006;47:1569-72

Methods of contraception that are affected by EIAEDs

- Combined oral contraceptives
- Combined contraceptive patch
- Progestogen only pill
- Progestogen implant

O'Brien Epilepsia 2006;47:1419

Methods of contraception that are not affected by EIAEDs

- Depo-Provera
- Hormone releasing intrauterine system
- Other intrauterine contraceptive devices
- Barrier meethods

O'Brien Epilepsia 2006;47:1419

Implications for AED treatment

- OC with high estrogen dose (50µg or more) is often recommended if inducing AEDs are considered.
- Intrauterine contraceptives a good alternative
- Lamotrigine plasma levels should be monitored and doses adjusted in patients on LTG that are given, or from whom estradiol containing OC are withdrawn
- Efficacy of lamotrigine may vary over the cycle with sequential pills *Sidhu et al Br J Clin Pharmacol 2006*

Treatment of epilepsy in women

- Reproductive function
- Contraception
- Pregnancy
- Catamenial epilepsy
- Menopause

AED treatment & pregnancy Basis for treatment strategy

- Uncontrolled tonic-clonic seizures are more hazardous to the mother and the fetus than AEDs
- AEDs are indicated during pregnancy if necessary for achieving control of tonic-clonic seizures
- The objective is to maintain seizure control throughout pregnancy with minimised risks to the mother, the fetus, and the new-born

Treatment issues in epilepsy and pregnancy

1. Adverse foetal effects of AEDs
   -Birth defects
   -Effects on postnatal cognitive development
2. The effect of pregnancy on seizure control
3. The effect of pregnancy on AED kinetics
4. Breast-feeding

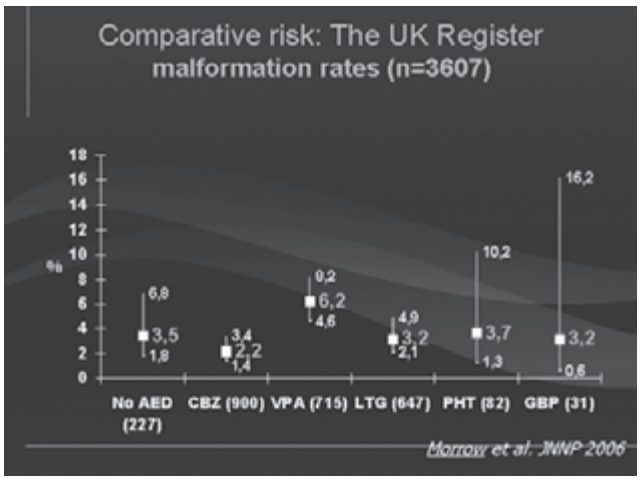
Epilepsy, AEDs and pregnancy outcome

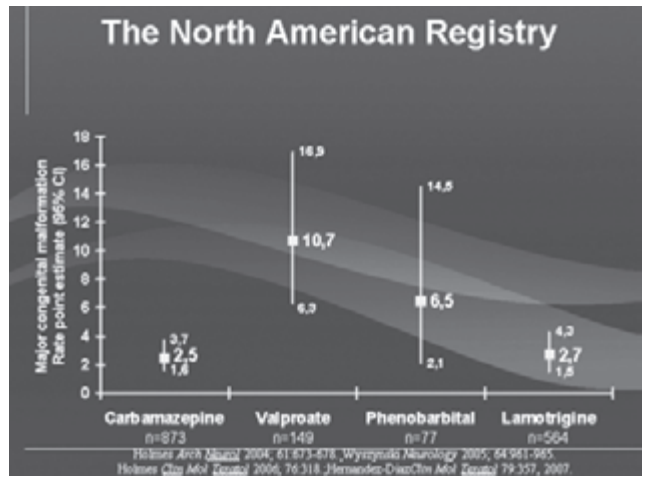
- Children of mothers treated for epilepsy during pregnancy have a 2-3 fold increased risk of major congenital malformations
- The reasons are multifactorial possibly including
  -socio-economic factors
  -genetic factors
  -seizures
  -AEDs

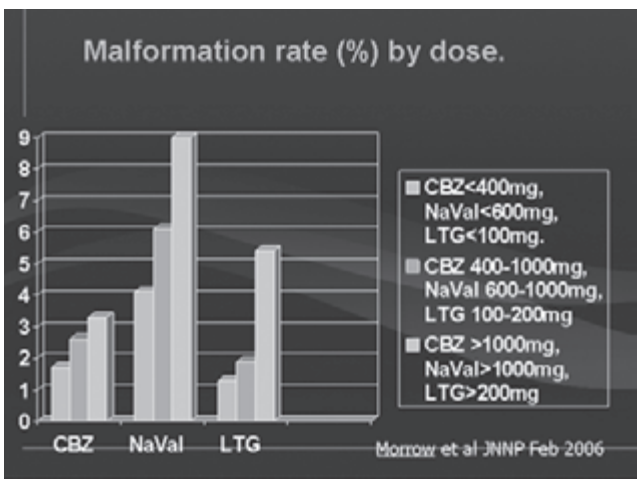
Treatment of epilepsy associated with increased rate of birth defects

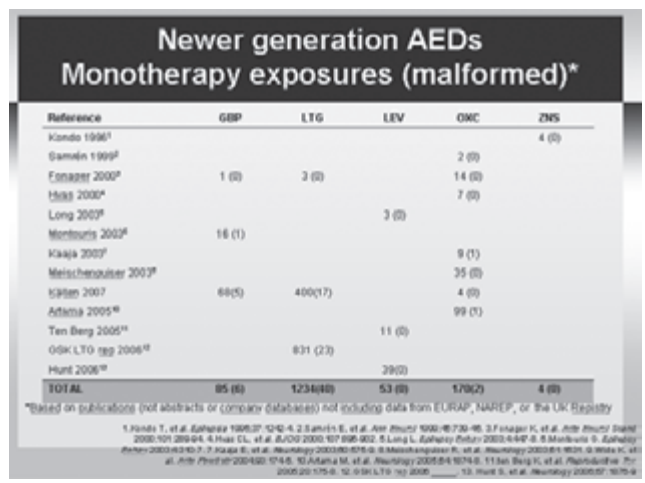
Offspring of treated mothers with epilepsy			Offspring of untreated mothers with epilepsy			Offspring of mothers without epilepsy		
Total	N	%	Total	N	%	Total	N	%
4630	284	6.1%	1292	36	2.8%	186438	40221	2.2%

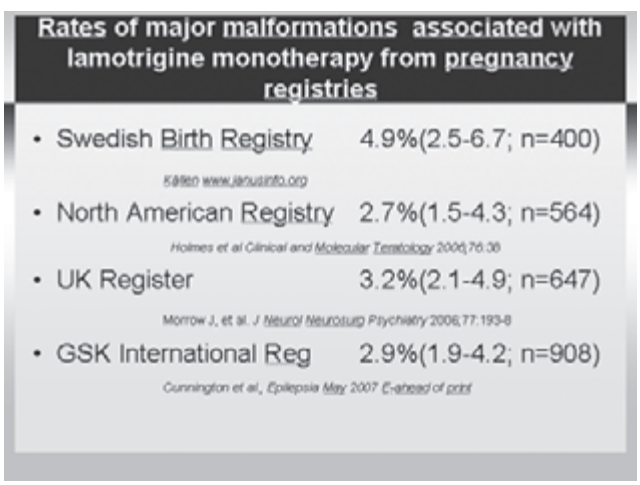
Pooled data from 26 studies

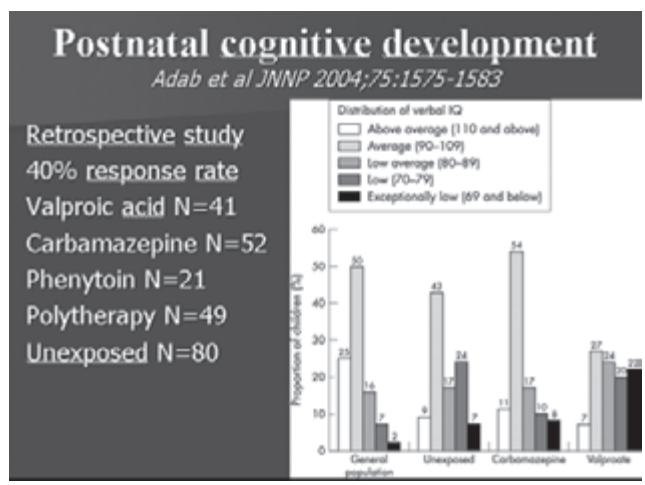

Comparative risk: The UK Register
malformation rates (n=3607)
%
No AED (227)
CBZ (900)
VPA (715)
LTG (647)
PHT (82)
GBP (31)
Morrow et al. JNNP 2006


The North American Registry
Major congenital malformation
Rate point estimate (95% CI)
Carbamazepine
n=873
Valproate
n=149
Phenobarbital
n=77
Lamotrigine
n=564


Malformation rate (%) by dose.
CBZ<400mg, NaVal<600mg, LTG<100mg.
CBZ 400-1000mg, NaVal 600-1000mg, LTG 100-200mg
CBZ >1000mg, NaVal>1000mg, LTG>200mg
CBZ
NaVal
LTG
Morrow et al JNNP Feb 2006


Newer generation AEDs
Monotherapy exposures (malformed)*
Reference
GBP
LTG
LEV
OXC
ZNS
TOTAL
85 (6)
1234(40)
53 (0)
170(2)
4 (0)


Rates of major malformations associated with lamotrigine monotherapy from pregnancy registries
• Swedish Birth Registry 4.9%(2.5-6.7; n=400)
Kaiser www.janusinfo.org
• North American Registry 2.7%(1.5-4.3; n=564)
Holmes et al Clinical and Molecular Teratology 2006;76:36
• UK Register 3.2%(2.1-4.9; n=647)
Morrow J, et al. J Neurol Neurosurg Psychiatry 2006;77:193-8
• GSK International Reg 2.9%(1.9-4.2; n=908)
Cunnington et al., Epilepsia May 2007 E-ahead of print


Postnatal cognitive development
Adab et al JNNP 2004;75:1575-1583
Retrospective study
40% response rate
Valproic acid N=41
Carbamazepine N=52
Phenytoin N=21
Polytherapy N=49
Unexposed N=80
Distribution of verbal IQ
Above average (110 and above)
Average (90-109)
Low average (80-89)
Low (70-79)
Exceptionally low (69 and below)
Proportion of children (%)
General population
Unexposed
Carbamazepine
Valproate

Dose effect of VPA monotherapy *in utero* on verbal IQ in children

	n	Mean Verbal IQ	95% CI
Mean AED dose in whole pregnancy			
VPA <800	11	90.7	80.6-101.4
VPA 801-1500	23	82.0	74.3-89.7
VPA >1500	6	73.8	60.2-87.4
Mean AED dose in final trimester			
VPA <800	6	88.7	67.1-110.2
VPA 801-1500	21	81.0	72.7-89.3
VPA >1500	7	75.9	63.8-87.9
Unexposed group	80	90.9	87.2-94.6

Adab et al. J Neurol Neurosurg Psychiatry 2004;75:1575-1583

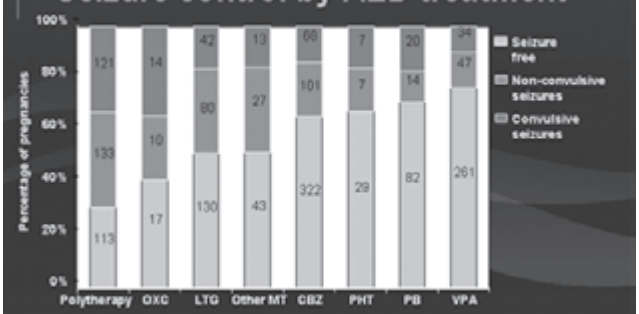
Postnatal Cognitive Development
Assessment of children exposed *in utero*

- Risk of impaired verbal IQ (<69) higher after exposure to VPA than after CBZ and in unexposed in retrospective UK study
- Trend toward lower verbal IQ in VPA exposed in prospective, small population based Finnish study
- Similar IQ trend with VPA in an independent Finnish population based study, but mothers using VPA also scored lower

Comparative teratogenic potential of AEDs

- Valproate appears to be associated with
  - -higher malformation rate
  - -and possibly lower verbal IQ
  - than carbamazepine
- How does VPA compare with other alternatives?
- How does low dose VPA compare with other AEDs?
- Role of confounders?
- Potential differences in teratogenic potential need to be weighed against risks associated with loss of seizure control

Effectiveness of treatment options: Seizure control by AED treatment

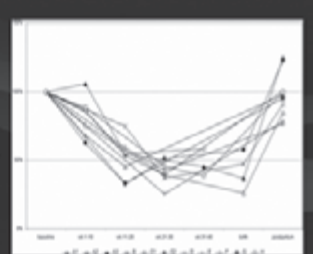


MT, monotherapies

EURAP Study Group. Neurology 2006;66:354-60

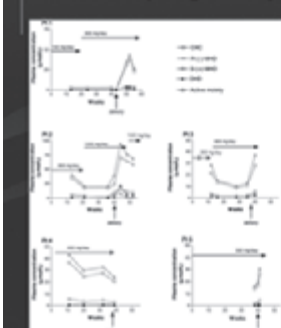
Effects of Pregnancy on the Pharmacokinetics of AEDs

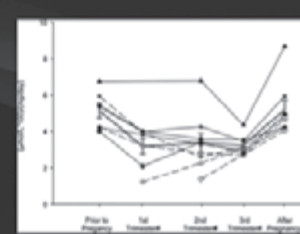
- Lamotrigine clearance increases by appr. 300% with marked individual variation
  Tomson et al Epilepsia 1997; Ohman et al Epilepsia 2000; De Haan et al Neurology 2004; Pennell et al., Neurology 2004;62:292-5
- Much more pronounced than for other AEDs



Disposition of oxcarbazepine in pregnancy and puerperium

- The dose-normalised concentrations of the active moiety decreased markedly during pregnancy, lowest after week 20, and increased several-fold after delivery in 4/5.





Mazzucchelli et al., Epilepsia 2006;47:504-9 *Christensen, J. et al. Neurology 2006;67:1497-1499*

Effects of pregnancy on AED plasma concentrations

AED	Total conc.	Unbound conc.
Phenobarbital	-10-20%	-10-20%
Phenytoin	-60%	-20%
Carbamazepine	-10%	minor
Valproate	-30%	minor
Lamotrigine	-30-75%	-30-75%
Levetiracetam	-40-50%	-40-50%?
Oxcarbazepine	-30-50%	-30-50%?
Other newer AEDs	?	?

Battino et al 1984, 1999; Yerby 1992, Tomson et al 1994, Tomson et al 1999;Ohman et al 2000; Tran et al 2001

Does it matter?

- Increase in LTG dose needed in 11/12 pregnancies
  Tran et al., 2002
- LTG dosage adjustment in all 14 pregnancies
  Pennell et al., 2004
- Seizure aggravation in 9/12 and 5/11 LTG pregnancies, respectively
  de Haan et al., 2004; Petrenaite et al., 2004
- Low concentrations of active OXC moiety associated with emergence of seizures in 2/4
  Mazzucchelli et a., 2006

Implications for AED treatment

- Data on comparative teratogenic potential still insufficient, in particular for the new generation AEDs
- All major changes in treatment before conception
- Use monotherapy at lowest effective dosage
- Avoid valproate if equally effective and safer AEDs are available
- In particular avoid VPA>1000 mg/day and combination with lamotrigine
- Establish pre-pregnancy AED level baseline and monitor in particular lamotrigine and oxcarbazepine
- Consider prescribing folate 4-5 mg/day, but explain lack of evidence for its efficacy
- Offer prenatal diagnosis

Breast-feeding and Old AEDs

AED	N	Milk/Plasma	Rel.dose*	Rel.conc.**
Phenobarbital	>25	0.3-0.8	10-40%	50-100%
Ethosuximide	>10	0.8-1.0	50-100%	40-60%
Phenytoin	>25	0.1-0.6	7-10%	<10%
Carbamazepine	>25	0.3-0.6	3-8%	10-20%
Valproate	>25	0.01-0.1	1-4%	<5%

*Infant dose/kg bw as percentage of maternal dose/kg bw
**Plasma concentration in nursed infant relative maternal plasma levels

After Wisner 1997

Breast-feeding and New AEDs

AED	N	Milk/Plasma	Rel.dose*	Rel.conc.**
Oxcarbazepine	1	0.5		7-12%
Lamotrigine	>20	0.4-0.8	6-15%	25-50%
Vigabatrin	2	0.1-0.9	1-4%	
Gabapentin	5	0.7-1.3	1-4%	4-12%
Topiramate	5	0.7-1.1	5-20%	9-17%
Tiagabine	0			
Levetiracetam	16	0.8-1.3	8%	<20%
Zonisamide	1	0.9		
Pregabalin	0			

*Infant dose/kg bw as percentage of maternal dose/kg bw
**Plasma concentration in nursed infant relative maternal plasma levels

Treatment of epilepsy in women

- Reproductive function
- Contraception
- Pregnancy
- Catamenial epilepsy
- Menopause

Catamenial epilepsy

Herzog et al 1997

- 2-fold increase in seizure frequency during either
  1. Perimenstrual cycle days -3 to +3
  2. Preovulatory cycle days 10 to -13
  3. Second half of inadequate luteal phase cycles
- 1/3 of the women meet these criteria
- Cyclic variation in levels of neuroactive reproductive steroids may be pathophysiological factor
- Progesterone (100-200 mg/day, days 15-28) or clobazam (10-20 mg/day intermittently) often used, definitive studies are lacking

Treatment of epilepsy in women

- Reproductive function
- Contraception
- Pregnancy
- Catamenial epilepsy
- Menopause

Epilepsy in the menopause

- Retrospective, unvalidated questionnaire studies of small numbers of selected menopausal, perimenopausal and premenopausal women with epilepsy
- Suggest no consistent change in seizure control in menopause

  Abassi et al. Epilepsia 1999, Harden et al Epilepsia 1999
- Small RCT (n=21) indicates dose-dependent deterioration in seizure control with HRT (CEE/MPA=estrogen and medroxyprogesterone)

  Harden et al. IEC Paris 2005
- No implications for AED selection

AEDs and Bone Health

- Decreased bone mineral density (BMD) and risk of fractures reported at higher frequency in people with epilepsy
- May be of particular importance for women and in post-menopause
- Enzyme-inducing AEDs, but also valproic acid have been associated with reduced BMD and increased bone turnover
- Lack of studies comparing different AEDs

Bone Mass and Turnover in Pre-menopausal WWE on AEDs

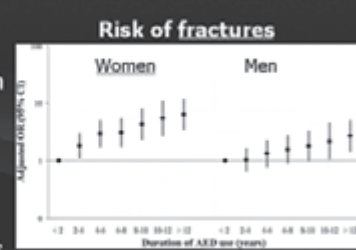
- Cross-sectional comparative study including ambulant WWE on monotherapy with CBZ (n=37), PHT (n=19), LTG (n=19) or VPA (n=18)
- BMD was normal and similar across the groups
- Patients on CBZ, PHT, and VPA significantly lower s-Calcium, and PHT significantly higher bone-specific alkaline phosphatase compared to LTG
- However, use of LTG considerably shorter (21 months) compared to VPA or CBZ (66), or PHT (97)
- Implications for AED selection uncertain

Pack et al., Ann Neurol 2005;57:252-7

Gender aspects on risk of fractures and use of AEDs

Case-control study
Cases: epilepsy pts with fracture (n=1,018)
Controls: epilepsy pts without (n=1,842)

No difference between exposure to ez-inducers vs. non-inducers



Souverein, P. C. et al. Neurology 2006;66:1318-1324

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Approach to AED therapy in women Conclusions

- Many issues involved and as always, the therapy needs to be individually tailored
- The phases in life that are unique to women prompt a more proactive approach with structured information and planning
- Much essential information for evidence-based strategies is lacking.

The elderly
Emilio Perucca (Italy)

The Elderly: Treatment Issues

Emilio Perucca
Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE Course, 12 February 2008

Epilepsy in the Elderly: An Exploding Epidemiological Phenomenon

- The incidence of epilepsy increases exponentially in old age
- 22-34 % of all incident cases occur above 70 years
  - Worldwide increase in life expectancy
  - Increased prevalence of neurological morbidity
  - Decreasing mortality associated with epilepsy

Epidemiology of AED Use in the Elderly

- 11% of 10,168 nursing home residents in the US received AEDs for a seizure disorder (unclassified in 54% of cases)
- In one out of 5 patients, AEDs were given for non-epilepsy indications (e.g., psychiatric conditions, chronic pain)
- Phenytoin most widely used AED (52%), followed by carbamazepine (12%) and phenobarbital (7%)

Schachter et al., 1998

Treating Epilepsy in the Elderly
Why do We Need Age-Specific Drug Trials?

- Aetiologies of epilepsy in the elderly are different
- Natural history and risk / benefit ratio of treating after a first unprovoked seizure may differ
- Pharmacokinetics and brain sensitivity to AEDs differ
- There are age-sensitive issues related to comorbidities, risk of drug interactions, and compliance

Most Desirable Features for an AED in the Elderly

- Predictable pharmacokinetics
- Not a cause nor a target for drug interactions.
- Not an enzyme inducer
- Not an enzyme inhibitor
- Excellent tolerability
- High efficacy
- Availability of a parenteral formulation

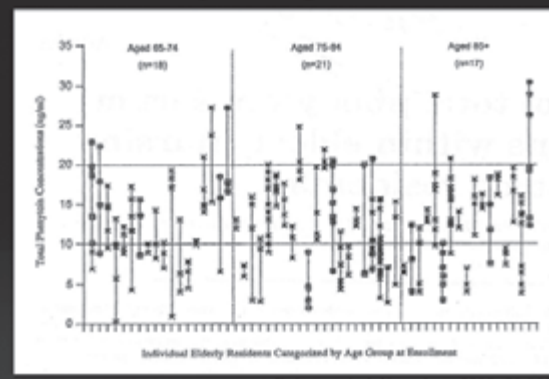
Pharmacokinetic (PK) Variability of AEDs: Why is Important?

- AEDs have a narrow therapeutic index, i.e. therapeutic and toxic doses are close
- Dosage requirements differ greatly across individuals, partly as a result of PK variability
- Controlling PK variability may facilitate clinical management

PK Changes in Old Age: Absorption

- Old age is associated with increased gastric pH, decreased g.i. motility and decreased g.i. blood flow
- Usually, no major alterations are seen in average extent of drug absorption (unless atrophic gastritis is present) - absorption rate may be decreased
- Is variation in bioavailability larger in the elderly?

Day to-Day Variability in Serum Phenytoin Level in 56 Elderly Nursing Home Residents



Birbaum et al, Neurology 2003; 60:555-9

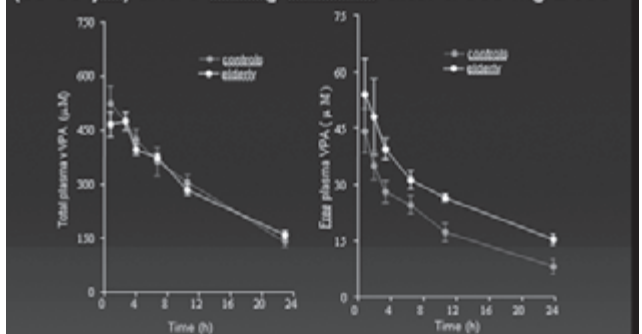
PK Changes in Old Age: Distribution

- Binding to plasma proteins may decrease
  - ✓ Related to reduction in plasma albumin
  - ✓ Endogenous binding inhibitors may contribute when renal function is impaired
  - ✓ Displacing effect of highly bound comedication, e.g. NSAIDs
- Body fat/lean mass ratio is increased
  - ➢ Vd increases, half-life increases, drug concentration does not change

Relevance of Changes in Plasma Protein Binding in the Elderly

- Significant only for highly bound AEDs: PHT, VPA, TGB
- Unless metabolizing capacity is impaired, free (active) concentration is unchanged
- Total drug concentration underestimates free concentration

Free and Total VPA Concentrations in 6 Elderly Patients (68-89 yrs) and 6 Young Controls after a 800 mg Dose



Perucca et al, Brit J clin Pharmacol 1984; 17:665-669

PK Changes in Old Age: Biotransformation

- Reduced metabolizing capacity for drugs cleared by P450 enzymes (1A2, 2C9, 2C19, 2D6 and 3A4) - however, large inter-subject variability
- Reduced metabolizing capacity also for drugs eliminated by conjugation

Carbamazepine Clearance in Old Age

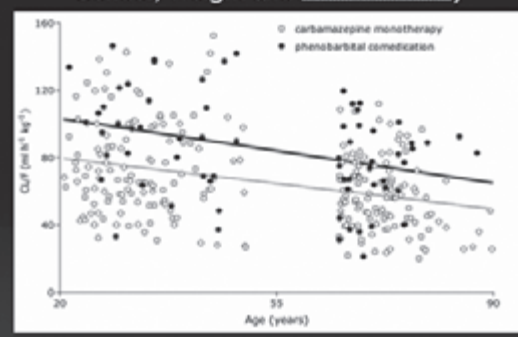
	CBZ clearance (ml h^{-1} kg^{-1})	
	Elderly patients*	Controls
CBZ monotherapy (n = 123 per group)	57.1 ± 20.6*	74.6 ± 28.3
PB comedication (n = 34 per group)	74.7 ± 25.5*	98.7 ± 34.9

* P < 0.01 vs controls, mean age of elderly patients, 72 ± 5 yrs

Battino et al, Epilepsia, 2003; 44: 923-9

Relationship of CBZ Clearance with Age

(157 Elderly Patients and 157 Controls Matched for Gender, Weight and Comedication)



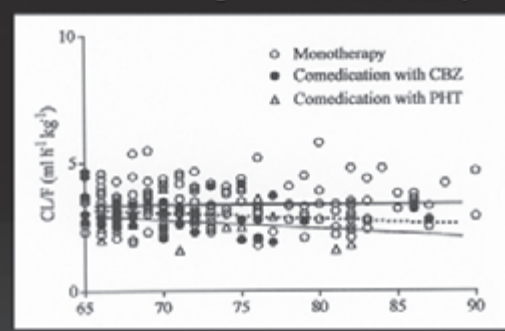
Battino et al, Epilepsia 2003; 44: 923-9

PK Changes in Old Age: Renal Excretion

- Glomerular filtration rate decreases with age
- Renal drug clearance decreases in parallel
- Elimination of drugs cleared by renal excretion is impaired

Relationship of PB Clearance with Age

(116 Elderly Patients and 157 Controls Matched for Gender, Weight and Comedication)



Messina et al, Epilepsia 2005; 46:372-7

Clearance of First Generation AEDs in Old Age*

Drug	Mean % difference in CL/F (vs adults)	Reference
Phenytoin	- 25 %**	Bachmann, 1999
Carbamazepine	- 25-40%	Battino, 2004
Valproic acid	- 40%**	Perucca, 1984
Phenobarbital	- 22%	Battino, 2005

* Inter-patient variability can be large
* Free drug clearance. Effect may not be apparent from total plasma concentration measurements

Clearance of New AEDs in Old Age

Drug	Mean % difference in CL/F (vs adults)	Reference
Lamotrigine	- 37 %	Posner, 1991
Oxcarbazepine	- 25-35%	V. Heiningem, 2001
Tiagabine	- 30%	Snel, 1997
Felbamate	- 10-20%	Richens, 1997
Levetiracetam	- 20-40%	Pellock, 2001
Topiramate	- 20%	Doose, 1998
Zonisamide	no change?	Shah, 2002
Gabapentin	- 30-50%	Armijo, 2004
Pregabalin	No data	-
Vigabatrin	- 50-90%*	Haegele, 1988

*study included patients with renal failure

Perucca E. Clin Pharmacokinet 2006; 45, 351-63

Old age is less a period of predictable change than of increased variance between individuals….

Tallis RC, in: The Treatment of Epilepsy, Shorvon, Perucca, Fish & Dodson, Eds, Blackwell, Oxford, 2003

Predicting PK Changes in Old Age: Patient-Related Factors

- CLcr, plasma proteins
- Frailty
- Dietary changes
- Co-morbidity
- Co-medication (drug interactions)

Altered Pharmacodynamic Responsiveness in the Elderly

- Greater vulnerability to CNS side effects
  - Confusion, sedation, irritability, cognitive dysfunction (BZDs, VGB, FBM)
  - Dizziness, coordination difficulties, falls, fractures (BZDs, CBZ, PB, PHT)
- Greater vulnerability to cardiac toxicity (CBZ, PHT)
- Increased risk for "metabolic" side effects
  - Hyponatremia (OXC, CBZ)
  - Bone demineralization (PHT)

Increased Pharmacodynamic Sensitivity in Old Age?

VA Cooperative Studies #118 & #264

Mean Plasma Concentration in Patients With Adverse Effects (μg/mL)

Age	CBZ	VPA
<40	7.4	79.5
40-64	5.9	83.7
≥65	3.6	66.3

Ramsay et al. *Epilepsia*. 1994;35(suppl 8):91A.

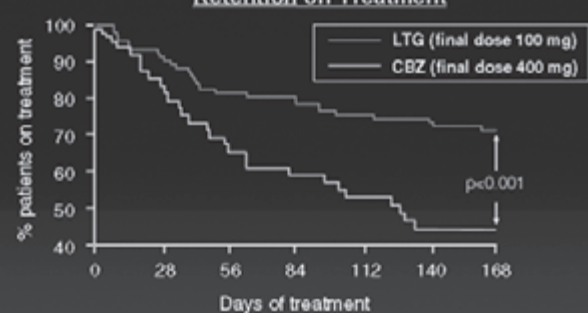
Treating Epilepsy in Old Age Studies with Older-Generation AEDs

- Good prognosis for seizure control, usually at low doses
  - ◆UK retrospective study, 73 pts (Cameron, 1995[1])
  - ◆US retrospective study, 94 pts (Hasegawa, 1995[2])
  - ◆UK randomised PHT-VPA trial, 38 pts (Tallis, 1994[3])
  - ◆VA randomised trial, PHT-CBZ-PB-PMD (Ramsay, 1994[4])
- Poor prognosis in terms of survival
  - ◆UK NGPSE Study (Cockerell, 1997[5])

[1]*Epilepsy Res* 1995;21:149-57; [2]*Clin Neuropharmacol* 1995;18:13-22; [3]*Epilepsia* 1994;35:381-90; [4]*Epilepsia* 1994;35 (suppl. 8):91A; [5]*Epilepsia* 1997;38:31-46

CBZ vs LTG in the Elderly The UK Randomised Trial

Retention on Treatment



Brodie et al. *Epilepsy Res* 1999;37:81-87

LTG *vs* CBZ in the Elderly
The UK Randomised Trial

Strengths

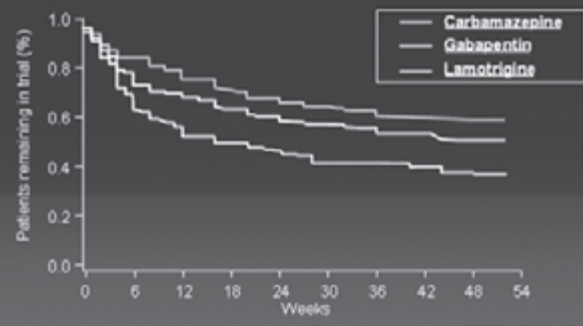
- Previously untreated patients
- Target dosages not excessive
- Slow titration
- Dose adjustments permitted

Weaknesses

- Low sample size (50 patients in the CBZ group)
- Short follow-up (24 weeks)
- Immediate-release CBZ, given twice daily

CBZ vs LTG vs GBP in the Elderly
The U.S. (VA #428) Randomised Trial

Retention on Treatment



Rowan et al. Neurology 2005;64:1868-1873

GBP *vs* LTG *vs* CBZ in the Elderly
The VA #428 Randomised Trial

Strengths

- Large sample size, good power!
- t.i.d. dosing for CBZ and GBP
- Flexible dosages
- One-year follow-up

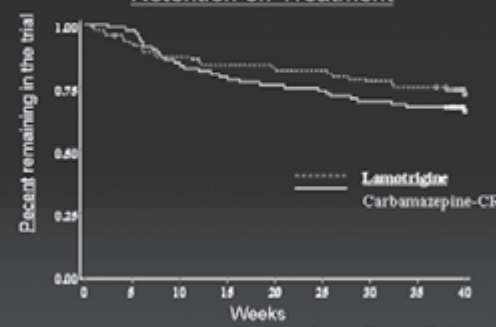
Weaknesses

- Lower age limit at 60
- 43% previously treated, usually with PHT - selection bias against CBZ?*
- Fast titration, high target dosages, biased against CBZ?
- Immediate-release CBZ

* 141 patients refused enrolment because "satisfied with current treatment"

CBZ-CR vs LTG in the Elderly
The European (LAM #40089) Randomised Trial

Retention on Treatment



Saetre E et al, Epilepsia, in press

LTG *vs* CBZ in the Elderly
The European LAM #40089 Randomised Trial

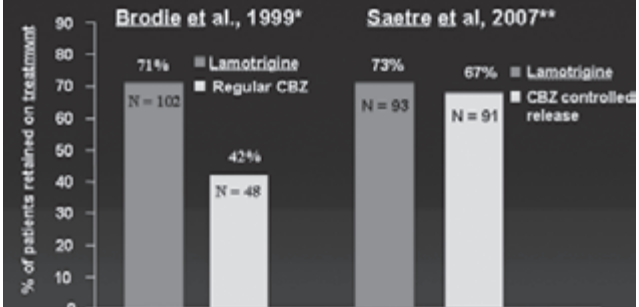
Strengths

- Previously untreated patients
- Target dosages not excessive
- Slow titration
- Sustained-release CBZ
- Dose adjustments permitted

Weaknesses

- Modest sample size
- Duration of follow-up <12 months

What Difference can a Formulation Make?
Treatment Retention in 2 Double-blind RCTs in Elderly People with New Onset Epilepsy



* 20 wk trial, Epilepsy Res. 1999;37:81-87 ** 40 wk trial, Epilepsia 2007;48:1292-1302
Dosing and titration schemes were identical in both trials

Conclusions

- Aging influences the pharmacokinetics of AEDs, but interindividual variability is considerable
- Pharmacodynamic (PD) sensitivity also changes, and therapeutic and adverse effects occur at lower AED concentrations than in younger adults
- Interpretation of blood levels needs to consider changes in protein binding and PD sensitivity
- Results of RCTs in younger populations do not necessarily apply to the elderly

Conclusions (2)

- Few RCTs have been conducted in the elderly, and many AEDs have not been properly tested
- Most completed studies have methodological shortcomings, such as small sample size, and use of suboptimal formulations or dosing regimens
- Findings confirm that elderly persons differ from younger people in their response to AEDs
- Further studies with an improved design are clearly needed

THE NEUROBIOLOGICAL BASES OF AED RESISTANCE

LAZAROWSKI ALBERTO[1,2], CZORNYJ LILIANA[3], D`GIANO CARLOS[4], VAZQUEZ SILVIA[4] AND GIRARDI ELENA[2,5]

ACKNOWLEDGEMENT

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SUMMARY

It is estimated 20-25% of the epileptic patients fails to achieve good control with the different antiepileptic drugs (AEDs) treatments, developing refractory epilepsy (RE).

The activity of the transporters as P-glycoprotein (P-gp), multidrug-resistance-associated proteins (MRPs) and breast cancer resistant protein (BCRP), are directly related with the multidrug resistance (MDR) phenomenon. According with other authors, we have observed the over-expression of these all transporters in the brain of patients with RE. Several experimental epilepsy models have demonstrated the inducible P-gp overexpression on blood brain barrier (BBB) and brain parenchyma cells (astrocytes, neurons) related with MDR phenotype and the impairment of brain AEDs access. Early P-pg detection in vessel-related cells and later additional P-gp detection in neurons, correlated with the gradual loss of protective effect of phenytoin, depending on intensity and time-constancy of seizure-injury. The expression of P-gp and other multidrug-transporters in excretory organs suggests they have a central role in drug elimination. Persistent low levels of AEDs in plasma or increased liver clearance of ^{99m}Tc- MIBI (a P-gp substrate) in RE surgically treated cases that showed P-gp brain over-expression were documented by our group. Additionally, changes in known AED's targets (voltage-gated sodium channels, hyperpolarization-activated current (IH) and GABA receptors) were also reported. P-gp neuronal expression described in both clinical and experimental reports suggests an alternative mechanism related with lower membrane potential ($\Delta\psi 0$ = -10 to -20) observed in P-gp-expressed cells as compared to normal physiological $\Delta\psi 0$ of -60 mV. Under this situation and irrespective to the P-gp pharmacoresistant property, MDR+ neurons could increase their sensitivity to new seizures perhaps as an epileptogenic mechanism. The understanding of properties of these multidrug-transporters can offer new tools for better selection of more effective preventive or therapeutic strategies and avoid the invasive surgical treatments for RE.

KEY WORDS: Refractory epilepsy, MDR, BCRP, MVP. 99mTc-MIBI

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Introduction

Epilepsy is a neurological disorder affecting 1-2% of the general population (1 Commission on Classification and Terminology of the International League Against Epilepsy 1981). Despite considerable advances in the pharmacotherapy of epilepsy, about 30% of epilepsy patients are refractory to antiepileptic drugs (AEDs) (Collaborative Group for the Study of Epilepsy 1992; Temkin 2001). These patients can't to control the seizures after use of several antiepileptic drugs (AEDs), even at maximum tolerated doses administrated (Kwan & Brodie 2000; Sander & Sillanpaa 1998) (Fig.1). In most cases, a patient who is resistant to one major AED also is refractory to other AEDs, although these drugs act by different mechanisms.

Reasoning and making decision in epilepsy, each new diagnosed epilepsy case requires a good identification of his epileptic syndrome, and according with the corresponding classification, the treatment is started. So, in ~ 60% of epileptic patients, administration of one or two AEDs, is enough to seizures control. However, ~40% of epileptic patients repeatedly fail to control the seizures with one AED after another or their combinations, defining the Multidrug Resistance (MDR) Phenotype. (Kwan & Brodie. 2000).

Which key mechanisms govern efficacy of CNS drugs?

Anti-epileptic drugs (AEDs) are lipophilic compounds that with adequate serum levels have to traverse the blood-brain barrier (BBB) via the lipid membranes. BBB is formed by the endothelial cells lining the brain microvessels and complex tight junctions linking adjacent endothelial cells make these brain capillaries tighter than peripheral capillaries to small hydrophilic molecules.

AEDs have to bind to one or more target molecules to exert their desired action. Thus, pharmacoresistance could be caused by modifications on drug target molecules, building the "target theory" for pharmacoresistance. Many channels, particularly those that shape the ongoing electrical behavior of a neuron, are voltage-dependent channels. The frequency with which such channels open and close depends on the membrane potential. Different types of channels may either increase or decrease the amount of time that they spend in the open state as the voltage across the membrane is made more positive. Upon depolarization of the membrane, the Na+ channels activate and give rise to a fast 'transient' inward Na+ current responsible for the rising phase of the action potential, and-in some

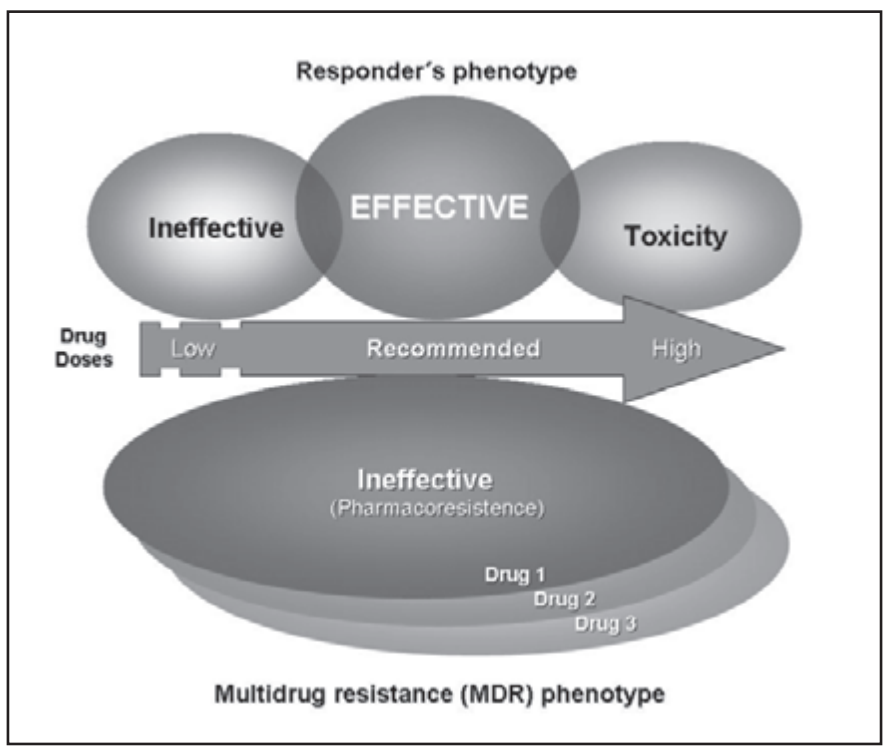

Figure 1: Behavior of responders and refractory patients

cells-a slowly-inactivating 'persistent' current, corresponding to the major targets of several first-line AEDs. These AEDs block Na+ channels in their resting state at hyperpolarized membrane potentials with a voltage-dependent enhancement of the block towards more depolarizing potentials. The drugs acting on INaT channels display voltage-dependent inhibition, associated with a shift of the steady-state inactivation curve in a hyperpolarized direction. This shift decreases the availability of the Na+ channel during an action potential and, therefore, reduces the excitability of the cell. In this context, several mechanisms can account for an altered sensitivity of Na+ channels in epileptic tissue. One possibility may be an altered subunit composition of these channels, where the downregulation of accessory Na+ channel 1 and 2 subunits following experimentally induced status epilepticus appears to be a consistent finding. However, available data indicate that altered sensitivity of Na+ channels may not be able to account for altered efficacy of other AEDs such as valproic acid or lamotrigine (Remy et al., 2003). This finding may indicate that resistance to AEDs in epilepsy patients is a complex phenomenon that possibly relies on multiple mechanisms.

The pilocarpine model of epilepsy has been frequently used to study changes in pharmacosensitivity of drug targets. Leite and Cavalheiro (1995) have provided some evidence that high doses of common AEDs such as carbamazepine, PHT and valproate reduce the spontaneous seizure frequency in these animals. This is in apparent contradiction to the finding that Na+ channels in the same model are resistant to carbamazepine. Similarly, experiments with kindled rats based on their responsiveness to

PHT (Loscher et al., 1998), when rats responsive to PHT were compared to a group of rats that were not, no difference in PHT sensitivity of INaT emerged. (For full revision of these mechanisms see recently published article by Stefan Remy and Heinz Beck, 2006).

All these data, suggests that other mechanisms should be addressed to explain the Multidrug resistant phenotype observed in refractory epilepsy.

P-gp is predominantly located on the endothelial luminal membrane of BBB and it is estimated that lipophilic AEDs are also potential substrates for efflux carriers of the BBB, particularly P-gp. According with this observations, studies in Mdr1a knockout (7/7) mice showed a dramatic increase in the brain distribution of compounds known to be P-gp substrates (Schinkel et al 1994). However, it is important to notices that the only presence of P-gp at BBB level, as normally described (Schinkel et al 1994; van Asperen et al 1997), is not enough to produce the impairment of AED's entrance in the brain, as suggested by the treatment success in the epileptic responders' patients. An overexpression or functional up-regulation of P-gp at BBB and/or brain parenchyma cells, together with other transporters should be present to explain the multidrug resistance phenotype observed in refractory epilepsy. The mechanism of multidrug resistance (MDR), initially described in tumor cells, is due to the action of the P-glycoprotein, an ATP- and Ca2+-dependent detoxifying pump that extrudes potentially toxic compounds out of the cells and can confer resistance levels of 1000-fold or more to the expressing cells (Ling 1989, Gottesman & Pastan 1993).

Tishler et al. (Tishler et al. 1995) illustrated the high expression of P-gp in the brain of refractory epileptic patients that display MDR phenotype, and this was subsequently confirmed by others (D'Giano C et al. 1997; Lazarowski et al. 1997; Sisodiya et al. 1999; Dombrowski et al 2001; Sisodiya et al 2002).

ABC TRANSPORTERS: STRUCTURES AND MECHANISMS OF ACTION

The multidrug resistance (MDR) phenotype is a multifactorial phenomenon that is conferred by distinct proteins belonging to one large named "ABC transporters superfamily". Currently, 48 different members have been identified in the human genome, 22 of them have been associated with physiologic or pathological functions. Particularly the P-gp, the multi-drug-resistance-associated proteins (MRP1-7) and the Breast Cancer Resistant Protein (BCRP) have been related with the MDR phenotype. Most ABC-transporters have two transmembrane domains (TM) and two cytosolic nucleotide-binding domains (NBDs) (□tefaková et al. 2004). The breast cancer resistance protein (BCRP), has only one TM domain and one NBD, and is assumed to function as a dimmer (Ejendal & Hrycyna 2002) (Fig. 2).

P-gp and others ABC-transporters are most highly expressed in the apical membrane of epithelial cells in the liver, kidney, intestine, colon,

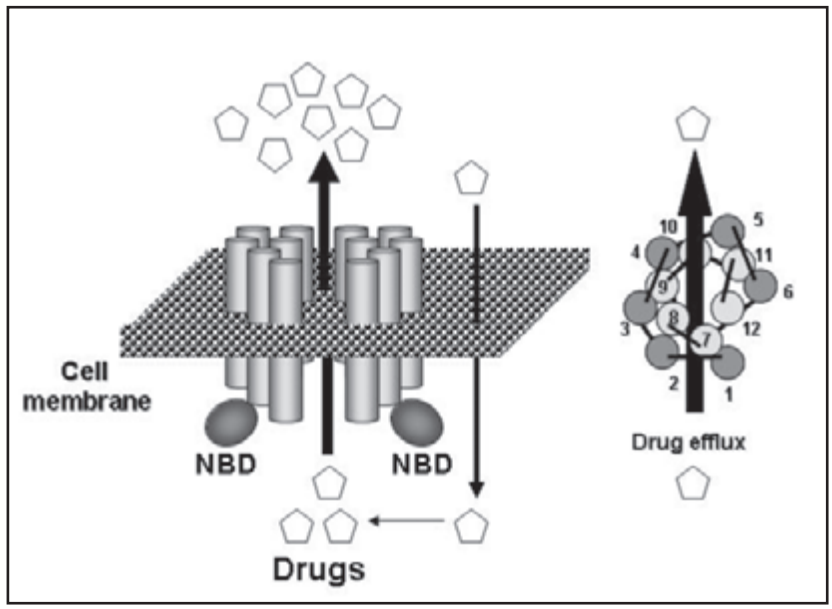

Figure 2: Typical structure of the ABC- transporters

brain, testis, and placenta (Cordon-Cardo et al. 1990), suggesting that it plays a role in protecting tissues against potential toxins.

Differentiating agents, hormones, oncogenes, and transcription factors know to be evolved in apoptosis, stress, inflammation and hypoxia (e.g. p53, NFkB, NF-IL6, AP-1, HIF-1α) (Fig. 3) (Cornwell & Smith 1993; Goldsmith et al. 1995; Combates et al. 1994; Labialle et al 2002; Comerford et al. 2002), can up-regulate the expression of these transporters in previously non-expressive cells as neurons (Ramos et al 2004, Lazarowski et al 2007) or cardiomiocytes (Lazarowski et al 2005a, Laguens et al 2007), suggesting that P-gp and other MDR-like proteins may be also involved in cell survival-death related biological processes (Friesen et al 1997; Hirose & Kuroda 1998; Abolhoa et al. 1999).

ABC TRANSPORTERS IN NORMAL BRAIN AND IN CLINICAL REFRACTORY EPILEPSY

P-gp, MRPs and BCRP are normally expressed in the BBB or the blood-CSF barrier (BCSFB), playing all together a combined role to reduce the brain penetration of many drugs. P-gp is expressed on the apical side of the choroids' plexus epithelia (Rao et al 1999) and at the abluminal membrane of vascular endothelial cells of the blood brain barrier (BBB) (Beaulieu et al. 1997) and it is also co-localization of P-gp with glial fibrillary acidic protein (GFAP), rather than the endothelial marker (GLUT1) suggesting that P-gp is present at the astrocyte foot-ending-processes on the luminal side of the endothelium. MRPs proteins, which mediate the ATP-dependent cellular export of organic anions, are expressed in the brain microvessel endothelial cells; however, whether MRP4 and MRP5 confer refractoriness to AEDs is still unknown (Recently revised by Loscher and Potschka (Loscher & Potschka 2005). BCRP is normally located at the BBB, mainly at the luminal surface of microvessel endothelium. Thus, BCRP may give an additional barrier to drug access to the brain (Cooray et al. 2002; Eisenblatter et al. 2003; Zhang et al, 2003).

About one-half of newly diagnosed patients with epilepsy obtain full seizure control with the first AED tried, and 13% more enter remission with the addition of a second drug. The remaining patients are not likely to obtain satisfactory seizures control with any single drug or drug combination (Collaborative Group for the Study of Epilepsy 1992) (Fig.4).

After the potential association between P-gp over-expression in the brain and refractory epilepsy described by Tishler et al. (Tishler et al. 1995), several reports illustrated high levels of P-gp and MRPs expression in epileptogenic brain specimens from patients with refractory epilepsy (RE). In these studies, P-gp was highly expressed not only in vascular endothelial cells but also in brain parenchymal cells (D'Giano et al. 1997; Lazarowski et al. 1999; Sisodiya et al. 1999; Dombrowski et al 2001; Sisodiya et al 2002). However it is still unclear whether this overexpression of efflux transporters is

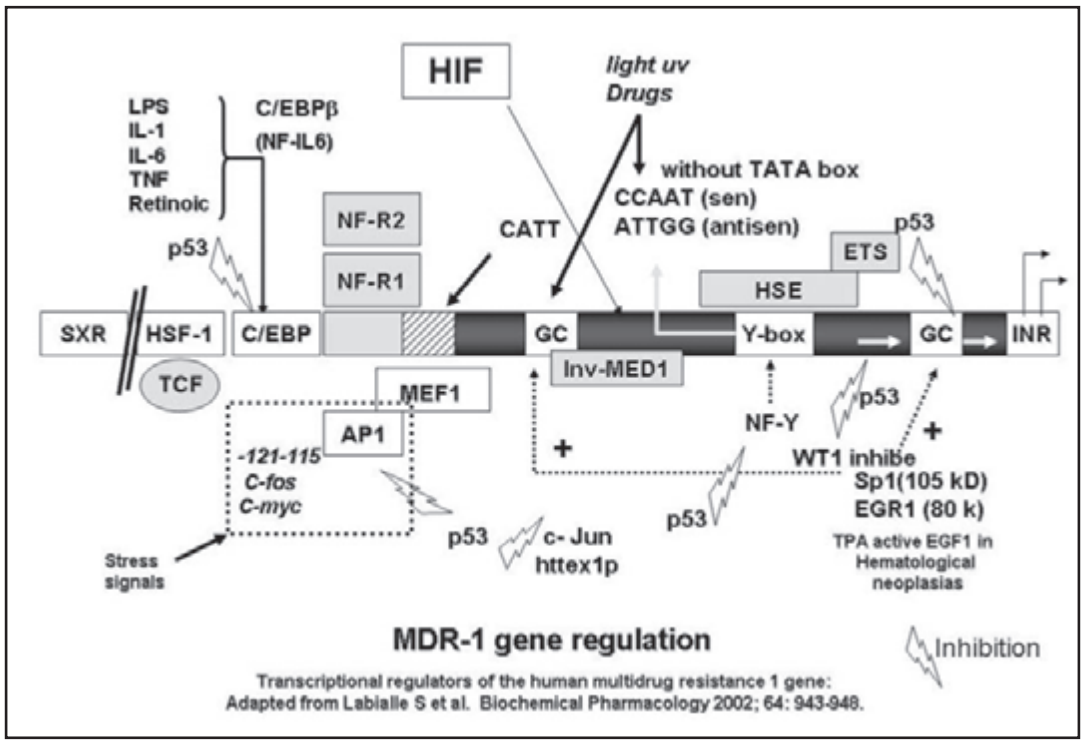

Figure 3: Transcription factors that up-regulates the MDR-1 gene expression

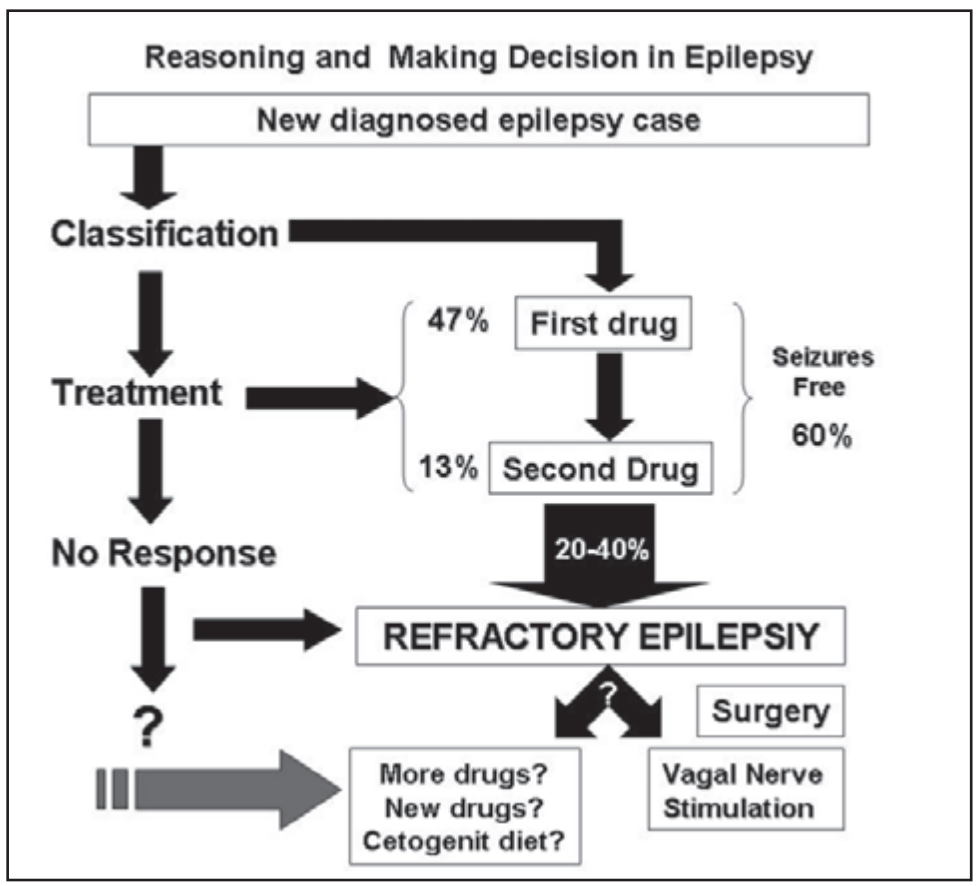

Figure 4: Reasoning and taking decisions in epilepsy

constitutive and exists before the onset of epilepsy or is a consequence of epileptic seizures, or drug treatments, or both. The nature of ABC transporter genes indicates that their expression can be induced in previously non-expressive cells. Consequently, overexpression of these proteins could be observed in BBB-related cells and brain parenchyma cells, including neurons from clinical end experimental studies, however, the pharmacological role of P-gp as expressed in neurons still remains unclear (D'Giano et al. 1997; Aronica et al. 2003; Volk et al. 2004; Lazarowski et al. 2004a; Lazarowski et al 2004b).

The abnormal parenchyma cells presents in the epileptogenic tissues from different RE syndromes such as dysembryoplastic neuroepithelial tumors, focal cortical dysplasias and hippocampal sclerosis, could express P-gp or MRP1 constitutively (Sisodiya et al. 2002). However it is not known if these P-gp or MRP1 positive parenchyma cells are also epileptogenic cells. Recently, in 3 cases of tuberous sclerosis with refractory epilepsy, P-gp and MRP1 were detected immunohistochemically in abnormal balloon cells and dysplastic neurons, as well as in normal parenchyma cells presents in brain lesions from the epileptogenic cortical tubers but not at normal brain areas (Lazarowski et al. 2004c). These results indicates that in RE, the brain expression of these transporters could be secondary to constitutive mechanisms in abnormal cells as well as induced mechanisms in normal cells, and their presence only observed in the cortical tubers, could also suggest a still non-described potential epileptogenic-associated role.

Additionally, in the same 3 cases of tuberous sclerosis mentioned, BCRP was only detected at BBB level, however, a cytosolic non-ABC transporter multidrug resistant protein named MVP (mayor vault protein), was detected in the cytoplasm of few ballooned cells in one of these cases (Lazarowski et al. 2006). This last observation is in according with previous reports from Marroni M et al. and Sisodiya (Marroni et al 2003; Sisodiya et al 2003a).

The hypothesis of an inducible mechanism was demonstrated in experimental epilepsy model of our group (see below), and supported by most recent clinical data from Sisodiya et al. (Sisodiya & Thom 2003b), who studied P-gp and MRP1 expression in brain specimen from a fatal case of human staus epilepticus. A net up-regulation of both transporters in the hemisphere with cortical dysplasia was found. Additionally, there was also a widespread up-regulation of both transporters in glia from the normal hemisphere reinforcing the idea that seizures can induce the expression MDR transporters.

BCRP and/or MVP (Mayor Vault Protein) overexpression have been documented in some clinical reports of different RE cases (Sisodiya et al. 2003b; Vogelgesang et al 2004; Lazarowski et al 2005b; Sisodiya et al 2006). And MVP was also overexpressed in an experimental epilepsy model (van Vliet et al. 2004). Strikingly, we have been recetly documented highly expressed BCRP in the BBB and dysplastic and/or ballooned neurons without brain P-gp overexpression, in two children with RE due to transmantel cortical dysplasia and refractory fatal satus epilepticus respectively (Czornyj et al. 2004; Czornyj et al. 2005).

Whether over-expression of the P-gp and MRP are demonstrated to be also a consequence of the seizure-induced stress, this concept will give a rational support to the criteria that "the repetitive uncontrolled seizures are a high risk factor to develop refractory epilepsy".

Persistent sub-therapeutic AEDs blood levels or ^{99m}Tc-MIBI-liver clearance in patients with refractory epilepsy and brain MDR-1 gene over-expression.

Refractory epilepsy is described in patients whom have adequate therapeutic levels of AEDs, without control of seizures. In spite that therapeutic levels of phenytoin (PTH) in blood and CSF can be achieved 2 hours after conventional loading doses of i.v. administration of PTH (Rabinowicz et al 1997), in some cases, patients can have persistent low plasmatic levels of PHT (or at least one of the AEDs administered), despite their scrupulous compliance with the prescribed drugs regimen. In these cases, often non-detectable errors for AEDs measurement procedures methods are assumed. However, the persistent low plasmatic levels of PHT (or other AEDs) in spite of adequate drug administration and their relationship with the brain expression of P-gp in two pediatric patients with refractory epilepsy were first reported by our group (Lazarowski et al. 1997; Lazarowski 1999a; Lazarowski et al. 2004a).

In both cases described, over-expression of P-gp in the brain do not explain the inappropriate

blood levels of AEDs obseerved but the results might indicate that, at least in these cases, P-gp over-expression could be a more general phenomenon that results in the accelerated clearance of AEDs not only from the epileptic lesions but also from the blood and peripheral tissues, perhaps in concert with other active metabolic and excretory mechanisms. We suggest that a systemic P-gp (or other ABC-transporters) over-expression should be considered as a potential additional mechanism responsible for drug resistance to pharmacological epilepsy treatment, and highly suspected in patients with persistent sub-therapeutic drug plasma levels in their laboratory controls.

Most drug metabolizing enzymes produce either covalent modifications of functional groups or conjugation of xenobiotic substrates with endogenous co-substrates to facilitate drug metabolism and excretion. The abundant expression of P-gp in tissues where drug alteration takes place suggests that P-gp plays central role facilitating drug elimination or their metabolites. Bile flow plays important functions during drug metabolism. A large number of endogenous "waste products" and xenobiotic are secreted into the bile, often following oxidative or conjugative metabolism by hepatic detoxifying systems. Most canalicular transport elements involved in bile formation are members of the ABC transporter super-family, among them the glycoprotein P-gp and MRPs. In this regard it was recently documented that P-gp is overexpressed in the liver of chronic epileptic rats without influences on phenytoin kinetics (vanVliet et al 2007).

^{99m}Tc-hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) is used as a myocardial perfusion imaging agent (Boucher et al. 1980). However, ^{99m}Tc-MIBI has been reported to be a transport substrate for P-gp as not metabolized compound and it is used for in vivo functional detection of P-gp activity in different tumors (Hendrikse et al. 1998; Lazarowski 1999b; De Moerloose et al. 1999; Lazarowski et al 2006b). The normal distribution of ^{99m}Tc-MIBI correlates with the active efflux mediated by P-gp in excretory organs [Fig. 3]. For this reason, irrespective to the AED's plasma levels of the patients, ^{99m}Tc-MIBI-HB-T½ could be a more robust parameter to evaluate the excretory systems dependent of ABC-transporters. The individuals with higher excretory function of drugs could be porters of high expression of active P-gp in these excretory systems. According with all these properties of ^{99m}Tc-MIBI, we recently observed that the ^{99m}Tc-MIBI hepatic clearance showed a differential accelerated pattern in patients with pharmacorresistant epilepsy (Vazquez et al. 2004). In this preliminary study, the renal ^{99m}Tc-MIBI kinetic measurements did not show differences between pharmacoresistant epileptic patients and controls. However, in patients with RE, ^{99m}Tc-MIBI hepatic clearance (MIBI-HC) was significantly shorter than normal controls and responder cases ($p<0.001$), indicating that hepatic, but not the kidney excretion, could somehow be involved with additional pharmacokinetic changes favoring the development of a pharmacoresistant phenotype.

To assess the potential relationship between this accelerated kinetics and the brain over-expression of P-gp, in a retrospective study, we investigated five of cases with RE and faster MIBI-HC. These patients had mesial temporal sclerosis and were surgically treated. In brain specimens P-gp overexpression was documented in vascular endothelium, glial cells and neurons in several hipocampal areas investigated by immunohistochemistry and RT-PCR methods, but in contrast with previous report (Aronica et al. 2004), MRP was not detected

USE OF CALCIUM CHANNEL BLOCKERS

In the pioneer report of Tishler and col. (Tishler et al. 1995), it was documented that phenytoin did not accumulate in MDR-1 expressing DAOYAR2 cells but, pre-incubation of these cells with verapamil resulted in cellular accumulation of phenytoin to concentrations similar to those observed in DAOY (MDR-1 negative) control cells.

Our group has recently studied several pediatric cases with persistent sub-therapeutic AEDs blood levels and refractory epilepsy. Nimodipine administration, together with AEDs, resulted in notable improvement of both medical condition and blood levels of AEDs. Importantly, one of these patients described above (Lazarowski et al. 2004a) showing P-gp over-expression in brain, the combined therapy with phenytoin and nimodipine resulted in increased plasmatic levels of phenytoin and a decreased PHT clearance.

Recently, it was described an 11-years-old boy who developed status epilepticus after a prolonged right-side simple partial motor seizure, which was unresponsive to long term aggressive

treatment with several AEDs (Ianetti et al. 2005). The control of seizures was achieved at a plasma valproic acid level of 108 g/ml, but electrical status epilepticus persisted, and the child remained comatose. On day 37, a treatment with verapamil (a calcium L-channel blocker) was started, and 1.5 hour after the initiation the infusion, the patient regained consciousness, was able to breathe spontaneously, and the electrical status, promptly disappeared. The authors suggested that verapamil, a known P-gp inhibitor acted by facilitating the brain penetration of AEDs simultaneously administrated to the patient, however, because surgical treatment was not developed, brain over-expression of P-gp can't be confirmed in this case.

It is interesting to remark that the use of nimodipine, showed a significant increasing T½ of ^{99m}TC MIBI-liver-clearence of two RE patients from the previously mentioned ^{99m}Tc-MIBI kinetic study, which had an initial T½ of 99mTC MIBI-liver-clearence of 1636 sec. and 1583 sec, and after 2 months of nimodipine treatment, the T½ were increased to 2134 sec. and 2565 sec. respectively. The outcome in a year follow up both patients had an important clinical improvement associated the kinetic changes, diminishing the frequency seizures up 50%. One of them was seizure free for four months (D'Giano et al. 2005). Several progresses are coming from use of more specifics and effective inhibitors of P-gp and others ABC transporters. According with the result related here, in association with AEDs this stratagem could be an alternative treatment in refractory epilepsy.

Multidrug resistance gene (mdr-1) in experimental epilepsy models

The brain expression of mdr-1 gene can be induced in experimental models of epilepsy. Several groups have demonstrated the over-expression of P-gp in different epileptic models, such as a single dose of intra-cerebroventricular kainate, chronic epilepsy, and status induced, where the P-gp expression on brain parenchyma cells as astrocytes and neurons, was documented. (Seegers et al. 2002; Rizzi et al. 2002; Lazarowski et al. 2002)

Recently, a very original study (Kwan et al. 2002) have investigated both mdr-1a and mdr-1b rodent isoforms genes expression, in genetically epilepsy-prone rats, after single audiogenic stimulation. This model eliminates the induction of mdr-1 gene produced by drugs, physical restraint or implantation of electrodes. The authors suggested that: 1) the expression of P-gp is increased along with the seizure axis and 2) the short-term audiogenic stimulation can induce the expression of mRNA mdr-1a gene for periods as long as seven days.

In our experience with a rat model of 3-mercaptopropionic acid (MP)-induced seizures, the daily induction of one convulsive episode for 4 consecutive days (MP-4), P-gp immunosatining carried out using two different monoclonal antibodies, resulted in high expression of P-gp in vascular endothelial cells and adjacent astrocytes located in the cortex, striatum and hippocampus. However while some vessels showed negative immunoreactivity, few neurons were immunoreactive (Lazarowski et al. 2002). In a second study a more extensive MP stimulation was performed during 7 consecutive days (MP-7)(Lazarowski et al 2004b). The immunostaining was more enhanced in vessel-related cells compared with MP-4 treatment. Additionally, immunoreactivity selectively spread to distal neurons. However, astrocytes neighboring these positive distal neurons and some vessels were negative. Results observed in these experiments indicated that mdr-1 over-expression depends on the seizure-stress frequency. Also, this expression exhibits a selective sequential pattern in term of the type of cells affected: as the frequency of the induced-seizures increased, more cells i.e. endothelial cells, astrocytes and surrounding neurons, became mdr-1 positive.

The early detection of P-pg in vessel-related cells with the persistent non-reactive vessels and, later the additional P-gp immunostaining in neurons suggest that the expression of P-gp in previously non-expressing cells is a progressive process of selective cellular induction depending on intensity and time-constancy of seizure-injury. This observations are in agreement with the potential develop of "P-gp-positive seizure-axis" as proposed previously (Kwan et al. 2002). In this context it is worth noting that in a recent prospective study with 525 epileptic patients, it was shown that the development of RE directly correlated with the number and frequency of epileptic crisis before initiation of drug therapy (Sander & Sillanpaa 1998).

Because MDR1 gene expression is under control of various transcriptional factors including NF B and AP-1, found at high levels in the brain of epileptic rats as well as in brain tissues of patients with

temporal lobe epilepsy, further suggests that sustained seizures may induce mdr-1 expression independently from AEDs administration. However, recently it was reported that the treatment with the more common AEDs, could result in higher P-gp brain expression as demonstrated in an experimental model of Coriaria lactone-induced status epilepticus (Wang et al. 2003).

A more recent experiment of our experimental group, demonstrated that long term treatment with 3.MP (13 days), animals developed refractory epilepsy to phenytoin treatment and death in status on 13th day. However, additional treated with nimodipine (2mg/kg, ip) clearly reversed the refractory phenotype (Girardi et al. 2005) and was also able to restore the normal hippocampal pharmacokinetics of PTH. (Lazarowski et al. 2006c; Hocht et al. 2007). The increasing neuronal expression of P-gp paralleled with the progressive loss of protective effect of PTH and the death in status epiepticus. Perhaps, the presence of P-gp in neurons could play a role in the easier development of new seizures or more severity of them. In this regards, an alternative mechanism to the classic pumping function of P-gp was observed in cells expressing MDR-1 gene. These cells exhibit significantly low membrane potential ($\Delta\psi 0$ = -10 to -20) compared to the physiological potential ($\Delta\psi 0$ of -60 mV), leading to reduced (~30%) binding of the drug (Wadkins & Roepe 1997, Roepe 2000). In a speculative consideration, this potential membrane alterations ($\Delta\psi 0$), not only could contribute to develop the refractory phenotype, but also, and as consequence of the electric nature of neuronal function sensitive to the membrane depolarization, P-gp expressed neurons may play a role in the intrinsic mechanisms of the epileptogenicity. Because a significant and stable membrane depolarization occurs in MDR1-expressed cells which exhibit significant low membrane potential ($\Delta\psi 0$ = -10 to -20) compared to normal physiological $\Delta\psi 0$ of -60 mV, in case of neurons over-expressing P-gp in epileptogenic tissues, this will lead to a persistent reduced threshold to lower glutamic stimuli triggering more seizures (Fig. 5). Is this mechanism consistent with the "target hypotheses" mentioned above?

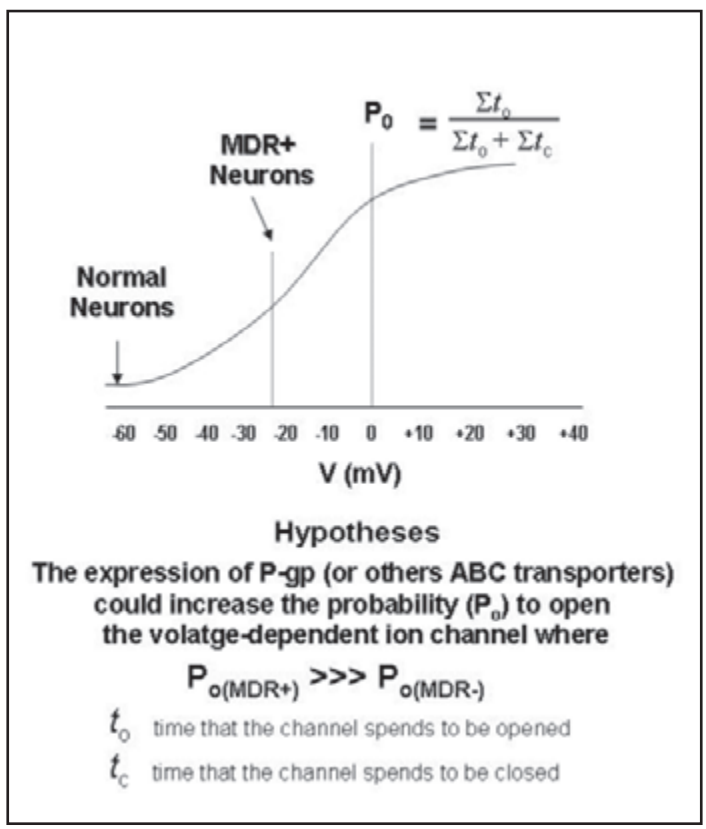

Figure 5: Hypothesis: Are P-gp positive neurons' predepolarized?
In these conditions, low glutamic acid stimuli could induce a new seizure.

CONCLUSIONS:

The ABC transporters as MDR-1, MRP-1 and BCRP and additionally, the cytosolic MVP protein, are related with the epileptic refractory phenotype, and the understanding of their molecular properties can give to us, new tool for better selection of more effective therapeutic strategies, and avoid the invasive surgical treatments for Refractory Epilepsy

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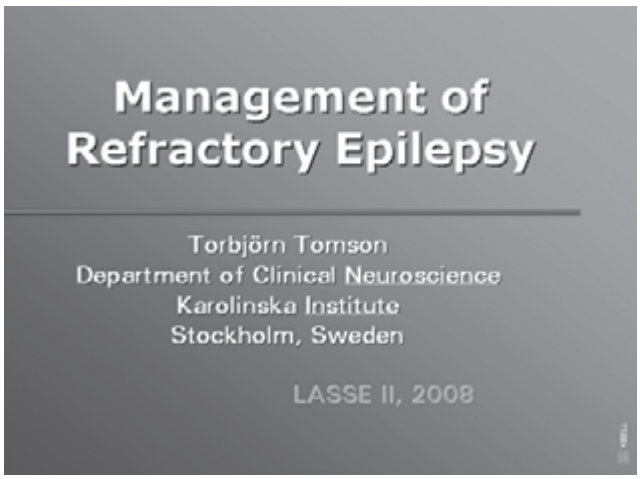
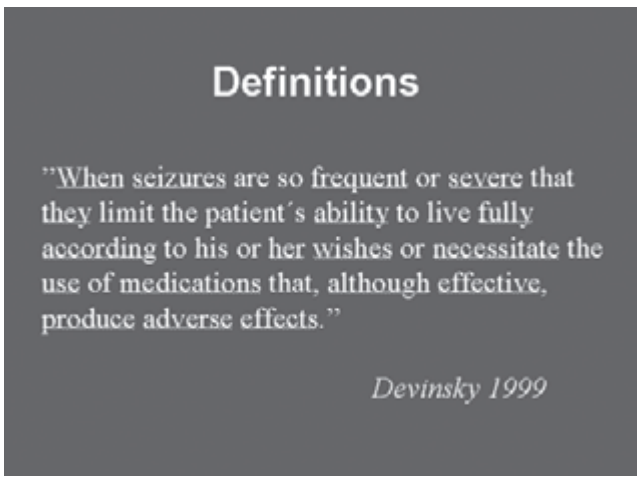
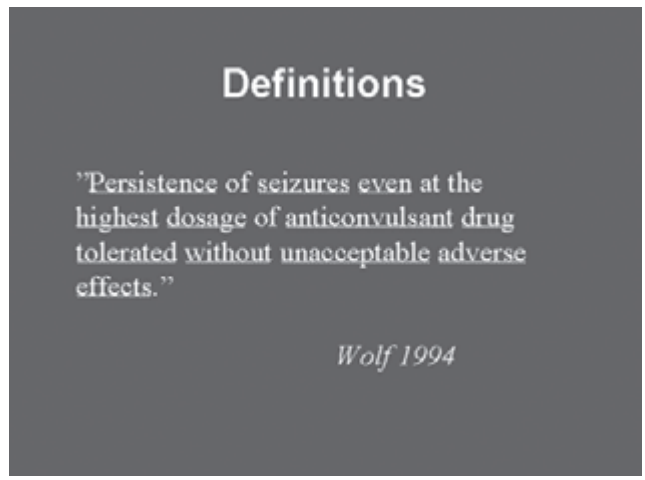
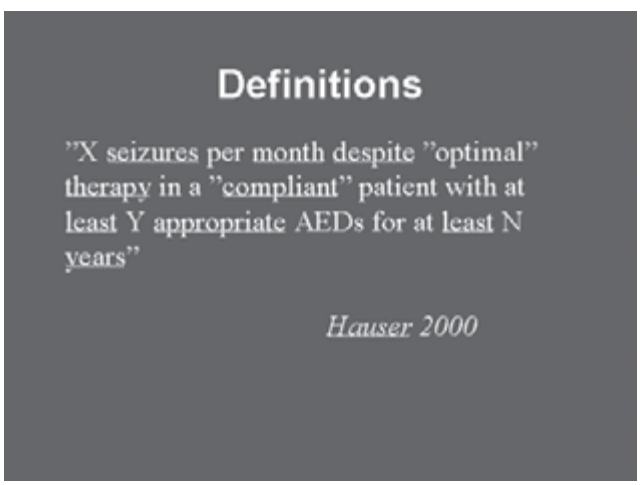
Clinical management of refractory epilepsies

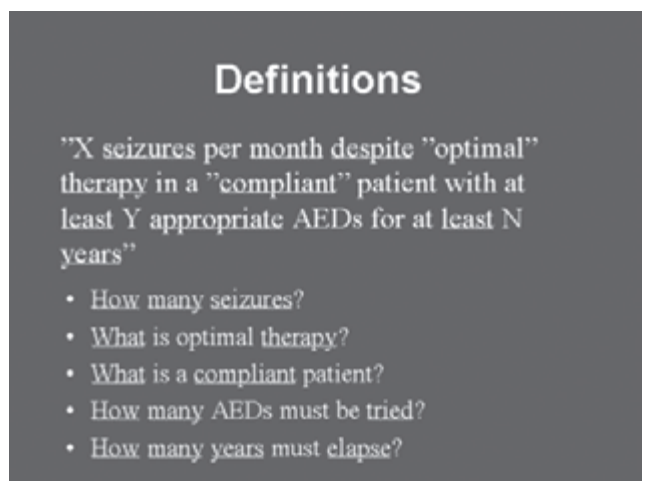
Torbjörn Tomson (Sweden)











Frequency of Intractable Seizures

- Incidence: 5-6/100,000/year
- Prevalence:
  - 3/1000 in the general population
  - 30% of the prevalence population

Hauser 2000

Intractability Score

(Schmidt 1986)

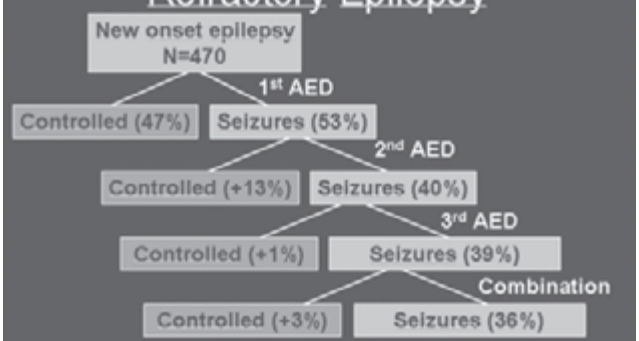
Persistent seizures on treatment with	Score
Other than primary drug in any dose	0
Primary drug below recommended dose	1
Primary drug within recommended dose	2
Primary drug with plasma levels within range	3
Primary drug with maximum tolerated dose	4
Two or more drugs with maximum tolerated dose in subsequent single-drug treatment	5

Pharmacoresistance Grading

(Perucca 1998)

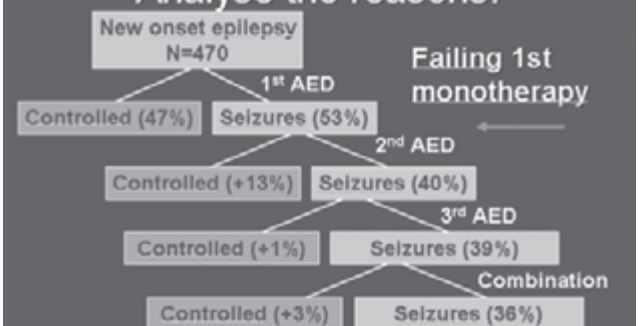
Grade	Definition
I	Resistance to 1 primary drug
II	Resistance to 2 primary drugs (A) used sequentially or (B) in combination
III	Resistance to 3 or more primary drugs (A) used sequentially or (B) in combination

Early Identification of Refractory Epilepsy



Kwan & Brodie (2000)

First action in treatment failure Analyse the reasons!



Kwan & Brodie (2000)

Why did first monotherapy fail?

1. True or pseudo-failure? Re-evaluate patient!
   - Correct diagnosis?
   - Seizure provoking factors?
   - Adequate dosage?
   - Compliance?
2. Failure due to adverse effects?
3. Failure in efficacy?

Reasons for Intractability
The Specialist Clinic Perspective

- Incorrect diagnosis (non-epileptic attacks)
- Unidentified underlying structural pathology
- Unrecognized psychosocial problems including inappropriate lifestyle
- Unreliable recording of seizures
- Erroneous interpretation of adverse effects
- Poor compliance
- Inappropriate choice of drugs
- Inadequate dosage or regimen

"Refractory Epilepsy" Referred to Specialist Clinic

- **94 patients referred with "refractory epilepsy"**
- **Only 7 considered to have genuinely refractory epilepsy**
- **12 had pseudoseizures**
- **Main cause of pseudo-refractoriness was failure to recognise idiopathic generalised epilepsy**

Smith et al (1999)

NEWLY DIAGNOSED EPILEPSY
Outcomes from July 1982 to May 2003
(n=780; age 9-93)

- Responder – seizure-free for a minimum of 12 months
- Immediate responder – no seizures after starting treatment
- Remission – no relapse after becoming seizure-free
- Relapse – controlled for at least one year then refractory
- Non-responder – never seizure-free for any 12 months

Courtesy of Brodie MJ

NEWLY DIAGNOSED EPILEPSY
Response with monotherapy

First	393	(50.4%)
Second	57	(7.3%)
Third	8	(1.0%)
Other choices	4	(0.5%)
	462	(59.2%)

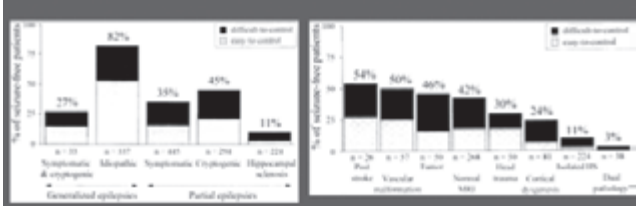
Mohanraj R, Brodie MJ. Eur J Neurol 2006;13:277-82

NEWLY DIAGNOSED EPILEPSY
Predictors of refractoriness
(multivariate analysis)

	Odds ratio	95% CI	p value
Family history	1.89	1.15-3.00	0.011
Febrile seizures	3.36	1.58-7.18	0.002
Traumatic brain injury	3.26	1.59-4.69	<0.001
Psychiatric comorbidity	2.17	1.33-3.55	0.002
Recreational drug use	4.26	2.03-8.94	<0.001
10 or more seizures	2.77	1.98-3.89	<0.001

Hitiris N et al, Epilepsy Research 2007; 75: 192-6

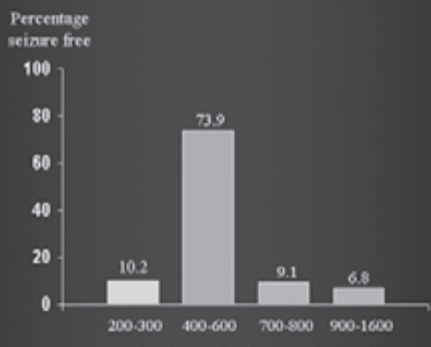
Treatment response depends on syndrome and etiology



Semah et al. Neurology 1998

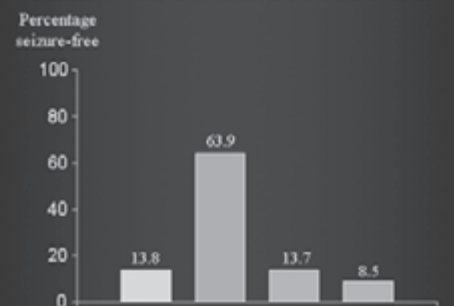
Has the drug been tried at adequate dosage?

CARBAMAZEPINE MONOTHERAPY IN SEIZURE FREE PATIENTS



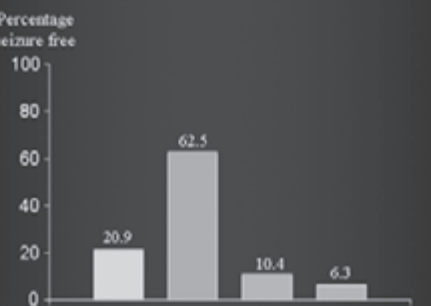
Kwan P and Brodie MJ, Epilepsia 2001; 42: 1255-60

VALPROATE MONOTHERAPY IN SEIZURE FREE PATIENTS



Kwan P and Brodie MJ, Epilepsia 2001; 42: 1255-60

LAMOTRIGINE MONOTHERAPY IN SEIZURE FREE PATIENTS



Kwan P and Brodie MJ, Epilepsia 2001; 42: 1255-60

Analysis at Treatment Failure

- Repeat seizure history from patient/witness
  - Different seizures, provoking factors
- Review medical records for analysis of seizure development over time
- Review etiological work-up
  - Is it adequate and up to date?
- Review EEGs
  - Type(s) of seizures/type of epilepsy?
- Review previous and current treatment
  - Which AED have been tried, doses, concentrations, relationships AED/efficacy/adverse effects

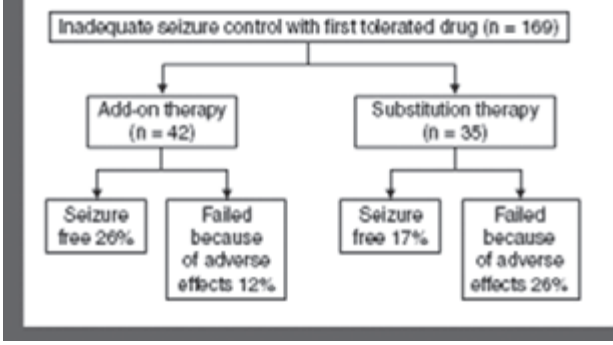
Formulate treatment plan

- A realistic goal based on the reanalysis of diagnosis
- Determine sequence of drug changes – change, addition and withdrawal
- Duration of each treatment trial
- Consider timing of surgical evaluation, VNS etc.

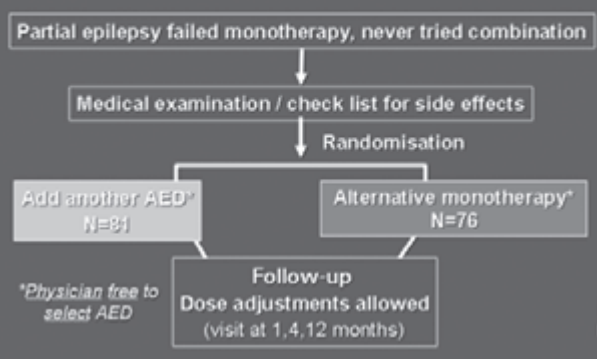
What to do after a true failure on 1st monotherapy?

- Choice of treatment strategy
  - Change to another monotherapy?
  - Add-on therapy?

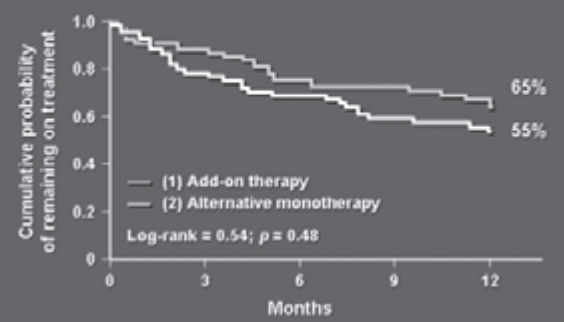
Failure after 1st monotherapy: Retrospective data (Kwan& Brodie, 2000)



Alternative monotherapy or add-on? BASE Study

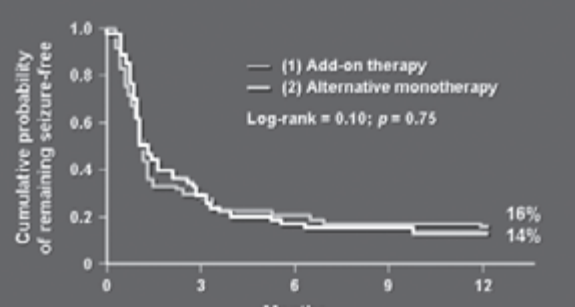


Retention rates (Primary endpoint)



Beghi et al. Epilepsy Res 2003;57: 1-13

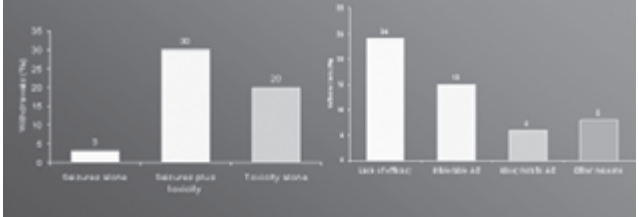
Seizure free rates



Beghi et al. Epilepsy Res 2003;57: 1-13

Strategy may depend on Reasons for failing 1st AED

Reasons for discontinuation of 1st monotherapy,% of all patients



(Mattson et al., NEJM 1985;313:145-51) (Kwan & Brodie, NEJM 2000;342:314-9)

Why did first monotherapy fail?

1. True or pseudo-failure? Re-evaluate patient!
   - Correct diagnosis?
   - Taking prescribed dose?
   - Adherent therapy?
   - Compliant?
2. Failure due to adverse effects?
3. Failure in efficacy?

Outcome on 2nd AED after failing 1st AED

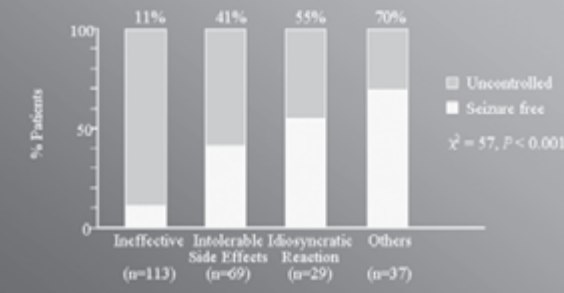


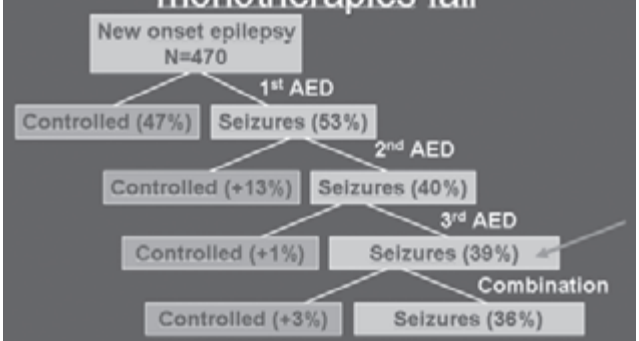
Figure on top of bar represents percentage seizure free

(Kwan and Brodie)

What to do after 1st failed monotherapy?

Idiosyncratic effects	Alternative monotherapy
Other adverse effects	Alternative monotherapy
Lack of efficacy	Alternative monotherapy?
Insufficient efficacy	Add-on?

Combining AEDs when monotherapies fail

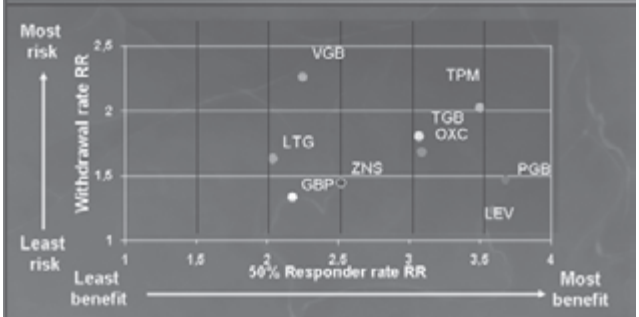


Kwan & Brodie (2000)

Benefit from AED combination therapy

- Some 10 to 50 % of patients with refractory epilepsies are expected to *benefit* from AED combinations
- All licensed newer generation AEDs have shown efficacy (compared with placebo) as add-on treatment in short term trials
- Few data comparing different add-on treatments (most studies are against placebo)
- No data comparing current add-on drugs after 1st AED has failed

Risk/benefit as add-on in refractory partial epilepsy, can we compare AEDs?



Rosito P et al. Presented at IEC, Paris, 2006.

The real efficacy of newer AEDs in refractory epilepsy

- 23 placebo controlled add-on trials of newer AEDs in refractory partial seiures
- 67 out of 2,390 patients (2.8%) rendered seizure free during 8-16 weeks treatment period
- Highest proportion seiure free on any AED was 5.5%

From Perucca

Long term efficacy of AEDs

Open follow-up of add-on to patients with refractory partial seizures

Lhatoo et al Epilepsia 2000 Krakow et al Neurology 2001

Selection of AED combinations

- With 15 AEDs available, avialable combinations are numerous
- Drugs differ in modes of action and side effect profiles – different combinations are expected to produce different effects
- Pharmacokinetic and pharmacodynamic interactions also differ depending on the combination chosen

Criteria for selecting AED combination therapy

- Consider AED combinations for which there is clinical indication of a favorable therapeutic index
  - supra-additive efficacy + additive toxicity
  - additive efficacy + infra-additive toxicity

General apects to take into consideration when combining AEDs

- Side effect profile
  -avoid combining AEDs with similar AE profiles
- Pharmacokinetic interactions
  -in general negative, and often best avoided
- Pharmacodynamic interactions
  -positive or negative
- Combining AEDs with different modes of action appears to be better than combining e.g.two sodium channel blockers
- Patient's specific co-morbidity

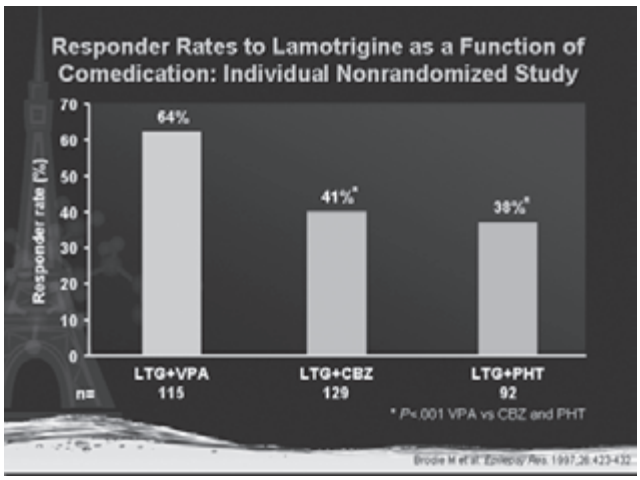
Favourable and poor AED Combinations

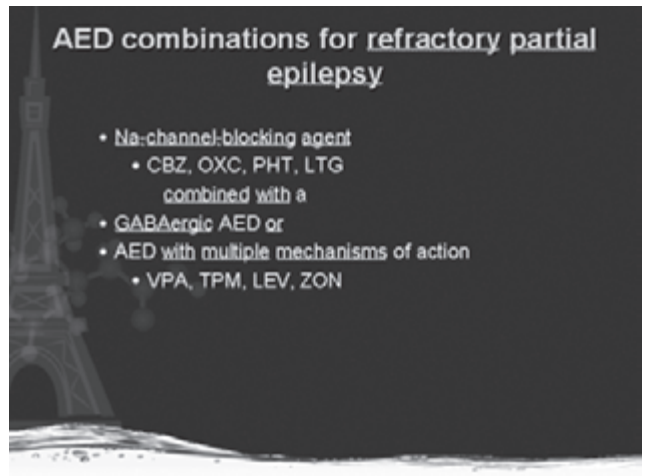
Combinations with improved therapeutic index

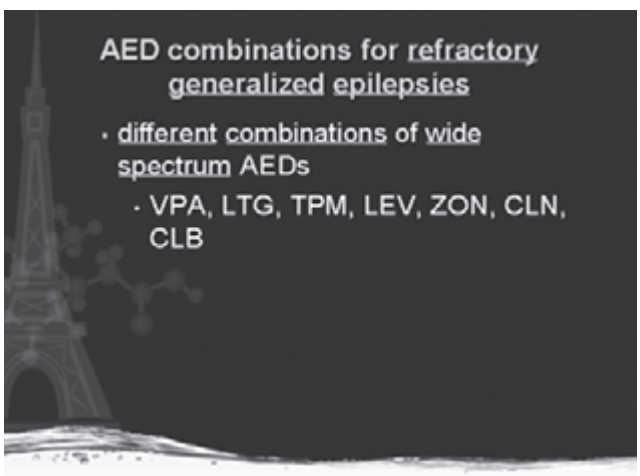
Combination	Evidence	Ref.
Valproate + Lamotrigine	+ + +	Pisani 1999
Valproate + Ethosuximide	+ +	Rowan 1983
Valproate + Carbamazepine	+ +	Brodie 1999
Carbamazepine + Vigabatrin	+ +	Brodie 1999

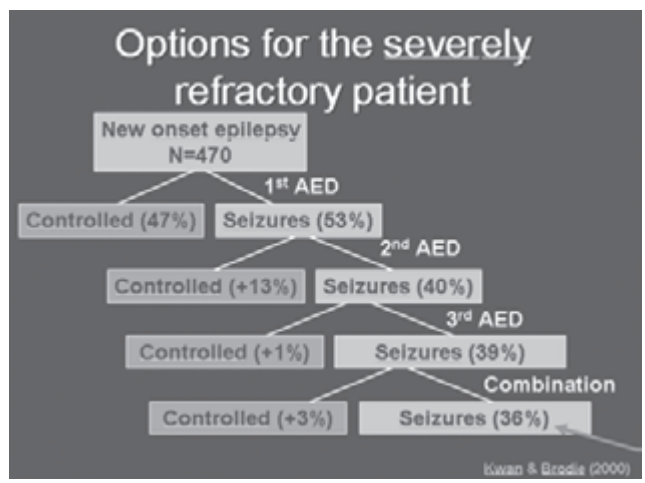
Combinations with reduced therapeutic index

Combination	Evidence	Ref.
Oxcarbazepine + Carbamazepine	+ + +	Barcs 2001
Lamotrigine + Carbamazepine	+ +	Besag 1998









The severely refractory patient: questions

- Is the epilepsy diagnosis correct?
- Is the diagnosis of epilepsy syndrome correct?
- Have the AED treatments been adequate?
- Is there a compliance problem?
- Is there a lifestyle problem?

Further treatment options

- Epilepsy surgery
- Vagal nerve stimulation
- Ketogenic diet

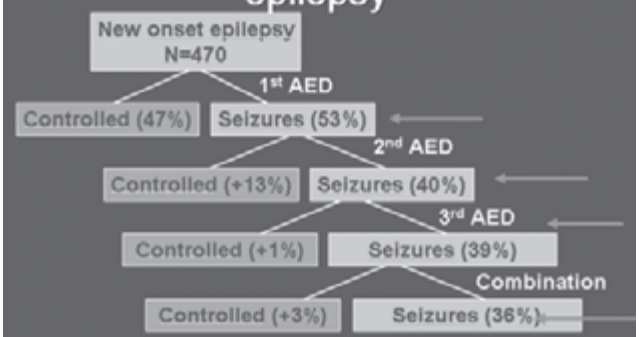
Who might be epilepsy surgery candidates?

- Appr. 30% of patients with epilepsy are not controlled with AED
- It has been estimated that appr. 3% of patients with intractable epilepsy might benefit from surgical treatment
- There are well defined epilepsy syndromes where epilepsy surgery should be considered early

The surgical menu

- Resective surgery
  - Lesionectomy
  - Lobectomy
  - Multilobar resections
  - Hemispherectomy
- Non-resective procedures
  - Callosotomy
  - Multiple Subpial Transection (MST)

Management of refractory epilepsy



Kwan & Brodie (2000)

Acute repetive seizures and status epilepticus

Torbjörn Tomson (Sweden)

Management of Repeated Seizures and Status Epilepticus

Torbjörn Tomson
LASSE 2
2008

Management of Status Epilepticus

- **Definitions and classifications**
- Diagnosis
- Prognosis and outcome
- Treatment

Definitions of Status Epilepticus

- 'a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition' (ILAE 1964)
- 'a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.' (ILAE 1981)
- Operational definition: 'two or more seizures without full recovery of neurological function between seizures.'But how long?
  - 30-60 minutes (Gastaut 1967)
  - >20 minutes (Bleck 1991)
  - >5 minutes (Lowenstein et al 1998)

Simplified classification of SE

- Generalised convulsive SE
- Non-convulsive SE (NCSE)
  - Complex partial SE (CPSE)
  - Absence SE
- Simple partial SE

Treiman & Delgado-Escueta 1980

Revised classification of SE

- SE confined to early childhood
- SE confined to later childhood
- SE occurring in childhood and adult life
- SE confined to adult life

Shorvon 1994

Suggested definitions of NCSE

- 'NCSE is a term used to denote a range of conditions in which EEG seizure activity is prolonged and results in nonconvulsive clinical symtoms' Oxford consensus meeting
- 'EEG seizure activity and behavioural change or obtundation for >30 min without tonic-clonic or myoclonic movements'

Kaplan 2007

Classification of nonconvulsive status epilepticus (NCSE)

- Complex partial SE
- Absence SE
- NCSE in patients with learning difficulties
- NCSE in coma
  - NCSE after GTCSE
  - NCSE with subtle clinical signs
  - NCSE with no clinical signs

Walker 2001,2003

Frequency of SE

'If one cannot easily define a condition or indeed satisfactorily classify it, clearly any estimate of its frequency must be of doubtful validity; this is the position with status.'

Shorvon 1994

Epidemiology of SE

- Incidence ~18-36/100 000 person-years. Rates higher in learning disability, structural pathology, frontal pathology
- Age-specific incidence
  - Highest during first year of life and after 65 years
  - 65% of cases of SE occur de novo due to acute cerebral or metabolic/drug-induced cause; Acute symptomatic
- In epilepsy, GCSE is often precipitated by AED reduction/withdrawal, intercurrent illness, metabolic disturbance or progressive illness
- SE occurs in 5% of all adults and 10-25% of all children with epilepsy

Management of Status Epilepticus

- Definitions and classifications
- **Diagnosis**
- Prognosis and outcome
- Treatment

Diagnosis of SE

- Clinical features
  - Clinically apparent recurrent seizures without full recovery between seizures, *or*
  - Continuous seizure state
- EEG
  - Sequence of five patterns of EEG discharges in GTCSE (Treiman et al 1990)
  - Heterogeneous patterns in NCSE

Diagnostical problems

- Clinical features
  - Variable especially in CPSE, difficult in coma
  - Problems with evaluating recovery between seizures in acute symptomatic SE
  - Pseudo-SE
- EEG
  - Most often not available in GTCSE and in emergency room setting
  - May be difficult to interpret in NCSE, e.g. PLEDS

NCSE in coma

- When monitoring patients in coma with no history of epilepsy and no signs of seizure activity with EEG, up to 8% meet criteria for SE

  Towne et al 2000
- Controversial whether this should be regarded as NCSE or as a different entity characterised predominantly by the coma as a consequence of brain damage rather than coma produced by seizure activity

  Kaplan 2002, Walker 2003

Management of Status Epilepticus

- Definitions and classifications
- Diagnosis
- **Prognosis and outcome**
- Treatment

Mortality and morbidity in SE

- Mortality and morbidity higher in hospital-based than in community-based studies
- Largely determined by the underlying etiology, only a fraction estimated to be caused by SE
- May be increased by inadequate treatment

Mortality in GCSE

- 15-22% in adults (Aminoff et al 1980, DeLorenzo et al 1996, Logroscino et al 1997)
- 3-15% in children (Aicardi et al 1970, Maytal et al 1989, DeLorenzo et al 1996, Lacroix et al 1994)

Predictors of mortality and morbidity in GCSE

- Old age
- Acute symptomatic SE (especially anoxia and stroke)
- Long duration of SE (>60 min)
- Continuous (vs intermittent) szs

Towne et al 1994, Logroscino et al 1997, Waterhouse et al 1999,Claassen et al 2002

Prognosis in NCSE

- NCSE heterogeneous condition with major diagnostic difficulties
- NCSE may *per se* be associated with mortality, morbidity and neuronal injury

  (Westerlain et al 1993, Krumholz et al 1995, DiGiorgio et al 1996)
- Mortality and morbidity mainly related to underlying etiology, degree of mental status impairment and rate of complications

  (Kaplan 1999, Drislane 2000, Schreiber and Fountain 2003)

Acute morbidity and mortality in NCSE

- Retrospective study of 100 consecutive patients in NCSE defined as:
  - Mental status impairment >30 min, mild or severe
  - EEG criteria: typical SW, atypical SW, multiple SW, rhythmic delta mixed with sharp waves. Not PLED/PED
- Specific etiologies divided in three groups: acute medical, epilepsy and cryptogenic
- Outcome: Mortality 18%
  - 14/52 in the acute medical group
  - 1/31 in the epilepsy group
  - 3/17 in the cryptogenic group

Shneker and Fountain 2003

Acute morbidity and mortality in NCSE

- Complications in 39%, most commonly infectious and respiratory
- Mortality was higher :
  - In patients with severe versus mild mental status impairment
  - In patients with acute complications, especially respiratory
- Presence of generalised SW discharges on EEG did not correlate with mortality

Shneker and Fountain 2003

Management of Status Epilepticus

- Definitions and classifications
- Diagnosis
- Prognosis and outcome
- **Treatment**

Treatment of GTCSE

Aims of treatment in GTCSE:

- Halt seizure activity
- Maintain homeostasis
- Treat complications

Stages of GTCSE

- Premonitory stage
- Early SE (0-30 min)
- Established SE (30-60 minutes)
- Refractory SE (>60 min)

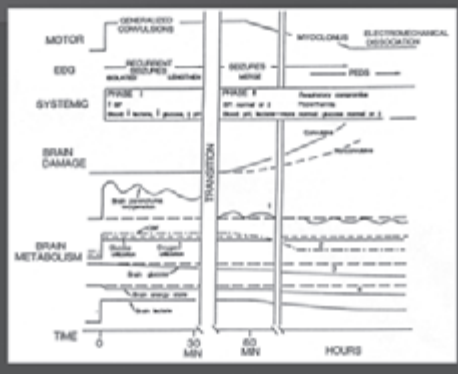
Shorvon 1994

Progressive changes in GTCSE

- Premonitory stage
  - -increasing seriel seizures and EEG correlates
- Biphasic pattern of physiological change
  - -phase of compensation
  - -phase of decompensation
  - -progressiv clinical and EEG changes
  - -compensated to decompensated stage 60-120 min.
- Window of opportunity for treatment
  - -risk of cerebral damage increases with time after 60-120 minutes

Shorvon

Evolution of GTCSE



Early systemic effects of GTCSE

- Massive release of plasma chatecholamines
- Cardiac arrhythmias
- Hyperthermia
- Cerebral and systemic hypoxia
- Lactic acidosis
- Neurogenic pulmonary oedema

Late systemic effects of GTCSE

- Fall in blood pressure
- Loss of cerebral autoregulation
- Hypoglycemia
- Rhabdomyolysis
- Hyperkalaemia
- Renal failure
- Hepatic failure
- Disseminated Intravascular coagulation

GCSE - Staged treatment approach

- Stage 1: Premonitory/Early SE
- Stage 2: Established SE
- Stage 3: Refractory SE
- Treatment protocols improve outcome
- Staged use of drugs of increasing strength/toxicity
- Speed: Stage 3 by 2 hours

Shorvon 1994

General measures

1st stage (0– 10 minutes)	• Assess cardiorespiratory function • Secure airway and resuscitate • Administer oxygen
2nd stage (0–60 minutes)	• Institute regular monitoring • Emergency AED therapy • Set up intravenous lines • Emergency investigations • Administer glucose and/or thiamine where appropriate • Treat acidosis if severe
3rd stage (0–60/90 minutes)	• Establish aetiology • Identify and treat medical complications • Prosecute therapy when appropriate
4th stage (30–90 minutes)	• Transfer to intensive care • EEG monitoring • ICP monitoring where appropriate

Stage 1- premonitory/early SE (0-30/60 minutes)

- BZD drugs of choice:
  - Lorazepam, 4 mg iv, may be repeated after 10 min
  - Diazepam, 10-20 mg iv (5mg/min), may be repeated after 10 minutes
  - midazolam, clonazepam
- Out-of-hospital therapy
  - Rectal diazepam
  - Buccal/intranasal/im midazolam

Out-of-hospital RCT of GCSE

- Design: Double-blind, randomised, multicenter parallel group trial comparing two i v regimens or placebo as pre-hospital treatment
- Patients: 205 patients were randomised to treatment with lorazepam (LZM) 2 mg (N=66), diazepam (DZM) 5 mg (N=68) or placebo (N=71)

Alldredge et al 2001

Out-of-hospital RCT of GCSE

- Definitions:
  Continuous seizure activity >5 min. or 2 GTCS with incomplete recovery
- Evaluation:
  SE was considered to end at the time convulsive seizures ceased if the patient regained consciousness

Alldredge et al 2001

Primary Outcome: Status epilepticus at ED arrival

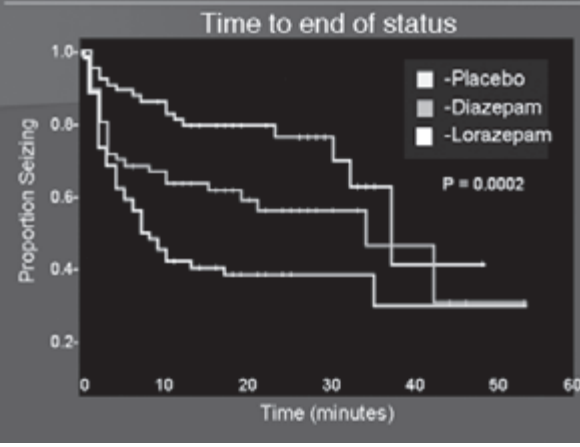
	Placebo	Diazepam	Lorazepam
NO	15 (21%)	29 (43%)	39 (59%)
YES	56 (79%)	39 (57%)	27 (41%)

Chi-Square = 0.001

	PLC-LZP	DZP-LZP
Odds Ratios (97.5% CI)	5.4 (2.3 - 13.1)*	1.9 (0.9 - 4.3)
Adjusted Ratios (PreRx Int, PostRx Transport, Total dose, Etiology)	4.8 (1.8 - 13.9)*	2.7 (1.1 - 7.1)*

* - P < 0.5

PHTSE



Secondary Outcomes:

Prehospital Complications
(Hypotension, Dysrhythmia or Airway Change)

	Placebo	Diazepam	Lorazepam
NO	55 (77%)	61 (90%)	59 (90%)
YES	16 (23%)	7 (10%)	7 (10%)

Chi-Square = 0.08

Intubation (Yes/No)	9/62	1/67	4/62

Chi-Square = 0.02

The New England
Journal of Medicine

VOLUME 345 AUGUST 30, 2001 NUMBER 9

A COMPARISON OF LORAZEPAM, DIAZEPAM, AND PLACEBO FOR THE TREATMENT OF OUT-OF-HOSPITAL STATUS EPILEPTICUS

BRIAN K. ALLDREDGE, PHARM.D., ALAN M. GELB, M.D., S. MARSHAL ISAACS, M.D., MEGAN D. CORRY, E.M.T.-P., M.A., FAITH ALLEN, M.D., SUEKAY ULRICH, R.N., M.S., MILDRED D. GOTTWALD, PHARM.D., NELDA O'NEIL, R.N., M.S.N., JOHN M. NEUHAUS, PH.D., MARK R. SEGAL, PH.D., AND DANIEL H. LOWENSTEIN, M.D.

Conclusions Benzodiazepines are safe and effective when administered by paramedics for out-of-hospital status epilepticus in adults. Lorazepam is likely to be a better therapy than diazepam. (N Engl J Med 2001; 345:631-7.)

In-hospital RCT of buccal MDZ vs rectal DZM in children

- Design: Open, randomised, multicentre, parallel group trial
  Randomisation of weekly blocks of tx with buccal MDZ or rectal DZM
- Patients: 177 children (219 episodes) median age 3 yrs, 109 episodes treated with MDZ, 110 with DZM
- Definitions:
  Pats presenting to hospital with active seizures and without iv access

McIntyre et al Lancet 2005

In-hospital RCT of buccal MDZ vs rectal DZM in children

- Duration of SE: MZM: mean 30 min (10-49)
  DZM: mean 41 min (10-61)
- Treatment: Dosage of MDZ or DZM related to age designed to give about 0.5 mg/kg
- Evaluation: Therapeutic success: cessation of szs within 10 min, no resp depression and no more szs within one hour

McIntyre et al Lancet 2005

In-hospital RCT of buccal MDZ vs rectal DZM in children

- Results: Therapeutic success
  - 56% for buccal MDZ
  - 27% for rectal DZM.
  - Rate of resp depression low and did not differ between groups

After adjusting for centre, age, known epilepsy, prior tx, length of SE, MZM was more effective than DZM

McIntyre et al Lancet 2005

Stage 2- established SE

- Conventional treatment:
  - Phenytoin/fosphenytoin iv at 50/100mg/min
  - Phenobarbitone, 10mg/kg iv at 100 mg/min
- Alternatives:
  - Valproate, levetiracetam, benzodiazepine infusion

In-hospital RCT of GCSE

- Design: Double-blind, randomised, multicenter parallel group trial comparing four i.v.regimens
- Patients: 570 with GCSE, verified in 518, overt (n=384) or subtle (n=134)
- Definitions:
  Overt: Continuous seizure activity >10 min. or 2 GTCS with incomplete recovery
  Subtle: Coma and ictal EEG discharges

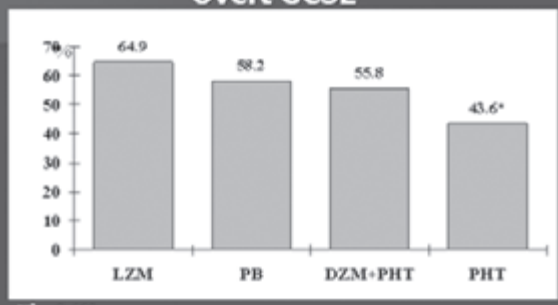
Treiman et al 1998

In-hospital RCT of GCSE

- Treatment : Diazepam (0.15 mg/kg)+ Phenytoin (18mg/kg)
  Lorazepam (0.1 mg/kg)
  Phenobarbital (15 mg/kg)
  Phenytoin (18 mg/kg)
- Evaluation : Treatment was considered successful if all clinical and electrical evidence of seizure activity stopped within 20 minutes after the start of the infusion and did not recur during the period from 20 to 60 minutes after the start of treatment

Treiman et al 1998

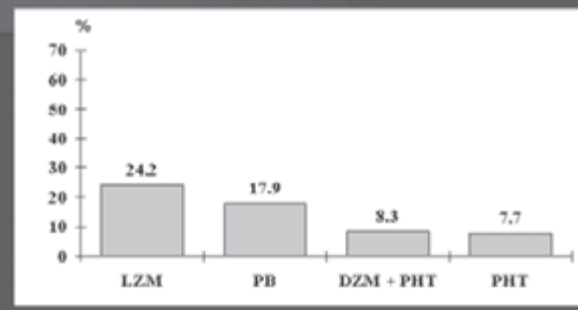
Success as first treatment
Overt GCSE



$X^2 = 9.663$
$p = 0.02$ * $p = 0.002$

Treiman et al., *NEJM*, 339:792-8, *1998*

Success as first treatment
Subtle GCSE



$X^2 = 9.663$
$p = 0.02$ * $p = 0.002$

Treiman et al., *NEJM*, 339:792-8, *1998*

In-hospital RCT of GCSE
Short term outcome (30 days)

	Overt GCSE (N=384)	Subtle GCSE (N=134)
– Discharged	50.1%	8.8%
– In hospital	22.9%	26.5%
– Dead	27.0%	64.7%

Treiman et al 1998

In-hospital RCT of GCSE
Causal factors

	Overt GCSE (N=384)	Subtle GCSE (N=134)
– Remote neurol	69.5%	34.3%
– Acute neurol.	27.3%	37.3%
– Life-threatening medical cond.	32.0%	56.7%
– Cardiopulm. arrest	6.3%	38.1%
– Drug related	6.3%	5.2%
– Alcohol withdrawal	6.5%	0.7%

Treiman et al 1998

Is valproate an alternative?

- No RCT
- Side effects and toxicity
  - No fall in BP, Heart rate, ECG abnormalities
  - No local reaction at infusion site
  - Other side effects – hyperammonemia, platelet function, problems if comedication with lamotrigine?

Experience with valproate

- Efficacy – rates of seizure control
  - Case series of >350 patients, good response in majority, better if early
- Dose – no consensus
  - 25-60 mg/kg in adults (at 3-6 mg/kg/min)
  - 30-60 mg/kg in children
- RCT needed!

Experience with levetiracetam

- Iv formulation licensed for replacement therapy – not for SE
- Pharmacokinetics established based on 1500 mg over 15 minutes
- Small series and case reports in >150 patients with varying types of SE
- Dose varied between 500-2000 mg iv bolus

Experience with levetiracetam

- No effect on cardiovascular or respiratory function
- No adverse effects at infusion site
- Reported efficacy – reported good response in majority
- RCT needed!

Time to treatment in GCSE

- The longer the duration, the harder SE is to stop - 'time is brain'
- Duration of SE before treatment:
  - Treiman et al 1998
    - Overt SE: mean 2.8 hours
    - Subtle SE: mean 5.2 hours
  - Pellock et al 2004
    - 59% of 889 patients recieved treatment after >30 minutes of seizures

Stage 3: Refractory status epilepticus – definition/frequency

- **The stage of SE reached when seizures have continued despite treatment for 60 minutes or more**
- **The purpose of therapy is to control seizures in order to prevent seizure-induced cerebral damage**
- **Time chosen as it represents the period after which excitotoxic cerebral damage (due to electrographic activity) may occur**
- **Frequency approx 2-5/100,000 persons/year**

Stage 3 – refractory GTCSE (>90 minutes)

- General anaesthesia is the definitive treatment used for RSE
- Conventional protocol:
  - Thiopenthone
  - Propofol
  - Midazolam
- No RCT

Review of refractory SE

- Review of studies using midazolam (MZM), propofol (PRO) or pentobarbital (PTB) for RSE
- Peer-reviewed studies 1970-2001 of adults with SE refractory to first and 2nd line treatment
- Main outcome measures: treatment failure (szs 1 to 6 hours after starting therapy) and mortality
- 28 studies describing 193 patients:MZM (n=54), PRO (n=33), PTB (n=106)

Claassen et al 2002

Refractory SE - which anaesthetic?

	Midazolam (n=54)	Pentobarb (n= 106)	Propofol (n=33)
Failed Sz control	20 %	8 %	27 %
Breakthough Szs	51 %	15 %	12 %
Withdrawal Szs	63 %	43 %	46 %
Hypotension	30 %	77 %	42 %
Mortality	46 %	48 %	52 %

"Meta-analysis" (Claasen et al Epilepsia 2002 43 146)

Review of refractory SE

- Primary causes of SE were similar in the three treatment groups
- Mortality (48%) was not associated with choice of agent or titration goal (burst suppression or sz suppression)
- Mortality associated with older age, etiology and SE duration
- PTB associated with less frequent breakthrough szs and higher frequency of hypotension

Claassen et al 2002

Stage 3 – refractory GTCSE

- Thiopentone

  100-240 mg iv bolus over 20 secs followed by 50 mg bolus every 2-3 mins then iv infusion 3-5 mg/kg/hr to burst suppression
- Propofol

  2 mg/kg iv bolus, repeated, then iv infusion of 5-10 mg/kg/hr to burst suppression
- Midazolam

  0.1-0.3 mg/kg iv bolus (rate not>4 mg/min) then iv infusion 0.05-0.4 mg/kg/hr to burst suppression

Management of GCSE

Pragmatic advice

- Reduce time from start of SE until initiation of treatment - 'time is brain'
- Carefully consider clinical diagnosis - beware of pseudostatus!
- If GCSE – treat promptly according to protocol and investigate possible causes – remember that most cases are acute symptomatic!

Management of NCSE
what do we know?

- Clinical diagnosis often difficult and EEG patterns variable
- There is no good evidence that aggressive treatment improves the prognosis of NCSE
- No RCT in NCSE
- In some instances, aggressive treatment may carry a worse prognosis than no treatment
  - Treatment with BZD i v associated with increased risk for death in the critically ill elderly
  - Patients with epilepsy as the only cause of NCSE are more likely to die from complications of treatment than from NCSE

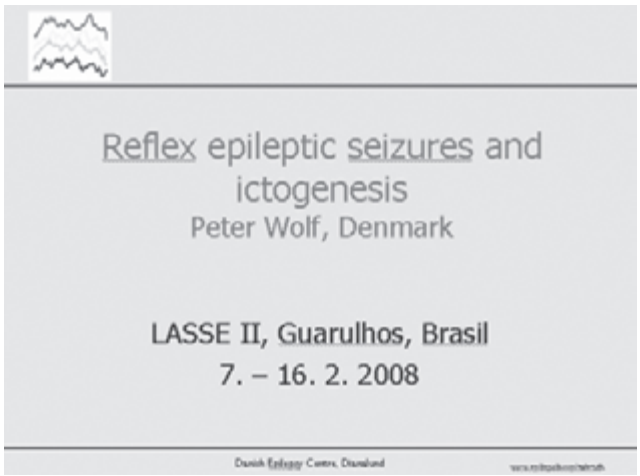
(Litt et al 1998, Schneker and Fountain 2003)

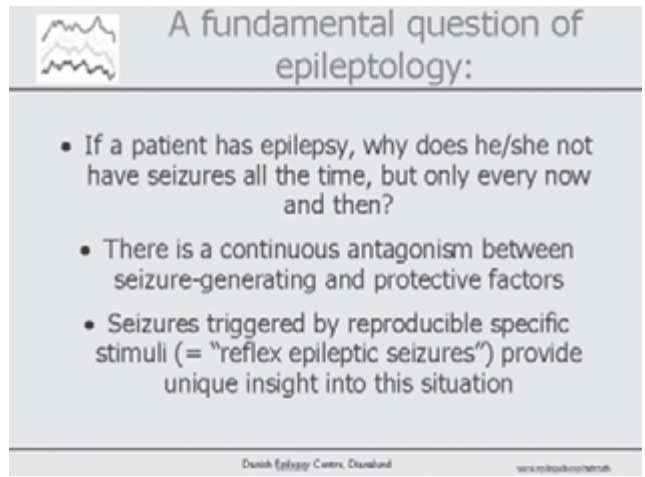
Management of NCSE
Pragmatic advice

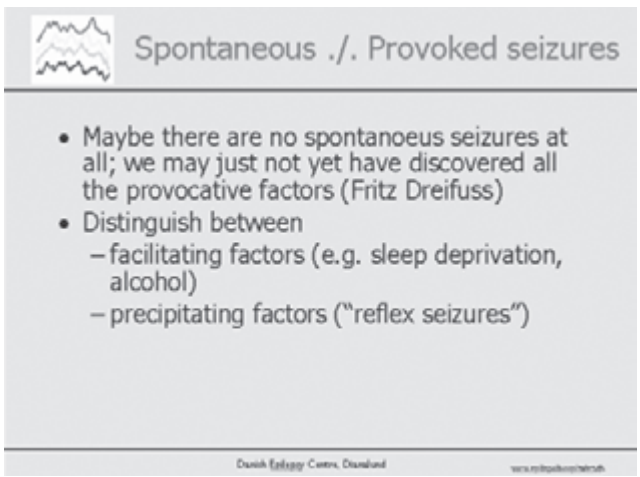
- Early recognition of NCSE is important and treatment with oral or rectal BZD can be effective
- Intravenous therapy with DZP/LZP followed by PHT/fosPHT are drugs of choice
- Although evidence is lacking, reasonable to consider VPA or LEV as next steps
- Anesthetic agents or iatrogenic coma only in unusual cases – but no consensus about which cases!

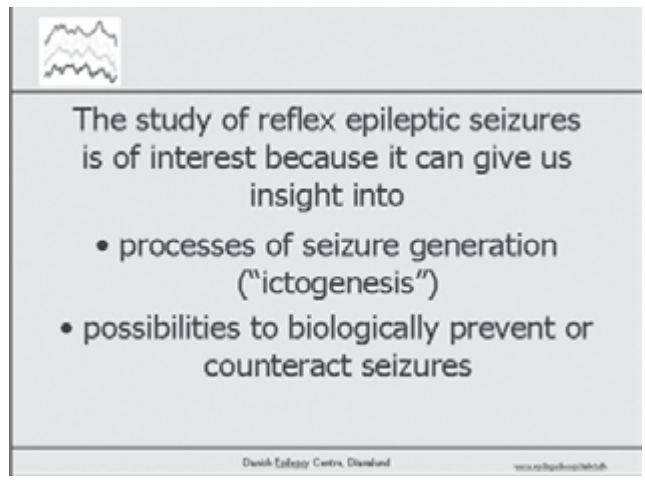
Interactive case discussions
G. Avanzini/E Perucca/T Tomson/ M. Bialer

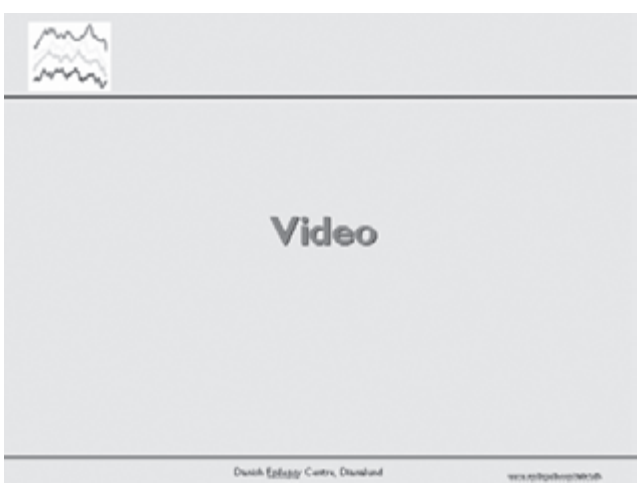
Reflex epileptic seizures and ictogenesis
Peter Wolf (Denmark)

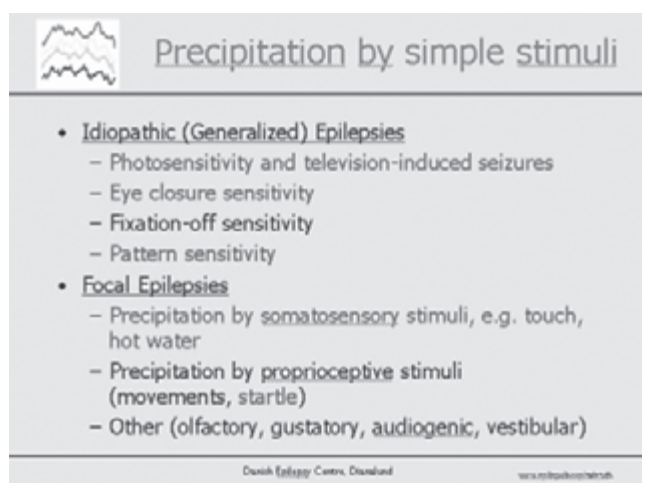












Precipitation by complex stimuli

- Oro-facial reflex myocloni (ORM)
- Praxis-induced seizures
- Seizures precipitated by eating
- Other complex sensorimotor triggers
  - (Hot water epilepsy?)
  - Seizures precipitated by tooth-brushing
- Complex auditory stimuli
  - Musicogenic seizures
  - Other (musical pitch, voices of radio speakers)
- Complex visual stimuli (own hand, safety pin etc.)
- Emotional precipitation, psychogenic epileptic seizures

Danish Epilepsy Centre, Dianalund

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Danish Epilepsy Centre, Dianalund

Reflex epileptic mechanisms: why idiopathic > symptomatic ep.?

- Because idiopathic epilepsies are genetically determined, and the frequent reflex epileptic mechanisms are genetic traits that are part of the etiopathogenesis of polygenic conditions like JME, at least as a manifestation factor
- Symptomatic epilepsies often have ill-connected focal pathologies.
- Exception: startle epilepsy with early spastic hemiparesis from infarction: why?

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Photosensitivity

- Inherited age-dependent trait
- Most often seen in Idiopathic Generalised Epilepsies, especially Juvenile Myoclonic Ep.
- Homogeneous?
- Myoclonic sz > absences > GTC > focal occipital
- Stimulation of occipital cortex
- Response quantitative and variable, rapid with right frequency (~ 14 - 30 hz) but rarely immediate
- No short-loop response but some intermission

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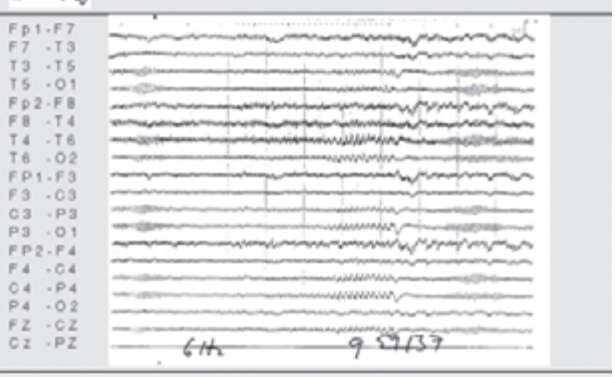
Patient with television - induced GTC seizures only: suspicion of photosensitivity at 6 Hz



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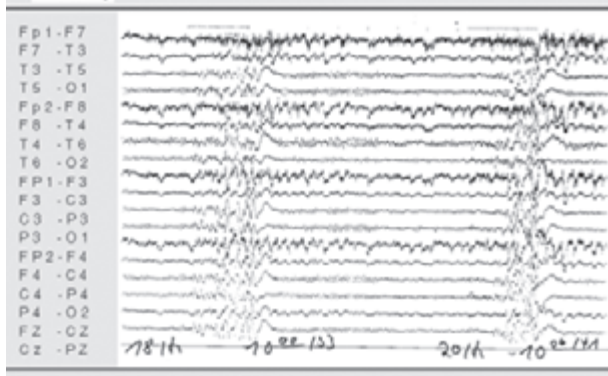
Photosensitivity in patient with television - induced GTC seizures only



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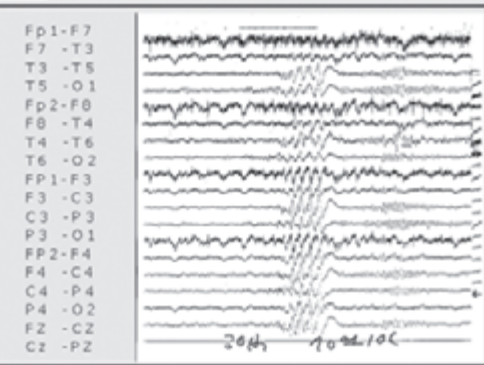
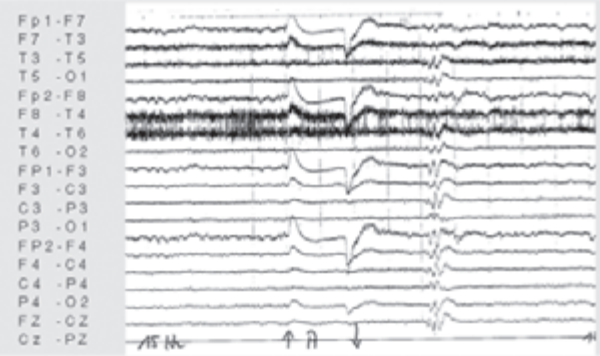
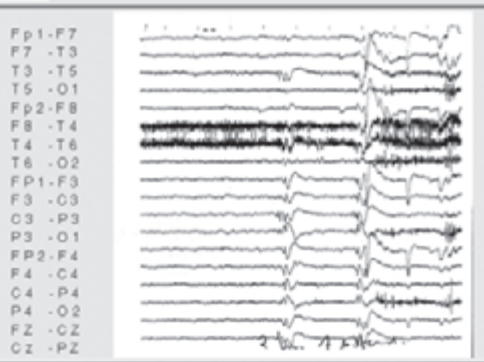
Patient with photo- and television sensitivity



Photosensitivity: attenuation by dark glasses (- 30%)



Television-sensitive patient viewing small screen from 2 m distance, for 1 min 10 sec



Eye closure sensitivity

- SW within 2 (-3) sec after eye closure (= immediate, qualitative)
- mostly occipital dominant
- often overlapping, but not identical with photosensitivity
- found in about 3 - 4% of IGE
- related to absences with eyelid myocloni (seizure type) or eyelid myclonus with absence (syndrome): short reflex loop
- Visual factor? Dark and lit environment!

Pattern sensitivity

Definition: precipitation of seizures (mostly absences) or spike-wave activity by vertical stripes of strong contrast.

Response immediate and qualitative

Environmental: heater grids, striped clothing, wall-papers, escalators etc etc

Self-induction of seizures: trance-like states with continuous SW patterns

Simple stimuli: conclusion

The reflex epileptic traits in idiopathic (generalized or localization-related) epilepsies are all related to the visual system and to stimulation of the occipital cortex.

The typical epileptic responses do not present the same relation but are "generalized" (absences or myoclonic)

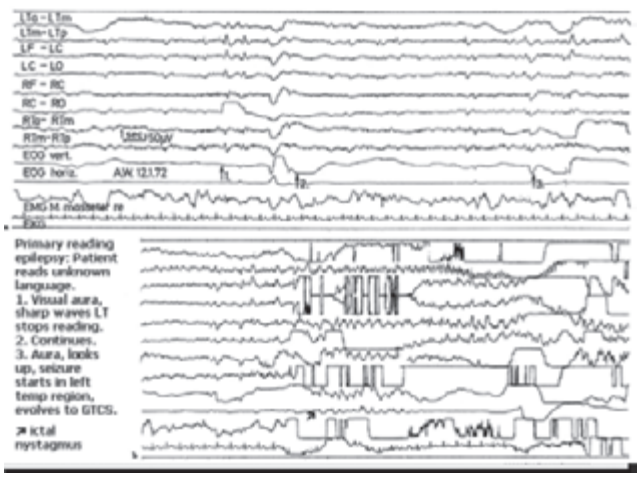
Praxis-induced seizures

Precipitating factors in 91 patients with praxis-induced seizures (Inoue et al)

Calculating	51
Writing	30
Playing cards	29
Spatial constructing	23
Playing chess	22
Complicated manipulation	20
Drawing	19
Reading	13
Speaking	1

ORM: Primary reading epilepsy

- Idiopathic localisation-related epilepsy of adolescence
- Age-related onset: 12 - 25 years
- Frequently hereditary
- Hallmark: orofacial reflex myocloni (ORM) precipitated by reading >> talking >> other language-related activities
- Rare: visual / oculomotor / dyslexic aura
- High risk of secondarily generalized TCS
- Quantitative relation to difficulty of performance
- Semantics irrelevant
- Decisive: transcoding
- System needs to be "warmed up"



ORM in JME

- Occurs in ~ 1/3 of patients
- Phenotype identical with PRE
- Precipitation always by talking, and sometimes (~ 40%) by reading
- Tuning of system, then short reflex loop in speech musculature (proprioception ⇒ myocloni), like in PRE

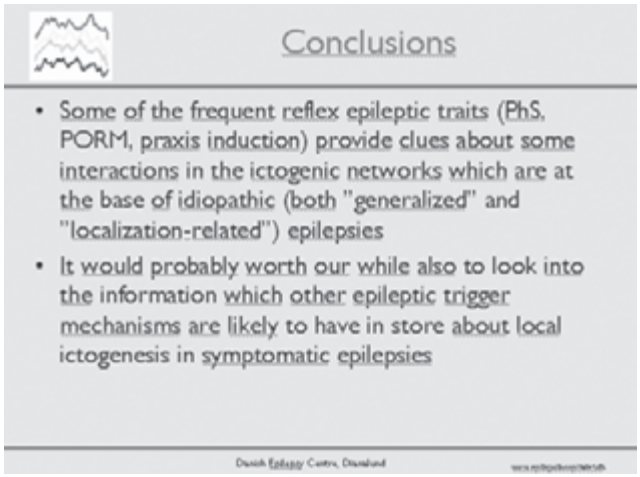
Reflex epileptic traits in JME and their significance

- Photosensitivity (40-50%)
  - occipital ⇒ motor cortex
- Eye closure sensitivity (4-5%)
  - sensorimotor reflex loop: role of occipital cortex?
- Praxis induction (30%; Japan: 50%)
  - complex visuomotor coordination as "tuner" ⇒
  - sensomotor reflex loop
- Orofacial reflex myoclonias (25-30%)
  - complex visuo-audio-motor "tuner" ⇒
  - sensomotor reflex loop
  - phenotypically = PRE, but difference of tuner

All reflex epileptic traits suggest interactions of functional anatomic networks

Reflex epileptic traits in JME and their significance

- All 4 reflex epileptic traits are most probably genetically determined and independent.
- We can therefore expect to find dysfunctional receptors or ion channels,
- which will presumably have specific patterns of distribution.
- The hypothesis is, that these can be related to functional anatomic networks that newer functional and advanced imaging studies indicate to exist in IGE.


Conclusions
• Some of the frequent reflex epileptic traits (PhS, PORM, praxis induction) provide clues about some interactions in the ictogenic networks which are at the base of idiopathic (both "generalized" and "localization-related") epilepsies
• It would probably worth our while also to look into the information which other epileptic trigger mechanisms are likely to have in store about local ictogenesis in symptomatic epilepsies
Danish Epilepsy Centre, Dianalund

Programa – 13.02.2008

Morning session – 9:00 – 13:00

- Generic products of AEDs: Is it an issue? – M. Bialer (Israel)
- Are the adverse effects of phenobarbital overestimated? -T. Tomson (Sweden)
- Stopping AED treatment: When and how? - G. Avanzini (Italy)

Afternoon session – 14:30-18:30

- Guidelines for drug therapy of the epilepsies – Carlos Guerreiro (Brazil)
- The AEDs of the future – M. Bialer (Israel)
- Alternative therapy in childhood epilepsies – Jaderson Costa da Costa (Brazil)

Generic products of AEDs: Is it an issue?

Meir Bialer (Israel)

Generic AEDs: Is There a Problem? Can we Separate the Science from the Politics?

Prof. Meir Bialer
Hebrew University
Jerusalem, Israel

LASSEII Sao Paulo (13.02.2008)

1

New Drug - NDA Generic Product - ANDA

- A new drug has to prove efficacy & safety (NDA)
- A generic product of an existing drug has to be bioequivalent to the brand (reference) product by demonstrating the same *in vivo* (absorption) performance (ANDA)

2

Bioequivalence

- Bioequivalence studies are designed to assess the relative bioavailability of a drug from test (generic) and reference (brand) formulations
- Ideally, the test and reference formulations should give essentially superimposable plasma concentration versus time profiles, but practically it is impossible
- Bioequivalent generics are regarded as essentially similar to the brand product

Midha et al, *Eur J Pharm Sci.* 1996

3

Generic Products - ANDA

A generic product has to be bioequivalent to the brand (reference) product by demonstrating the same *in vivo* (absorption) performance

4

The Three Major PK Parameters to Assess Bioequivalence are:

1) AUC - extent of absorption

2) Cmax - rate (but also extent) of absorption

3) tmax - rate of absorption

5

AUC & Bioavailability

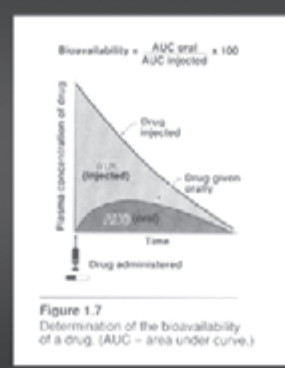


Figure 1.7
Determination of the bioavailability of a drug. (AUC = area under curve.)

6

Area Under the Curve (AUC)

- AUC is a robust parameter which takes into consideration all the experimental points collected in each phase of a bioequivalence study
- AUC is the principal criterion to characterize the extent of absorption and to assess bioequivalence
- This applies to single and to multiple dose studies of immediate and CR formulations

7

Bioavailability & Bioequivalence

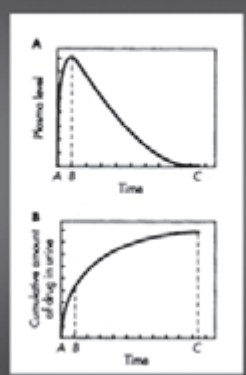
Absolute bioavailability $F = \frac{AUCpo / Dpo}{AUCiv / Div}$

Relative bioavailability (Bioequivalence) $F' = \frac{AUCtest / Dtest}{AUCref / Dref}$

AUC is calculated by numeric (non-compartmental) method
Absorption rate : Cmax and tmax are determined by visual inspection of the experimental plasma data

8

Bioequivalence – Extent of Absorption

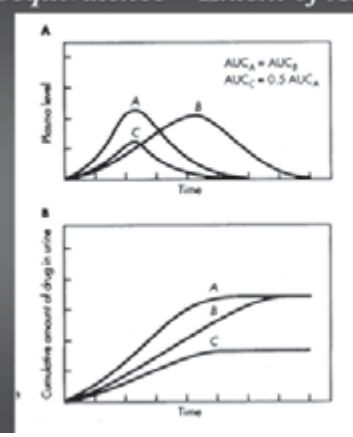


Plasma data-AUC

Urine data-Cumulative amount excreted unchanged in urine (Δe)

9

Bioequivalence – Extent of Absorption

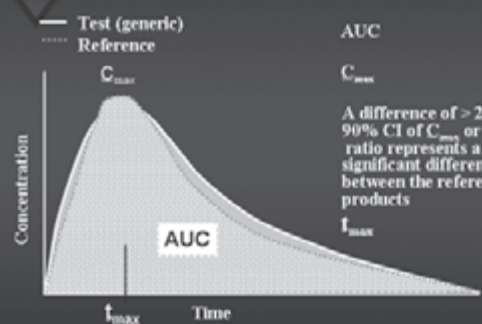


Plasma data

Urine data

10

Bioequivalence Criteria



AUC

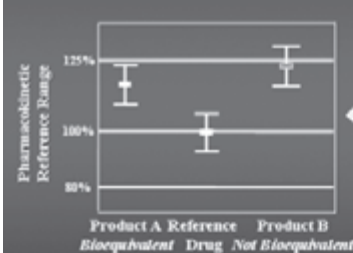
C_{max}

A difference of > 20% in the 90% CI of C_{max} or the AUC ratio represents a significant difference between the reference & test products

t_{max}

11

FDA Requirements for Bioequivalence



- Product A is bioequivalent if the 90%CI of its AUC ratio (AUCtest/AUCref) and Cmax ratio falls within 80-125%
- Product B is not bioequivalent if the 90%CI of its AUC ratio (AUCtest/AUCref) and Cmax ratio falls outside 80-125%

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Bioavailability (BA) & Bioequivalence (BE)

- Bioavailability (BA) is measured by assessing the rate and extent to which an active drug or active drug moiety is absorbed from the drug product and becomes available at the site of action
- Bioequivalence (BE) is the science of comparing the bioavailability of a drug from two different formulations of that drug
- Within-subject variability (WSV) is more important in BE than in BA

Within-Subject Variability (WSV)

- WSV or intrasubject variability is a measure of variability in response within the same subject, when the subject is administered two doses of a solution (preferably) on two different occasions
- WSV may be intrinsic to the drug substance and/or formulation
- WSV is more important in BE than in BA, since BE is concerned with interchangeability within a subject

Within-(WSV) vs Between-Subject Variability (BSV)

WSV is estimated from ANOVA

The fixed effects in the ANOVA model are typically:

Formulation
Period
Sequence
Subject (Sequence)
} These account for all the BSV

Residual Variance (MSE) } WSV

Many drugs have a large BSV, but BE is concerned with interchangeability. Therefore, WSV and not BSV is a critical determinant for BE

PK Parameters to Assess Bioequivalence: Systemic Exposure Concept

- AUC - A measure of total exposure, assesses extent of absorption
- Cmax - A measure of peak exposure, assesses rate (but also extent) of absorption
- tmax- assesses rate of absorption
- AUC_t- Partial AUC truncated at tmax, a measure of early exposure (MR, rapid onset)

Meeting the acceptable 90%CI of 80-125%, implies that plasma levels (AUC) of a bioequivalent generic with linear PK will not differ by >5-7% from those observed with the brand product

Perucca et al, *Epilepsia*, 2006; Bialer, *Epilepsia*, 2007; Midha & McKay, *BA & BE Conference*, Athens, October 1-2, 2007

Residual (WSV) Variance

- The residual variance has four components:
- True PK WSV plus a component of analytical variability
- Within formulation (tablet to tablet) variability
- Subject by formulation interaction
- Unexplained random variation

These variance components cannot be separated in a standard two-period design

Standard vs Replicate Designs

Standard 2-period Design

- 2-formulations, 2-period, 2-sequence crossover design
- The two sequences are: TR & RT

Replicate Design

- The test & reference formulations are given twice
- A 4-period replicate design with two sequences is: TRTR & RTRT

Physicians' Concern

Concern persists that the criteria used to establish bioequivalence of generic drug products may not adequately guarantee the interchangeability of drugs, particularly CR formulations

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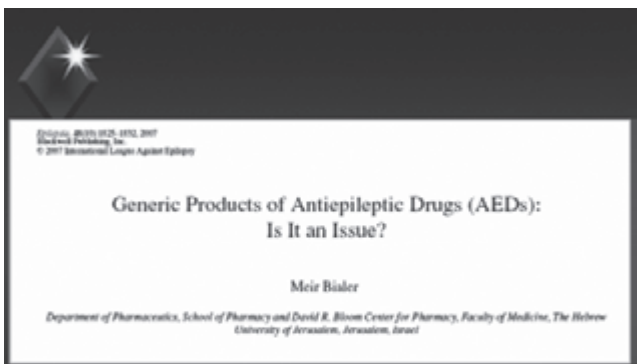
Bioequivalence is a More Demanding Criterion than Therapeutic Equivalence

"The present requirements to prove bioequivalence, at least in the US and Canada, are already so rigorous and constrained that there is very little possibility, even for NTI drugs, that dosage forms meeting regulatory criteria could lead to therapeutic problems"

Benet & Goyan, *Pharmacotherapy*, 1995

20



Generic Products of Antiepileptic Drugs (AEDs):
Is It an Issue?

Meir Bialer

Department of Pharmaceutics, School of Pharmacy and David R. Bloom Center for Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Do bioequivalent generic AEDs work as well as brand AEDs?
Can generic AEDs be used as substitutions for brand AEDs?
Can generic AEDs be used interchangeably?

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Issues Specific to Epilepsy & Generic Products of AEDs

- **Epileptic patients require consistency in their AED treatment**
- **This is particularly true for seizure-free patients**
- **The generic switch itself may cause breakthrough seizures as patients are averse to changes**
- **Patients prescribed with generics may face switches from one generic product to another**
- **In an unpredictable subset of epileptic patients generics may have a higher intrasubject variability (WSV) than the brand AEDs**

Bialer, *Epilepsia*, 2007

22

Average vs Individual Bioequivalence (BE)

- **Average BE- Compares population means between the test (generic) and reference (brand) products**
- **Individual BE- Can evaluate switchability**
- **Individual BE Concept: Each patient has an individual therapeutic window & intrasubject variability (WSV)**
- **Individual BE models are more complicated**

Bialer, *Epilepsia*, 2007

23

Individual Bioequivalence (BE)

Individual Difference Ratio

IDR=T-R/R-R

Difference in bioequivalence metric (AUC, Cmax) between test & reference

Difference between reference & reference

Replicate Design
For individual BE analysis the generic and brand products must be administered twice to the same group of subjects

Chen & Lesko, *Clin Pharmacokinet*, 2001; Bialer, *Epilepsia*, 2007

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Individual & Average Bioequivalence (BE)

Individual BE

(Difference of means)^2+Interaction+ Difference of variances ≤ (Preset limit)^2

Average BE

Lower preset limit (80%) ≤ Difference of means ≤ Upper preset limit (125%)

When the within subject variances of the generic & brand products are the same and there is no interaction: Individual BE=Average BE

Schall & Luus, *Stat Med*, 1993; Endrenyi et al, *Eur J Pharm* Sci. 1998

25

Individual Bioequivalence - Has its Time Come?

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FDA Current Thinking on BE of Highly Variable Drugs (HVD)

- An FDA survey: 20% of the acceptable bioequivalent generics between 2003-2005 were HVD
- What % were generic AEDs?
- Are AEDs except phenytoin HVD?
- BE studies of HVD enrolled 50% more subjects
- HVD – WSV (root mean square error-MSE) or %CV>30%

B. M. Davit, *OGD, CEDAR*, FDA

27

FDA Current Thinking on Bioequivalence (BE) of Highly Variable Drugs (HVD)

- It is possible to reduce number of study subjects when the 90%CI are adjusted to the within-subject variability (WSV) of the reference product
- The WSV is determined in a partially replicate crossover study (generic product administered once, reference administered twice)
- The FDA would also impose a point estimate constraint on the generic/reference mean ratio to eliminate the potential for approving a generic product with a large T-R difference

B. M. Davit, *OGD, CEDAR*, FDA

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Average vs Individual Bioequivalence (BE) - Conclusions

- Approved generic AEDs with documented average BE data are prescribable & represent a valuable choice for drug "naïve" patients
- The switch to generic is well tolerated by many patients and is cost-effective but is less likely to be published than case reports with bad news
- Until we have individual BE data or the tool to *apriori* identify susceptible patients, seizure-free patients should not be switched

Bialer, *Epilepsia*, 2007

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Average vs Individual Bioequivalence (BE): Questions

- Did average BE fail to assess BE of generic AEDs, aside from anecdotal reports?
- Is subject-by-formulation interaction important in BE analysis?
- What is the right population for individual BE, healthy subjects or patients?
- Is the within subject variability of patients to a switch from a brand to generic greater than from one batch to another?

Bialer, *Epilepsia*, 2007

30

Generic AEDs: We Must Separate the Politics from the Science

Politics

- A pressure against generic AEDs by physicians & patients associations
- Only "bad news" get published. A soft substitution from brand to generic does not merit publication
- Many Pharmas produce a "manufacturer's own" generic identical to the brand. Is it a problem?
- AEDs global sales rose from $4.4 billion in 2000 to $10.7 billion in 2005
- Pharmas want to keep up this this trend. Governments and HMOs do not!

Kramer et al, *Epilepsy Behav*, 2007; Bialer, *Epilepsia*, 2007

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Industry Fights Switch To Generics for Epilepsy Drug Makers Help Patient Groups Lobby; More Attention to States

In state legislatures across the country, the Epilepsy Foundation (EF) has been campaigning for bills that would make it harder for pharmacists to switch patients to inexpensive generic epilepsy pills. The effort is getting behind-the-scenes support from drug companies - a sign of how the industry, long & potent lobbying force in Washington, is increasingly looking to states to achieve its goals.

EF, a nonprofit group supported by the drug industry, says switching to generics could cause dangerous seizures. The FDA says it hasn't seen persuasive evidence for that, and it believes each generic is equivalent to the brand-name drug it copies.

Sarah Rubenstein, *The Wall Street Journal*, July 13, 2007

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National Guidelines for Generic Prescription of AEDs

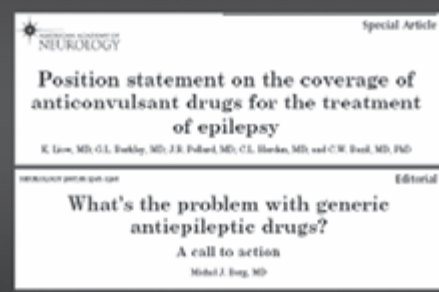
Country	Principal recommendations
England	Small differences in absorption can result in large differences in therapeutic effect
Germany	Never switch patients who are well controlled
Italy	In seizure free patients switching is not recommended
Sweden	A switch between formulations is considered to carry a risk of unstable seizure control
The Netherlands	Generic substitution of AEDs is risky. SR formulations should not be substituted

Kramer et al, *Epilepsy Behav*, 2007

33

Generic Products of AEDs: What is so Specific?

The patients, the disease pattern, the AEDs?


NEUROLOGY

Special Article

Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy

K. Liow, MD; G.L. Barkley, MD; J.R. Pollard, MD; C.L. Hawkes, MD; and C.W. Reed, MD, PhD

Editorial

What's the problem with generic antiepileptic drugs?

A call to action

Michel J. Berg, MD

34

AAN Position Statement on Generic AEDs

- AAN believes that formulary policies should support complete physician autonomy in prescribing & epileptic patients in accessing the full range of AEDs
- AAN opposes policies that would result in arbitrary switching among AEDs
- AAN supports legislation that would require informed consent of physicians and patients before generic substitutions of AEDs are made at the point of sale

Liow et al, *Neurology* 2007

35

AAN Position Statement on Generic AEDs

- AAN believes that the use of AEDs in epilepsy should be distinguished from their use in other disorders
- Unlike other diseases, a single breakthrough seizure due to change in delivered medication dose (formulation) can have devastating consequences including loss of driver's license, injury, and even death

Liow et al, *Neurology* 2007

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French League's (LFCE) Considerations on Generic AEDs

- Epilepsy differs from chronic diseases. A single seizure may have serious and even irreversible consequences
- AEDs are a particular class whose substitution in epilepsy is problematic (all AEDs?)
- FDA acceptable range for bioequivalence is too large for epileptic patients and thus does not guarantee therapeutic equivalence (disagree)
- Seizure recurrence after substitution of a brand by a generic AED (no prospective studies)
- Ambiguity in terms of legal responsibility in case of an accident

LFCE, *October,* 2007

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LFCE Recommendations on Generic AEDs

- AEDs are a particular class whose substitution in epilepsy is problematic
- No substitutions of AEDs without the agreement of the physician and the patient especially in seizure-free patients
- Opposed to the practice that allows substitution of an AED at the point of sale
- Autonomy of prescriptions and free access of the patients to the prescribed treatments remain basic principle of medical practice

LFCE, *October,* 2007

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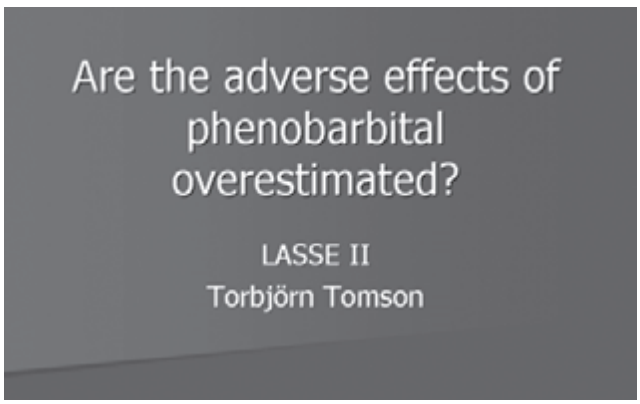
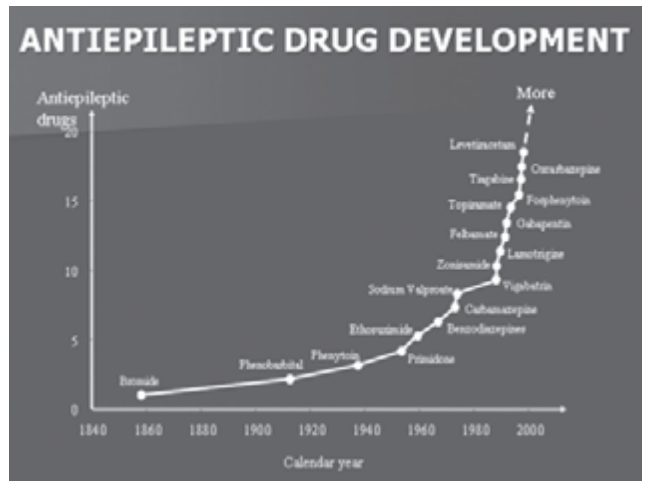
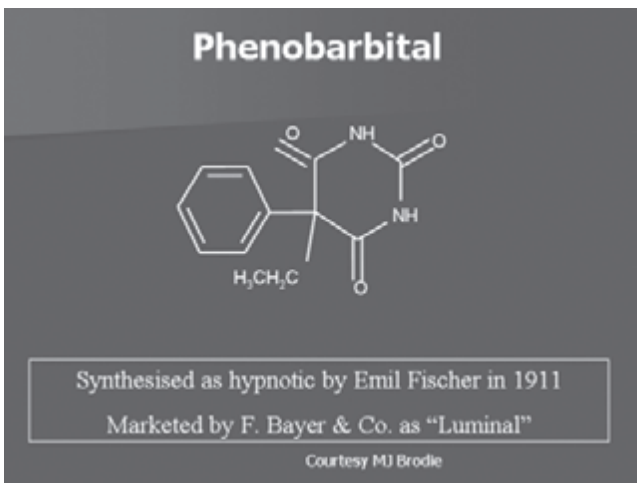
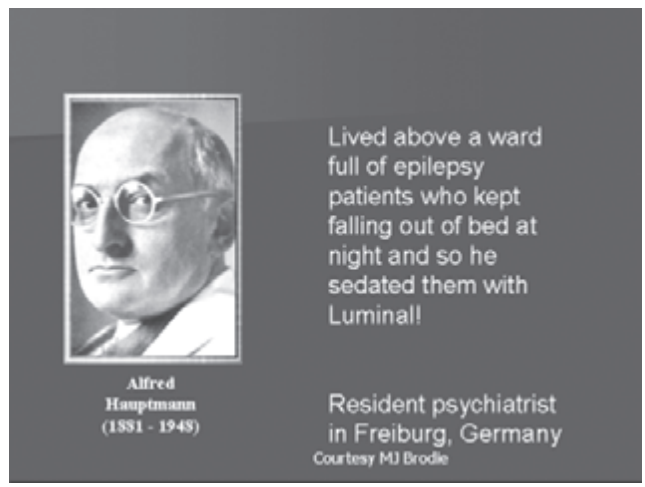
Are the adverse effects of phenobarbital overestimated?

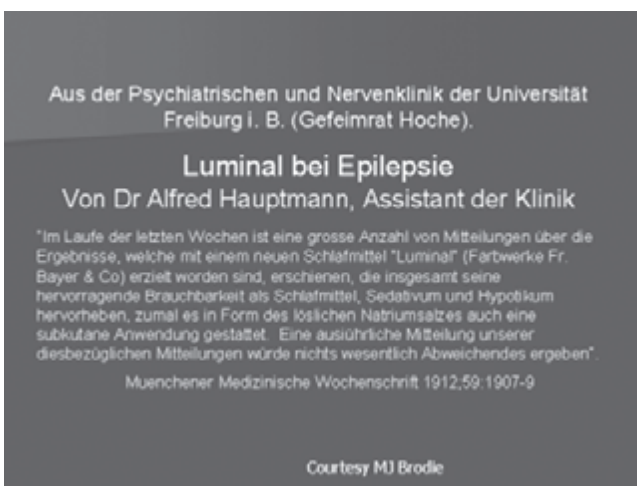
Torbjörn Tomson (Sweden)

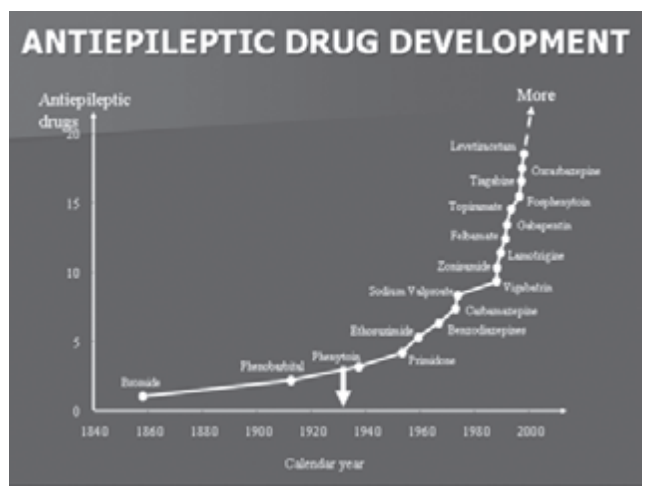








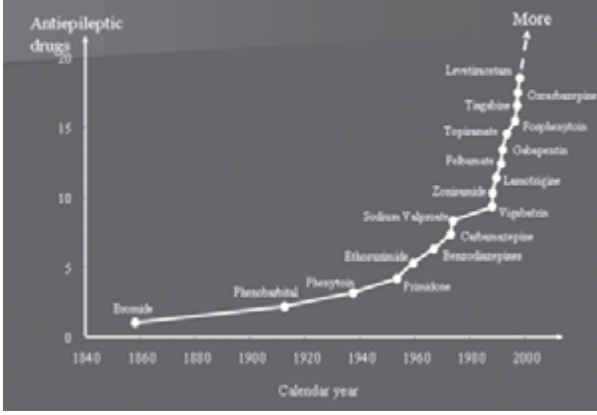




The Epilepsies
William G Lennox
Tice's Practice of Medicine, 1937

"Of the various barbituric acid derivatives, phenobarbital is the most effective. It is sold under the trade name "luminal" which costs more than phenobarbital but has not been proven to be more effective. Dispensed in tablets, the usuasal dose is 1½ grains (=100 mg) daily. The amount must be varied to suit the needs of the patient, 3 or ewen 6 grains (=200 to 400 mg) daily may be used. The dosage should be less than the amount required to produce a feeling of sleepiness."

ANTIEPILEPTIC DRUG DEVELOPMENT



Properties of an ideal AED and of phenobarbital

- Effective in high proportion of patients ■ +
- Safe, few severe idiosyncratic reactions ■ +
- Extensive experience ■ +
- Favourable kinetics ■ +
  - once daily dosing
  - linear kinetics
  - low protein binding
- Affordable ■ +

Properties of an ideal AED and of phenobarbital

- Effective in high proportion of patients ■ +
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  - once daily dosing
  - linear kinetics
  - low protein binding
  - no interactions -
- Affordable ■ +
- High tolerability ■ ?

Systematic Review
CBZ vs. PB monotherapy for epilepsy
Tudor Smith et al Cochrane Database 2003

- Data available for 684 participants from four trials
- "No overall difference for time to 12 months remission or time to first seizure. Phenobarbitone is significantly more likely to be withdrawn, indicating that it is less well tolerated than carbamazepine."

Systematic Review
PB vs. PHT monotherapy for partial onseet seizures and generalized onset tonic-clonic seizures
Tudor Smith et al Cochrane Database 2003

- Data available for 599 participants from four trials
- "The results of this review favour phenytoin over phenobarbitone, as phenobarbitone was significantly more likely to be withdrawn than phenytoin. Given that no significant differences for seizure outcomes were found, the higher withdrawal rate with phenobarbitone may be due to adverse effects."

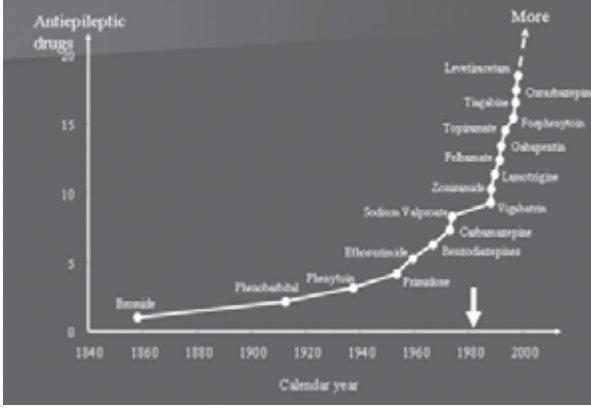
Systematic Review

Phenobarbital for childhood epilepsy

Pal Paediatr Perinat Drug Ther 2006

- RCTs of PB vs other AEDs or placebo conducted 1970-2005 were reviewed
- "There is no evidence for a difference in antiepileptic efficacy between phenobarbital and any other compared AED, yet no evidence for absolute efficacy. No convincing evidence exists for an excess of behavioural adverse effects, over other AEDs, attributal to phenobarbital. Masked studies of phenobarbital in childhood epilepsy have shown no significant differences in behavioural or cognitive adverse effects compared to other AEDs. This is in contrast to the excess of such adverse effects reported in open to observer bias."

ANTIEPILEPTIC DRUG DEVELOPMENT



Comparison of CBZ, PB, PHT, and PRM in Partial & Sec. GTCS

- No significant difference between CBZ, PHT and PB in retention
- Significantly better retention with PB compared with PRM
- 36-month retention for those with tonic-clonic seizures as successful for PB as for CBZ and PHT
- Higher retention with CBZ or PHT than with PB or PRM for partial seizures only
- Most PB and PRM failures occurred early

Mattson et al NEJM 1985

Comparing CBZ, PHT, PB, and PRM Reasons for drug failures

Reason	CBZ N=101	PB N=101	PHT N=110	PRM N=109
Toxicity alone	12	19	18	36
Toxicity + seiz	30	33	29	35
Seizures alone	3	4	1	3
Total failures	45	56	48	74

Mattson et al NEJM 1985

VA RCT comparing CBZ, PHT, PB, and PRM

AED	Mean plasma concentration at 24 months (mg/L)	Reference range
CBZ	8.4	5-12
PHT	14.0	10-20
PB	25.8	10-40

Mattson et al NEJM 1985

Mean composite scores for seizure frequency and toxicity*

	12 months	24 months	36 months
CBZ	22	27	31
PB	26	31	33
PHT	21	24	29
PRM	31	35	36

*50 points assigned to patients whose drug failed. Lower score indicates a better outcome.

Mean composite scores among patients remaining in study

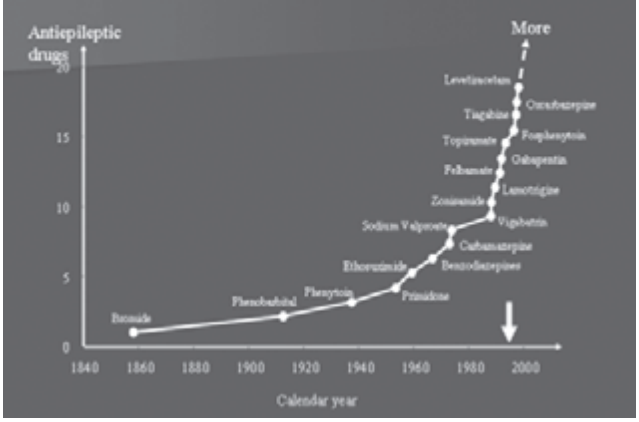
	24 months, all	24 months, those still on study drug
CBZ	27	11
PB	31	13
PHT	24	12
PRM	35	9

50 points assigned to patients whose drug failed. Lower score indicates a better outcome.

Adverse effects

- Phenobarbital associated with lowest incidence of motor disturbance early in treatment
- Phenobarbital associated with lowest incidence of gastrointestinal problems
- Systemic toxicity scores for PB 33% lower months 7-24 compared to 1-6

ANTIEPILEPTIC DRUG DEVELOPMENT



PB, PHT, CBZ, or VPA for newly diagnosed adult epilepsy *Heller et al, JNNP 1995*

- Open label RCT, n=243, mean follow up time 30 months (1-91)

Results

	PB	PHT	CBZ	VPA	Total
N	58	63	61	61	243
1 year remission	52%	59%	59%	59%	57%
Withdrawal for AE	22%*	3%	11%	5%	10%

*Drowsiness and lethargy accounted for 8/13 withdrawals on PB

Dosing

AED	Start dose mg/day	Incremental dose, mg	Conc. range* mg/L
PB	60	30	20-40
PHT	200	50	10-20
CBZ	400	200	4-11
VPA	400	200	50-100

*Drug dose increased until seizures ceased or plasma concentration in the top half of the concentration range

PB, PHT, CBZ, or VPA for newly diagnosed childhood epilepsy

de Silva et al Lancet 1996

- Open label RCT, n=167
- Of the 10 first patients assigned PB, 6 experienced unacceptable side effects (cognitive or behavioural) and further recruitment to this treatment arm was stopped

Dosing

AED	Start dose mg/kg day	Incremental dose, mg/kg	Conc. range* mg/L
PB	3	2	20-40
PHT	5	2	10-20
CBZ	8	4	4-11
VPA	15	5	50-100

*Drug dose increased until seizures ceased or plasma concentration in the top half of the concentration range

PB or CBZ for GTCS in semi-urban Kenya

Feksi et al, Lancet 1991

- Open label RCT, n=302, 6-65 years of age
- CBZ n=152; PB n=150
- CBZ slowly titrated to minimum maintenance dose (600 mg for adults)
- PB started at minimum maintenance dose (60 mg for adults)

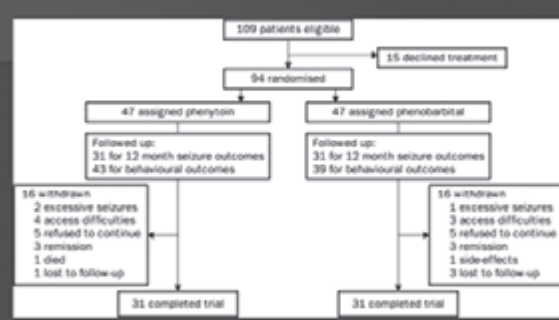
Results

	CBZ	PB
Withdrawn, total, n	26	27
Withdrawn, side effects, n	8	5
Seizure free, % of remaining	52	54

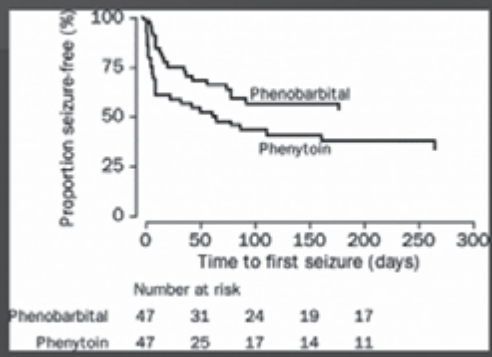
PB or PHT for childhood epilepsy in rural India

Pal et al, Lancet 1998

- Open label RCT, n=94, 2-18 years of age
- PHT, n=47; minimum maintenance dose 5.0mg/kg/day
- PB, n=47; minimum maintenance dose 3.0mg/kg/day
- 12 months follow up



Time to first seizure



Side effects

	PHT (n)	PB (n)
No side-effects	33	34
Behavioural	6	6
Sleep disturbance	2	2
Anorexia/nausea	1	
Dizziness	1	
Several side-effects	4	5

PB or PHT for partial or generalised tonic-clonic seiures in India

Mani et al., Lancet 2001

- Open non-randomised, n=135 up to 5 years follow up
- PHT, n=60; at "lowest effective dose"
  - <15 y 50-200 mg/day
  - >15 y 100-250 mg/day
- PB, n=68; at "lowest effective dose"
  - <15 y 30-60 mg/day
  - >15 y 30-90 mg/day
- Outcome measure: Absence of seizures for at least 2 years

PB or PHT for partial or generalised tonic-clonic seiures in India

Mani et al., Lancet 2001

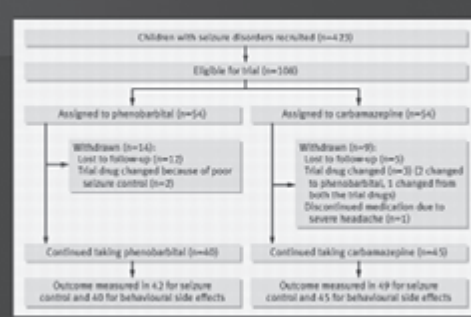
- Terminal remission in 50 to 66%
- Only 3 (4%) out of 75 reported adverse effects with PB
  - -dullness, hyperkinesia, somnolence
- 29 (43%) out of 67 reported adverse effects with PHT
  - -mainly gingival hyperplasia

Comparison of side effects of PB and CBZ in childhood epilepsy in Bangladesh

Banu et al., BMJ 2007

- De blind RCT, n=108, 2-15 years old
- Generalized T-C (n=51) or partial +/- generalisation (n=57)
- CBZ, starting dose 5 mg/kg/day
  initial maintenance dose 16 mg/kg/day
- PB, starting dose 1.5 mg/kg/day
  initial maintenance dose 3 mg/kg/day
- Outcome measure: Behavioural side effects at 12 months

Flow of children through the trial



Banu, S. H et al. BMJ 2007;334:1207

BMJ

Results

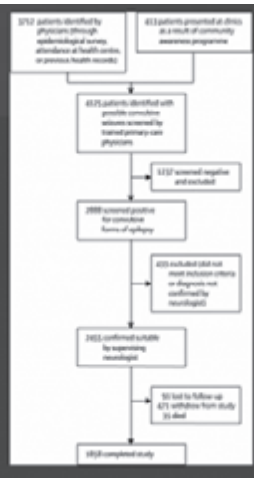
	PB (n=40)	CBZ (n=45)
Seizure free last 3 months	32	39
Behavioural outcome unchanged	28	31
Behavioural outcome improved	8	8
Behavioural outcome deteriorated	4	6

Efficacy of phenobarbital in epilepsy in rural China

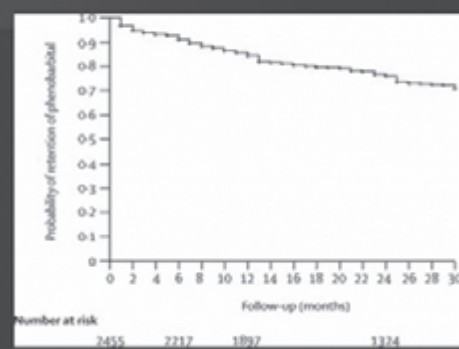
Wang et al Lancet Neurol 2006

- Open non-randomised study of PB in convulsive forms of epilepsy
- N=2,455, > 2 years of age

Age, years	Median, mg/day	Range, mg/day
2-5	30	15-90
6-10	60	15-210
11-15	75	15-270
>15	120	60-300



Retention on PB



Adverse events over time

	1-3 mo	7-12 mo	19-24 mo
Drowsiness	27%	13%	8%
Dizziness	13%	9%	5%
Headache	8%	5%	3%
Ataxia	7%	4%	2%
Anxiety	6%	4%	2%
Hyperactivity	2%	2%	1%

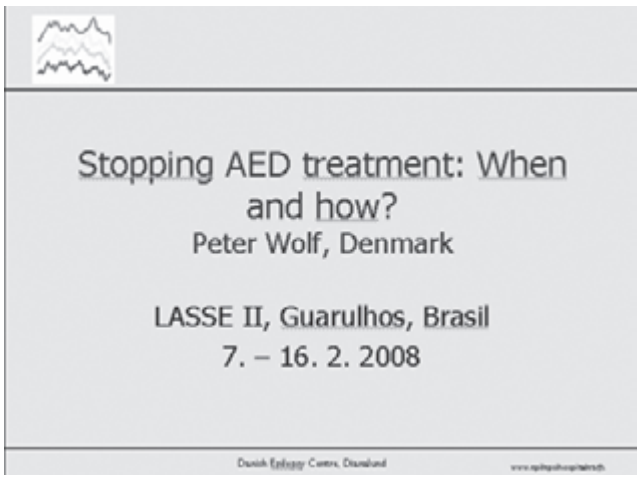
5% withdrew from treatment due to adverse events

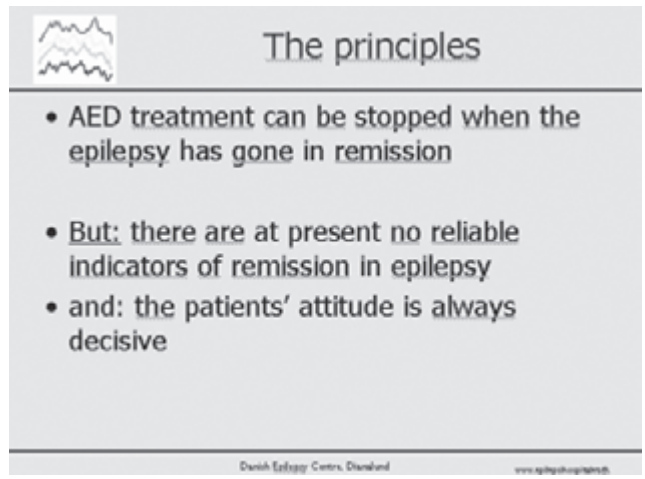
Conclusions

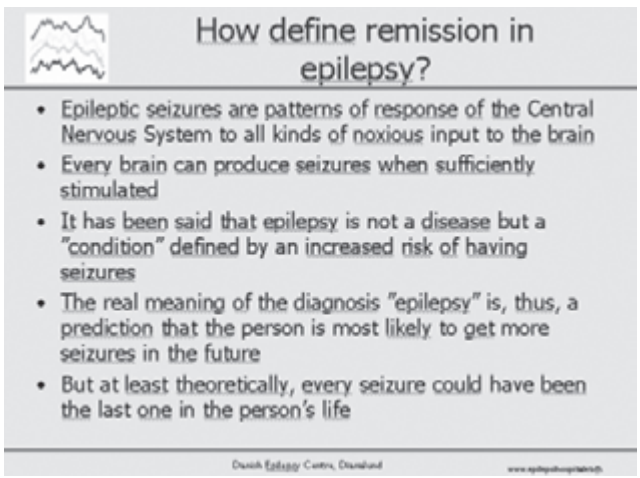
- AEs with PB not markedly higher than with other AEDs in large double-blind studies
- Some AEs reported to be more common with PB in some open studies from western countries
- No consistent similar pattern from developing countries
- Possible explanantions for discrepancies :
  - -dosing strategies?
  - -expectations?
  - -regional differences in risk/benefit analysis

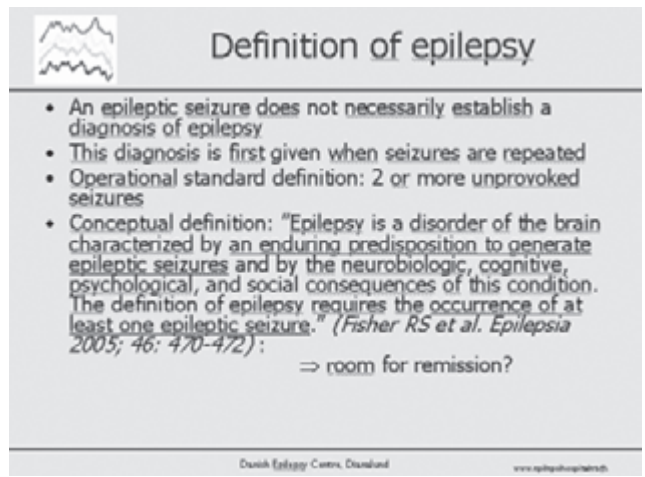
Stopping AED treatment: When and how?

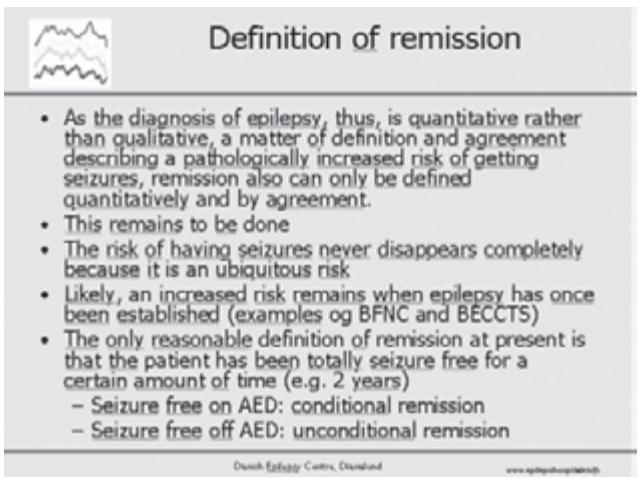
G. Avanzini (Italy)

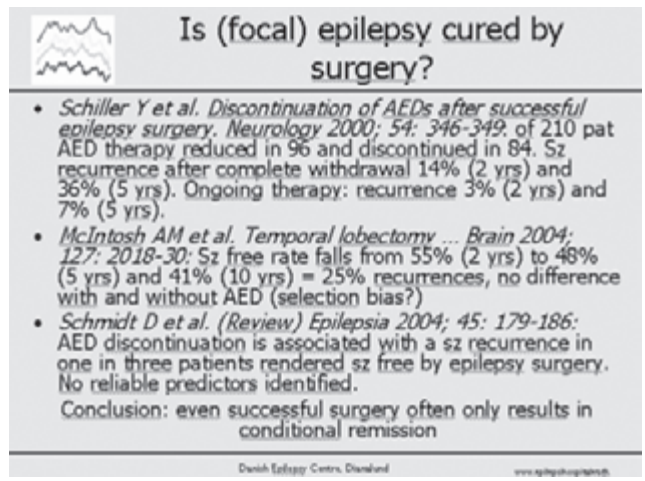












Remission with medical therapy?

- Risk of relapse at discontinuation of AED: 30% - 70%
- Possible risk factors
  - age at onset
  - age at withdrawal
  - family history of epilepsy
  - etiology
  - syndrome
  - abnormal neurological findings
  - abnormal psychiatric findings
  - EEG abnormalities
  - number of seizures preceding remission
  - duration of seizure free period

AED discontinuation in sz free patients: predictors of remission and relapse?

Medical Research Council AED Withdrawal Study Group, Lancet 337 (1991) 1175-80 (n = 1013, randomised, prospective)

"The most important factors determining outcome were
- longer seizure-free periods (risk ↓),
- more than one AED (risk ↑)
- and a history of tonic-clonic seizures (risk ↑).
- Other factors (e.g. history of neonatal seizures, specific electroencephalographic features) seemed to have smaller effects, but even in such a large study the confidence intervals for these observations were wide."

AED discontinuation in sz free patients: predictors of remission and relapse?

Specchio et al. JNNP 72 (2002) 22-25 (n = 225, not randomised, monotherapies)

"A relation was found between relapse and
- duration of active disease,
- number of years of remission while on treatment, and
- abnormal psychiatric findings."

The concept of seizure propensity

- Seizure propensity is a time-honoured terminology which refers to the quantitative differences in the risk of having seizures.
- Sz propensity is a function of many factors, only some of which are known and may fluctuate e.g. in relation to time (age, sleep-wake cycle, menstrual cycle), alertness, tension vs relaxation, lack of sleep, stress, previous seizure activity ("seizures beget seizures") etc.
- Others are largely unknown.
- There are external influences (e.g. alcohol).
- Most are difficult to measure and quantify which makes the matter of sz propensity somewhat elusive.
- Bickford et al attempted a semi-quantified description:

The concept of seizure threshold

- Whereas "seizure propensity" sums up all the factors which facilitate the generation of seizures,
- "seizure threshold" sums up all intrinsic factors which counteract generation of seizures. In Bickford's graph a straight line but in reality probably also fluctuating.
- These factors are less well known.
- A seizure would occur when the seizure propensity mounts above the seizure threshold,
- in other words: when the sum of facilitating factors is higher than the sum of protective factors:
- Epilepsy needs to be seen as a dynamic condition.

The concept of *therapeutic* treshold

- Whereas seizure propensity and seizure threshold are to some extent theoretical concepts that can help us to understand the dynamics of ictogenesis but cannot be measured,
- the therapeutic threshold can be calculated.
- It is the level of antiepileptic drug (AED) action which needs to be surpassed to prevent seizures at the time when the interaction of facilitating and protective factors is most unfavourable for the patient, i.e. when the risk of a seizure is highest.

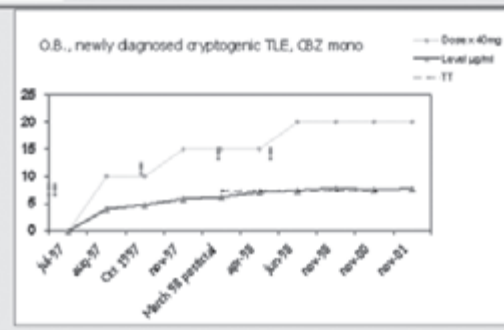
Definition of the therapeutic treshold

- At present there is no generally accepted definition, and no direct determination is possible
- An operational definition has been proposed which sets the therapeutic threshold as the mean of the highest AED plasma level at which seizures still occurred (subtherapeutic level) and the lowest level at which seizures were controlled (therapeutic level)

Wolf P et al. Epilepsy & Behavior 2006; 8: 384-390

Danish Epilepsy Centre, Dianalund

The therapeutic threshold is an individual measure



It is an indicator of the patient's seizure propensity

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Seizure propensity, thresholds and remission

- A high therapeutic threshold reflects a high seizure propensity or a low seizure threshold or both
- Remission could be due to a decrease of sz propensity or an increase of sz threshold
- In either case it would be reflected by a decrease in the therapeutic threshold
- This we have attempted to study with longitudinal antiepileptic drug monitoring in seizure free patients undergoing reduction and discontinuation of AEDs

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Lessons to learn from relapses

- Traditionally, relapse is just considered as failure of a therapeutic strategy.
- Alternatively, if AED levels are determined, a relapse can be used as a source of information about the present therapeutic threshold (TT).
- By following the development of the therapeutic AED threshold, indirectly the development of the seizure propensity can be investigated.
- This is what we have attempted in our study.

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Own study: definition of new therapeutic threshold (TT) at relapse

- AED plasma levels were determined routinely after every dose decrement.
- Following relapses, the AED plasma levels were measured as closely as possible after the event (postictal drug levels).
- The new TT was defined as the mean of the last dose / plasma level before the relapse and the postictal dose / plasma level.

Wolf P, Pastuchova T, Mataringa M. Decline of seizure propensity in seizure free patients as reflected in the evolution of the therapeutic AED threshold (Epilepsy & Behavior 2006; 8:384-390)

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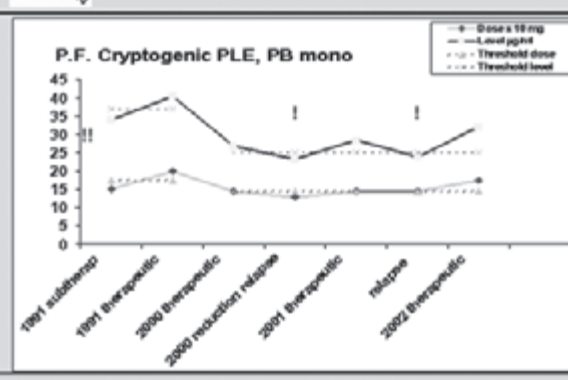
An example of threshold development



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Own investigation: observational

Evaluation of 201 adults where, after prolonged periods of seizure control, the antiepileptic medication was tapered and, if possible, terminated.

Start of taper: after seizure free periods of 2 years (cases with good response to treatment) to 5 years (difficult-to-treat cases).

Analysis of recurrences: the TT

The initial therapeutic threshold (of serum level, dose or both) could be determined in 51 cases, and could not be determined in 66.

Reasons:

- Seizure control achieved by first dose / level at onset of therapy (less severe cases),
- After failure of previous drug, seizure control achieved during switch of drugs

(uncontrolled influences of positive or negative pharmacodynamic and pharmacokinetic interactions, and of withdrawal effects).

Advance of reduction in 117 fully successful monotherapies

Progress of reduction	All cases (n = 117)
< 50 %	50 (42.7 %)
≥ 50 %	32 (27.4 %)
off AEDs	35 (29.9 %)

Procedure: very slow after 2 – 5 years

Advance of reduction in 117 fully successful monotherapies

Progress of reduction	All cases (n = 117)	ITT known (n = 51)	ITT unknown (n=66)
< 50 %	50 (42.7 %)	29 (56.8 %)	21 (31.8 %)
≥ 50 %	32 (27.4 %)	15 (29.4 %)	17 (25.8 %)
off AEDs	35 (29.9 %)	7 (13.7 %)	28 (42.4 %)

Reasons for missing ITT: full response to first target dose or change from other AED with phase of bitherapy

In cases with unknown ITT, reduction is more advanced. All immediate responders are in this group

Fisher's exact test p =< .002

Relapse: known and unknown TT

TT known (51)		**TT unknown (66)**
• **Relapse**:	32 (62.7%)	• 19 (28.8%)
• **No relapse**:	19 (37.3%)	• 47 (71.2%)
– *No drugs*:	*5 (9.8%)*	– *25 (37.9%)*

Relapses less frequent when initial therapeutic threshold is unknown ($p < .01$)

Relapses: in what stage?

	TT known (51)	**TT unknown (66)**
– **1st reduction:**	4 (7.8%)	– 1 (1.5%)
– **<50% reduction**	23 (45.1%)	– 5 (7.6%)
– **≥50% reduction:**	3 (5.9%)	– 10 (15.2%)
– **at termination:**	2 (3.9%)	– 3 (4.5%)

Conclusions:

1. With prolonged seizure control the seizure propensity almost always decreases
2. Seizure propensity falls substantially more in people with a good initial response ($p < .001$)
3. Remission often is not a qualitative but a quantitative process

Conclusions

During a long seizure free period the seizure propensity usually falls.

This is true for at least 90% of cases.

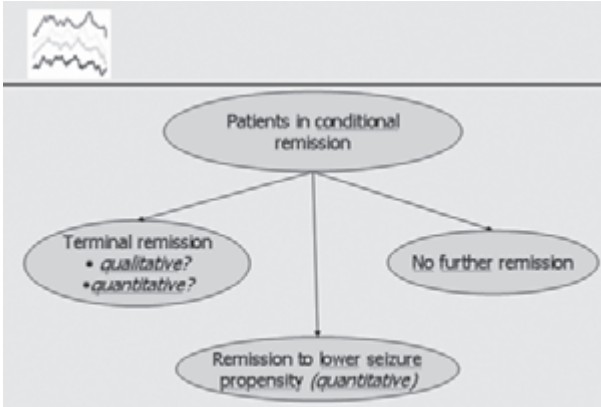
The fall in SP is more pronounced in patients who responded immediately to a moderate AED dose:

They relapse more rarely and at a later stage although their reduction is more advanced.

They probably represent a relatively benign segment where unconditional remission is more likely to occur.

Gradual decrease of seizure propensity?

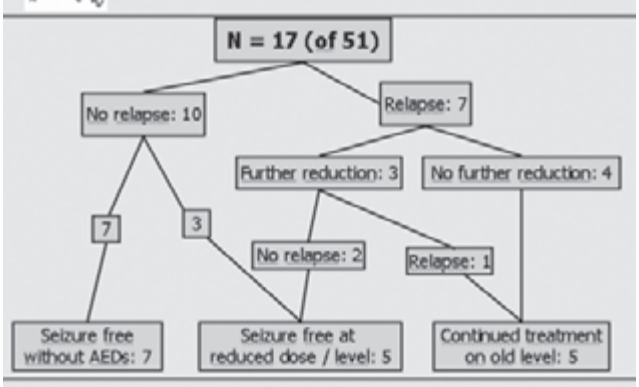
- If the fall of SP were always qualitative, or quantitative but limited, the patient would either become seizure free without drugs or require continuous treament above a new TT.
- If the fall of SP is quantitative and gradual, it would be possible, in these cases, to continue AED taper even after a relapse.



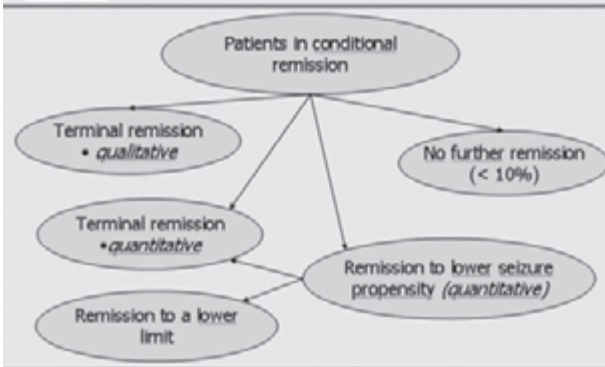
Remission limited or unlimited? Pats. with 2nd withdrawal (17/51)

- Further relapse at dose / serum level comparable to 1st relapse: TT and SP have remained the same = limited remission
- No relapse in spite of dose / level below previous relapse: ongoing process of remission
- AED completely withdrawn without relapse: processes of remission have continued to terminal remission

Course after 2nd reduction



Conclusion



Predictors of 2.relapse: known TT?

TT known	32
2. reduction	10
2. relapse	5
TT unknown	19
2. reduction	7
2. relapse	2

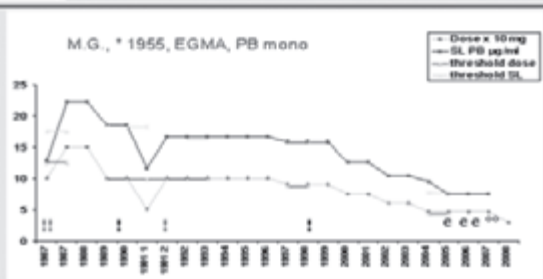
The big difference from 1. reduction has disappeared. Those with the best prognosis were already filtered out.

Predictors of 2.relapse: 1. relapse with reduction of < 50%?

Relapse with reduction < 50%	33
2. reduction	4
2. relapse	3
Relapse with reduction > 50%	18
2. reduction	13
2. relapse	5

(n.s.)

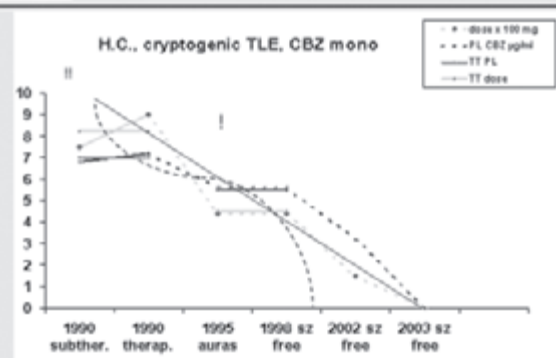
Remission type 2: progressive



! = unprovoked seizures ! = seizures with non-compliance
e = runs of generalized spike – waves for 40 sec, subclinical

ITT (1987) 125 mg (17.5), TT_e (1991) 100 (16.3), last TT (2006) 45 mg (7.7)

Progression to terminal remission



Stopping AED treatment: When and how?

- AED treatment can be stopped when the epilepsy has gone into remission
- In some patients, remission is a built-in feature of their epilepsy, and part of these can be identified
- In others, remission occurs relatively rapidly, and stepwise withdrawal after 2 sz free years over 2 – 6 months is possible
- Most of these patients initially responded to the first dose of the first drug, but not all rapid responders belong to this group
- No other predictors at present

Stopping AED treatment: When and how?

- In a substantial proportion of cases, remission of epilepsy is a slowly progressive process
- It may be limited to a regression to a lower threshold, or it may proceed to terminal remission
- It involves probably multiple factors
- Reduction and eventual stopping of treatment in these cases may take many years
- They are typically identified by a recurrence at a first attempt to taper
- Recurrence at small dose reduction is probably negative prognostic sign

Guidelines for drug therapy of the epilepsies

Carlos Guerreiro (Brazil)

Guias para a Terapia Medicamentosa das Epilepsias

Carlos A. M. Guerreiro, M.D., PH..D
Professor de Neurologia- UNICAMP (Universidade Estadual de Campinas), SP, Brasil

O que é medicina baseada em evidência (MBE)?

- MBE: ".. a integração da melhor evidência de pesquisa com *expertise* clínico e valores do paciente para conseguir a melhor conduta possível"
- MBE substituiu o termo "epidemiologia clínica"
- Também chamado de "prática baseada em evidência"
- MBE é sobre resultados clínicos reais

(D. Sackett et al., Mc Master Univ Ontario, Ca)

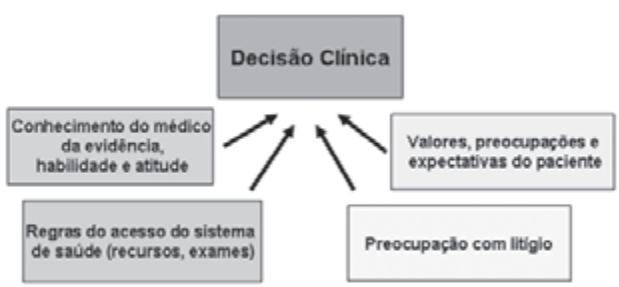
Histórico- Guias Médicos

- 1754 – primeiro ensaio clínico controlado

Histórico

- 200 anos após -1.o ensaio clínico controlado-
- 1950 – Ensaio clínico randomizado
- Ronald Fisher (pai da estatística)
- Austin Bradford Hill (1947)- Metodologia estatística em medicina
- Archie Cochrane (1971)- revisões sitemáticas
- Dave Sackett (anos 90)- introduziu o termo medicina baseada em evidência

Componentes da Decisão Clínica



Interesse Mundial em Guias

- North America
  - Canada (CCOPGI)
- Asia
  - Singapore (NMRC)
- Australia/Oceania
  - Australia (NHMRC)
  - New Zealand (NZGG)

- Europe
  - Denmark (DSAM)
  - England (CHSR, RCP London)
  - Finland (Duodecim)
  - France (ANAES, FNCLCC)
  - Germany (AWMF)
  - Italy (ARHS)
  - Netherlands (CBO)
  - Scotland (SIGN)
  - Sweden (SBU)

Interesse nos EUA em Guias

• ACR	108	• ACCP	42
• CDC	94	• AAN	37
• AAP	79	• AGA	30
• ICSI	55	• IDSA	25
• USPSTS	45	• CCHMC	23

Professional organizations

Government agencies

Non profit organizations

National Guideline Clearinghouse

Guias Recentes AAN sobre Epilepsia

- Avaliação da primeira crise não febril em crianças (2000)
- Tratamento da criança com a primeira crise não febril (2003)
- Ressecções de lobo temporal e neocortical localizadas para epilepsia (2003)
- Eficácia e tolerabilidade das novas DAE I: Tratamento de epilepsia recém diagnosticadas (2004)
- Eficácia e tolerabilidade das DAE II: Tratamento de epilepsia refratária (2004)
- Uso da prolactina sérica no diagnóstico de crise epiléptica (2005)
- Reavaliação: Neuroimagem na emergência no paciente que apresenta crise epiléptica (out/2007)
- Parâmetro Prático: Avaliação de uma aparente primeira crise epiléptica não provocada em adulto (nov/2007)

Importância dos Guias Baseado em Evidência

- **Interesse mundial em guias**
- **Objetivo dos guias: melhorar a qualidade da assistência médica e da eficiência no uso dos recursos em saúde**
- **Orientar aqueles que desenvolvem política, auditoria, perfil, monitoram qualidade e administram revisões de conduta**
- **Guias tornaram-se uma necessidade para os neurologistas**

Terminologia

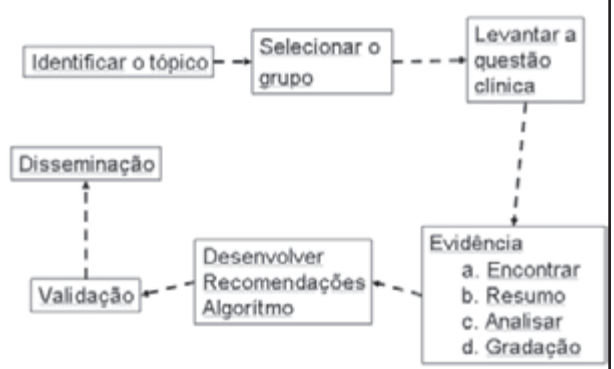
- Guia Prático: afirmações sistematicamente desenvolvidas para ajudar nas decisões dos agentes de saúde e patientes sobre o cuidado médico apropriado para circunstâncias específicas (IOM)
- Parâmetro prático: "estratégias para a conduta do paciente, criado para ajudar o médico na sua decisão...incluindo padrões, guias, e outras estratégias" (AMA)
  - Deve ser abrangente, integrado, evidência integrada à experiência clinica, atual e amplamente divulgado

Quando os guias vão além da evidência...

National Institute for Clinical Excellence (NICE)

- "As novas DAE gabapentina, levetiracetam, oxcarbazepina, tiagabina, lamotrigina, topiramato, e vigabatrina, com suas indicações aprovadas, são recomendadas na conduta de epilepsia em pessoas que não se beneficiaram do tratamento com DAE antigas como CBZ e VPA, ou para os quais CBZ e VPA são inadequados"

Desenvolvimento de Guia
Resumo das atividades



Fatores Críticos na Seleção de DAE

- Eficácia
- Espectro de atividade
- Tolerabilidade
  - EA de curto prazo
  - EA de longo prazo
- Taxa de titulação
- Interações/ farmacocinética
- Segurança
- Esquema de dosagem
- Potencial para teratogenicidade
- Custo

Guias para Epilepsia Recém-diagnosticadas

- Internacional
  - ILAE Treatment Guidelines: Evidence-based Analysis of Anitepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes by Glauser, Ben-Menachem, Bourgeois, Cnaan, Chadwick, Guerreiro, Kälviäinen, Mattson,Perucca and Tomson. Epilepsia 47(7):1-27,2006
- Nacional
  - AAN (Efficacy and tolerability of the new AEDs I and II)
  - NICE (Diagnosis and management of the epilepsies in adults and children in primary and secondary care)
  - SIGN (Diagnosis and management of epilepsy in adults)

Guia Metodologia

- Tópico
  - Monoterapia inicial ótima para pacientes com epilepsia recém-diagnosticadas ou não tratadas
- Grupo
  - 10 membros
    - Epileptologistas
    - Farmacologistas clínicos
    - Estatícista
    - Metodologista
  - 6 países

Guia de Monoterapia Inicial ILAE Questões Clínicas (n=8) :

- Q1-Q3: Pacientes (adultos/idosos/crianças) com crises de início parcial
- Q4-Q5: Pacientes (adultos/crianças) com crises tônico-clônicas de início generalizada
- Q6: Crianças com síndromes e epilepsias idiopáticas localizadas (BECTS)
- Q7-Q8: Crianças com epilepsias idiopáticas generalizadas (CAE, JME)

Guias: Metodologia

- Evidência – Variáveis chaves na avaliação
  - Randomização
  - Avaliação do resultado cego (Mínimo potencial para tendenciosidade)
  - Variável do resultado claramente definida eficácia/efetividade
  - Análise estatística apropriada
  - Uso de comparador adequado
  - Duração mínima de tratamento apropriado
  - Diferença detectável minimamente aceitável

Guias Metodologia

- Comparador adequado
  - Sensibilidade do ensaio
  - Critérios: DAE superior a outra droga, ou uma outra dose da mesma droga, ou um outra modalidade de tratamento ou placebo
- Mínima duração do tratamento apropriado
  - Estabelecido em 48 semanas

Guias
Metodologia-estatística

- Mínima diferença detectável aceitável
  - Estabelecida em 20% pelo guia da ILAE 1998.
  - Estabelecida como diferença relativa para este projeto
    - Supondo que taxa comparativa de pacientes livres de crises seja 50%.
    - DAE com taxa livre de crises ≤ 40% ou ≥ 60% (50% ± 0.2 x 50%) seria clinicamente significante.
  - Proteção contra DAE inefetiva rotulada como efetiva
  - Diferença minimamente detectável calculada para todos os ensaios clínicos randomizados (RTC) baseados no poder de 80%. p estabelecido em ≤ 0,05 e análise de não-inferioridade.

Guias Epilepsia

- Classificação – 4 Classes
  - Classe I: Um RCT cego, satisfazendo todos os critérios das variáveis chaves
  - Classe II: Um RCT cego prospectivo combinando com estudo de cohort numa população representativa que preenche todos os critérios chaves ou RCT numa população representativa que falte um dos critérios variáveis chaves
  - Classe III: todos os outros ensaios controlados numa população representativa, aonde a variável do resultado é independente do tratamento do paciente
  - Classe IV: Evidência de estudos não controlados, série de casos, relato de casos ou opinião de especialista

French JA, Epilepsia 2004, 45(5):401-409 and 410-423

Critérios para Classe I -ILAE

- Ensaio clínico, controlado, randomizado, prospectivo (RCT) ou meta-análise de RCTs, numa população representativa que preencha os seis critérios abaixo:
  1. Variável de resultado primário (Primary outcome variable): eficácia ou efetividade
  2. Duração do tratamento: ≥ 48 semanas (dados livres de crise por >24 semanas para eficácia ou >48 semanas de retenção para efetividade)
  3. Desenho do estudo: duplo cego
  4. Demonstrada superioridade ou, se não demonstrada a superioridade, o tamanho real da amostra foi suficiente para mostrar não inferioridade com diferença relativa menor que 20% na eficácia/efetividade
  5. Saída do estudo: não forçada por um n.o predeterminado de crises
  6. Análise estatística apropriada

Critérios para Classe II -ILAE

- Classe II: RCT ou meta-análises de acordo com os critérios da classe I exceto:
  1. Superioridade não demonstrada e a amostra real do estudo foi suficiente para mostrar não inferioridade na diferença relativa de 21-30% na efetividade/eficácia

  OU

  2. Duração do tratamento: ≥24 semanas mas ≤ 48 semanas

Critérios para Classe III-IV -ILAE

- Classe III: RCT ou meta-análise não preenchendo os critérios para classe I e II
- Classe IV: Evidência de estudos não randomizados, prospectivos, controlados ou não, descrições de casos ou relatos de *experts*

Metodologia do Guia:
Graduação da evidência para cada DAE

- Recomendações – 6 Níveis
  - Nível A: ≥ 1 Classe I RCTs **OU** ≥ 2 Classe II RCTs
  - Nível B: 1 Classe II RCTs **OU** ≥ 3 Classe III RCTs
  - Nível C: 2 Classe III RCTs
  - Nível D: Classe III, ou IV RCTs **OU** opinião de especialista
  - Nível E: Ausência de evidência clínica
  - Nível F: Evidência positiva de falta de eficácia *OU* Risco significante de agravamento das crises

Relação entre o Nível de Evidência e as Conclusões

Evidência (Nível)	Conclusões
• A	• DAE estabelecida eficaz ou efetiva como monoterapia inicial
• B	• DAE provavelmente eficaz ou efetiva como monoterapia inicial
• C	• DAE possivelmente eficaz ou efetiva como monoterapia inicial

Relação entre o Nível de Evidência e as Conclusões

Evidência (Nível)	Conclusões
• D	• DAE potencialmente eficaz ou efetiva como monoterapia inicial
• E	• Nenhum dado disponível para avaliar se a DAE é efetiva como monoterapia inicial
• F	• DAE estabelecida ineficaz ou risco significante de agravamento de crises

Recomendações (baseadas nos dados de eficácia e efetividade somente)

Evidência Nível A-B

DAE deveria ser considerada como monoterapia inicial – Candidato a monoterapia de 1.a linha

Evidência Nível C

DAE pode ser considerada como monoterapia inicial – Candidatos alternativos às monoterapias de 1.a linha

Recomendações (baseadas nos dados de eficácia e efetividade somente)

Evidência Nível D

Dados disponíveis de eficácia/efetividade fracos para apoiar o uso da DAE como monoterapia inicial

Evidência Nível E

Não há dados ou os dados são inadequados para decidir se a DAE deveria ser considerada como monoterapia inicial

Evidência Nível F

DAE não deveria ser usada como monoterapia inicial

GUIA ILAE

Baseado na melhor evidência disponível, qual é a monterapia inicial ótima para pacientes com epilepsia recém-diagnosticada ou não tratada?

Crises Parciais: Adultos Evidência Disponível

- Um total de 33 RCTs e 5 meta-análises foram examinados para monoterapia inicial de adultos com crises de início parcial
- Divisão dos ensaios
  - Classe I (n=2)
  - Classe II (n=1)
  - Classe III (n=30)

Crises Parciais em Adultos
Listagem das RTCs Class I-III Duplo cego

Classe I

Mattson (1985) CBZ, PB, PHT, PRM

Chadwick (99) CBZ, VGB

Classe II

Mattson (92) CBZ, VPA

Classe III (Devido ao baixo poder –DNB- ou saida forçada)

Brodie (95)	CBZ, LTG	Chadwick (98)	GBP
Brodie (02)	GBP, LTG	Sachdeo (00)	TPM
Christe (97)	OXC, VPA	Gilliam (03)	TPM
Bill (97)	OXC, PHT	Privitera (03)	CBZ,TPM,VPA
Dam (89)	CBZ,OXC	Arroyo (05)	TPM
Brodie (02)	CBZ, REM	Steiner (99)	PHT, LTG
Ramsay (83)	CBZ, PHT	Gibberd (82)	PHT, PNT
Mikkelsen (81)	CBZ, CLP		

Crises Parciais: Adultos
Recomendações

Nível A: CBZ, PHT

Nível B: VPA

Nível C: GBP, LTG, OXC, PB, TPM, VGB

Nível D: CZP, PRM

Nível E: Outras

Nível F: Nenhuma

Crises Parciais: Crianças
Evidência Disponível

- Um total de 25 RCTs e 1 meta-análises examinada para monoterapia inicial de crianças com crises de início parcial
- Divisão dos ensaios
  - Classe I (n=1)
  - Classe II (n=0)
  - Classe III (n=17)

Crises Parciais: Crianças
Classe I-III RCTs

Classe I

Guerreiro (97) OXC, PHT

Classe II 0

Classe III

TPM (n=2), CBZ/CZP (n=1), CBZ/ CLB (n=1), TPM/VPA/CBZ (n=1)

Crises Parciais: Crianças
Recomendações

Nível A: OXC

Nível B: Nenhuma

Nível C: CBZ, PB, PHT, TPM, VPA

Nível D: LTG,VGB

Nível E: Outras

Nível F: Nenhuma

Crises Parciais: Idoso
Evidência Disponível

- Um total de 30 RCTS participantes idosos para monoterapia inicial para crises de início parcial
- Divisão dos ensaios
  - Classe I (n=1)
  - Classe II (n=1)
  - Classe III (n=2)

Crises Parciais: Idoso
Classe I-III RCTs

Classe I
Rowan (05) CBZ, GBP, LTG

Classe II
Brodie (99) CBZ,LTG

Classe III
Privitera (03) CBZ, TPM, VPA

Nieto-Barrera (01) CBZ, LTG (Estudo aberto)

Crises Parciais: Idoso
Recomendações

Nível A: GBP, LTG

Nível B: Nenhuma

Nível C: CBZ

Nível D: TPM, VPA

Nível E: Outras

Nível F: Nenhuma

Crises Tônico-clônicas Generalizadas
Evidências Disponíveis

- Um total de 23 RCTs e 5 meta-análises examinadas para monoterapia inicial de adultos com crises tônico-clônicas generalizadas
- Divisão dos ensaios
  - Classe I (n=0)
  - Classe II (n=0)
  - Classe III (n=10):CBZ, GBP, LTG, OXC, PB, PHT, TPM, VPA

Crises Tônico-clônicas Generalizadas: Adultos
Recomendações

Nível A: Nenhuma
Nível B: Nenhuma
Nível C: CBZ*,LTG,OXC*,
PB, PHT*,TPM,VPA
Nível D: GBP,VGB
Nível E: Outras
Nível F: Nenhuma

*=pode agravar crises tônico-clônicas e mais comumente outros tipos de crises generalizadas; devem ser usadas com cautela

Crises Tônico-clônicas Generalizadas: Crianças
Evidência Disponível

- Um total de 20 RCTs examinadas como monoterapia inicial de crianças com crises tônico-clônicas de início generalizadas
- Divisão dos ensaios
  - Classe I (n=0)
  - Classe II (n=0)
  - Classe III (n=14): CBZ, CLB, OXC, PB, PHT, TPM, VPA

Crises Tônico-clônicas Generalizadas: Crianças
Recomendações

Nível A: Nenhuma
Nível B: Nenhuma
Nível C: CBZ*,PB, PHT*,TPM,VPA
Nível D: OXC*
Nível E: Outras
Nível F: Nenhuma

* =pode agravar crises tônico-clônicas e mais comumente outros tipos de crises generalizadas, devem ser usadas com cautela

Epilepsia Ausência da Infância: Evidência Disponível

- Um total de 6 RCTs examinadas para monoterapia inicial de crianças com epilepsia ausência da infância
- Divisão dos ensaios
  - Classe I (n=0)
  - Classe II (n=0)
  - Classe III (n=6) -3 Duplo Cego

    ETX, LTG, VPA

Epilepsia Ausência Infância: Recomendações

Nível A: Nenhuma
Nível B: Nenhuma
Nível C: ESM, LTG, VPA
Nível D: Nenhuma
Nível E: Outras
Nível F: CBZ, GBP, OXC, PB, PHT,TGB,VGB

Monoterapia Inicial para Síndromes Epilépticas Idiopáticas Localizadas: Epilepsia Benigna com Pontas Centro-temporais (BECTS)

BECTS: Evidência Disponíveis

- Um total de 3 RCTs examinadas para monoterapia inicial de crianças com BECTS, 2 –Duplo cego
- Divisão dos ensaios
  - Classe I (n=0)
  - Classe II (n=0)
  - Classe III (n=2)

BECTS: Recomendações

Nível A: Nenhuma

Nível B: Nenhuma

Nível C: CBZ, VPA

Nível D: GBP,STM

Nível E: Outras

Nível F: Nenhuma

Monoterapia Inicial para Síndromes Epilépticas Generalizadas Idiopáticas: Epilepsia Mioclônica Juvenil

Epilepsia Mioclônica Juvenil (EMJ): Evidência Disponível

- Um total de 0 RCTs examinadas para monoterapia inicial de crianças com EMJ
- Divisão dos ensaios
  - Classe I (n=0)
  - Classe II (n=0)
  - Classe IIII (n=0)

Epilepsia Mioclônica Juvenil : Recomendações

Nível A: Nenhuma
Nível B: Nenhuma
Nível C: Nenhuma
Nível D: CZP, LTG*, LEV, TPM, VPA, ZNS
Nível E: Outras
Nível F: CBZ*, GBP, OXC*, PHT*, TGB, VGB

*pode agravar crises mioclônicas, devem ser usadas com cautela

Epilepsia Mioclônica Juvenil

- Drogas a ser evitadas
- Evidência clínica sugere que PHT, CBZ, OXC, VGB, TGB, GBP (PRE?) podem agravar crises de ausência e mioclônicas
- LTG pode agravar epilepsias mioclônicas severas na infância e na EMJ
  Nível de Evidência III-IV,
  Recomendação C

Resumo das Evidências e Recomendações Crises de início Parcial

Tipo de crises ou síndrome epiléptica	Classe I	Classe II	Classe III	Nível de Evidência de Eficácia e Efetividade (em ordem alfabética)
CIP: Adultos	2	1	30	Nível A: CBZ, PHT, (LEV) Nível B: VPA Nível C: GBP, LTG, OXC, PB, TPM, VGB
CIP: Crianças	1	0	17	Nível A: OXC Nível B: None Nível C: CBZ, PB, PHT, TPM, VPA
CIP: Idoso	1	1	2	Nível A: GBP, LTG Nível B: None Nível C: CBZ

Resumo das Evidências e Recomendações Crises de início generalizadas

Tipo de crises ou síndrome epiléptica	Classe I	Classe II	Classe III	Nível de Evidência de Eficácia e Efetividade (em ordem alfabética)
CTCG: Adultos	0	0	23	Nível A: Nenhuma Nível B: Nenhuma Nível C: CBZ, LTG, OXC, PB, PHT, TPM, VPA
CTCG: Crianças	0	0	14	Nível A: Nenhuma Nível B: Nenhuma Nível C: CBZ, PB, PHT, TPM, VPA
Crises de Ausência	0	0	6	Nível A: Nenhuma Nível B: Nenhuma Nível C: ESM, LTG, VPA

Resumo das Evidências e Recomendações Síndromes Epilépticas

Tipo de crises ou síndrome epiléptica	Classe I	Classe II	Classe III	Nível de Evidência de Eficácia e Efetividade (em ordem alfabética)
BECTS	0	0	2	Nível A: Nenhuma Nível B: Nenhuma Nível C: CBZ, VPA
EMJ	0	0	0	Nível A: Nenhuma Nível B: Nenhuma Nível C: Nenhuma

Variáves na Seleção Inicial de DAE

Variáveis específicas das DAE	Variáveis ligadas ao paciente	Variáveis reacionadas ao país
Eficácia/Efetividade específica da crise/síndrome epiléptica	"Background" genético	Disponibilidade de DAE
Efeitos adversos (efeitos dose-dependentes, reações idiosincráticas, toxicidade crônica, teratogenicidade e carcinogenicidade)	Idade	Custo de DAE
Farmacocinética	Co-medicações	
Potencial interação	Co-morbidades	
Formulações	Cobertura de seguro	
	Capacidade de engolir pílulas/tabletes	

Participants in the ILAE Subcommission on Antiepileptic Drug Guidelines

- Elinor Ben-Menachem, Chairman
- Tracy Glauser, USA
- Blaise Bourgeois, USA
- David Chadwick, UK
- Avital Cnaan, USA
- Carlos Guerreiro, Brazil
- Reetta Kalviainen, Finland
- Richard Mattson, USA
- Emilio Perruca, Italy
- Torbjörn Tomson, Sweden

Epilepsia Refratária: Resumo do Guia baseado em Evidência da AAN (recomendação nível A ou B)

DAE	Parcial, adjunctiva, adulto	Parcial Monoterapia	Generalizada Primária	Generalizada Sintomática	Parcial, Pediátrica
Gabapentina	**Sim**	**Não**	**Não**	**Não**	**Sim**
Lamotrigina	**Sim**	**Sim**	**Sim*(ausência)**	**Sim**	**Sim**
Levetiracetam	**Sim**	**Não**	**Não**	**Não**	**Não**

* Não aprovado pelo FDA para esta indicação

Neurology Volume 62, #8; 2004

Epilepsia Refratária: Resumo do Guia baseado em Evidência da AAN (recomendação nível A ou B)

DAE	Focal, adjunctiva, Adulto	Focal, Monoterapia	Generalizada Primária	Generalizada Sintomática	Focal, Criança
Oxcarbazepina	**Sim**	**Sim**	**Não**	**Não**	**Sim**
Tiagabina	**Sim**	**Não**	**Não**	**Não**	**Não**
Topiramato	**Sim**	**Sim***	**Sim**	**Sim**	**Sim**
Zonisamida	**Sim**	**Não**	**Não**	**Não**	**Não**

* Não aprovado pelo FDA para esta indicação

Neurology Volume 62, #8; 2004

Resumo do Guia Baseado em Evidência da AAN (Recomendação Nível A ou B)

DAE	Monoterapia para Epilepsia Focal/Mista Recém-diagnosticada	Ausência Recém-diagnosticada
Gabapentina	Sim*	Não
Lamotrigina	Sim*	Sim*
Topiramato	Sim*	Não
Tiagabina	Não	Não

* Não aprovada pelo FDA para esta indicação

Neurology Volume 62, #8; 2004

Resumo do Guia Baseado em Evidência da AAN (Recomendação Nível A ou B)

DAE	Monoterapia para Epilepsia Focal/Mista Recém-diagnosticada	Ausência Recém-diagnosticada
Oxcarbazepina	Sim	Não
Levetiracetam	Não	Não
Zonisamida	Não	Não

Neurology Volume 62, #8; 2004

Comparação

Variável	ILAE	AAN / AES
Tópico	Recém diagnosticada somente Adultos, idosos, crianças	New onset, refractory Adults, children
Equipe	N=10, 6 países	N=24, 1 país
DAE examinadas	23 DAE	7 novas DAE US
Anos abrangidos	1940-presente	1987-2003
Sistema de "score"	Sistema ILAE	Sistema AAN
Reanálise dos dados	Sim, usado para graduar	Não
Variáveis chaves	Graduação, cego, poder	Grupo controle
Dose efetiva	Não discutida	Discutida
Custos	Não considerados	Não considerados

Guias baseados em evidência

CONCLUSÕES

- Limitados pela disponibilidade de ensaios clínicos válidos
- Em muitos aspectos ensaios clínicos não são possíveis ou não foram realizados

-BASE DA EVIDÊNCIA NÃO É TÃO ROBUSTA COMO GOSTARÍAMOS

- Ausência de evidência não é equivalente à evidência de ausência
- Quando não há dados disponíveis, julgamento clínico (experiência) e análise risco-benefício terão papel preponderantes na decisão clínica

Guias baseados em evidência

CONCLUSÕES

- Difícil comparar guias sobre o mesmo tópico
  - Diferentes questões PECOT levantadas
  - Variabilidade na gradação e classificação das escalas de evidências
  - Variabilidade nos critérios de recomendação

The AEDs of the future
Meir Bialer (Israel)

The AEDs of the Future

Prof. Meir Bialer
Hebrew University
Jerusalem, Israel

Latin-American Summer School on Epilepsy (LASSE II)
February 7-16, 2008, Sao Paulo, Brazil

1

AEDs of The Future: What Can We Expect?

Where is the AED market going in 5-10 years?

- "After the prophet Malachi, prophecy has been given to the children, deaf and fools"
- The expectation for AEDs of the future: They must be better than existing drugs in efficacy, safety, broad utilization and disease modification

2

Lancet Neurol 2007; 6: 793–804

Development of new antiepileptic drugs: challenges, incentives, and recent advances

Emilio Perucca, Jacqueline French, Meir Bialer

Despite the introduction of many second-generation antiepileptic drugs (AEDs) in the past 15 years, a third of patients with epilepsy remain refractory to available treatments, and newer and more effective therapies are needed. Although our understanding of the mechanisms of drug resistance is fragmented, novel AED targets have been identified, and models of refractory epilepsy have been developed that can help to select candidate compounds for development. There are more than 20 compounds with potential antiepileptic activity in various stages of clinical development, and for many of these promising clinical trial results are already available. Several incentives justify further investment into the discovery of newer and more effective AEDs. Moreover, developments in clinical trial methodology enable easier completion of proof-of-concept studies, earlier definition of the therapeutic potential of candidate compounds, and more efficient completion of trials for various epilepsy indications.

3

AEDs In Development

Presented at: EILAT VIII (September 10-14, 2006)
Will be presented at: EILAT IX (June 15-19, 2008)

Brivaracetam (ucb 44212)	phase II
Carisbamate (RWJ-333369)	phase III
Eslicarbazepine acetate (BIA 2-093)	phase III
Fluorofelbamate	phase I
Ganaxolone	phase I
Lacosamide	phase III
NS-1209	phase II (injectable)
Retigabine	phase III
Rufinamide	approved 01/2007
Seletracetam (ucb 34717)	phase I
Valnoctamide	phase II (bipolar)
Valrocemide	phase II
XP-13512	phase II (restless leg)
YKP3058	phase I

Bialer et al, Epilepsy Res, 2004 & 2007; Bialer, Expert Opin Investig Drug, 2006

4

Do We Need More AEDs?

- Epilepsy is a common, ancient and chronic disease
- About 30% of the epileptic patients are therapy-resistant despite the availability of ~ 20 AEDs
- All current AEDs have side effects
- The "near future" goal is to make 90% of the patients seizure free

5

An Industrial Concern

"If there is no flour there is no Torah"

- Are there too many AEDs?
- How to improve the chances of a new AED to be efficacious and safe in patients?
- Can a new AED generate revenue to support its development?
- How can we develop a magic bullet?

6

Answers to the Industrial Concerns

- PK-based design of new AEDs that are second-generation to existing AEDs
- There is "room" for both. CBZ & OXC global 2005 sales are $560 & $700 million, respectively
- Development of reliable animal models for bipolar disorder and migraine
- Industry-academia partnership (e.g. fosphenytoin, tiagabine, lacosamide, valrocemide). Otherwise, even the most brilliant academic initiative will remain in the test-tube

7

Developing New AEDs: The Hurdles

- Development of New Drugs is costly & risky
- Only 10 % of the drug candidates that reached that IND stage will be approved
- The duration between IND and NDA approval is >5 years and the cost >$100 millions
- Incomplete knowledge of the mechanisms of AED resistance, prevents mechanism-driven drug development

8

Animal Model-Based Design of New AEDs: Pros & Cons

Pros

- Screening in animal models is the engine that has driven AED discovery since phenytoin (1938)
- Anticonvulsant animal (mice, rats) models are efficient & effective in identifying new AEDs and provide insight into their PK-PD relations (D & Css)
- The MES and scMet tests remain the "gold standard" in early stages of testing (NIH-NINDS-ASP). Compounds active in the MES and scMet tests have been generally efficacious in clinical trials
- Animal models with a similarly high predictive value do not exist in other CNS disorder ("The compare-to-what principle")

Rogawski, Epilepsy Res, 2006; Schmidt & Rogawski, Epilepsy Res, 2002; Bialer et al, Epilepsy Behav, 2004

Animal Model-Based Design of New AEDs: Pros & Cons

Cons

- Conventional models (e.g. MES & scMet) are likely to identify more of the same ("me to") new AEDs
- New drugs that are "me to" AEDs are unlikely to have an effect on refractory epilepsies
- Animal models do not predict toxicity or side effects in patients or human tolerability
- No reliable animal models for epileptogenesis

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Rogawski, Epilepsy Res, 2006; Schmidt & Rogawski, Epilepsy Res, 2002

Future AEDs: The Incentive

- AEDs treat the symptoms (seizures), and therefore, have to be taken for many years
- NIH-ASP provides free screening of drug candidates
- Orphan Drug Act gives market exclusivity & benefits
- New AEDs have found utility in other non-epileptic CNS disorders:
  - Migraine
  - Neuropathic pain
  - Bipolar disorder
  - Stroke, Alzheimer's & Parkinson's (a VPA analogue ONO-2506)
  - Cancer (VPA via HDAC inhibition -Savicol®)

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Future AEDs:The Economic Incentive ("Flour")

- US AEDs market value in all indications is >3 times higher than AEDs market value in epilepsy alone
- AEDs in epilepsy are less "vulnerable" to a switch to generics

A PK analogy to AEDs' sales

- The time to peak sales (tmax) for a new AED is reached slowly
- The peak sale value (Cmax) is lower than in "flashier" drug classes
- However, the sales' half-life (t1/2) is long and the overall exposure (AUC) is large in epilepsy alone (e.g. PHT, CBZ, VPA)

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AEDs In Development

Presented at: EILAT VIII (September 10-14, 2006)
Will be presented at: EILAT IX (June 15-19, 2008)

Brivaracetam (ucb 44212)	phase II
Carisbamate (RWJ-333369)	phase III
Eslicarbazepine acetate (BIA 2-093)	phase III
Fluorofelbamate	phase I
Ganaxolone	phase I
Lacosamide	phase III
NS-1209	phase II (injectable)
Retigabine	phase III
Rufinamide	approved 01/2007
Seletracetam (ucb 34717)	phase I
Valnoctamide	phase II (bipolar)
Valrocemide	phase II
XP-13512	phase II (restless leg)
YKP3058	phase I

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Bialer et al, Epilepsy Res, 2004 & 2007; Bialer, Expert Opin Investig Drug, 2006

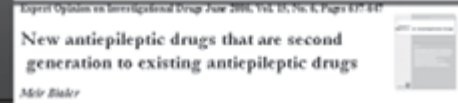
New AEDs: Second Generation

Progress report on new antiepileptic drugs: A summary of the Eighth Eilat Conference (EILAT VIII)

Meir Bialer[a,*], Svein I. Johannessen[b], Harvey J. Kupferberg[c], René H. Levy[d], Emilio Perucca[e], Torbjörn Tomson[f]

Valproic Acid: Second Generation

Meir Bialer & Boris Yagen



New antiepileptic drugs that are second generation to existing antiepileptic drugs

Meir Bialer

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EILAT Conferences on New AEDs

Epilepsy Research

Conference Review

Progress report on new antiepileptic drugs: a summary of the Seventh Eilat Conference (EILAT VII)

Meir Bialer[a,*], Svein I. Johannessen[b], Harvey J. Kupferberg[c], René H. Levy[d], Emilio Perucca[e], Torbjörn Tomson[f]

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journal homepage: www.elsevier.com/locate/epilepsyres

Progress report on new antiepileptic drugs: A summary of the Eighth Eilat Conference (EILAT VIII)

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EILAT IX will take place on June 15-19, 2008

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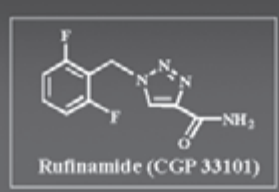
NINTH EILAT CONFERENCE ON NEW ANTIEPILEPTIC DRUGS (EILAT IX)

Sitges, Spain, June 15-19, 2008

www.eilat-aeds.com

Rufinamide

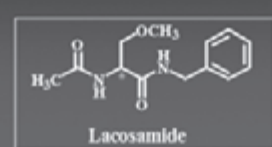


Rufinamide (CGP 33101)

- Linear PK (40-1600 mg/day); nonlinear >1600 mg/day
- V=50-60L; $t_{1/2}$=6-10h
- Major metabolite: the corresponding acid (fm=85%)
- F=60% increases by 40% with food
- Approved by EMEA for LG on 1/2007

Rosenfeld & Karolchyk, in EILAT V Summary, Epilepsy Res, 2001; Jain,EXOIT, 2000; Arzimanoglou, in EILAT VIII Summary, Epilepsy Res, 2007

Lacosamide (LCS)



Lacosamide

- Linear PK (100-800 mg/day); fe=40%; $t_{1/2}$=13h
- Complete oral absorption
- Major metabolite: O-desmethyl-LCS (inactive)
- Second Phase III epilepsy trial showed that add-on LCS (400 & 600 mg/day) significantly reduced seizure frequency in refractory patients

Doty et al , in EILAT V III Summary, Epilepsy Res, 2004; Doty & Whitesides, in EILAT VIII Summary, Epilepsy Res, 2007

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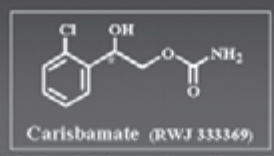
Carisbamate (RWJ-333369)

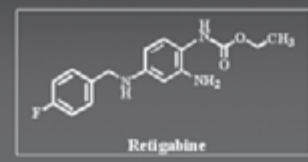


Carisbamate (RWJ 333369)

- Phase III clinical trials began in epilepsy in 9/2006
- Linear PK (doses 100-1500 mg)
- CL/F=2.9-3.7 L/h; V/F=52-66 L; t1/2=11.5-13.9 h
- CBZ decreased RWJ-333369 AUC by 35% due to enzyme induction
- Glucuronidation is a major metabolic pathway
- No PK drug interactions with VPA and LTG

Chien et al, Epilepsia, 2006; Yao et al, Epilepsia, 2006; Novak et al, in EILAT VIII Summary, Epilepsy Res, 2007

Retigabine



Retigabine

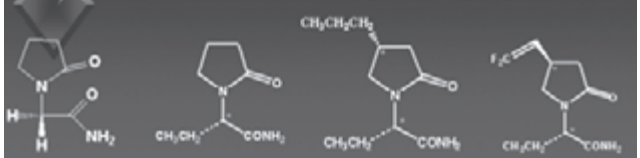
It activates K^+ channels in cortical neurons

- $t_{1/2}$ = 9h
- Linear PK (50-600 mg)
- Metabolism : N-glucuronidation & acetylation
- No interaction with lamotrigine
- Successful Phase III clinical trials

Porter & Nohria, in: EILAT VIII Summary, Epilepsy Res, 2007; French et al, in EILAT VII Summary, Epilepsy Res, 2004

20

LEV & its 2nd Generation AEDs



Piracetam | Levetiracetam (LEV) | Brivaracetam (ucb 34714) | Seletracetam (ucb 44212)

	ED_{50} (mg/kg)	ED_{50} (mg/kg)
Kindled rat	7.3	1.2
Frings mice	30	2.4

- Levetiracetam (LEV) is a second generation of piracetam, ucb 34714 & 44212 are second generation of LEV
- ucb 34717 has been granted orphan drug status for PME

Matagne et al, in: EILAT VII, 2004; Bialer, Expert Opin Investig Drug, 2006

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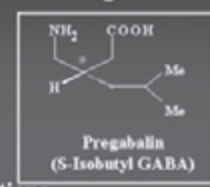
Pregabalin (PGB) vs Gabapentin



Pregabalin (S-Isobutyl GABA)

- In the future PGB will have to compete with:
  - Generic GBP, CR GBP formulations
  - XP13512 (Xenoport & GSK)
  - A transported GBP prodrug designed to utilize endogenous GI (food) transporters & thus resulting in superior PK and therapeutic utility

22

An Incentive for a Second Generation Carbamazepine (CBZ)

- CBZ global (2005) sales are $700 million
- A CBZ analogue that does not produce:
  - skin rash
  - diplopia
  - hyponatremia

can capture the majority of CBZ market share

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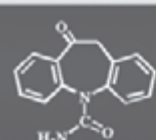
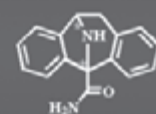
Second Generation Carbamazepine (CBZ)

PK-based design	PD-based design
	
Oxcarbazepine	ADCI
• Lack of induction • Minimal oxidative metabolism	• A combination of CBZ & MK-801

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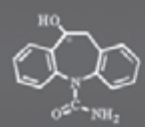
Second OXC (& Third CBZ) Generation AEDs

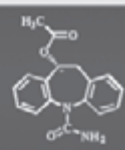
PK-based design



Licarbazepine (MHD)

OXC is a prodrug to MHD
OXC ⟶ MHD is stereoselective

PK/PD-based design

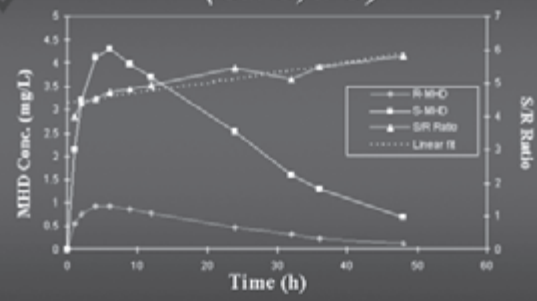


Eslicarbazepine acetate (BIA 2-093)

t1/2 20 - 24 h
Only 5% chiral inversion
F' of S-MHD is 16% greater than that of OXC

Sources: da Silva in: EILAT VII, 2004; Elger in EILAT VIII, 2007; Benes et al, 1999

S- and R-MHD - Humans (OXC, PO)



Volosov et al, Clin Pharmacol Ther, 1999

26

An Incentive For a Second Generation Valproic Acid (VPA)

- VPA is a simple molecule with US sales >$1.5 billion
- A CNS-active VPA analogue that:
  - does not produce weight gain
  - is non-teratogenic
  - is non-hepatotoxic

  can capture the majority of VPA market share
- The ultimate goal is to design a new non-teratogenic, broad-spectrum CNS-active VPA derivative with greater potency, lower toxicity and optimal PK profile as a beneficial successor of VPA

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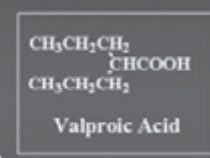
Valproic Acid (VPA)

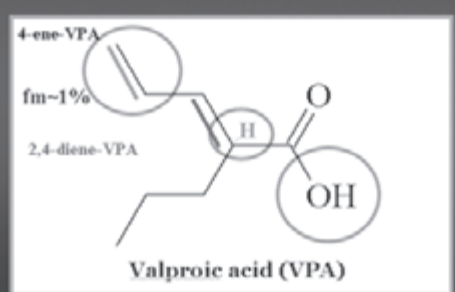
- Broad spectrum anticonvulsant
- Useful also in:
  - Migraine prophylaxis
  - Bipolar disorders
  - Neuropathic pain
  - Cancer (clinical trials)
- Least potent AED (ED_{50})
- Poor brain penetration
- Serious adverse events:
  - Teratogenicity
  - Hepatotoxicity



Valproic Acid

28

Structure-Activity Relationships of VPA Teratogenicity & Hepatotoxicity



Valproic acid (VPA)

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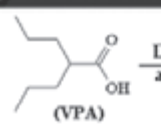
Design of 2nd Generation VPA

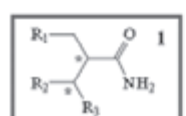


(VPA)

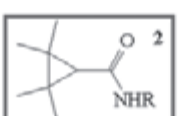
Design of "stable" amide derivatives

No acidic function
Minimal conversion to the acid

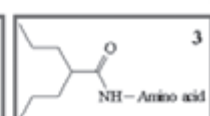
Three Strategies for design of a better and safer VPA



1 Aliphatic amide analogs

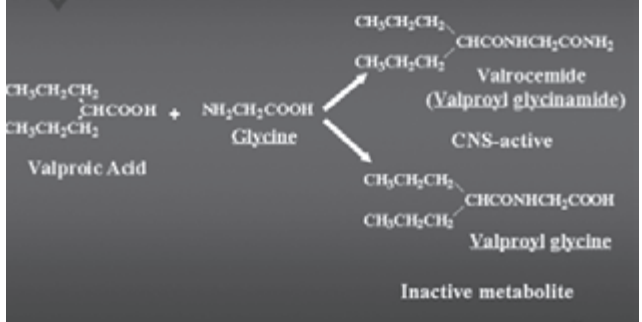


2 Cyclic derivatives



3 Amino acid conjugates

Valrocemide (VLR)



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Anticonvulsant Activity ED_{50} (mg/kg) VLR vs. VPA

Test	MES	6Hz (32mA)	6Hz (44mA)	scMet	scBic	scPic	Erings
VLR	151	237	317	132	248	276	52
VPA	272	126	310	149	360	386	155

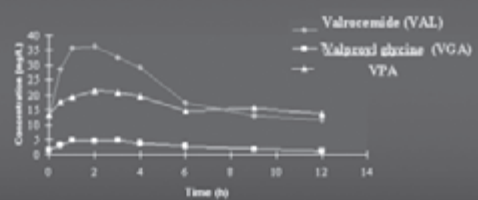
In kindled rats:

- 300mg/kg ip significantly reduced seizure score & after discharge duration
- 400 mg/kg increased after discharge threshold

Isoherranen et al, Epilepsia, 2001

32

VLR Phase II Data in Epileptic Patients(2g bid)



Bialer et al, EILAT VII & VIII Summaries, Epilepsy Res, 2004 & 2007

33

Valrocemide (VLR)

- VLR has a broad anticonvulsant spectrum
- Only 5% was biotransformed to VPA
- VGA is a major inactive metabolite (a possible inducible formation)
- Based on animal data - the active entity is the parent compound
- Phase I clinical studies show VLR to have favorable safety &PK profiles (linear PK - 0.25-4g)
- Shire licensed VLR from Yissum on July, 2006

Bialer et al, EILAT VIII Summary, Epilepsy Res, 2007

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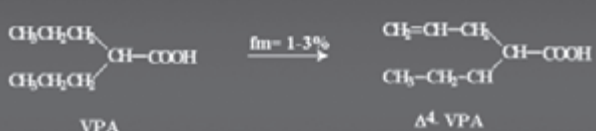
4-ene Valproic Acid- Δ^4-VPA



The above metabolic pathway serves as a rationale to design CNS-active VPA derivatives that cannot form putative hepatotoxic metabolite(s) with a terminal double bond

35

CNS-Active Cyclopropylamide Analogs of VPA

MTMCD & TMC-Urea are the lead compounds

NIH-NINDS Epilepsy Branch issues a Red Book on TMC-Urea on 21/11/2006

Sobol et al, J Med Chem, 2004; Bialer & Yagen, Neurotherapeutics, 2007

MTMCD & TMC-Urea Anticonvulsant Activity (Rats)

	VPA	MTMCD	TMC-Urea
MES (ED_{50};mg/kg)	485 (PI=1.6)	82 (PI=2.0)	29 (PI=19) 24 (ip,PI=6)
scMet (ED_{50};mg/kg)	646 (PI=1.2)	45 (PI=3.6)	92 (PI=6) 56 (ip,PI=2.6)
Kindling (ED_{50};mg/kg)		39	59 (ip,PI=2.5)
Tox (TD_{50};mg/kg)	784	163	538 ip,146

Sobol et al, *J Med Chem*, 2004; Sobol et al, Neuropharmacology, 2006

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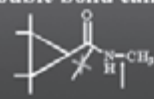
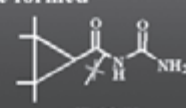
MTMCD & TMC-Urea

- Achiral molecules produced by a two step synthesis
- More potent than VPA (2-20 times)
- Non-teratogenic
- No formation of the corresponding acid – TMCA (non-teratogenic, inactive)
- An hepatotoxic metabolite with a terminal double bond cannot be formed



MTMCD



TMC-Urea

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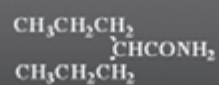
Valpromide-VPD (Depamide®)

- For >30 years in Europe - Epilepsy & Bipolar Disorder
- More potent than VPA (2-30 times)
- Non-teratogenic (mice)
- A prodrug of VPA (humans)



Valpromide (VPD)

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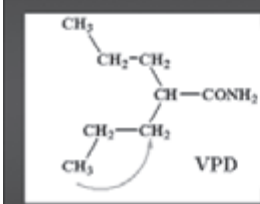
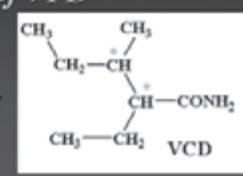
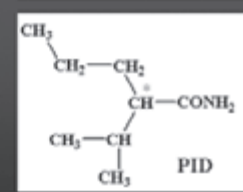
VCD & PID: "Stable" Non-Teratogenic Isomers of VPD



VPD



VCD



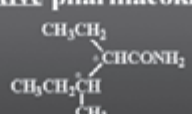
PID

PID enantiomers –Jazz Pharmaceuticals, Palo Alto, CA, USA
VCD stereoisomers- Neurocrine Biosciences, San Diego, CA, USA

40

Valnoctamide-VCD (Nirvanil®)

- OTC for >30 years (Europe) -Tranquilizer
- Minimal conversion to VCA in humans
- More potent AED than VPA (2-30 times) & active in bipolar patients
- Racemic mixture of 4 stereoisomers
- Stereoselective pharmacokinetics



Valnoctamide (VCD)

41

VCD (Racemate) in Mania

A phase II Clinical Study

This study is currently recruiting 80 patients

http://www.clinicaltrials.gov/ct/show/NCT00140179

Sponsors & Collaborators:

a) Beer Sheva Mental Health Center

b) Stanley Medical Research Foundation

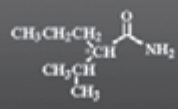
VCD-Dose 400 mg tid for 5 weeks

Applebaum et al, Bipolar Disorder, 2005 (abstract)

42

Propylisopropyl Acetamide (PID)

- More potent AED than VPA (3-30 times)
- Not commercially available
- No biotransformation to its corresponding acid PIA in mice, rats & dogs
- One chiral center (two enantiomers)



Propylisopropyl acetamide (PID)

43

(R,S)-PID Anticonvulsant Activity (Rats, po)

	VPA	VPD	VCD	PID
MES, ED_{50}	490	32	29	22
sc Met, ED_{50}	180	59	-	>26
Neurotoxicity, TD_{50}	280	87	58	>53
PI, MES	0.6	2.7	2	>2.4
PI, sc Met	1.6	1.5	-	2

ED_{50}, TD_{50} in (mg/kg)
PI (protective index)= TD_{50}/ED_{50}

Bialer et al, Pharm World Sci, 1994

44

Anticonvulsant Profile (ED_{50} mg/kg) of Aliphatic Amide Analogs of VPA (Mice)

Drug	MES	scMet	Rat-MES	6Hz (22mA)	6Hz (32mA)	6Hz (44mA)	Tox
VPA	263	220	590	42	126	310	398
VPD	56	55	32	20	61	71	81
VCD (rac)	58	32	29		37	67	77
PID (rac)	122	77	31	23	44	73	112
(R)-PID	110	67	16*	11*	46*	57*	111
(S)-PID	145	80	25	20	73	81	97

Levetiracetam-ED_{50} at the 6Hz (44 mA) model is 1089 mg/kg
(Barton et al., 2001)

R-PID is better than S-PID in the rat-MES & 6Hz models

Isoherranen et al, Brit J Pharmacol & Pharm Res, 2003

45

Potency in Neuropathic Pain (SNL) Model

Compound	ED_{50} (95%CI, mg/Kg)
VPA	269 (227-310)
VPD	61 (44-77)
VCD	52 (20-84)
(R)-PID	46 (14-57)
(S)-PID	48 (14-60)
(R,S)-PID	42 (14-52)
MTMCD	41 (13-69)
TMCD	85 (38-206)
Gabapentin	32 (18-50)

Winkler et al, Brit J Pharmacol, 2005 & Neuropharmacology, 2005

46

Propylisopropyl Acetamide (PID)

- (R)-PID and (S)-PID have a wide anticonvulsant activity in various animal models and are 3-30 times more potent than VPA
- In the SNL model for neuropathic pain (R)-PID, (S)-PID & (R,S)-PID were more potent than VPA
- Based on preclinical studies (kindling), PID has a potential use in bipolar disorder

Bialer et al, EILAT VIII Summary, Epilepsy Res, 2007

47

Activity in Bipolar Models

- Reduction of human brain inositol phosphate synthase activity (%)

  VPA (1.0 mmol/L) -100%

  Valpromide -VPD (1.4 mmol/L) - 34%

  MTMCD (1.3 mmol/L)- 93%
- MTMCD (1 mM) & the corresponding acids of VCD & PID showed similar activity to VPA (3 mM) and LiCl (2 mM) on median growth cone area from rat DRG

Shaltiel et al, Biol Psychiatr, 2004; Shimshoni et al, Mol Pharmacol, 2007

48

VPA Amide Derivatives Conclusions

- VPA amide derivatives have a broad spectrum of anticonvulsant, antiallodynic activity & are more potent than VPA
- VPA amide derivatives have a potential in epilepsy, neuropathic pain & bipolar disorder
- The amide derivatives of VPA are not teratogenic (mice) and may be non-hepatotoxic
- Valrocemide, PID enantiomers, VCD stereoisomers, MTMCD and TMC-Urea have a promising potential to become second generation to VPA

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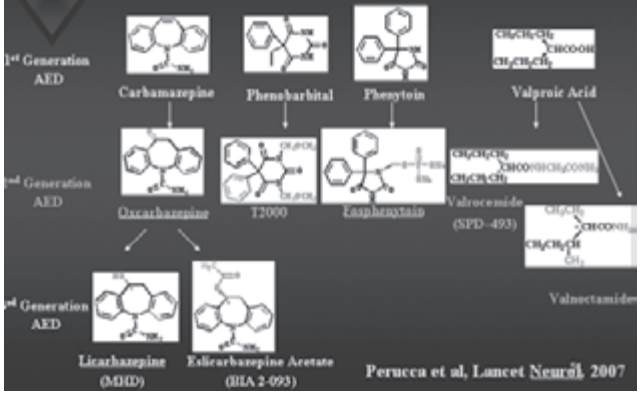
PK-Based Design of VPA Derivatives

- PK-based design of VPA derivatives circumvents: VPA teratogenic structural requirements and formation of hepatotoxic metabolite(s)
- PK-based design can increase potency and minimize toxicity of existing AEDs
- PK-based drug design should be implemented at early stages of development for future new AEDs, especially second generation of existing CNS drugs

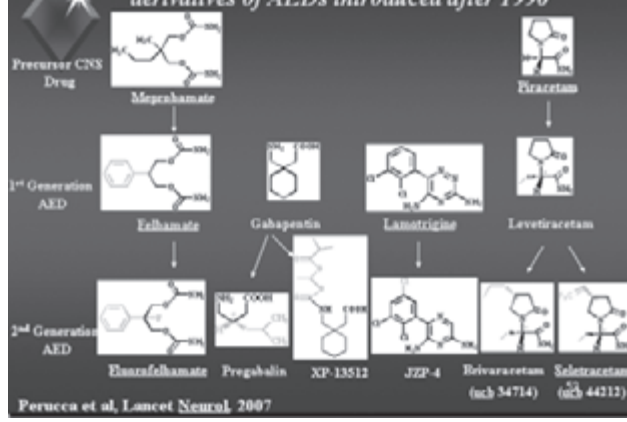
50

Compounds which are second or third generation derivatives of AEDs introduced before 1970



Perucca et al, Lancet Neurol, 2007

Compounds which are second generation derivatives of AEDs introduced after 1990



Perucca et al, Lancet Neurol, 2007

The AEDs of the Future: Academia Industry Partnership:

- Academia's answer to high throughput screening is: academician's expertise in one discipline
- Be more attuned to industry needs and modes of working
- Without industry partnership even the most brilliant academic initiative will remain in a preclinical stage or in the test-tube

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The AEDs of the Future: What Can We Expect?

"Send out your bread upon the water, so after many days you will get it back"

Ecclesiastes, Chapter 11, Verse 1

The completion of doing starts with the conception of thought

54

Alternative therapy in childhood epilepsies

Jaderson Costa da Costa (Brazil)

Programa – 14.02.2008

Morning Session – 9:00 – 13:00

- The normal and the pathologic hippocampal formation – Alexandre Valotta da Silva
- Neuroimaging in epilepsies – Fernando cendes (Brazil)
- Neuropsychological evaluation of the epilepsies – Cândida Pires de Carmargo (Brazil)

Afternoon Session – 14:30-18:30

- Neurocisticercosis and epilepsy – Marco Tulio Medina (Honduras)
- Constructing guidelines for the study of the epilepsies – Arturo Carpio (Equador)
- Discussão de casos clínicos – genética das epilepsias – Iscia Lopes Cendes
- Síndromes epilépticas geneticamente determinadas: Aspectos clínicos e moleculares – Iscia Lopes Cendes
- Genetic of the epilepsies – Iscia Cendes
- Epilepsy genetics: Genotyping can help clinical practice – A. Delgado-Escueta

The normal and the pathologic hippocampal formation

Alexandre Valotta da Silva

O hipocampo normal e patológico

The normal and pathological hippocampus

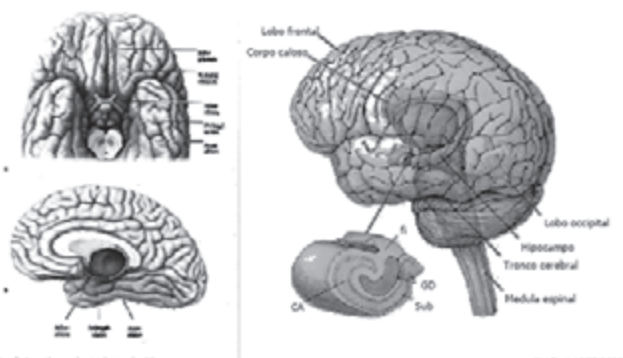
Prof. Dr. Alexandre Valotta da Silva
Departamento de Biociências
UNIFESP-EPM

O hipocampo normal

The normal hippocampus

Formação hipocampal

hippocampal formation



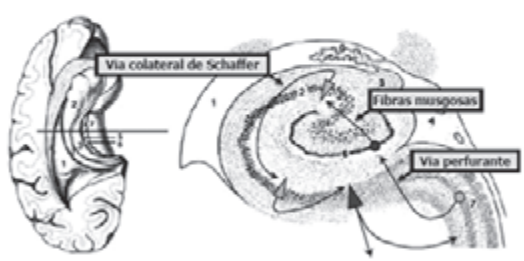
Formação hipocampal

hippocampal formation

- Córtex Entorrinal (CE)
- Giro Denteado (GD)
- Corno de Ammon (CA)
- Subículo (Sub)

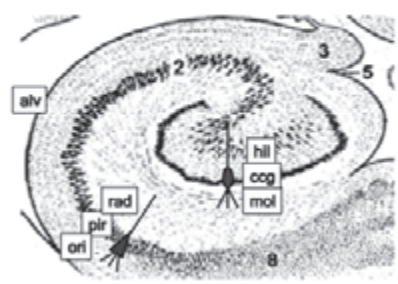
Formação hipocampal

hippocampal formation



Camadas do hipocampo

hippocampal layers



Camadas do hipocampo

hippocampal layers

- Giro denteado
  - Cam. Molec. Ext.: aferências (inputs) CE Lat. (olfato)
  - Cam. Molec. Int.: aferências (inputs) CE Med.
  - Cam. Granular: sinapses inibitórias
  - Hilo: interneurônios (+) e (-)
- Corno de Ammon
  - Estr. Lacunoso: V.Perfurante
  - Estr. Radiado: V.C.Schaffer, fibras comissurais
  - Estr. Lucido (CA3): fibras musgosas
  - Estr. Piramidal: sinapses inibitórias
  - Estr. Oriens: aferências (inputs): Septo medial
    eferências (outputs): Fímbria/Fórnix
    fibras comissurais

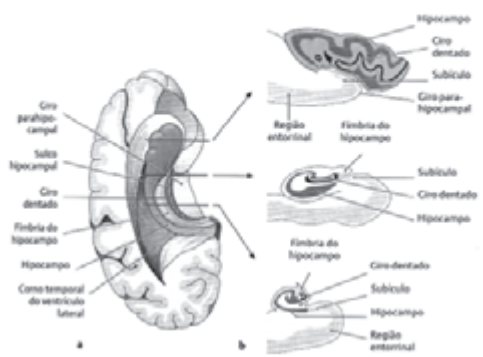
Conexões do hipocampo

hippocampal conectivity

- EXTRÍNSECAS
  - AFERÊNCIAS (inputs)
    - **Diretas**: Ctx entorrinal (Glu), nn. septais (ACh), hipotálamo mamilar, tálamo anterior, nn. rafe (5HT), locus ceruleus (NA)
    - Indiretas (via CE): bulbo olfatório, amigdala, neoctx temporal, ctx pré-frontal
  - EFERÊNCIAS (outputs)
    - **Sub** - Fórnx Pós-comissural - Tál. anterior / Hipotal. mamilar
    - CA - Fórnix Pré-comissural - Septo medial
- INTRÍNSECAS
  - Fibras comissurais: homotópicas e heterotópicas

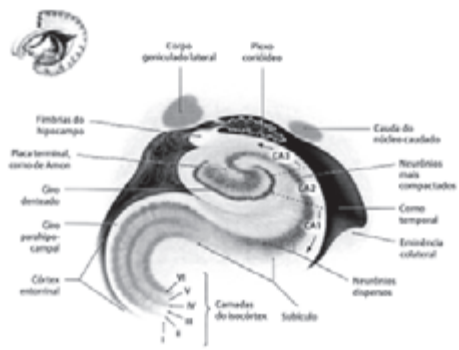
O hipocampo normal

The normal hippocampus



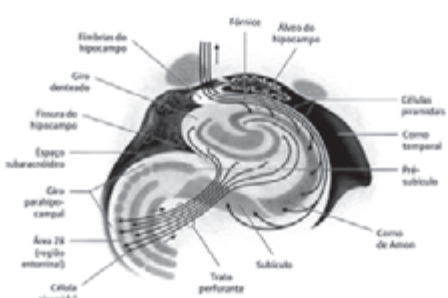
O hipocampo normal

The normal hippocampus



O hipocampo normal

The normal hippocampus



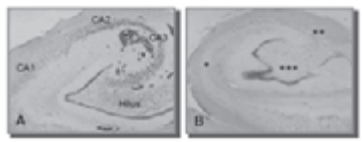
O hipocampo patológico

The pathological hippocampus

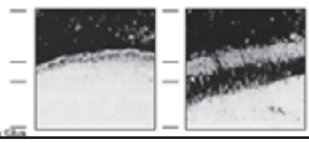
Esclerose hipocampal

Hippocampal sclerosis

- Perda neuronal e gliose



- Brotamento das fibras musgosas

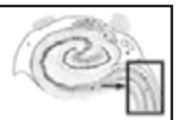


Hiperexcitabilidade hipocampal

hippocampal hyperexcitability

- Alterações no Córtex Entorrinal (CE)
- Alterações no Giro Denteado (GD)
- Alterações no Corno de Ammon (CA)
- Alterações no Subículo (Sub)

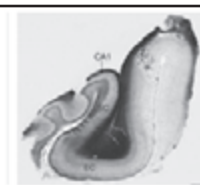
Alterações no Córtex Entorrinal

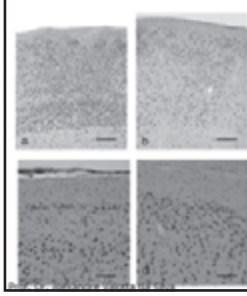


- Perda neuronal variável
- Proliferação astrocitária (gliose)
- Atividade espontânea *in vivo* ("fast ripples")

Quantitative Neuropathology of the Entorhinal Cortex Region in Patients with Hippocampal Sclerosis and Temporal Lobe Epilepsy

Stephen Dawodu and Mario Thom

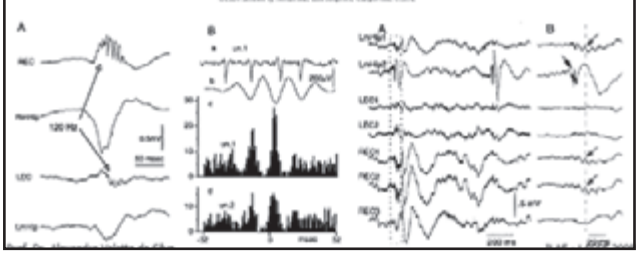




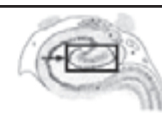
Laboratory Research

Hippocampal and Entorhinal Cortex High-Frequency Oscillations (100–500 Hz) in Human Epileptic Brain and in Kainic Acid–Treated Rats with Chronic Seizures

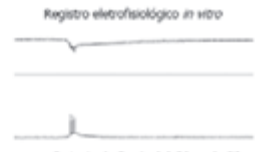
*†Anatol Bragin, *†Jerome Engel, Jr., *†Charles L. Wilson, ‡Rehak Fried, and *†Gary W. Mathern



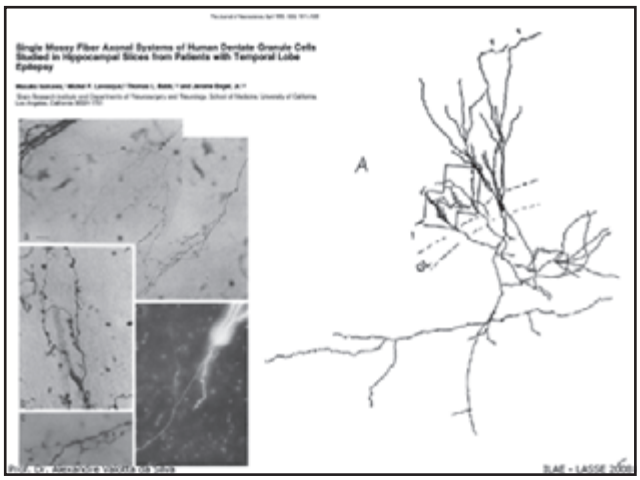
Alterações no Giro Denteado

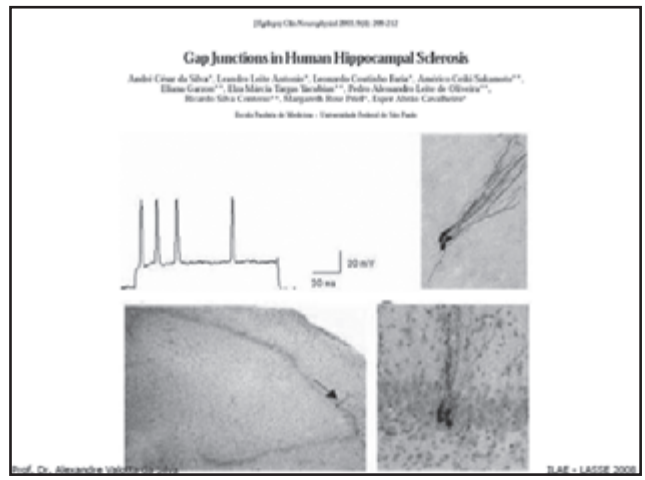


- Perda neuronal (>50%)
- Dispersão das células granulares
- Aumento da arborização dendrítica
- Brotamento axonal ("sprouting")
- Hiperexcitabilidade
  - Diminuição da inibição
  - Aumento da excitação

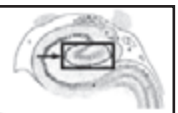


Cortesia do Dr. André César da Silva





Alterações no Giro Denteado
Diminuição da inibição



- Diminuição dos receptores de dinorfina
- Perda de interneurônios inibitórios
  NPY, Substância P, Somatostatina, GABA(?)
  - mec. compensatório: ⇑ Y2R e ⇓ Y1R
- Diminuição de receptores GABA-A
  - mec. compensatório: ⇑ GABA-B
- Diminuição da atividade GABAérgica *in vitro*

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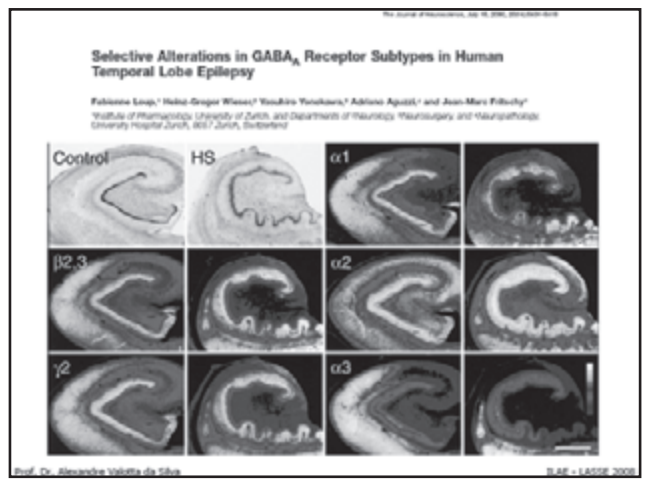
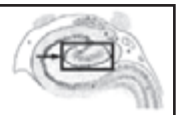


Alterações no Giro Denteado
Aumento da excitação



- Aumento da arborização dendrítica
- Brotamento axonal ("sprouting")
- Aumento de receptores GluR1
- Alteração dos GLUTs
- Alteração do controle da $[K^+]_e$ pelos astrócitos

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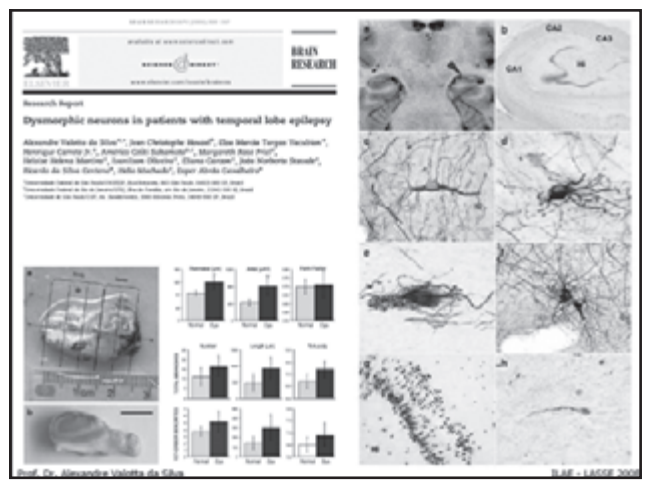

Alterações no Corno de Ammon

- Perda neuronal intensa
- Reorganização de interneurônios GABAérgicos (PV e CB)
  - ⇧ inibição sobre inibição
  - Hipersincronização anormal
- Proliferação astrocitária (gliose)

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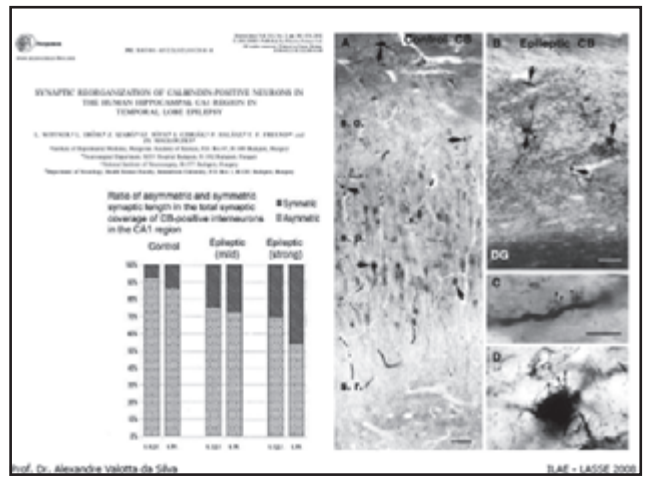

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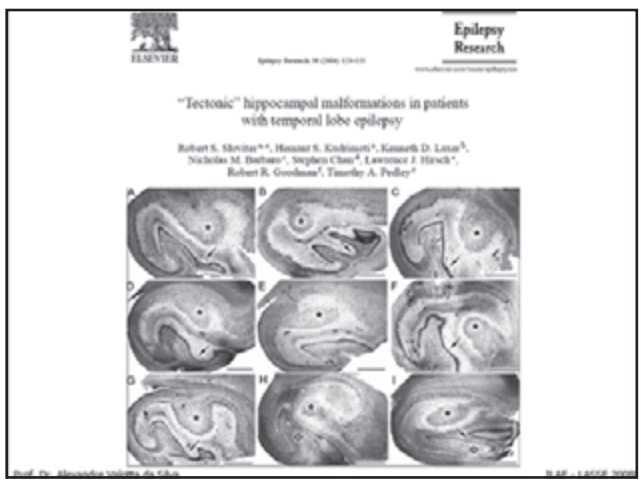

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Alterações no Subículo

- Via de saída da formação hipocampal
- Preservado, mesmo em casos de ELTM
- Atividade rítmica espontânea *in vitro*
  - Mediada por glutamato e GABA

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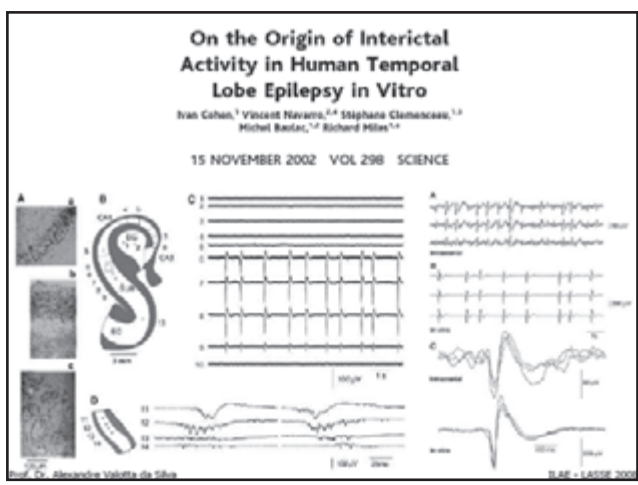

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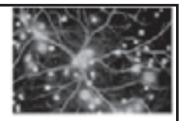
Hiperexcitabilidade hipocampal

hippocampal hyperexcitability

Alterações astrocitárias



- Aumento de canais de Na^+
- Alteração do controle da $[K^+]_e$
- ⇑ de receptores GluR1
- ⇓ da glutamina sintetase
- Alteração no transporte de água (AQP4) e acoplamento neurovascular

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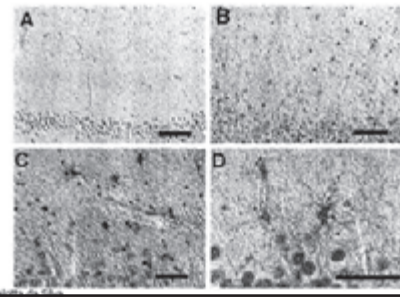
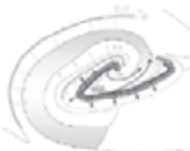
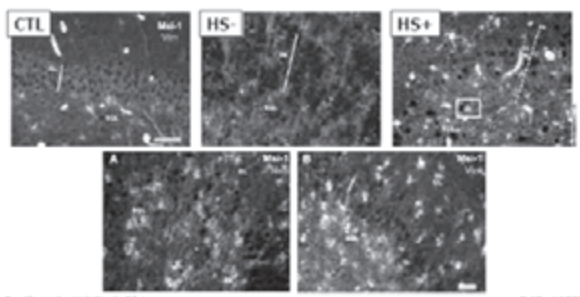
Glycosaminoglycan levels and proteoglycan expression are altered in the hippocampus of patients with mesial temporal lobe epilepsy



Neurobiology of Disease

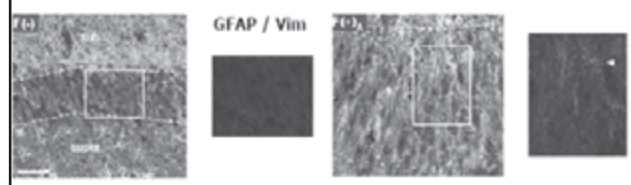
Increased number of neural progenitors in human temporal lobe epilepsy





Neuroscience Letters

Immature-like astrocytes are associated with dentate granule cell migration in human temporal lobe epilepsy

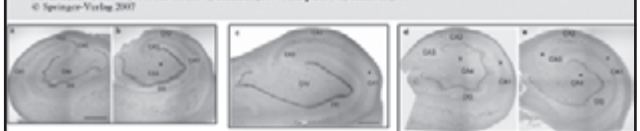


Acta Neuropathol

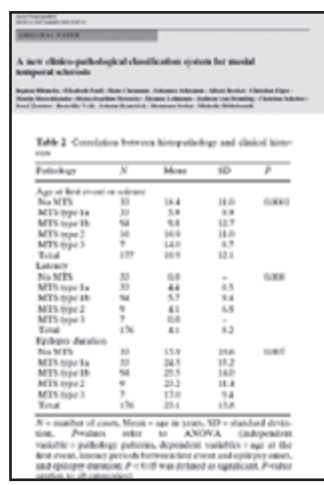
ORIGINAL PAPER

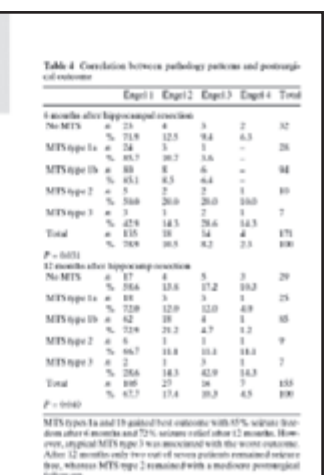
A new clinico-pathological classification system for mesial temporal sclerosis

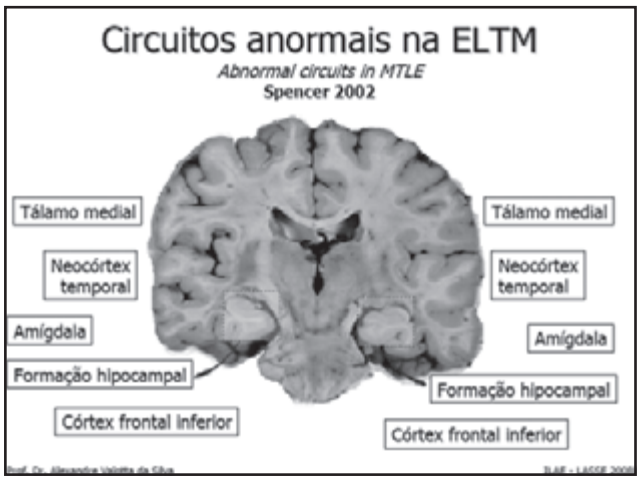
178 casos ELTM



A new clinico-pathological classification system for mesial temporal sclerosis






Circuitos anormais na ELTM
Abnormal circuits in MTLE
Spencer 2002
Tálamo medial
Tálamo medial
Neocórtex temporal
Neocórtex temporal
Amígdala
Amígdala
Formação hipocampal
Formação hipocampal
Córtex frontal inferior
Córtex frontal inferior


UNIFESP
Baixada Santista
SANTOS
Brasil

Neuroimaging in epilepsies

Fernando Cendes (Brazil)

MRI evaluation in epilepsies

Fernando Cendes, MD, PhD

UNICAMP, Campinas - SP, Brazil

Neuroimaging of patients with epilepsy

1. Aims and rationale
2. Techniques
3. The acute situation
4. The nonacute situation: *ideal practice*
5. The nonacute situation: *minimum standards*
6. Presurgical evaluation
   - Approaches in specific clinical syndromes
     - TLE
     - Extra-TLE
     - Generalized epilepsies

* Commission on Neuroimaging of the ILAE
Epilepsia 1997; 38:1255-6
Epilepsia 1999; 39: 1375-6

Aims and rationale of neuroimaging

- To identify underlying pathologies
  - e.g. tumors, granulomas, malformations, traumatic lesions, etc.
- To aid the formulation of syndromic and etiological diagnosis
- To help clinical treatment and prognosis
- Presurgical localization

Magnetic resonance imaging (MRI) and radiographic CT for etiological diagnosis

- MRI is clearly the structural imaging of choice
- Occasionally, CT may be useful as a complementary technique for cortical calcifications
- Conventional isotope brain scans (e.g. SPECT) do not provide sufficient information about brain structure
  - not recommended for etiological diagnosis

The acute situation

- CT scan is an appropriate initial investigation
  - new onset seizures with focal neurological signs
  - head injury, intracranial hemorrhage, encephalitis, etc
- Advantages
  - readily available in most emergency rooms; cost
  - scanners dedicated to emergency evaluation
  - compatible with peacemaker, conventional respirator, easier for anesthesia, ready access to the patient during scanner
  - adequate for most gross acute lesions: blood, tumors, infection (contrast enhancement)

The nonacute situation

- *Ideal situation*: MRI in all patients with epilepsy
- *Particularly indicated*:
  - any age with evidence of partial seizure onset on history or EEG
  - onset of unclassified or generalized seizures in the first year of life or adulthood
  - focal deficit on neurological examination
  - difficulty in obtaining seizure control with first-line drugs
  - loss of control of seizures or change in seizure pattern

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Presurgical evaluation

- Delineation of structural and functional abnormalities in the epileptogenic region
- Prediction of the nature of structural pathology
- Detection of abnormalities distant from the putative epileptogenic region (dual pathology)
- Emerging goals
  - identification of regions essential to normal brain function
  - relation of these areas to the epileptogenic region
  - prognostication regarding post-operatory functional status and seizure control

Presurgical evaluation *General considerations* - I

- Correct seizure and epilepsy syndrome diagnoses
- Strict standards for technique and interpretation must be used
- Imaging results must be placed in the context of all available clinical and laboratory data
  - history, neurological exam, video-EEG recordings, neuropsychology
- Images should be reviewed by physicians experienced in the evaluation of patients with epilepsy

Presurgical evaluation *General considerations* - II

- The several neuroimaging modalities now available provide data of a differing and complimentary nature
- To improve resolution, functional images can be co-registered with structural MRI
- No technique is clearly superior
  - the choice of a functional imaging procedure depends on resources and experience as well as the clinical situation
- A negative functional study does not preclude surgery if EEG data provide adequate localization

Presurgical evaluation - MRI

- MRI is essential for presurgical evaluation
- Surgery should never be contemplated without an MRI
- Both T1 and T2-weighted images should be obtained
- Coronal as well as axial slices; always
- Slices as thin as possible
- 3-D volume acquisition is highly recommended
  - allows multiplanar reformatting, quantitative segmentation
- Other sequences may add in specific situations
  - Inversion recovery (IR); FLAIR

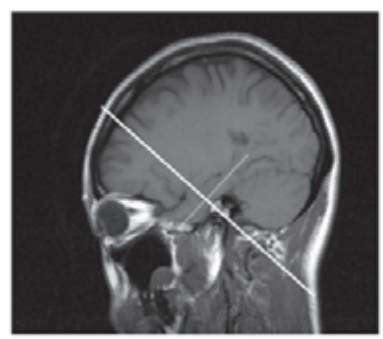
Presurgical evaluation - Functional imaging

- Magnetic resonance spectroscopy (MRS)
- Functional MRI (fMRI)
- Ictal single photon emission tomography (SPECT)
- Positron emission tomography (PET)

Approaches in specific clinical syndromes - TLE

- **Thin coronal MRI** slices, perpendicular to the axis of the hippocampus, give the best images for determining mesial temporal sclerosis (MTS) and other subtle pathologies in the temporal lobes
- **Proton MRS** can reliably localize and lateralize epileptic foci in patients with TLE
- **Interictal FDG-PET** shows focal and regional glucose hypometabolism
- **Ictal SPECT** using 99m Tc HMPAO or ECD is highly sensitive to identify temporal foci, as long as the tracer is injected as soon as possible after seizure onset

MRI in TLE



TLE and MRI

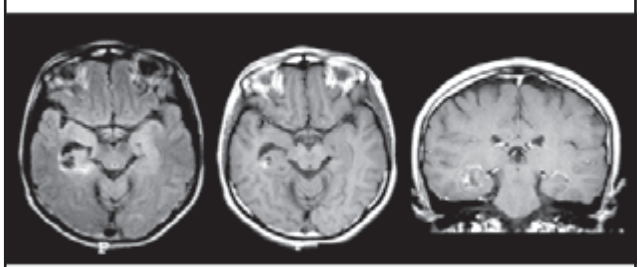
- I. Unilateral mesial temporal atrophy
- II. Bilateral mesial temporal atrophy
- III. Normal MRI
- IV. Other structural lesions:
  - Tumors
  - Malformations
  - Traumas
  - Infections

Oligodendroglioma

- On MRI, oligodendroglioma is nonspecifically hypointense on T1-weighted and hyperintense on T2-weighted images. Calcifications tend to be underestimated or inapparent. Occasionally, foci of increased signal on T1-weighted images reflect intratumoral hemorrhage. Enhancement on CT or MR is variable, with edema recognizable on CT in about 30%. On CT, calcifications are expected and may be shell-like, ring-like, or nodular. Up to 40% result in recognizable calcifications on plain skull films.

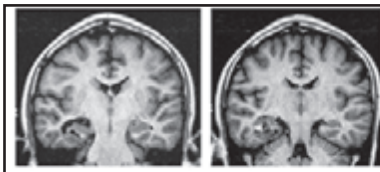
  The differential diagnosis in adults primarily includes other gliomas, particularly astrocytoma. In children, astrocytoma, ganglioglioma/gangliocytoma, neuroblastoma, or other primitive neuroectodermal tumors (PNET) could have a similar radiographic appearance

TLE - Oligodendroglioma

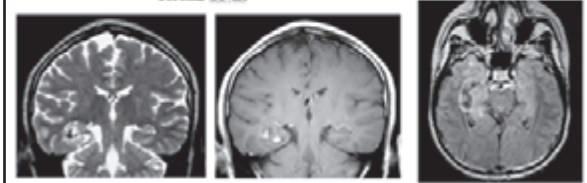


Axial FLAR | Axial T1 | Axial T1 After gadolium

TLE - Oligodendroglioma

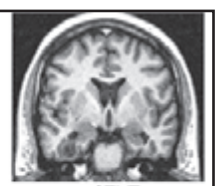


coronal T1-IR

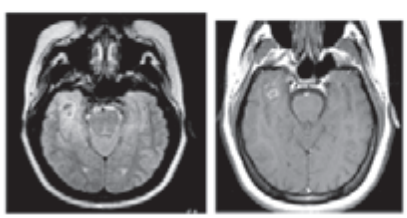


Coronal T2-FSE - Note hypointense signal (calcification) | Coronal T1 After gadolium | Axial FLAR

TLE - Oligodendroglioma



coronal T1-IR

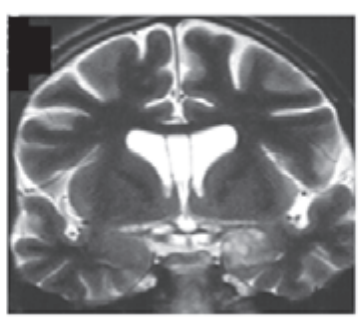


Axial FLAR | Axial T1 After gadolium | Coronal T1 After gadolium

Ganglioglioma

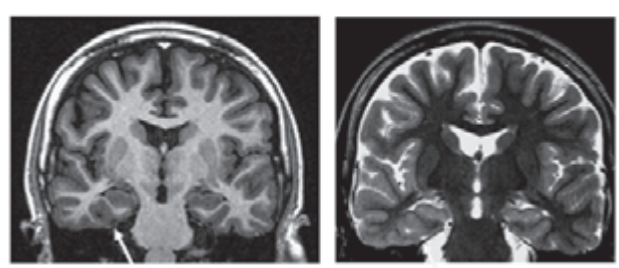
- By either CT or MR, approximately 40% of lesions are cystic. The remaining 60% are solid.
- On MR, T1-weighted images generally show the lesions to have a variable nonspecific appearance. On T2-weighted images gangliogliomas are slightly hyperintense.
- Following iodinated contrast administration, CT shows enhancement in half of gangliogliomas. Calcifications are seen in 30% of cases (especially in the cystic lesions).
- Ganglioglioma should be considered when a when a poorly defined, slightly enhancing mass is present in the temporal lobes.

TLE - Ganglioglioma

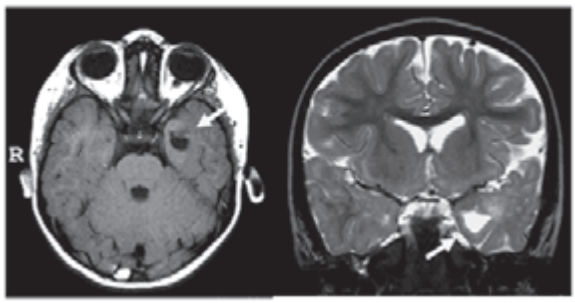


Coronal T2 W

Ganglioma in the right temporal lobe



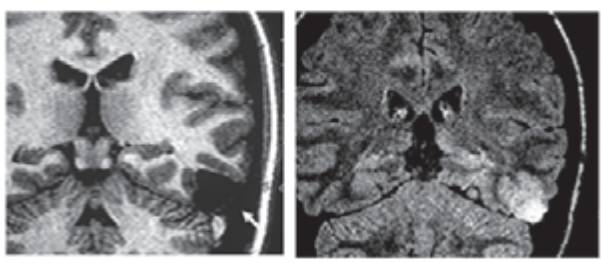
Ganglioma in a child with TLE



Dysembryoplastic Neuroepithelial Tumor – DNET

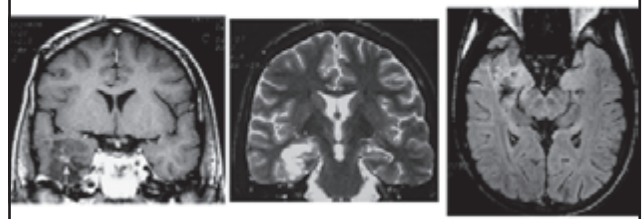
- DNETs are benign masses that are more common in the temporal lobes and usually present with seizures.
- The tumors are solid but often have cystic or microcystic components. They usually do not enhance with contrast. Calcification may be present.
- They are usually cortical tumors
- They may be associated with focal cortical dysplasia

DNET in a patient with temporal lobe seizures

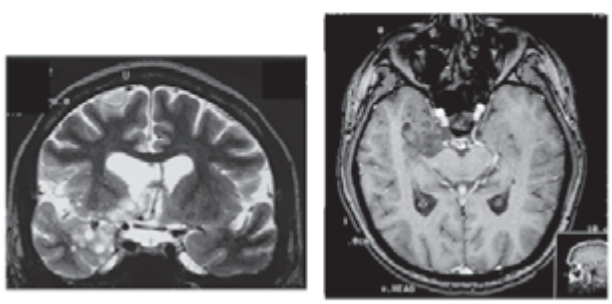


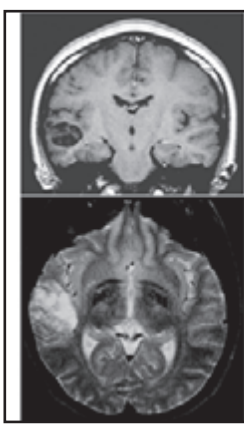
T1-IR FLAIR

DNET – Associated with focal cortical dysplasia in the right TL.
23 years old Patient with refractory partial seizures since age of 9 years

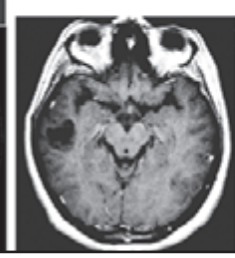


DNET in the right medial temporal lobe region





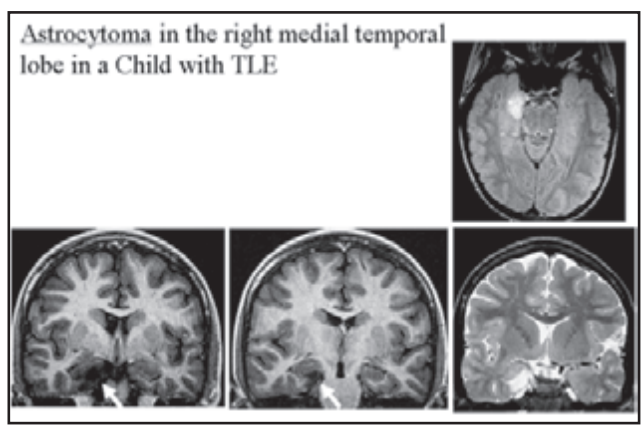
DNET –in the right TL in a 26 years old woman with seizures since childhood



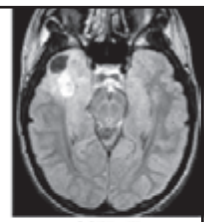
Hemispheric Astrocytomas

- They can be solid, solid with a necrotic center, or cystic with a mural nodule
- Although they tend to occur deep in the hemispheres they may be found in the temporal lobes as well
- Low grade astrocytomas are usually homogeneous and well circumscribed with little edema, whereas high grade astrocytomas are heterogeneous and surrounded by extensive edema. However, these characteristics are not absolute.

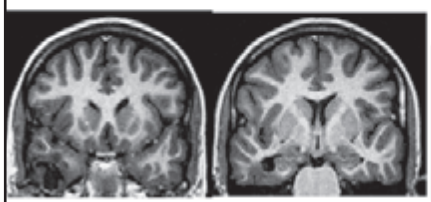
Astrocytoma in the right medial temporal lobe in a Child with TLE



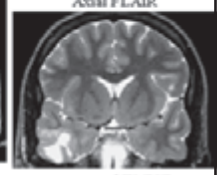
Astrocytoma in the right medial temporal lobe



Axial FLAIR



coronal T1-IR

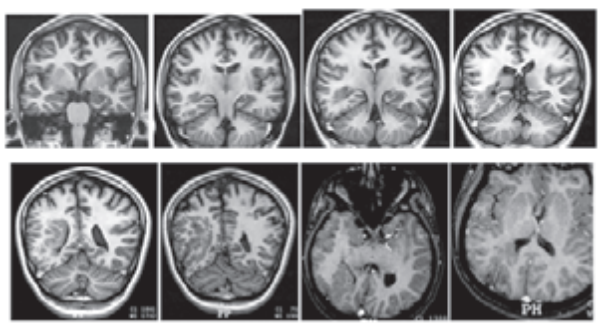


coronal T2 FSE

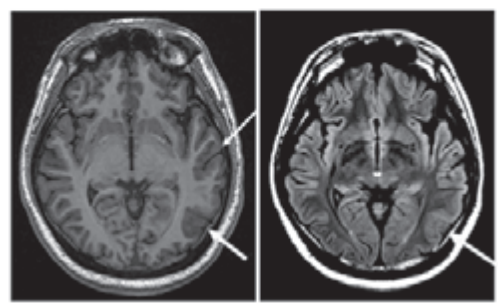
Malformation of cortical development in patients with TLE

- Heterotopias
- Focal cortical Dysplasia

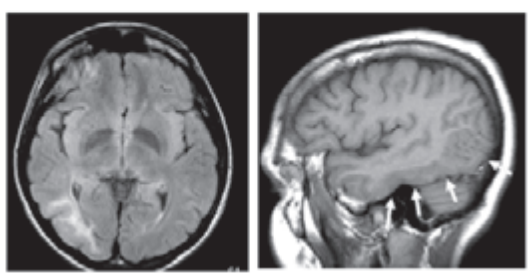
Periventricular and subcortical nodular heterotopia presenting with temporal lobe seizures



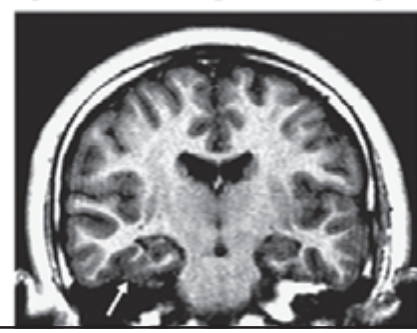
Focal cortical dysplasia in the left temporal lobe



Focal cortical dysplasia in the right posterior-inferior Temporal region and occipital lobe



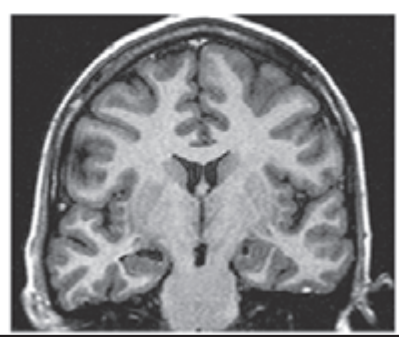
Transmantle focal cortical dysplasia in the right medial temporal lobe region

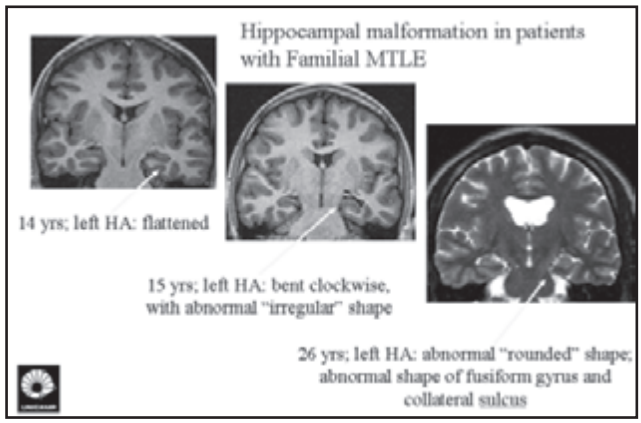


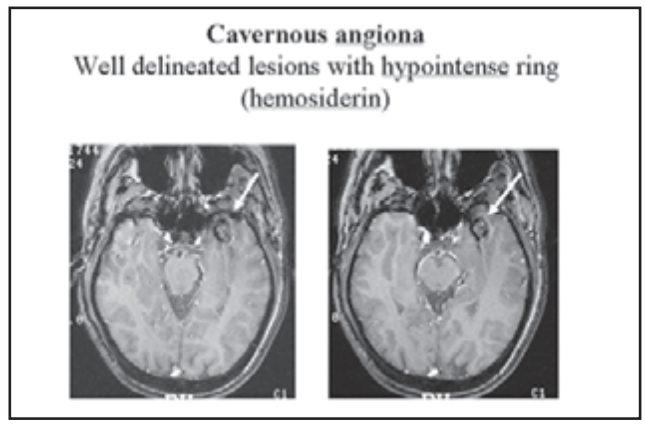
Hippocampal malformation

- Hippocampal malformation include hippocampi that are abnormally round, pyramidal in shape, with abnormal rotation or vertically orientated

Abnormal rotation of the left hippocampus (hippocampal malformation) in a patient with familial MTLE

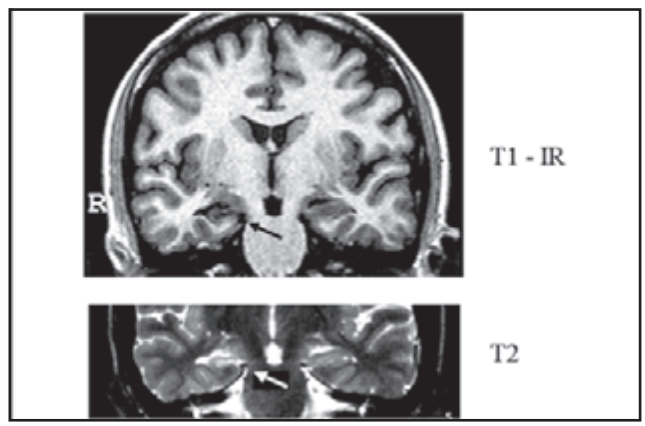


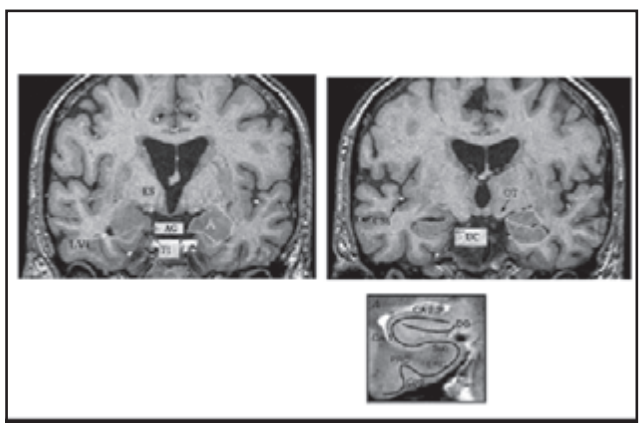


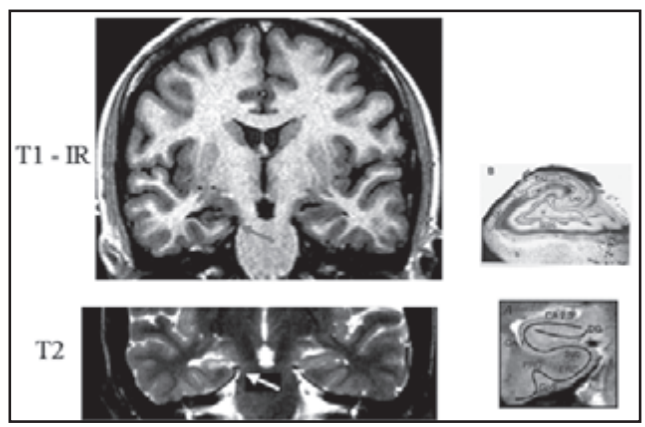


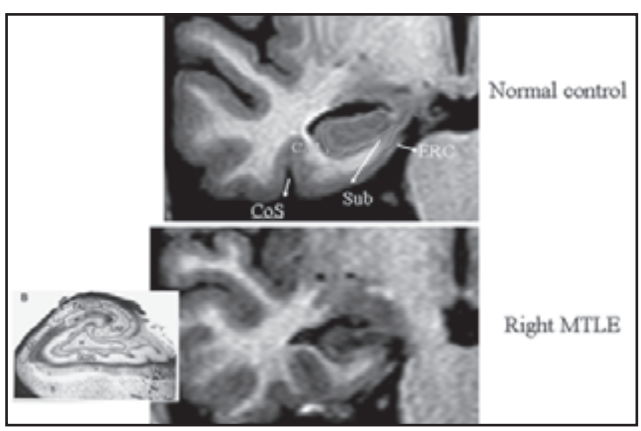
Approaches in specific clinical syndromes - TLE

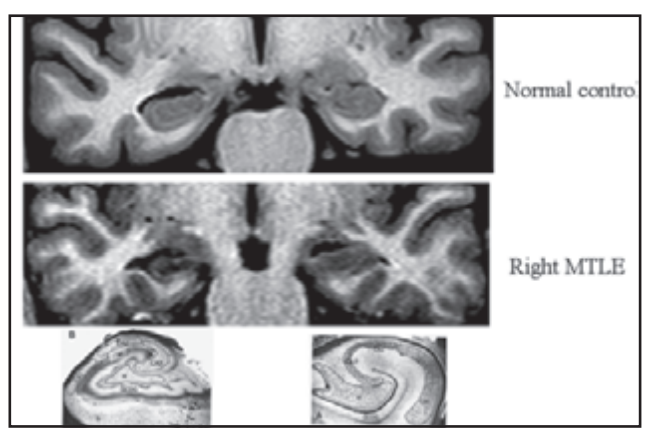
- MRI features of MTS, detectable by visual inspection of the images, are:
  - hippocampal smallness (atrophy) which is the most specific and reliable feature
  - increased T-2 signal and loss of internal structure
  - abnormal shape and rotation of hippocampal formation



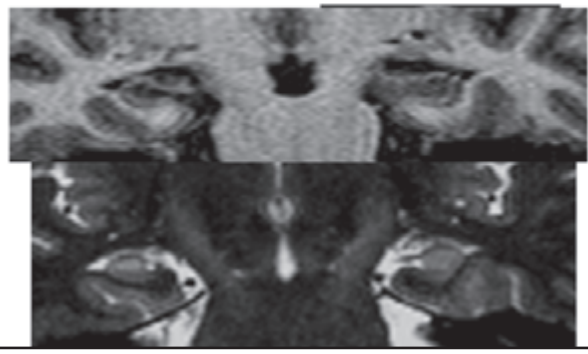




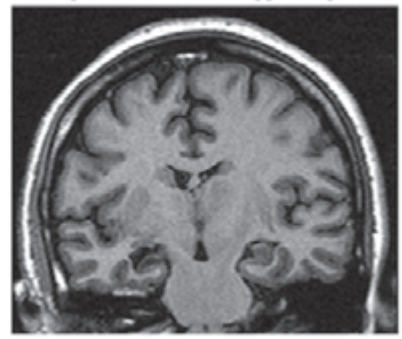




Bilateral MTS



Abnormal shape and rotation of hippocampal formation



Familial Mesial Temporal Lobe Epilepsy

Approaches in specific clinical syndromes
MRI features of MTS - II

- There may also be asymmetry of the horns of the lateral ventricles, which is variable and may lead to false lateralization
- Atrophy of the anterior temporal lobe which is non-specific
- T2 mapping is an objective method for measuring abnormal T2 signal which may be difficult to detect visually

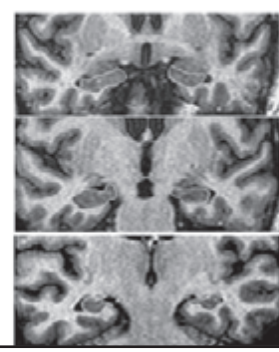
Approaches in specific clinical syndromes - TLE

- Most patients with MTS undergoing presurgical evaluation have one hippocampus which is clearly smaller than the other on visual inspection, and which has increased T-2 signal, along with a normal appearing contralateral hippocampus
  - volume measurement is not necessary for clinical purposes in this situation
- The visual binary paradigm breaks down in the presence of symmetric bilateral atrophy or mild unilateral disease
  - in these cases volumetric MR analysis of the hippocampus are very sensitive and specific for identifying MTS

Approaches in specific clinical syndromes - TLE

- MRI measurements of hippocampal volumes are a surrogate for the presence and severity of neuronal loss in hystopathology
- This may give useful prognostic information concerning postoperative seizure control
- Surgical treatment of strictly unilateral HS should give >90% excellent outcome

Hippocampal volumetry



Approaches in specific clinical syndromes - TLE

- Proton magnetic resonance spectroscopy (MRS) lateralizes most patients with temporal lobe epilepsy with normal MRI and detects bilateral abnormalities more often than does volumetric MRI

Summary: Imaging of MTS

MRI
- Detects Most Moderate - Severe MTS
- Abnormalities Highly Specific to MTS
- Insensitive to Epileptogenicity

MRS
- Detects Metabolic Changes in Mild - Severe MTS

Interictal FDG PET
- Detects Metabolic Changes in Mild - Severe MTS
- Highly Sensitive to Epileptogenicity, Not Specific to MTS

Ictal SPECT
- Highly Sensitive to Epileptogenicity, Not Specific to MTS

MRI in Extra-Temporal Epilepsies

Clique para adicionar um subtítulo

Epilepsies due to neocortical lesions

- In patients with suspected neocortical TLE or extratemporal epilepsies, subtle structural lesions can be missed unless MRI is performed with optimal technical quality and is expertly interpreted
- Correlation of structural and functional imaging data is essential

Techniques and sequences

- FLAIR (fluid-attenuated inversion recovery) and T2-weighted turbo-/fast- spin echo imaging should be performed in all patients in the coronal or axial planes
- These pulse sequences should be performed with the highest possible spatial resolution while still including enough slices to cover the entire brain.
  - MCDs frequently cause mild prolongation of the T2-relaxation time and account for subtle hyperintensity in the subcortical and possibly the deep white matter on both pulse sequences.

Techniques and sequences

- The combination of the FLAIR and T2-weighted sequences can also aid in the characterization of subcortical or periventricular masses such as heterotopic gray matter or to demonstrate that the identified dysmorphic cortex is actually an abnormally thickened gray matter rather than a glioma.

Techniques and sequences

- In addition to the conventional turbo-/fast spin echo studies, a high-resolution T1-weighted, gradient echo, volume acquisition is recommended for all patients with previously "normal" MRI
- The thin contiguous slices (1-2mm) provide the needed spatial resolution to depict subtle abnormalities in cortical morphology that may not be apparent on conventional spin echo images.

MRI investigation in epilepsy

- Further review of the digital data from the original acquisitions can also be of great benefit.
- On many occasions, adjusting the display of the images to accentuate the contrast between gray and white matter can make the lesion more obvious.

MRI investigation in epilepsy

If nothing is found, reexamination by an experienced observer may reveal a subtle lesion such as cortical dysplasia

- Multiplanar reconstruction and 1 mm re-slicing.
- 3 mm coronal inversion recovery images, and thin T2-FSE sequence may be helpful at this point.
- In the absence of MRI findings no imaging technique is specific for dysplasia. In such cases, cortical dysplasia may be discovered at surgery.

MRI investigation in epilepsy

- If focal findings appear, comparison of ictal and interictal SPECT images or PET may add additional information on the localization of the epileptogenic zone
  - Local expertise in performing and interpreting this procedure is important given the complexity of many cortical dysplasia syndromes

Presurgical evaluation - Functional imaging

- Magnetic resonance spectroscopy (MRS)
- Functional MRI (fMRI)
- Ictal single photon emission tomography (SPECT)
- Positron emission tomography (PET)

Ictal SPECT: interests

- Non invasive technique
- High sensitivity
- Localizing value validated
- Helpful for placing intracranial electrodes
- May avoid intracranial EEG in some patients
- Helpful for studying seizure semiology in children

Approaches in specific clinical syndromes
Extratemporal epilepsies

- In patients with suspected neocortical TLE or extratemporal epilepsies, subtle structural lesions can be missed unless MRI is performed with optimal technical quality and is expertly interpreted
- Correlation of structural and functional imaging data is essential

Malformation of cortical development

- cell proliferation
- migration
- organization

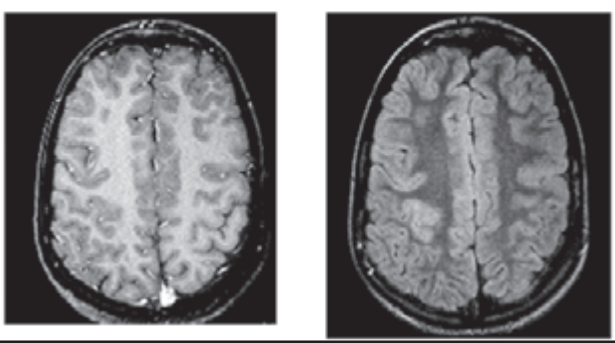
Disorders of cell proliferation

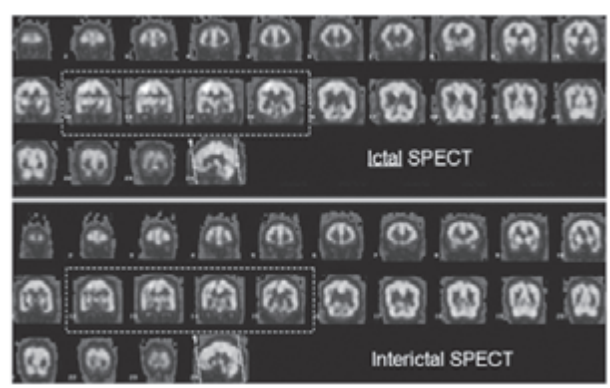
- **Non tumoral**
  - hemimegalencephaly
  - **focal cortical dysplasia**
  - tuberous sclerosis
- **Tumoral** (with cortical disorganization)
  - DNT
  - ganglioglioma

MRI diagnosis of Focal cortical dysplasia - FCD

- Cortical thickening and/or blurring of the gray-white matter junction
- Often accompanied by
  - Variable degrees of focal gyral abnormality
    - alteration in the width, length, height, shape, orientation, and size of gyri/ sulci
  - Prolongation of T2 relaxation times in the underlying WM
  - Radial signal abnormalities extending from the affected cortical surface towards the ipsilateral ventricle (transmantle sign)

10 year-old boy with seizures since 6 yrs, starting with tingling sensation in the left arm





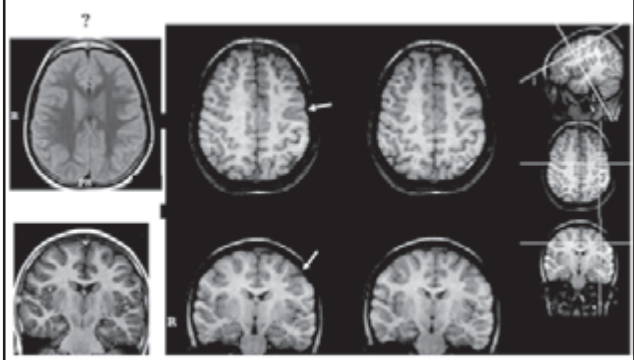
FCD and Epilepsy

- Gradient of morphologic changes
  - from dysplastic lesions that can be easily identified by conventional MRI techniques
  - to minor structural abnormalities
    - small areas of discrete cortical thickening and/or blurring of the gray-white matter interface
    - often go unrecognized

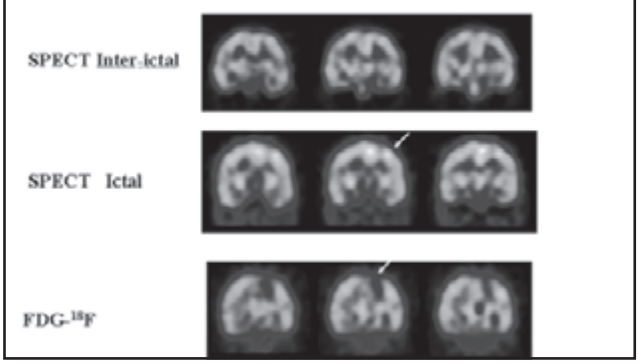
MRI - Multiplanar reformatting - MPR

- Subtle cortical lesions are being increasingly recognized by MRI
- 3D MRI with thin partition size has been helpful in identifying fine structural changes
- It provides good resolution and the ability to analyze the brain volume by MPR

MPR: 7 years old girl with partial motor seizures in the right hand



Coronal slices



Neuropsychological evaluation of the epilepsies

Cândida Pires de Camargo (Brazil)

Avaliação Neuropsicológica

Candida H. P. Camargo

Diretora do Serviço de Psicologia (1994-2005)

Unidade de Neuropsicologia / Reabilitação Neuropsicológica (1971-2005) - IPQ - HC/ FMUSP

Metas da Avaliação Neuropsicológica (NP)

- **Descrever o estado cognitivo pré e pós cirúrgico**
  - aumentar a confiança nos achados pré-operatórios
  - mapear a extensão e grau das disfunções
  - prover informações sobre os riscos/ benefícios potenciais do tratamento cirúrgico.

Metas da Avaliação Neuropsicológica (NP)

- Auxiliar na localização do foco/ ou área epileptogênica
  - nem sempre área epileptogênica coincide com a lesão estrutural
  - contribuir para o planejamento cirúrgico, adequação e sucesso do tratamento

Metas da Avaliação Neuropsicológica (NP)

- Auxiliar na determinação do hemisfério dominante para linguagem
- Estabelecer a extensão dos déficits pré-operatórios
- epilépticos freqüentemente tem localização anômala de linguagem: ↑ porcentagem de pacientes T. destros têm dominância cerebral D para linguagem
  - exame neuropsicológico freqüentemente levanta esta suspeita
  - hipótese deve ser confirmada por: - Audição Dicótica
    - WADA
    - Neuroimagem

Princípios Gerais da Avaliação

- utilizar ampla gama de testes visando estabelecer se há um padrão, isto é, dados convergentes que apontam a topografia das disfunções.
- Protocolos variam entre os autos, porém é dada atenção especial à:
  - **Funções Executivas**
  - **Memória**
  - **Linguagem**
  - **Habilidade Visuoconstrutiva**
  - **Nível Intelectual**
- Ref.: Lezak, M (1995) – Neuropsychological Assessment Spreen, Strauss (1998) – A Compendium of Neuropsychological Tests: Administration and Norms.

Problemas metodológicos

- Uso de testes não padronizados
- Efeitos das DAEs
- D.C.E.: atividade subclínica anormal, interictal

Testagem Formal

- Testes Neuropsicológicos
  - Bateria Mínima:
    - Atenção e Funções Executivas
    - Funções Motoras
    - Funções Visuais
    - Praxia Construtiva
    - Linguagem
    - Memória Verbal e Visual
    - Nível Intelectual

Testagem Formal

- Funções Motoras
- Objetivo:
  - identificar prejuízos sutis
  - integridade de cada hemisfério (performance pior contralateral à lesão
  - preferência manual
- Testagem dá pistas sobre lateralidade da linguagem

Testagem Formal

- Funções Motoras:
  - * Preferência:
    - mão usada para a escrita
    - Questionários (Annett Lezak 1995)
      - escrever
      - jogar bola
      - escovar dentes
      - etc.
  - Lúria: vários testes

Funções Motoras

- Preferência
  - nem sempre a performance com a mão preferida é mais eficiente;
  - 30% de sujeitos normais tem performance igual ou melhor com a mão não-preferida
  - não inferir prejuízo neurológico a partir disto.

Funções Motoras

- Preferência
  - Normais
    - 70% em H.D
    - 5% em H.E
    - 25% preferência mista
  - Lesionados precoces
    - Lesão E: > incidência de canhotismo
      - * canhotismo patológico
      - * desajeitamento com a M.D.
    - Lesão D: > incidência de dextrismo
      - * desajeitamento com a M.E.
      - * dextrismo patológico

Funções Motoras

- Medidas de Competência
  - Força: Dinamômetro: média de 2 tentativas alternar mão preferida x não
  - Velocidade: Finger Tapping – 10 seg cada mão
  - Dextreza: Purdue colocar pinos com D, E, ambas em 30seg.

Testagem Somatosensorial

- Porque?
  - Funções do córtex primário somatosensorial
  - Lobo Parietal → giro pós-central
  - Sensibilidade táctil varia conforme a parte do corpo
  - Proporcional à córtex sensorial relacionada à parte corporal
  - Mãos e face ocupam as maiores áreas.

Testagem Somatosensorial

- Geralmente feita nas mãos; pode ser também em outras partes do corpo;
- Realizada com exclusão da visão
  - olhos fechados
  - vendados
  - caixa-aparador

Efeitos de lesões na área das mãos

- Ambos hemisférios contribuem para o processamento da informação sensorial dos lados D e E do corpo
- Perda da sensibilidade táctil na mão contralateral
  - também possível na mão ipsilateral
  - menos severa neste caso
  - frequência igual em lesões D ou E

Efeitos de lesões na área da face

- Déficits sensoriais na face contralateral
  - < proporção tem déficits ipsilaterais
- Proporção de déficits é menor do que em área da mão
- Preservação sensorial relacionada à representação bilateral

Testagem: Discriminação Sensorial e Táctil

- Localização de Pontos
  - habilidade para julgar se dois estímulos simultâneos e/ ou sucessivos estão no mesmo ou em diferentes pontos
  - Senso de posição
    - julgar a direção do movimento ↓↑
    - 12 tentativas cada dedo
    - escore ≤ 57, deficitário

Esterognosia

- Reconhecimento Táctil
- Objetos diferentes em cada mão, simultaneamente
- Cada par testado duas vezes
- Reconhecimento Táctil de Formas (Benton, 1983)

Grafestesia

- Escrita na ponta dos dedos
  - Letras ou números
  - Direção de linhas em relação ao sujeito

Dupla estimulação (Extinção Táctil)

- Reconhecer em um ou dois estímulos tácteis aplicados á duas partes do corpo, simultaneamente
- Pressão igual e simultânea do tempo
- Usar os dedos ou pincel

Questões

- Vários testes disponíveis
- Sensibilidade > que exame neurológico
- Diferenças de gênero
- Lesões frontais:
  - falsos déficits
  - falta de concentração
  - dificuldades para inibir S irrelevantes

Percepção Visual e Processamento Não-Verbal de Informação

- ?: Localizam hemisfério não-dominante, especialmente quadrante posterior (O-P)
- Lesões F também produzem prejuízo em tarefas de percepção visual
  - déficits decorrentes de ↓ atenção;
    ↓ estratégia

Avaliação da Percepção Visual

- **Processamento de informação Não-verbal**
  - Componentes { recepção primária sensorial; interpretação secundária dos inputs visuais }
  - Métodos para investigar
    - apoiados em out put motor
    - tarefas sem componente motor

Avaliação Percepção Visual

- **Percepção Visual Primária**
  - Ep. Temporal pode ocasionar defeitos no quadrante visual contralateral superior
  - verificar Negligência Hemi-espacial
    - Desenhos
    - Testes de Cancelamento
    - Bissecção de Linhas

Avaliação Percepção Visual

- **Processamento Não-Verbal complexo**
  - Organização Visual
    - prejuízo localiza parietal não-dominante ou frontal – Teste de Hooper
  - Relações Espaciais
    - prejuízo localiza parietal e TP não-dominante - Julgamento de Orientação de Linhas (Benton)

Avaliação Percepção Visual

- **Processamento de Faces**
  - Tipicamente localiza LT inferior e Giro Fusiforme
  - * ambos hemisférios implicados
  - Integração Visomotora/ visuoespacial
    - * Cópia, desenho espontâneo e construções
      - Figura de Rey
      - Relógio
      - Cubos (WIS)

Percepção Visual e Processamento Não-Verbal

- Além de localizar as disfunções, tem implicações para os paciente cirúrgicos
  - Adaptação Funcional
  - Guiar
  - Qualidade de Vida
  - Funcionamento Social

Linguagem

- Avaliação das Habilidades Verbais
  - Funções Verbais Primárias
  - Raciocínio Verbal
  - Nomeação
  - Fluência verbal

Localização: L.T. e L. F., dominantes

Funções Verbais Primárias Afasia

- Fala Espontânea
  - Nomeação
  - Repetição
  - Compreensão Auditiva
  - Leitura
  - Escrita
- Localização: Região F inferior (Broca), T superior/ posterior (Wernicke); P inferior (giros angular, supra marginal); fasciculo arqueado.

Testes Afasia

- Diagnostico de Afasia de Boston
- Habilidades Comunicativas na Vida Diária
- Bateria de Afasia do Oeste (A. Herzog)
- "Token" Test.

Raciocínio Verbal

- Vocabulário
- Raciocínio Abstrato
- Conhecimento Adquirido
- Processamento Verbal Sequencial

  * localização: Lobo T e F dominantes

Testes de Inteligência Verbais

- **WASI:**
  - Vocabulário
  - Semelhanças
  - QI Verbal
- **Peabody Picture Vocabulary Test (PPVT-III)**
  - respostas por assinalamentos
  - escores idade-equivalentes

Nomeação

- Seletivamente ↓ em Epi T, mesmo com QIV normal
  - Pode ocorrer sem afasia
  - Piora após lobectomia T dominante
    - Localização: representação difusa no lobo temporal; nomeação visual – temporal + posterior;
- Testes: Boston NT
  - nomeação de itens descritos
  - correlação com "falha para achar palavras"

  * atenção ao viés cultural

Fluência Verbal

- **Geração de palavras dentro de restrições de tempo e de determinados tipos (via fonológica ou semântica)**
  - requer busca ativa na memória semântica
  - geração por via fonológica pode ser diferente da semântica no paciente

  * Localização: Lobo F dominante, porém ↓ em epi T dominante

- **Testes: FAS**

  * atenção à padronização

  * escores ajustados para idade/ escolaridade

  CATEGORIAS: Animais; Frutas; etc

Interpretação dos dados

- Sintomas Afásicos primários invalidam outros testes de linguagem
- Interpretação é feita junto com os demais testes
- Resultados em todos os testes verbais são suficientemente consistentes apontando ↓ T dominante?
- Evidência de lateralização anômala?
- Pode-se diferenciar entre F e T?

Memória e Aprendizagem

- Avaliação da Memória
  - Modalidades e Materiais Específicos

    Verbal x Não-Verbal

Verbal:	Não-Verbal
- Nomes	- Faces
- Listas de Palavras	- Desenhos geom/abstratos
- Histórias	- Localizações espaciais
	- Musicas

  - Aprendizagem x Retenção
  - Evocação x Reconhecimento
    - contornar falhas de atenção/ compreensão
    - uso de estratégias

Testagem para TE de TD

- Usar material altamente saturado, verbal ou não-verbal
- Aprendizagem em 4-5 tentativas
- Comparar resultados entre si (D – E)
- Diferencia os hemisférios

Aprendizagem Verbal

- RAVLT
- RVDLT
- SRT
- Lista de Palavras (WMS-III)
- Pares Associados (WMS-III)
- Faces
- Recuperação imediata
- Interferência
- Recuperação após 20 ou 30 min.
- Reconhecimento 24 horas

Memória Verbal

- **Histórias:**
  - Recuperação imediata "verbatim" 30 min
  - Reconhecimento
  - Memória Lógica, WMS III, R

Baterias de Memória: Vantagens e Desvantagens

- Itens balanceados, Verbal e Não-Verbal
- Padronizados
- Amplamente difundidas
- Pode não ser tão especifica para epi T
- Muito longas para administrar e corrigir

Baterias de Memória: Vantagens e Desvantagens

- Wechsler Memory Scale III (WMS-III)
- Memória Lógica I e II
- Pares Verbais Associados I e II
- Faces I e II
- Cenas de Família I e II
- Lista de Palavras
- Sequenciação Número/ Letra
- Span Espacial
- Controle Mental
- Reprodução visual I e II
- Dígitos

Epi T e WMS-III

- Chelune 1998

  Wilde e Chelune, Strauss 2001:

  - Epi TE: maior discrepância ente Pares Verbais e Faces
  - TD: Cenas de família x Pares Associados

  - Cenas: sensível na detecção de E.M.T.E

  * porém a utilidade do WMS-III em diferenciar pré-op TE de TD não está bem estabelecida

Avaliação da memória

- escolher testes apropriados para o nível e escolaridade
- Tarefas de aprendizagem verbais x não-verbais
- Evocação x Reconhecimento
- Tarefa Contextual História

- Excluir: problemas de: compreensão
  atenção
  percepção, etc.

Padrões Neuropsicológicos Pré-operatórios Relacionados com Sucesso Cirúrgico em Ep T.

- Lateralização Neuropsicológica no H.D.
- Disfunção apenas temporal
- Déficits neuropsicológicos coincidindo com área delimitada de disfunção nos outros exames
- Baixo grau de déficit neuropsicológico em geral
- Grau de integridade contralateral de memória quando a patologia envolve lobo TE
- Q.I. > 70

Padrões Neuropsicológicos Preditivos de Baixo Controle de crises ou Déficits no pós-operatório

- Indicação de disfunções neuropsicológicas de localização extra-temporal, além de envolvimento temporal
- Indícios sugestivos de alterações temporais bilaterais
- Baixo grau de integridade funcional no hemisfério contralateral
- Q.I. < 70
- Resultados mais altos nas medidas pré-operatórias de linguagem e memória, levando á déficits nestas áreas TE.

Padrões Neuropsicológicos Pós-operatórios em Cirurgia de Lobo Dominante

- Déficit de **Memória Verbal** em pacientes destros e dominância com a extensão da remoção hipocampal + excisão neocortical.
- Déficit de memória para trechos com significado variando de acordo com a **extensão da remoção** neocortical.
- Déficit de **Memória Verbal** quando as patologias do lobo temporal são diferentes de esclerose mesial temporal.
- Déficit de **Nomeação**, relacionado à excisão neocortical.

Padrões de Déficits Neuropsicológicos Pós-operatórios em Cirurgia de Lobo Não-Dominante

- Prejuízo de **Memória Verbal** quando a remoção hipocampal é extensa.
- Prejuízo de **Memória Visual** relacionada à materiais de difícil codificação verbal, variando de acordo com a extensão de hipocampo removido
- Prejuízo de **Memória Musical**
- Prejuízo de **Memória Espacial**
- Prejuízo na **Percepção Olfativa**

Neurocisticercosis and epilepsy

Marco Tulio Medina (Honduras)

Constructing guidelines for the study of the epilepsies

Arturo Carpio (Equador)

2nd Latin-American Summer School on Epilepsy (LASSE II)
"Epilepsy: increasing the knowledge and decreasing the treatment gap"
(São Paulo, 7-17 Feb 2008)

"Constructing guidelines for the study of the epilepsies"

Arturo Carpio, M.D.
Comprehensive Epilepsy Center
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Constructing Guidelines

- Practice guidelines consist of a formalized review of the literature that serves as the foundation for evidence-based practice recommendations.
- The literature review of a guideline is distinct from a typical literature review in that it is systematic and transparent.
- The recommendations of the guideline are also distinct in that they are fundamentally evidenced-based.

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Evidence-Based Medicine and Reviews:

- Cochrane Handbook (available at www.update-software.com/ccweb/cochrane/hbook.htm)
- Counsell, Carl. Formulating Questions and locating primary studies for inclusion in systematic reviews (Academia and Clinic: Systematic Review Series). Ann Intern Med, 1997;127:380-387.
- Evidence-Based Medicine (Sackett et al, 1997)
- Evidence-Based Principles and Practice (McKibbon, 1999)

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Evidence-Based Medicine and Reviews:

- National Guideline Clearinghouse at www.guidelines.gov
- The CATbank at http://cebm.jr2.ox.ac.uk/docs/catbank.html
- Regarding Using EndNote to Search Remote Databases:
- www.biomed.lib.umn.edu/endref.html
- Regarding Using EndNote to Create a Bibliography:
- www.biomed.lib.umn.edu/end.html

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Constructing Guidelines

ASK A CLINICAL QUESTION

↓

FIND AND ANALYZE RELEVANT EVIDENCE

↓

STATE CONCLUSIONS

↓

MAKE RECOMMENDATIONS

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Common Uses of Guidelines

- Improve health outcomes for patients
- Stay abreast of the latest in clinical research
- Provide medico-legal protection
- Advocate for fair reimbursement
- Determine whether one's practice follows current, best evidence
- Reduce practice variation

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Common Uses of Guidelines

- Affirm the role of neurologists in the diagnosis and treatment of neurological disorders
- Influence public or hospital policy
- Promote efficient use of resources
- Identify research priorities based on gaps in current literature

AAN Guideline Development Process

Select Guideline Topic
↓
Form Balanced Panel of Experts
↓
Develop Clinical Questions
↓
Comprehensively Review the Literature
↓
Rate Articles and Summarize Findings
↓
Write Guideline that Makes Explicit, Supported Practice Recommendations
↓
Distribute Draft for Extensive Peer Review by AAN, *Neurology*, and Others
↓
Obtain AAN Approval of Guideline

1. TOPIC DEVELOPMENT

1.1 Topic Nominations
1.2 Forming the Author Panel
1.3 Completing the Project Development Plan
- Potential clinical questions
- Terms and databases to be used in the literature search
- Inclusion and exclusion criteria for article selection
- Project timeline

Clinical Question Development:

Clinical questions should have three basic components:
- Population: The type of person (patient) involved
- Intervention: The type of exposure that the person experiences (therapy, test, risk factor, prognostic factor, etc.)
- Outcome: The outcome(s) to be addressed

Clinical Question Development:

a) Problem/Issue to be addressed
b) To what patient population does this apply?
c) What is the intervention (therapy, test, risk factor)?
d) What are the outcomes of interest?
e) State one or more answerable clinical questions that include the population, intervention and outcomes of interest

Clinical Question Development:

Examples:
- *What is (are) the best medication(s) for controlling seizures while minimizing side effects and providing a good quality of life for a patient who requires treatment for epilepsy?*
- *Does anticonvulsant prophylaxis decrease the risk of developing late seizures in patients with head injury?*

Evidence-Based Medicine-Related Terms for Searching MEDLINE

	MeSH Terms	MeSH subheadings	Textwords
Etiology	epidemiologic studies (exp), case-control studies, cohort studies, risk, risk assessment, risk factors, odds ratio	chemically induced complications, congenital embryology, epidemiology, etiology, genetics immunology, microbiology, parasitology, secondary transmission	Cohort risk causa$ predispos$

Evidence-Based Medicine-Related Terms for Searching MEDLINE

	MeSH Terms	MeSH subheadings	Textwords
Diagnosis	sensitivity and specificity double blind method single blind method	Used with disease terms or anatomical terms: diagnosis radiography radionuclide imaging ultrasonography Used with diagnostic techniques or methodologies: diagnostic use	Diagnosis diagnos$ sensitivity specificity predictive

Evidence-Based Medicine-Related Terms for Searching MEDLINE

	MeSH Terms	MeSH subheadings	Textwords
Treatment	clinical trials (exp) research design (exp) comparative study placebos double blind method	Used with disease terms: therapy drug therapy nursing prevention and control radiotherapy rehabilitation surgery transplantation Used with drugs and other therapeutic procedures: therapeutic use administration and dosage adverse effects contraindications poisoning toxicity	therap$ treat$ manag$ placebo$ random$

Evidence-Based Medicine-Related Terms for Searching MEDLINE

Publication types

- clinical trial
- randomized controlled trial
- multicenter study
- practice guidelines
- clinical guidelines
- consensus
- development
- reports
- overview
- meta-analysis

2- DATA REVIEW AND ANALYSIS DATA

2.1 Performing the Literature Search REVIEW

2.2 Selecting Articles for Inclusión

2.3 Data Extraction and Classification of the Evidence

2.4 Development of the Evidence Tables

2.5 Formulating Conclusions

2.6 Formulating Recommendations

2.1 Performing the Literature Search REVIEW

Criteria for Literature Search:

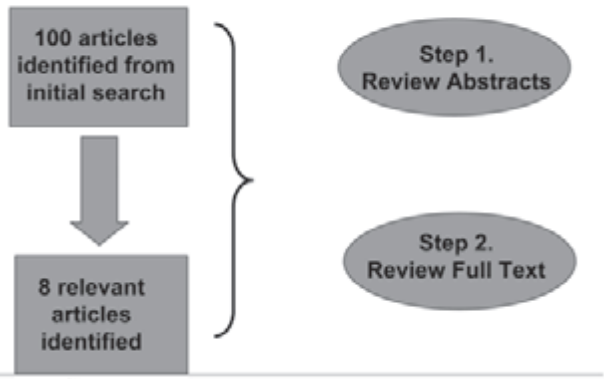
a) Key Text words and Index words for the condition or closely related conditions, if appropriate (linked by the word "OR"):

b) b) Key Text words and Index words for the intervention

c) Databases to be searched (e.g. MEDLINE, EMBASE, Current Contents)

d) Years to be included in the search

2.2 Selecting Articles for Inclusión



2.3 Data Extraction and Classification of the Evidence

- Citation information
- Items relevant to the study generalizability
- Elements relevant to the quality of evidence contained within the study
- Elements relevant to the study outcomes

2.3 Data Extraction and Classification of the Evidence

Quality-of-Evidence Indicators

- Use of a comparison (control) group
- Method of treatment allocation (randomized versus other)
- Method of allocation concealment
- Proportion of patients with complete follow-up
- Use of intent-to-treat methodologies
- Use of masking throughout the study (single-blind, double-blind, independent assessment)

2.3 Data Extraction and Classification of the Evidence

For screening questions critical elements include:

- Study design (prospective vs. retrospective)
- Setting (population-based, clinicbased or referral-center-based)
- Sampling method (selected or statistical)
- Completeness (all patients in the cohort underwent the intervention of interest)
- Masking (interpretation of the diagnostic test of interest was performed without knowledge of the patient's clinical presentation)

2.3 Classification of the Evidence: Patient Relevant Outcomes

Common Formulas for Calculating Effect Sizes for Therapeutic questions:

	Good	Poor
Treated	A	C
Untbreated	B	D

Relative Rate = [A / (A + C)] / [B / (B + D)].
Rate Difference = [A / (A + C)] - [B / (B + D)].

2.3 Classification of the Evidence: Patient Relevant Outcomes

Common Formulas for Calculating Effect Sizes for Diagnostic (Prognostic) Accuracy Questions:

	Disease (outcome) present	Disease (outcome) absent
Test (predictor) Positive	A	C
Test (Predictor) Negative	B	D

Relative Risk = [A / (A + C)] / [B / (B + D)].
Sensitivity = A / (A + B) *Positive Predictive value* = A / (A + C)
Specificity = D / (C + D) *Negative Predictive value* = D / (B + D)

2.3 Data Extraction and Classification of the Evidence

Classifying the evidence: the risk of bias

- class I: low risk of bias
- class II; moderate risk of bias
- class III: moderate to high risk of bias
- class IV: very high risk of bias

Classifying Evidence for:

Therapeutic Questions

- Comparison (Control) Group
- Treatment Allocation
- Completeness of Follow-Up
- Masking

Diagnostic or Prognostic Accuracy Questions

- Comparison (Control) Group
- Study Design
- Patient Spectrum
- Reference Standard
- Completeness
- Masking

Rating scale of evidence

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment. The following are required:

a) primary outcome(s) clearly defined
b) exclusion/inclusion criteria clearly defined
c) adequate accounting for drop-outs and cross-overs
d) relevant baseline characteristics

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above,

OR, a RCT in a representative population that lacks one criteria a-d.

Rating scale of evidence

Class III:

All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement

Class IV:

Evidence from uncontrolled studies, case series, case reports, or expert opinion.

2.5 Formulating Conclusions

- Class I studies only > Are *established* as safe and effective…
- Class II studies only or class I and II studies: > Are *probably* safe and effective…
- Class III studies only, or a combination of class III, II, and I studies > Are *possibly* safe and effective…
- Class IV studies > there is insufficient evidence to support a conclusion of effectiveness (or lack of effectiveness)

2.5 Formulating Conclusions

Four kinds of information need to be considered when formulating the conclusion:

- The class of evidence
- The effect (was the study positive or negative)
- Random error (the power of the study as manifested by the width of the confidence intervals)
- The consistency between studies

2.6 Formulating Recommendations

The formulation of recommendations lows from the conclusions: are best formatted in a way that clearly shows how they answer the clinical question. Thus,

- an "established as" (two class I) conclusion supports a "should be done" (level A) recommendation;
- a "probably effective" (two class II) conclusion supports a "should be considered" (level B) recommendation;
- a "possibly effective" (two class III) conclusion supports a "may be considered" recommendation.

Definitions for Classification of Evidence

Level	From evidence to recommendations	Conclusion
A	at least two consistent Class I studies (Should be done or, should not be done)	Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population
B	at least one Class I study or two consistent Class II studies (Should be considered or, should not be considered)	Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population

Definitions for Classification of Evidence

Level	From evidence to recommendations	Conclusion
C	at least one Class II study or two consistent Class III studies (May be considered or, may not be considered)	Possibly effective, ineffective or harmful for the given condition in the specified population
U	Studies not meeting criteria for Class I – Class III (Recommendation: None)	Data inadequate or conflicting. Given current knowledge, treatment (test, predictor) is unproven

Limitations and harms of clinical guidelines *

* Woolf s, et al. *BMJ* 1999;318;527-530

EVIDENCE-BASED MEDICINE *

- EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.
- The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research
- EBM is not restricted to RCTs and meta-analyses . . .

* http://www.cebm.net/index.asp •(Sackett et al., 1996).

EVIDENCE-BASED MEDICINE

- Many questions about treatment do not require RCTs, cannot wait for RCTs to be conducted or are not answerable by RCTs. . .
- Without clinical expertise, practice may become tyrannized by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient.
- Without current best evidence, practice risks becoming outdated, to the detriment of patients'

Concerns on Epilepsy Guidelines

- The blanket advice of many restrictive guidelines, based on a limited number of RCTs that are narrow in their scope, almost invariably ignores the fact that optimal therapy can differ in different syndromes and in different clinical settings.
- Commercially funded systematic reviews are prone to bias in favour of the sponsor and have been shown to score badly on scientific validity.
- Political interference, personal ego and prejudice are common in guideline committees.
- Guidelines are not regulations but often are treated as such

Concerns on Epilepsy Guidelines

- small numbers of published randomized trials,
- difficulty in identification of good data,
- selection of end points that do not fully inform treatment choice,
- lack of generalizability of studies, and
- too little attention to impact of mode of use.

As the ILAE guidelines states:

- ". . . It must ultimately remain for the individual physician to use his judgment and expertise when deciding on the most appropriate antiepileptic drugs for a specific patient . . . . . This document is only the first attempt to create a working framework rather than a rulebook about the treatment of new onset epilepsy . . ."

Constructing Guidelines Conclusions

- Clinical guidelines are increasingly part of current practice and will become more common over the next decade.
- Great care needs to be taken both to maximize the validity of guidelines and to ensure their use within clinical practice.
- Guidelines will not address all the uncertainties of current clinical practice and should be seen as only one strategy that can help improve the quality of care that patients receive.
- Guidelines will always need to be combined with the skill, knowledge, and the experience of the individual physician

Discussão de casos clínicos – genética das epilepsias

Iscia Lopes Cendes

2ª Escola Latino-Americana de Verão em Epilepsia
2ª Escuela latino-Americana de Verano em Epilepsia
2nd Latin-American Summer School on Epilepsy
São Paulo, SP, BRASIL **February 2008**

Caso 1: Paciente do sexo masculino de 23 anos estudante de engenharia refere que aos 15 anos iniciou com episódios nos quais ouvia um som semelhante a uma motocicleta, alguns desses episódios eram também acompanhados de visão distorcida (face ou objetos). Esses episódios acontecem pelo menos 1 vez a cada 6 meses. Nunca se importou muito com eles até porque seu pai apresenta "episódios" semelhantes e nunca procurou auxílio médico por essa razão, porém sua noiva que presenciou um desses "episódios" insistiu para que ele procurasse o neurologista. O paciente nega qualquer outro evento mesmo durante o sono (o que foi confirmado com a mãe), teve um desenvolvimento adequado e foi sempre ótimo aluno. O exame geral e neurológico é normal. A história familiar revela que o pai do paciente assim como 3 outros tios paternos (2 mulheres e 1 homem) também apresentam episódios muito semelhantes e uma das tias conta que também tem "episódios" nos quais sente uma "sensação estranha de familiaridade, como se já tivesse vivido aquela situação ou ido a lugares que nunca freqüentou antes". A outra tia paterna além dos "episódios" apresentou também em uma única ocasião uma "convulsão" durante o sono. Somente a tia que teve a convulsão usa medicação antiepilética os demais não usam medicação e consideram os episódios como "normais" ou "coisa da família".

Caso 2: Adolescente do sexo feminino de 16 anos de idade, natural de Monte Santo, MG e procedente de Franca, SP. Refere que a partir dos 6 anos iniciou com quadro de "tremores", que inicialmente apareciam apenas durante a movimentação. O quadro foi piorando com o aparecimento de "choques" principalmente em membros superiores (parecia que tinha levado um "susto"), seguido de perda de equilíbrio ao andar e dificuldade para pegar objetos ("errava o alvo"). Notou também que sua fala anda arrastada, como se estivesse embriagada. O quadro foi a acompanhado de sintomas de labilidade emocional (como choro fácil), mas não teve um declínio cognitivo perceptível até o momento. Refere também que há 1 ano iniciou com "convulsões" que têm se repetido pelo menos 1 vez por mês. Segundo a paciente o sintoma que mais a incomoda são os movimentos e os "choques". Fez uso de fenitoína por 4 meses depois do início das convulsões, mas teve que interromper, pois sentiu uma piora importante do equilíbrio. Nega outros casos na família, é a segunda filha de uma irmandade de 3 irmãos (ela e mais 2 irmãos homens). Nega consangüinidade nos pais, mas ambos são nascidos em Monte Santo, uma pequena cidade do sul de MG com 6.000 habitantes.

Caso 3: Criança do sexo masculino de 1 ano e 3 meses, o terceiro filho de casal não consangüíneo (tem outras 2 irmãs mais velhas) sendo que a mãe perdeu uma gestação antes do nascimento dele aos 6 meses de gravidez de um feto masculino. Procura o serviço de neurologia infantil por apresentar retardo do desenvolvimento neurológico identificado desde os primeiros meses (ainda não senta sozinho), acompanhado de crises convulsivas desde os 6 primeiros meses. Refere ter feito uso de várias medicações anticonvulsivantes sem um controle adequado das crises. Sua irmã mais velha (de 8 anos) também teve algumas crises somente durante o sono e hoje faz uso de medicação com bom controle. Nenhuma das 2 irmãs tem retardo mental. Mãe e pai são hígidos. Não há nenhuma outra criança com quadro semelhante na família.

Caso 4: Recém-nascido (10 dias de vida) de parto normal sem intercorrências, foi encaminhado ao neuropediatra por ter apresentado no berçário uma convulsão no terceiro dia de vida. Recebeu alta do berçário usando fenobarbital, mas não mais teve qualquer episódio. Atualmente país referem que a criança se comporta normalmente, com boa sucção e bom ganho ponderal. O pai está reticente em manter a medicação pois ele também teve uma convulsão única no período neonatal que nunca mais se repetiu. Todos os exames para alterações metabólicas e infecciosas estavam normais no momento da convulsão, mas mesmo assim a criança foi medicada com antibióticos e fenobarbital endovenoso. Nenhuma outra criança na família tem ou teve crises e os pais não são consangüíneos (mãe de origem italiana do interior de São Paulo e pai originário de Recife).

Caso 5: Criança de 6 anos com quadro de início aos 8 meses quando ocorreu a primeira tônico-clônica em presença de febre, que foi seguida de outros episódios de crises tônico-clônicas, sendo a maioria induzida por febre. Aos 2 anos apareceram também crises mioclônicas. As crises são freqüentemente prolongadas, tendo levado levando à ocorrência do *status epilepticus* em uma ocasião. O desenvolvimento neurológico foi normal antes do início das crises, mas atualmente é comprometido. Até o momento não foi conseguido um controle adequado das crises com medicação. Pais são hígidos sem consangüinidade, negam casos semelhantes na família.

Síndromes epilépticas geneticamente determinadas: Aspectos clínicos e moleculares

Iscia Lopes Cendes

O reconhecimento de que fatores genéticos são importantes na etiologia das epilepsias vem desde os tempos de Hipócrates. Na era moderna, vários estudos têm demonstrado de forma científica a importância desses fatores na determinação das epilepsias generalizadas idiopáticas. No entanto, as epilepsias focais eram vistas, até bem pouco tempo, como determinadas predominantemente por fatores ambientais. Recentemente, um número cada vez maior de relatos tem documentado a ocorrência de famílias segregando diversas formas de epilepsia focal.

1. Introdução

Epilepsia é uma das condições neurológicas mais comuns, ocorrendo em aproximadamente 1 a 1.5% da população geral[1]. A Classificação das Epilepsias e Síndromes Epilépticas, proposta pela ILAE (*International League Agaisnt Epilepsy*) divide as epilepsias em idiopáticas, sintomáticas e criptogênicas[2]. O grupo das epilepsias idiopáticas corresponde a aproximadamente 50% do total das epilepsias humanas[1]. É nas epilepsias idiopáticas que a predisposição genética se apresenta de maneira mais marcada. Inicialmente, acreditava-se que as epilepsias idiopáticas generalizadas apresentavam um forte componente genético, mas que as epilepsias parciais eram predominantemente causadas por fatores ambientais. Foram os estudos clínicos e eletrencefalográficos realizados por Andermann que chamaram a atenção para o envolvimento de fatores genéticos também nas epilepsias parciais[3,4]. Mais recentemente, com a identificação de síndromes especificas de epilepsia parcial familiar[5-7]os estudos de genética molecular das epilepsias idiopáticas parciais tomou novo impulso[8-10].

2. Estudos de epidemiologia genética

Desde os primórdios da medicina muito se tem especulado sobre a base genética das epilepsias[3,4]. Nos anos 50 e 60 vários estudos epidemiológicos demonstraram as primeiras evidências científicas para uma predisposição genética nas várias formas de epilepsia[11-13]. Nesses trabalhos se observou que o risco de desenvolver epilepsia era de 1.5 a 5 vezes maior nos indivíduos com antecedente familiar da doença do que na população geral [14,15]. Observou-se também em vários estudos que o risco para familiares de pacientes com epilepsia generalizada idiopática era aproximadamente 2 vezes maior do que o risco para indivíduos com história de epilepsia parcial[16-18]. Estudando mais de perto o tipo de fator genético envolvido na susceptibilidade para epilepsia, Lennox em 1951[11] e Inouye em 1960[17] demonstraram que a concordância clínica entre gêmeos monozigóticos, quando comparada com a concordância em pares dizigóticos, sugere a presença de um fator genético importante, mas demonstra também que o modelo de herança não é monogênico. Nos anos 70, Andermann[14] propôs o modelo multifatorial para as epilepsias, no qual fatores genéticos e ambientais interagem na determinação dos riscos de recorrência familiar da doença. Atualmente, as epilepsias, particularmente as idiopáticas, são vistas como doenças complexas do ponto de vista da herança genética[18]. Outros exemplos de doenças geneticamente complexas são: diabetes juvenil, hipertensão e doenças psiquiátricas como a esquizofrenia e a psicose maníaco-depressiva[19]. As doenças complexas são definidas como condições nas quais a correspondência entre o genótipo e fenótipo não é completa. Vários fatores são responsáveis pela "complexidade" dessas doenças, entre eles: penetrância incompleta, presença de fenocópias, heterogeneidade genética, herança poligênica ou multifatorial e alta prevalência na população geral[19-21].

3. A genética molecular e o estudo das epilepsias

Com os avanços recentes da biologia molecular as teorias sobre genes implicados na transmissão

das epilepsias poderão ser finalmente comprovadas experimentalmente.

Existem duas estratégias básicas para se localizar genes que causam doenças:

a) O teste de genes candidatos relacionados com a alteração metabólica ou os mecanismos fisiopatológicos da doença. **b)** A clonagem posicional realizada sem o conhecimento *a priori* das alterações metabólicas e/ou processos fisiopatológicos de base. Essa última estratégia utiliza técnicas de manipulação do DNA visando o mapeamento genético. A utilização das técnicas de clonagem posicional tem resultado em inúmeros sucessos no mapeamento genético das doenças neurológicas, cujos mecanismos são complexos e pouco conhecidos. As epilepsias são um bom exemplo dessa categoria de doenças.

Mesmo com o sequenciamento completo do genoma humano, anunciado desde o ano 2000, a estratégia de **clonagem posicional** permanece útil. Isso porque o conhecimento da seqüência do DNA não nos fornece informações precisas da localização física dos genes ou de sua função. Vale lembrar que o mapeamento do *locus* é apenas o passo inicial para a identificação de um gene que causa doença, e para alcançar tal mapeamento podemos nos valer basicamente de 2 tipos de desenho experimental: **estudos de ligação** e **análise de associação**[22]. A escolha de um ou outro método se baseia no tipo de efeito genético influenciando a doença em estudo. Seja esse efeito na forma de um gene maior ou de genes menores influenciando o fenótipo. Em geral na presença de um únic gene, responsável pela predisposição genética (herança monogênica) émais comum o encontro de recorrência familiar, levando à disponibilidade de grandes famílias com vários indivíduos afetados para o estudo. A situação oposta ocorre quando a característica em estudo é influenciada por fatores genéticos mais complexos, na forma de múltiplos genes influenciando o fenótipo (herança poligênica), ou quando existe a interação de fatores genéticos e ambientais (herança multifatorial) na determinação final das características clínicas da doença. Neste caso a recorrência familiar é menos freqüente, levando à necessidade do estudo de pacientes isolados não relacionados.

Para a primeira situação, ou seja de genes maiores determinando o fenótipo e levando a grande recorrência familiar utilizamos preferencialmente os **estudos de ligação**. O estudo de ligação, é baseado no conceito de recombinação e no princípio de que quando dois genes estão próximos no mesmo par cromossômico eles não se segregam independentemente. Dessa forma, pode-se usar a porcentagem de recombinantes como um indicador quantitativo da distância linear entre dois genes em um mapa genético[23]. Portanto, se dois genes estão ligados, significa que estão muito próximos entre si e, conhecendo a posição cromossômica de um desses genes, a posição cromossômica do segundo gene pode ser inferida. Uma das estatísticas mais comumente utilizadas para confirmar ou afastar ligação é o *lod score* (Z) [24].

Se ao contrário, não observamos grande recorrência familiar da doença e a maior parte dos casos é dita isolada, damos preferência aos **estudos de associação**, onde utilizamos material proveniente de indivíduos doentes, não aparentados, seguindo um desenho do tipo "caso-controle". No estudo de associação a freqüência dos alelos nos indivíduos afetados (casos) é comparada com a freqüência nos controles (indivíduos sem a doença)[22]. A análise de associação é mais útil do que a de ligação para confirmar a suspeita da participação de um determinado alelo na manifestação de uma certa característica ou de um alelo existente em um *locus* próximo ao responsável pela característica. As associações podem ocorrer porque o próprio gene marcador é o causador da patologia ou porque o alelo do gene marcador está em **desequilíbrio de ligação** com a mutação do gene relacionado à doença[25].

Segundo uma visão alternativa, podemos considerar que a utilização desses dois estudos na identificação de genes é complementar, uma vez que a análise de ligação visa encontrar *loci* possivelmente responsáveis pela expressão da doença e o estudo de associação indica a presença de um *locus* de susceptibilidade que aumenta a chance do indivíduo apresentar a doença, mas não garante que ela será expressa[25].

Atualmente são utilizados marcadores moleculares microssatélites na maioria dos estudos de ligação em humanos. Tais marcadores são seqüências de DNA repetitivo em *tandem* de dinucleotídeos[26]. Estes marcadores são mais informativos nos estudos de ligação, por serem numerosos e altamente polimórficos na população humana, características que auxiliam na análise das famílias genotipadas e conferem o máximo de informação para estudos de ligação[26].

Já nos estudos de associação, nos quais se têm como base a comparação da freqüência alélica

ou genotípica entre casos e controles o tipo de marcadores mais utilizados atualmente são os polimorfismos de base única ou SNPS[22,28]. Nesse tipo de estudo, em geral, são formuladas duas hipóteses: H_0 para não associação e H_1 para associação. Utilizando cálculos estatísticos adequados, como testes de χ^2, e analisando os resultados de *p-value*, rejeita-se ou não H_0. No caso de rejeição de H_0 fica mostrado associação entre gene ou *locus* estudado e a doença. Neste tipo de estudo, rejeita-se H_0 para valores de $p < 0,01$[22].

Os estudos de associação são utilizados na detecção de genes de susceptibilidade à determinada doença, os quais apresentam efeitos discretos ou moderados na sua determinação[22], o que torna estes testes estatísticos mais adequados para doenças poligênicas e multifatoriais[25].

4. Progressos recentes no mapeamento e identificação de genes implicados nas epilepsias.

Com o uso combinado das diferentes estratégias para a localização e identificação de genes implicados em doenças humanas vários loci para diferentes formas de epilepsia humana já foram localizados e alguns genes identificados. Como esperado, a maior parte das epilepsias mapeadas até o momento mostra uma herança genética Mendeliana clássica (autossômica dominante ou recessiva) ou são doenças degenerativas com alterações bioquímicas conhecidas cujos genes já haviam sido previamente identificados. Nessas doenças as estratégias que tiveram sucesso foram os estudos de ligação genética. As formas de epilepsia mais comuns e que apresentam herança genética mais complexa (poligênica e/ou multifatorial) ainda desafiam os pesquisadores da área e mesmo com os progressos nos estudos de associação resultados concretos e replicáveis ainda não estão disponíveis.

É importante diferenciar entre o mapeamento de um *locus* para a doença e a clonagem de um gene. O mapeamento do *locus* com a utilização dos estudos de ligação é o passo inicial para a identificação de um gene que causa doença. Mas somente com a identificação do gene cujas alterações (ou mutações) levam a doença podemos começar a compreender melhor os mecanismos básicos que levam ao aparecimento da epilepsia.

Com os avanços das técnicas de mapeamento, novos genes responsáveis pela transmissão das epilepsias deverão ser mapeados em um futuro bem próximo. O desenvolvimento de novos métodos de análise estatística e de novas técnicas de biologia molecular possibilitarão a localização de genes que predispõem as formas mais comuns de epilepsia e que apresentam uma herança genética complexa. Além disso, interações entre múltiplos genes e fatores ambientais poderão ser melhor investigadas. Isso possibilitará avanços importantes no entendimento dos mecanismos básicos responsáveis pela epileptogênese, o que por sua vez poderá resultar em terapêutica mais específica e eficiente.

Os Testes Moleculares

As mutações são em última instância as responsáveis pelas doenças genéticas. Hoje em dia já existem disponíveis testes moleculares específicos para uma série de mutações. Esses testes tem desempenhado um papel cada vez mais importante na prática clínica, já que apresentam uma alta sensibilidade e especificidade para o diagnóstico de uma série de doenças neurológicas.

Os testes moleculares podem ser realizados a partir do DNA, RNA e proteína, dependendo do tipo de teste ou mesmo do tipo de mutação envolvido. A característica principal do testes molecular é ser altamente sensível e específico, ou seja sua capacidade de fazer o diagnóstico é muito alta (em várias ocasiões chegando a 100%) e sua porcentagem de resultados falso positivos muito baixa. No entanto, o teste molecular é pontual, ou seja, o teste deve ser orientado por uma suspeita clínica bem firmada. Principalmente devido ao seu alto custo e necessidade de mão de obra altamente especializada, quando se decide por um teste molecular devemos saber o que estamos procurando, qual(ais) o(s) gene(s) possivelmente envolvido(s) ou até que tipo de mutação específica pode estar causando a doença.

Ainda não existe uma recomendação consensual sobre quando e como utilizar testes moleculares para epilepsias na prática clínica. Esse é um assunto que está sendo discutido por especialistas da ILAE e uma recomendação deve ser divulgada em breve. No momento, recomenda-se a utilização de muita cautela na indicação e interpretação de testes moleculares para as epilepsias (este assunto será discutido com mais profundidade nas aulas teóricas e nas discussões de casos durante o curso).

Uma grande dificuldade hoje em dia é se manter atualizado sobre quais os testes disponíveis e mesmo onde estão sendo realizados. Em nosso

país, esse tipo de informação não está compilado de maneira sistemática. Havendo interesse do clínico nesse tipo de teste, o ideal é procurar por grupos de pesquisa que têm interesse conhecido na área. Em geral, esses grupos poderão orientar sobre a disponibilidade dos testes moleculares para situações específicas e o local onde poderão ser realizados. Vale lembrar que nenhum teste molecular é atualmente coberto pelo **S**istema **Ú**nico de **S**aúde no Brasil.

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Genetic of the epilepsies

Iscia Lopes Cendes

Questões

- As epilepsias são geneticamente determinadas?
- Qual a proporção de epilepsias que são geneticamente determinadas?
- Quais são os tipos de epilepsia geneticamente determinadas?
- Qual a freqüência e quais as formas de epilepsia monogênica?

- A maioria das epilepsias tem etiologia genética
  - Alterações no DNA que levam ao mal funcionamento do neurônio e podem causar epilepsia (canalopatias)
  - Alterações em genes envolvidos no desenvolvimento do sistema nervoso central levando a **malformações** que podem causar epilepsia

Fatores Modificadores do Fenótipo

- Gravidade da epilepsia
- Idade de início
- Resposta ao tratamento (FARMACOGENÉTICA)

Genes Modificadores (herança poligênica)

↓

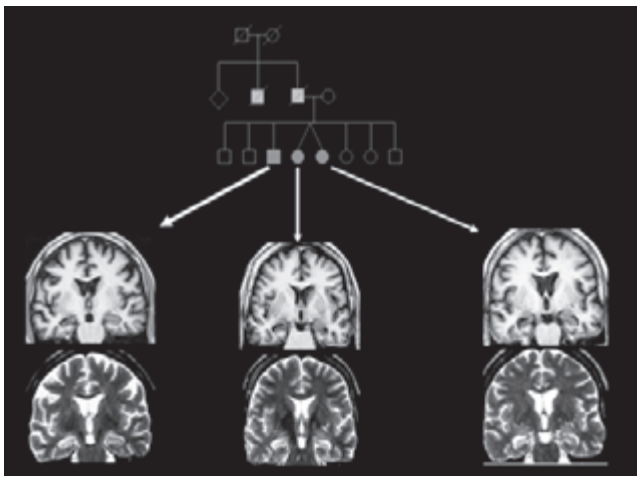
Doença Complexa

Genetic factors associated with seizure severity

Why patients get severe epilepsy?

Genetic predisposition to severe epilepsy

- Animal models: kindling in wild type animals leading to different response
- Marked variability in clinical presentation and seizure severity in monogenic seizure disorders



Pharmacogenetics and Pharmacogenomics

- Addresses the genetic differences in drug response: efficacy, metabolism and adverse effects (teratogenic effects)
- Applies new technology, or whole genome technology to these studies
  - *High output DNA sequence and gene expression studies*

Testes Genéticos

- Citogenética clássica: exame de cariótipo
- Citogenética molecular: método de FISH
- Testes bioquímicos de triagem: bateria de EIM e cromatografia de amino-ácidos
- Testes bioquímicos específicos: dosagens de metabólitos e dosagens enzimáticas

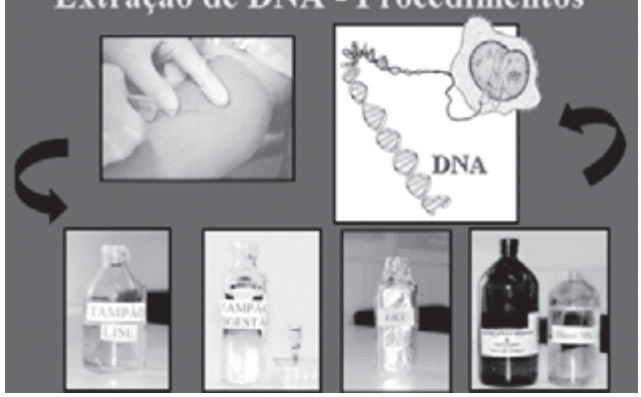
Testes Moleculares

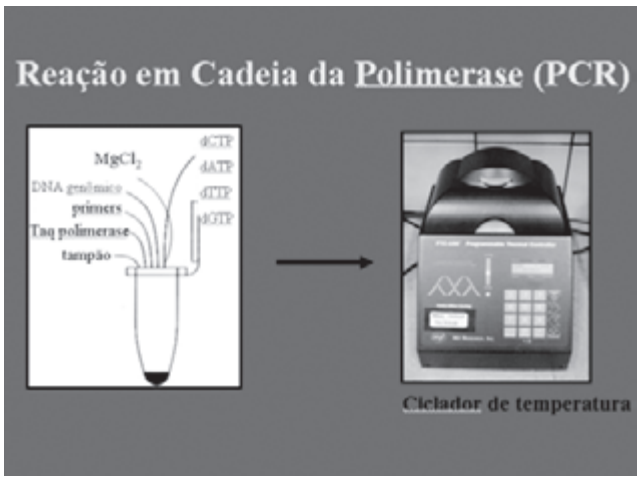
- Exames feitos a partir do DNA, RNA ou proteínas oriundas de pacientes e/ou familiares

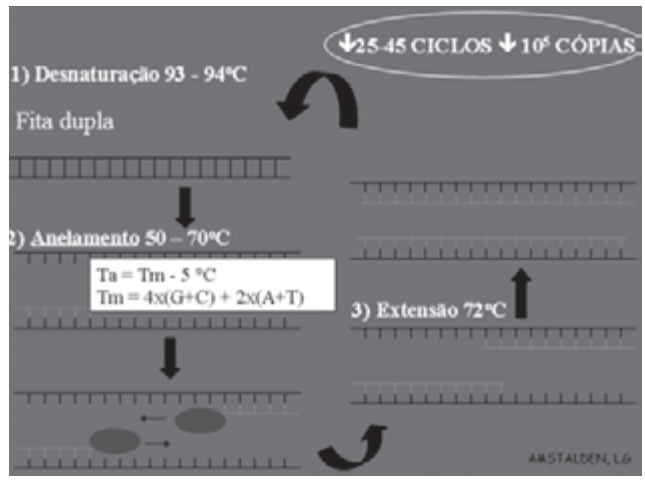
Alteração no DNA

- Mutação: qualquer alteração na seqüência normal do DNA → nocivo para o organismo
  - Durante o processo normal da vida da célula (erros na divisão celular)
  - Causada por fatores externos: radiação (raios-X, ultra-violeta, etc.), agentes químicos (armas biológicas)

Extração de DNA - Procedimentos

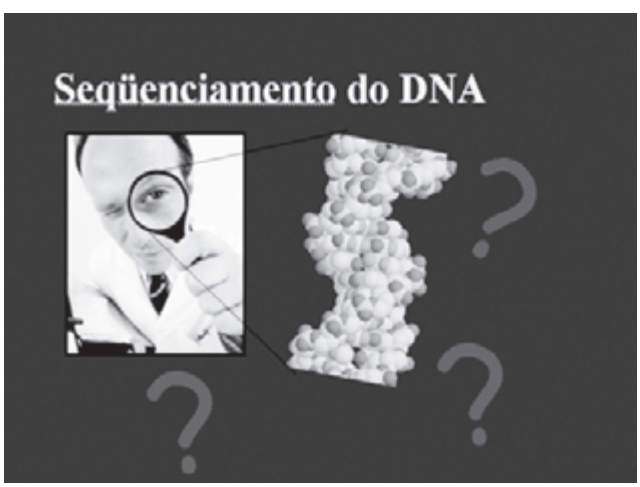



Reação em Cadeia da Polimerase (PCR)
$MgCl_2$
DNA genômico
primers
Taq polimerase
tampão
dCTP
dATP
dTTP
dGTP
Ciclador de temperatura


25-45 CICLOS 10⁶ CÓPIAS
1) Desnaturação 93 - 94ºC
Fita dupla
2) Anelamento 50 – 70ºC
Ta = Tm - 5 ºC
Tm = 4x(G+C) + 2x(A+T)
3) Extensão 72ºC
AMSTALDEN, LG

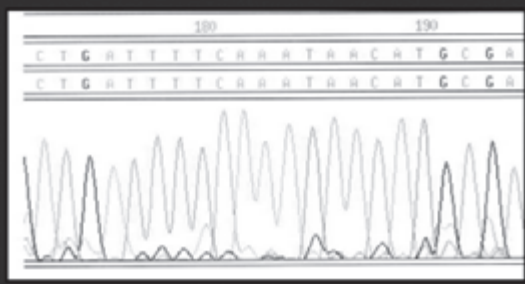

Digestão Enzimática
• Endonucleases de restrição
• Classes: I, II
• Mais de 1300 enzimas ident
MOLÉCULA DE DNA CLIVA
FRAGMENTOS DE TAMA
DIFERENTES


Eletroforese em gel
AMSTALDEN, LG


Seqüenciamento do DNA

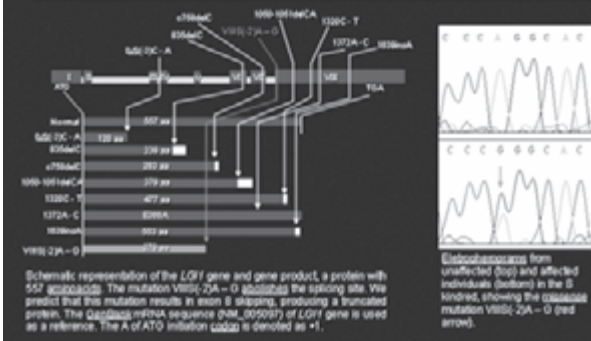

Gel electrophoresis

Eletroferograma



N.F. Santos, E.Kobayashi, F.R.Torres, R. Secolin, L.A.F.Sardinha, F.Cendes, I.Lopes-Cendes
Familial temporal lobe epilepsy with auditory auras: clinical and genetic heterogeneity

Mutation analysis of LGI1 gene



Schematic representation of the *LGI1* gene and gene product, a protein with 557 aminoacids. The mutation VIII9(-2)A – G abolishes the splicing site. We predict that this mutation results in exon 8 skipping, producing a truncated protein. The GenBank mRNA sequence (NM_005097) of *LGI1* gene is used as a reference. The A of ATG initiation codon is denoted as +1.

Electropherograms from unaffected (top) and affected individuals (bottom) in the S kindred, showing the missense mutation VIII9(-2)A – G (red arrow).

Estudo de Mutações na Prática Clínica

- Necessário para diagnóstico?
- Necessário para terapêutica?
- Testes preditivos?

Pergunta Central

- O diagnóstico molecular é sempre necessário?
- Em que situações o diagnóstico molecular é necessário?

Dois Pontos Importantes

- Necessário/Obrigatório
- Desejável (influenciado pela circunstância)
  - » Características clínicas
  - » História de vida
  - » Situação familiar

O Diagnóstico Médico

- Hipótese Diagnóstica (HD):
  - Baseada em dados clínicos (história clínica, história familiar e exame físico)
  - Corroborada por exames complementares (patologia clínica, imagem, testes bioquímicos, citogenéticos e moleculares)

Características do Teste Molecular

- Possibilidade de erro é pequena, para identificar a alteração no DNA
- Maior "eficiência" se dirigido por hipótese clínica bem fundamentada
- Implica em ter acesso ao material genético (DNA) do indivíduo e muitas vezes de familiares

Características do Teste Molecular

- Certeza x Probabilidade: interação entre fatores genéticos e ambientais na determinação da doença
- Expressividade variável ou variabilidade clínica: mesmo defeito genético levando a diferentes manifestações clínicas

Limitações do Teste Molecular

- Limitação técnica e econômica nas técnicas de triagem de mutações
- Heterogeneidade gênica: mutações em genes diferentes causando a mesma doença
- Heterogeneidade alélica: mutações de tipos diferentes no mesmo gene levando a mesma doença
- Falha em prever a gravidade da doença (heterogeneidade clínica), ou mesmo se vai haver doença (penetrância incompleta)

O Teste Molecular de Aplicação Clínica

- Teste diagnóstico (TD)
- Teste preditivo (TP)

TESTE PREDITIVO

➢ Detectar indivíduos saudáveis que mais tarde apresentarão ou poderão apresentar doenças genéticas

➢ Doenças monogênicas com alta penetrância

➢ Risco aumentado para detecção de desenvolvimento de doenças complexas

Fatores que influenciam a realização do TP

- Com possibilidade de tratamento
- Sem possibilidade de tratamento

Testes Preditivos em Doenças Complexas

- Não estão indicados se riscos atribuídos a mutação são baixos
- Podem ser realizados em sub-grupos Mendelianos dessas doenças:
  - Doença de Alzheimer: alelos APO E (4) podem ser usados até como auxílio no diagnóstico, mas o risco atribuível a esse fator de risco ainda não recomenda o seu uso para TP. No entanto, existem as formas AD da doença, que são passíveis de realização de TP.

Testes Preditivos em Doenças Complexas

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Epilepsy Genetics: Genotyping Can Help Clinical Practice

Antonio V. Delgado-Escueta

Epilepsy Genetics: Genotyping Can Help Clinical Practice

February 2008

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Epilepsy Center of Excellence, VA Greater Los Angeles Healthcare System
Los Angeles, California

Outline

I. Genotyping can help clinical practice
II. JME
- *(a) Subsyndromes and stages for epilepsy development*
- *(b) Myoclonin-EFHC1 functions*
  - ***(1) Susceptibility imbued by mutation effects on R type VDCC in dendrites***
  - ***(2) Epileptogenesis: Mutation reversal of apoptosis reduce pruning and disruption of neuroblast migration setup networks prime for epileptogenesis***

Lesson 1 - Genotyping Can Help Clinical Practice

YES	NO DATA YET
✓SCN1A	? Epitempin/LGI1
✓Laforin/Malin Lafora Disease	? Myoclonin/EFHC1
✓Cystatin B Unverricht-Lundborg	*But identification of synsyndromes may help treatment*
✓KCNQ2/KCNQ3 atypical BFNC – *Rarely helps*	
✓nACh Receptors: CHRA4 and CHRB2 (Nocturnal Frontal Lobe Epilepsy without family history) – *Rarely helps*	

Helps treatment and counseling

Why Genotype SCN1A?

26 exons in 100 kb in 100 kb genomic DNA; mutations cluster in 'C terminus', and loop between segments 5 and 6 of first three domains

Treatment-Response

AVOID sodium channel blockers: PHT, CBZ, OXC, LTG[1]

USE VPA+TPR *or* VPA+STR *or* VPA+LEV *or* VPA+Ketogenic Diet[2-4]

REFER to SMEI Online Parents Group

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SCN1A Mutations "Usual Clinical Suspects"

- Severe myoclonic epilepsy of infancy: 70%[1]
- Intractable GTC seizures of infancy (SME1B): 69%[2]
- GEFS+: 11% with SCN1A/SCN1B and SCN2A mutations[3]

1. Claes L, et al. *Am J Hum Genet.* 2001;68(6):1327-1332.
2. Fujiwara T, et al. *Brain.* 2003;126(pt 3):531-546.
3. Harkin LA, et al. *Brain.* 2007;130(pt 3):843-852.

Case Example – 1a

- 20 yo Iranian female whose 2-1/2 yo sister has the same epilepsy syndrome
- At 4 mo grand mal tonic-clonic convulsions started, resistant to treatment
- Between 6-12 mo, 3 bouts of convulsive status(afebrile and febrile)
- Phenobarbital, phenytoin, carbamazepine did not completely suppress convulsions
- At referral - 2 convulsions per week

Case Example – 1b

- AED history: phenytoin, carbamazepine, topiramate, zonizamide, depakote, trileptal, lyrica trials.
- Between 10-16 yo, convulsions stopped with depakote and zonizamide.
- At 16 yo, convulsions returned.
- Lamictal, zonizamide and lyrica used during consultation

Case Example – 1c

- EEG – interictal spikes phase reverse T3
- Video EEG – diffuse and bilateral single spike and slow wave complexes at 3 Hz heralded clonic jerks of the head to the left, then extensor posture during tonic phase followed by clonic convulsions for 56 seconds. Quick recovery.
- Diagnosis – Dravet Syndrome – SMEI-1B (Fujiwara T, et al. 2003)
- Treatment – IV depakone load and clobazam orally as lamictal, zonizamide and lyrica are discontinued.

SCN1A Mutations "Unusual Clinical Suspects"

- Cryptogenic generalized or focal epilepsy: 20%
- Vaccine encephalopathy: 11 of 14 cases (70%)[1]
- Adults with refractory epilepsy and intellectual disability onset in infancy: 10 of 14 cases (70%)[2]

Rarely -

- Myoclonic astatic epilepsy[3]
- Simple febrile seizures and temporal lobe epilepsy[4]

1. Berkovic SF, et al. *Lancet Neurol.* 2006;5(6):488-492.
2. Jansen FE, et al. *Neurology.* 2006;67(12):2224-2226.
3. Ebach K, et al. *Neuropediatrics.* 2005;36(3):210-213.
4. Colosimo E, et al. *Epilepsia.* 2007;48(9):1691-1696.

Genotype SCN1A (Nav1.1) When You See…

- …Febrile Convulsions in 1st year of life as prolonged or repeated seizure or status
- …Intractable GTC with onset at 1-2 years
- …Vaccine Encephalopathy, eg, pertussis
- …Refractory epilepsy and mild MR in adults with onset in infancy

AVOID PHT, CBZ, OXC, LTG

Why Genotype SCN1A?

26 exons in 100 kb in 100 kb genomic DNA; mutations cluster in 'C terminus', and loop between segments 5 and 6 of first three domains

Treatment/Intervention

AVOID sodium channel blockers: PHT, CBZ, OXC, LTG[1]

USE VPA+TPR *or* VPA+STR *or* VPA+LEV *or* VPA+Ketogenic Diet[2-4]

REFER to SMEI Online Parents Group

1. Guerrini R, et al. *Epilepsia.* 1998;39(suppl 3):S2-S10.
2. Striano P, et al. *Neurology.* 2007;69(3):250-254.
3. Ceulemans B, et al. *J Child Neurol.* 2004;19(7):516-521.
4. Korff CM, et al. *Nat Clin Pract Neurol.* 2007;3(9):505-516.

Why Genotype SCN1A?

26 exons in 100 kb in 100 kb genomic DNA; mutations cluster in 'C terminus', and loops between segments 5 and 6 of first three domains

CORRECT TREATMENT / INTERVENTION

AVOID sodium channel blockers: PHT, CBZ, OXC, LTG

USE VPA+TPR *or* VPA+STR *or* VPA+LEV *or* VPA+Ketogenic Diet

With correct treatment SMEI may not be as severe.

Why Genotype Laforin?

Intervention/Treatment

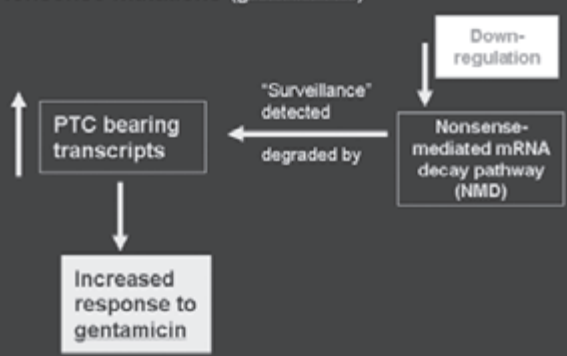
OFFER
Genetic counseling and psychosocial help to family

REFER
To Gene Therapy Trial (being organized)

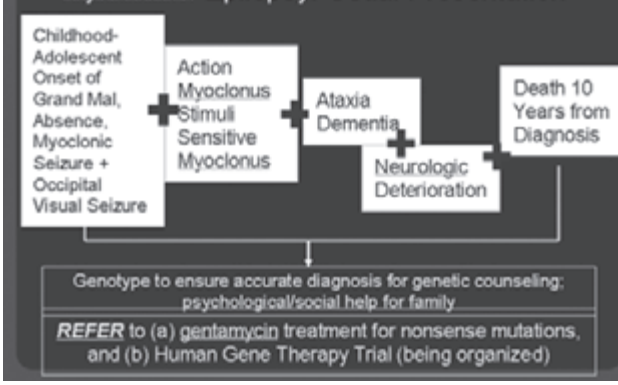
Why genotype?
Amnioglycosides and Nonsense Mutations (gentamicin)

- Nonsense mutations lead to premature termination codons (PTC)
- Aminoglycosides promote readthrough of PTC to enable expression of full-length functional protein
- Clinical trials in Duchenne Muscular Dystrophy, Becker Muscular Dystrophy and Cystic Fibrosis
- Clinical trials should be done in PME

REBUTTAL: Why genotype?
Generic Treatment with Amnioglycosides for Nonsense Mutations (gentamicin)



Laforin/Malin In Lafora Progressive Myoclonus Epilepsy: Usual Presentation



Genotype to ensure accurate diagnosis for genetic counseling; psychological/social help for family

REFER to (a) gentamycin treatment for nonsense mutations, and (b) Human Gene Therapy Trial (being organized)

Genotype Laforin In Progressive Myoclonic Epilepsy: Unusual Presentations With Family History of Lafora Disease

Childhood Learning Disorder: Dyslexia Between 5-10 Years; Failing Grades

Hepatic Failure In Childhood

Genotype to ensure accurate diagnosis for genetic counseling; psychological/social help for family

REFER to (a) gentamycin treatment for nonsense mutations, and (b) Human Gene Therapy Trial (being organized)

Case Example 2a

- 17 yr old female of Romanian descent with biopsy proven Lafora disease
- Mutation analyses
  (a) Nonsense mutation: *Transition C>T*
  Nucleotide Position: *721*
  Amino Acid Change: *Arginine>Stop codon*
  (b) Missense mutation: *Transition C>T*
  Nucleotide Position: *632*
  Amino Acid Change: *Proline>Leucine*

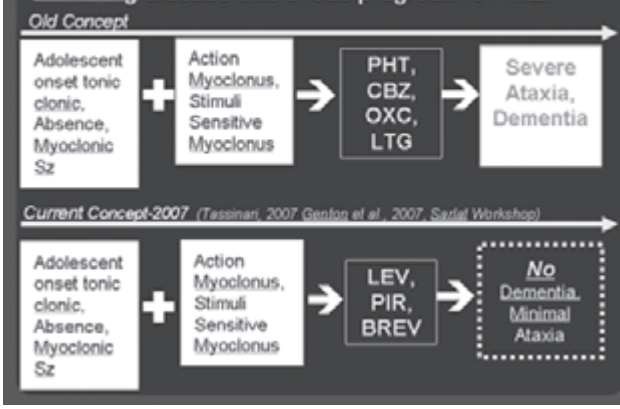
Case Example 3a

- 17 yr old female of Austrian (mother) and Russian Hebrew (father) descent with biopsy proven Lafora disease
- Mutation analyses
  (a) Nonsense mutation: *Transition C>T*
  Nucleotide Position: *163*
  Amino Acid Change: *Glutamine>Stop codon*
  (b) 32 bp deletion;
  Nucleotide Position: *108-139*
  Amino Acid Change: *Frame Shift*

Treatment for Case Examples 2 and 3

- IV gentamycin for 2 weeks at high doses
- Monitor glycogen synthase activity in skin fibroblasts
- Neurological examination to determine improvement in cerebellar signs
- Formal psychometric examination to determine improvements

Genotyping Changed our Concept on Unverricht Lundborg disease into a less progressive PME.



Genotype Cystatin B (Unverricht-Lundborg Disease)

Adolescent Onset Tonic Clonic, Absence, Myoclonic Seizure

+

Action Myoclonus, Stimuli Sensitive Myoclonus

AVOID PHT, CBZ, OXC, LTG[1]

USE LEV, PIR, BREV[2-4]

Prevent Severe Ataxia, Dementia

Genotype to ensure accurate diagnosis for genetic counseling: psychological/social help for family

REFER to Unverricht Lundborg family organization

1. Genton P, et al. *Epilepsia*. 2006;47(12):2083-2085. 2. Magaudda A, et al. *Epilepsia*. 2004;45(6):670-681. 3. Crest C, et al. *Neurology*. 2004;62(4):640-643. 4. Kasteleijn P, et al. *Neurology*. 2003;60(8):1394-1395.

SCN1A–The Epilepsy Gene Most Commonly Mutated In Different Epilepsies

"Location, Location, Location And Diagnosis"

52% truncations	→ 100% have SMEI of Dravet, a clinical Dx confirmed by SCN1A mutations
27% missense mutations	→ SMEI of Dravet in 75%
12% missense mutations in voltage sensor	→ GEFS+ SFS and TLE, SMEI, Doose Syndrome
10% other regions SCN1A, rarely	→ GEFS+
Cryptic genomic deletions 607 kb-4.7 mb	→ SMEI

Ceulemans BP, et al. *Pediatr Neurol.* 2004;30(4):236-243.

Case Example 4a

- 17 year old female referred for presurgical evaluation because of *"uncontrolled convulsions… 3 grand mal convulsions back-to-back last week"*
- History – febrile seizures at 6 months, staring with drooling at 7 months, *"Jumped out of chair during severe jerk at 1.5 years … Frequent jerks with falls"*
- AED trials – tegretol, topamax, keppra, zonizamide, trileptal, neurontin, dilantin, phenobarbital

Case Example 4ba

- EEG – 4-6 Hz spike wave complexes spontaneously, after 2.5 minutes of hyperventilation and during photic stimulation
- Video-EEG – pure clonic tonic clonic grand mal convulsions during 3.5-4.5 multispike wave complexes
- Family History – mother has febrile seizures, maternal grandfather has grand mal convulsions, maternal uncle has febrile seizures, grand mal convulsions and petit mal seizures; maternal uncle has a son and 2 daughters with grand mal seizures and petit mal seizures.
- Diagnosis – Generalized epilepsy with febrile seizures plus

Reminder: Why genotype?

Genotype SCN1A (Nav1.1) when you see…

…Febrile Convulsions in 1st year of life as prolonged or repeated sz or status

…Intractable GTC with onset at 1-2 yrs

…Vaccine Encephalopathy, e.g., pertussis

…Refractory epilepsy and mild MR in adults with onset in infancy

AVOID PHT, CBZ, OXC, LTG

Reminder – Genotyping helps clinical practice

YES
- ✓SCN1A
- ✓Laforin/Malin Lafora Disease
- ✓Cystatin B Unverricht-Lundborg

NO DATA
- ? Epitempin/LGI1
- ? Myoclonin/EFHC1

Treatment and counseling

Defines true phenotypes: With correct treatment SMEI and UL-PME may not be as severe

Prevents pre-surgical work-up and unnecessary brain surgery in JME, LD and UL-PMEs

Lesson 2 – Myoclonin/EFHC1 in JME

- Genotyping has separated
  - Classic JME
    - Has EFHC1 mutations
    - 70% success with treatment
  - CAE evolving to JME
    - Does not have EFHC1 mutations
    - Poor response to treatment

Martinez-Juarez IE, et al. *Brain.* 2006;129(Pt 5):1269-1280.

Lesson 3 - Treatment JME and Myoclonin EFHC1

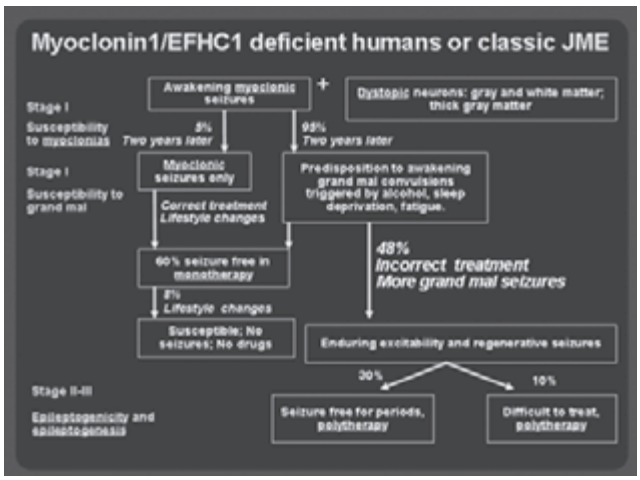
History and phenotypes

1. **Stages in genetic epilepsy: Susceptibility, epileptogenicity, and epileptogenesis**
2. **Myoclonin1/EFHC1: 20% of JME families and 9% of consecutive JME clinic cases**
3. **Susceptibility and calcium function and NMDA receptors: Amenable for treatment**
4. **Epileptogenicity predisposed by neuroanatomical systems produced by a developmental gene**
5. **Treatment algorithm:**
   - **Prevent epileptogenesis in classic JME**
   - **CAE evolving to JME: poor response to treatment**

Suzuki et al, Nat Genet 2004; Martinez et al, Brain 2006; Medina et al, Neurology 2007; de Nais et al, Exp Cell Res 2006

Lesson 3 (continued)– Three stages of JME

- **Susceptibility**
  - **decreased threshold for provoked seizures**
- **Epileptogenicity**
  - **decreased threshold for genesis of chronic epilepsy**
- **Established Epileptogenesis**
  - **enduring and regenerative chronic epilepsy**



Lesson 3 (continued): Treatment JME and Myoclonin EFHC1

- **Myoclonin1/EFHC1: 20% of JME families and 9% of consecutive JME clinic cases**

Suzuki et al, Nat Genet 2004; Martinez et al, Brain 2006; Medina et al, Neurology 2007; de Nija et al, Exp Cell Res 2006

Lesson 3 – Treatment JME and Myoclonin EFHC1

- **Treatment algorithm:**
  - **Prevent epileptogenesis in classic JME**
  - **CAE evolving to JME: poor response to treatment**

Suzuki et al, Nat Genet 2004; Martinez et al, Brain 2006; Medina et al, Neurology 2007; de Nija et al, Exp Cell Res 2006

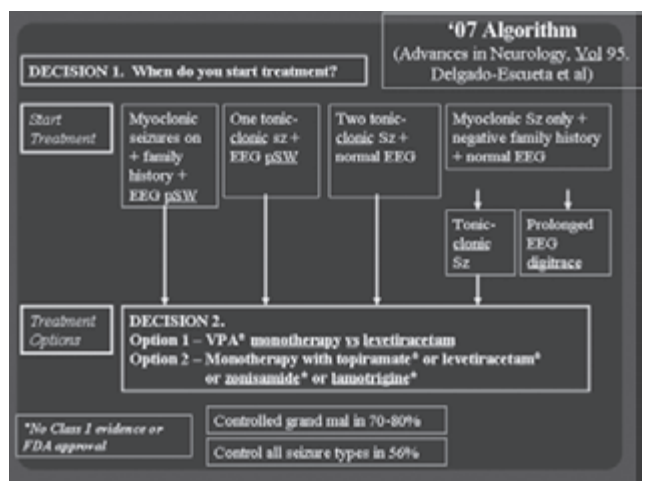
Clinical characteristics: JME

SUSCEPTIBILITY STAGE	EPILEPTOGENICITY EPILEPTOGENESIS STAGE
•Myoclonias and grand mal on awakening	•Myoclonias and grand mal on awakening + other hours of day
•Trigger: alcohol, sleep deprivation, fatigue, menses, ovulation…	•Occur without trigger
•Respond to AED monotherapy	•Require polytherapy
•Respond to lifestyle changes	•Occur even with life style changes

Long term follow-up of 222 JME patients (mean period 11.6 years)

	Myoclonias only	Myoclonias + TCS	Myoclonias + TCS + absence
Seizure free	80%	63%	46%

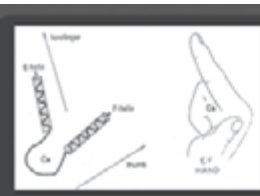
- Conclusion: the more seizure phenotypes, more progression to epileptogenicity, the lower success rate.
- Treatment during susceptibility stage has higher success rate.



CAE cy JME: poor response to treatment

Response to Treatment	Classic JME (n=161)	CAE/ JME (n=35)	JME with adolescent onset pharmacologic absence (JME/aPA) (n=18)	JME with astatic seizure (n=8)
All seizure types controlled*	93 (58%)	3 (7%)	10 (56%)	5 (63%)
Susceptible but in remission from all seizure types (>5 years without AEDs)	12 (8%)	-	-	-
Persisting Seizures	56 (35%)	32 (93%)	8 (46%)	3 (37%)

Martinez et al, Brain 2006

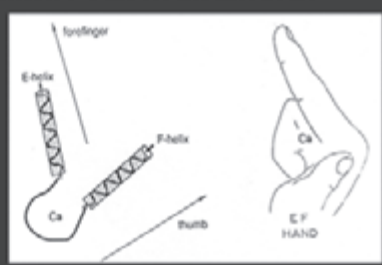


Lesson 4 – Functions Myoclonin1/ EFHC1

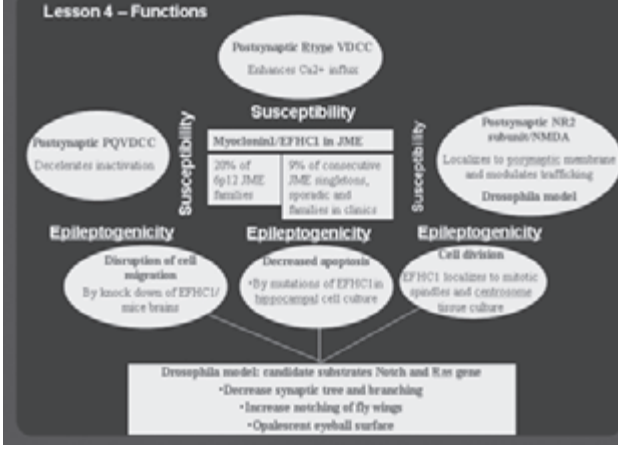
- C-terminal EF hands are found in neuronal calcium sensors, the calmodulin family, Ca^{2+}-ATPase, Ca^{2+}-activated K^+- and Ca^{2+}-channels, and various novel calcium binding proteins such as calsenilin and DREAM
- Modulates intracellular calcium concentrations and regulates excitability

Myoclonin/EFHC1

- Domain search through Interpro and Pfam databases revealed an EF hand motif connected by a calcium binding loop (Kretsinger et al., 1973) (pfam00036; E-value 0.00066) between amino acid residues 578 and 660 and three DM10 domains
- We named the gene myoclonin because function is still unknown and EFHC1 for EFH containing one EF hand.



Lesson 4 – Functions



Forward to the Future for JME and Myoclonin/EFHC1

- Targeted drug development against R-type Voltage dependent calcium channel
- Stem cell therapy to resculpture abnormal neuroanatomy produced during development by the JME gene

Programa – 15.02.2008

Morning session – 9:00 – 13:00

- Surgically treatable epilepsies and surgical treatment gap in Latin America – Américo Sakamoto (Brazil)
- Localization of the epileptogenic zone by non-invasive methods – Silvia Kochen (Argentina)
- Advanced multimodality imaging in the evaluation of intractable epilepsies – Csaba Juhásh (USA)
- Pathophysiology and management of infantile spasms - Harry Chugani (USA)
- Epileptogenesis of cortical dysplasia – Gary Mathern (USA)

Afternoon session – 14:30-18:30

- Surgical approach to adulthood epilepsies: temporal lobe – Ricardo Centeno (Brazil)
- Surgical approach to adulthood epilepsies: extratemporal epilepsies – Ney Azambuja (Brazil)
- Surgical approach to childhood epilepsies - Helio Machado (Brazil)
- Vagus nerve stimulation – Mario Alonso Vanegas (México)
- Future perspectives in the treatment of the epilepsies – Manuel Campos (Chile)

Surgically treatable epilepsies and surgical treatment gap in Latin America

Américo Sakamoto (Brazil)

Localization of the epileptogenic zone by non-invasive methods

Silvia Kochen (Argentina)

Advanced multimodality imaging in the evaluation of intractable epilepsies

Csaba Juhász (USA)

Pathophysiology and management of infantile spasms

Harry Chugani (USA)

EPILEPTOGENESIS OF CORTICAL DYSPLASIA
GARY MATHERN (USA)

Mechanisms Of Epileptogenesis In Pediatric Cortical Dysplasia

Gary W. Mathern

Neurosurgery, The Mental Retardation Research Center & Brain Research Institute

Collaborators

Mathern Laboratory: Julia Chang, Snow Nguyen, Marrissa Andres, Stella de Bode, My Huynh, P. Sarat Chandra.

Levine Laboratory: Carlos Cepeda; Veronique Andre; Mike Levine; and many others.

Neuroradiology: Noriko Salamon

Neuropathology: Harry V. Vinters, Hajime Miyata @ UCLA. Joao P. Leite and Luciano Neder @ Ribeirao Preto, Brazil

Pediatric Neurology: W. Donald Shields, Ramon Sankar, Susan Koh, Joyce Wu, Michele Van Hirtum-Das, Chris Giza, Sue Yudovin & others.

National Institutes of Health: Grants R01 NS38992 & P05 NS02808

Acknowledge ILAE Pediatric Epilepsy Surgery Sub-Commission 2004 Survey (Harvey et al., Epilepsia 2008, 49:146-155)

Centers (n=20)	Investigators
Europe (n=225 patients)	
Belgium, Brussels, ULBH-E	P. Van Bogaert, X. De Tiege
Finland, Helsinki, Hospital for Children	E. Gaily
France, Paris, Rothschild Foundation	O. Delalande, C. Bulteau, M. Fohlen
Germany, Bonn, USFS	R. Sassen
Germany, Vogtareuth, BHZ	H. Holthausen, T. Pieper
Netherlands, Wilhelmina Children's	O. Van Nieuwenhuizen
Sweden, Goteborg, Sahlgrenska Univ	B. Rydenhag
Sweden, Stockholm, Karolinska	P. Amark
United Kingdom, London, GOSH	J. H. Cross, W. Harkness, C. Dunkley
Australia (n=48 patients)	
Melbourne, Royal Children's	A.S. Harvey, W. Maixner
Sydney, Children's Westmead & Sydney	D. Gill, J. Lawson
USA (n=270 patients)	
Boston, Children's Hospital Boston	J. Riviello
Cleveland, Cleveland Clinic	D. Lachhwani, E. Wyllie
Chicago, Children's Memorial Hospital	D. Nordli
Los Angeles, UCLA	G.W. Mathern, S. Koh, W.D. Shields
Miami, Miami Children's	M. Duchowny, P. Jayakar
Minnesota, Minnesota Epilepsy Group	J. Gates, F. Ritter
New York, New York University	H. Weiner
Seattle, Seattle Children's Hospital	J. Ojemann, D. Kraemer

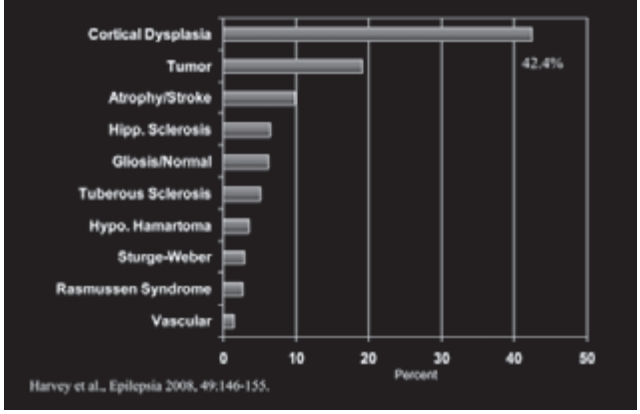
Learning Objectives

Characterize the clinical & pathological features of cortical dysplasia in pediatric epilepsy surgery patients.

Examine the morphological features relative to normal cortical development to determine the probable ontogenetic timing of cortical dysplasia cortical development.

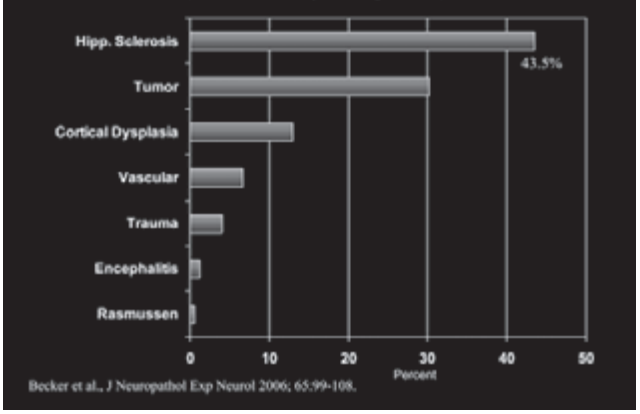
Characterize the electrophysiological properties by cell type and region in pediatric cortical dysplasia that suggest mechanisms of epileptogenesis involving immature GABA and glutamate neurotransmission.

Etiology/Substrates for Pediatric Epilepsy Surgery Patients Less Than 18 Years (ILAE Survey 2004; 20 Centers Europe, Australia, & USA; n=413)

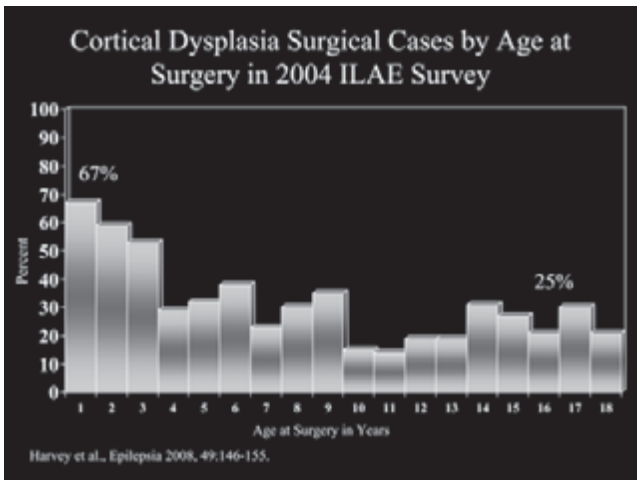


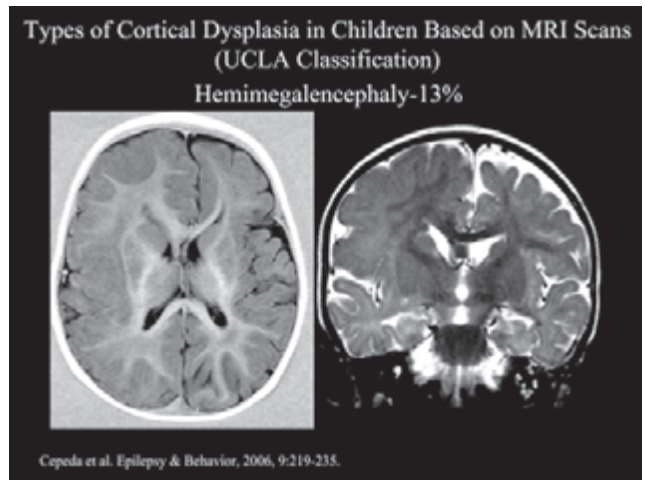
Harvey et al., Epilepsia 2008, 49:146-155.

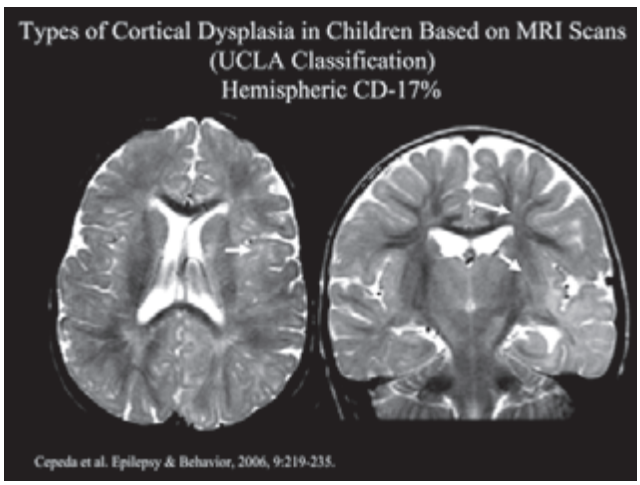
Etiology/Substrates for Adult Epilepsy Surgery Patients (N=2386 mostly adult patients)

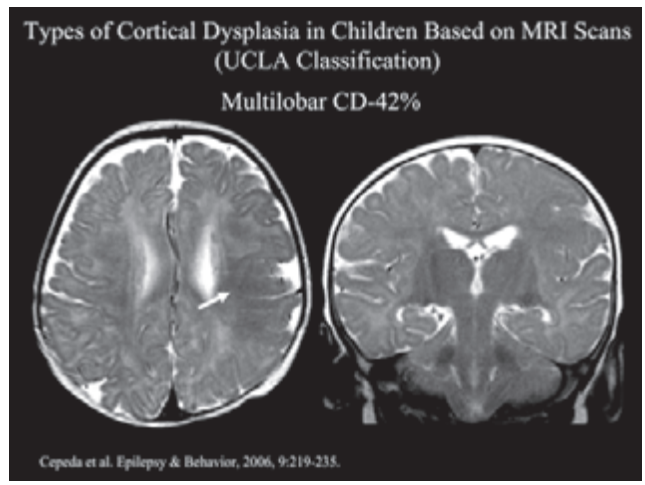


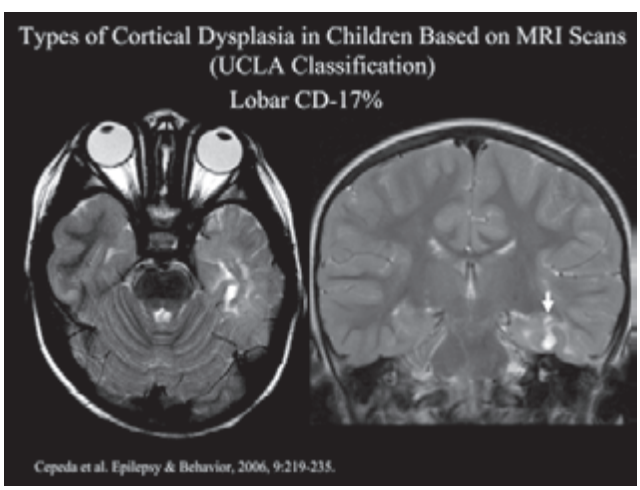
Becker et al., J Neuropathol Exp Neurol 2006; 65:99-108.

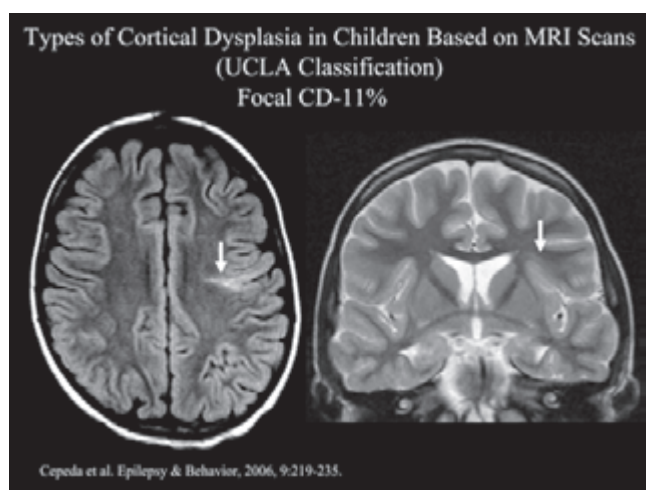

Cortical Dysplasia Surgical Cases by Age at Surgery in 2004 ILAE Survey
Percent
67%
25%
Age at Surgery in Years
Harvey et al., Epilepsia 2008, 49:146-155.

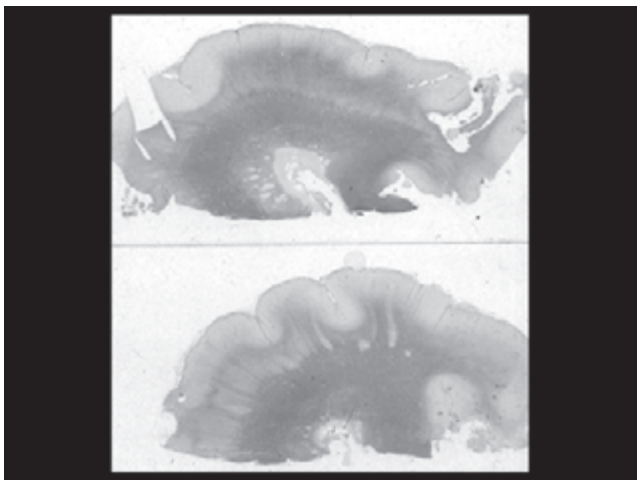

Types of Cortical Dysplasia in Children Based on MRI Scans
(UCLA Classification)
Hemimegalencephaly-13%
Cepeda et al. Epilepsy & Behavior, 2006, 9:219-235.

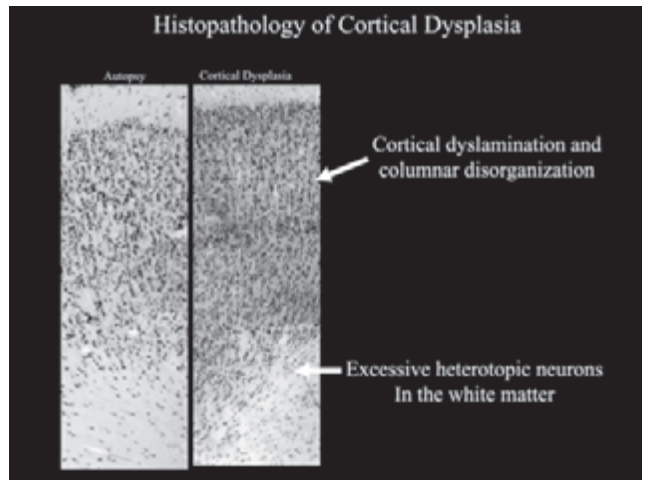

Types of Cortical Dysplasia in Children Based on MRI Scans
(UCLA Classification)
Hemispheric CD-17%
Cepeda et al. Epilepsy & Behavior, 2006, 9:219-235.

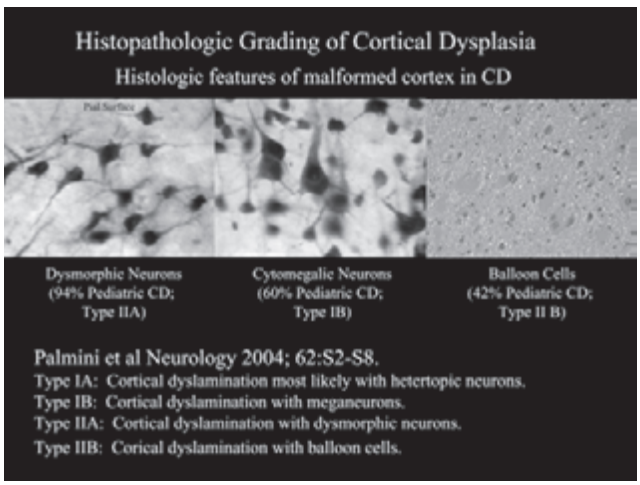

Types of Cortical Dysplasia in Children Based on MRI Scans
(UCLA Classification)
Multilobar CD-42%
Cepeda et al. Epilepsy & Behavior, 2006, 9:219-235.

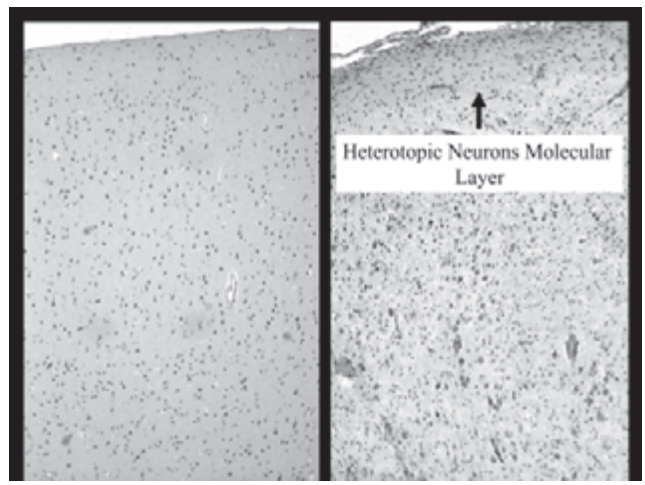

Types of Cortical Dysplasia in Children Based on MRI Scans
(UCLA Classification)
Lobar CD-17%
Cepeda et al. Epilepsy & Behavior, 2006, 9:219-235.

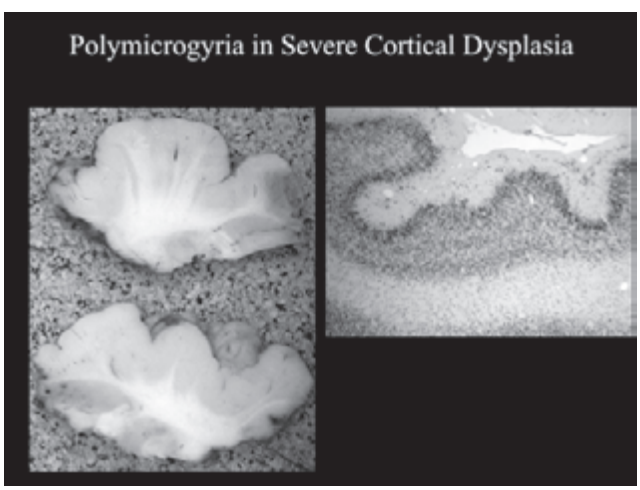

Types of Cortical Dysplasia in Children Based on MRI Scans
(UCLA Classification)
Focal CD-11%
Cepeda et al. Epilepsy & Behavior, 2006, 9:219-235.

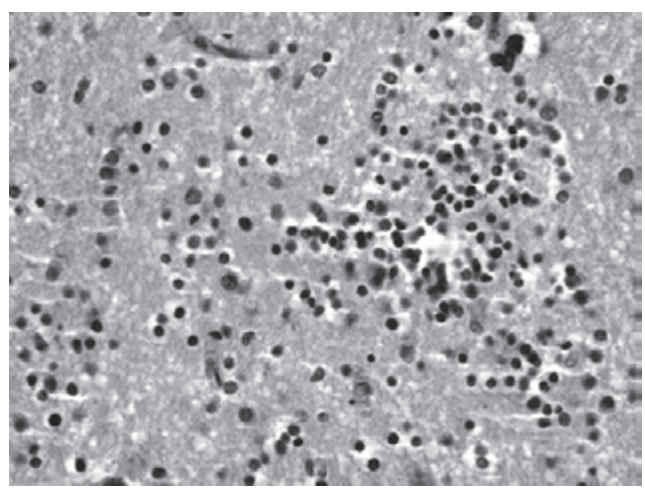



Histopathology of Cortical Dysplasia
Autopsy
Cortical Dysplasia
Cortical dyslamination and columnar disorganization
Excessive heterotopic neurons In the white matter


Histopathologic Grading of Cortical Dysplasia
Histologic features of malformed cortex in CD
Pial Surface
Dysmorphic Neurons (94% Pediatric CD; Type IIA)
Cytomegalic Neurons (60% Pediatric CD; Type IB)
Balloon Cells (42% Pediatric CD; Type II B)
Palmini et al Neurology 2004; 62:S2-S8.
Type IA: Cortical dyslamination most likely with hetertopic neurons.
Type IB: Cortical dyslamination with megancurons.
Type IIA: Cortical dyslamination with dysmorphic neurons.
Type IIB: Corical dyslamination with balloon cells.


Heterotopic Neurons Molecular Layer


Polymicrogyria in Severe Cortical Dysplasia



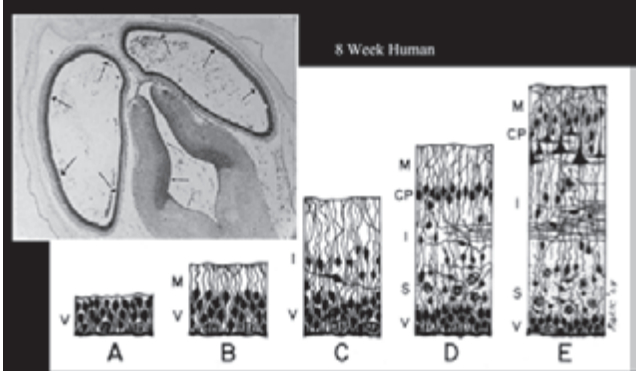
Histopathology by MRI CD Classification

Pathologic Finding (Incidence)	HME N=9	Hemi CD N=11	Multilobar N=14	Lobar N=12	Focal N=9	P-Value
Heterotopic Neu WM (100%)	100%	100%	100%	100%	100%	P=0.99
Dysmorphic Neurons (94%)	89%	100%	93%	92%	100%	P=0.66
Cytomegalic Neurons (60%)	89%	36%	71%	42%	67%	P=0.15
Polymicrogyria (53%)	**78%**	**64%**	**78%**	25%	11%	**P=0.001**
Heterotopic Neu Mol Lay (44%)	**100%**	**54%**	36%	25%	11%	**P=0.001**
Balloon Cells (42%)	44%	18%	43%	33%	**78%**	**P=0.017**
Immature Neurons (18%)	**56%**	**27%**	14%	0%	0%	**P=0.009**

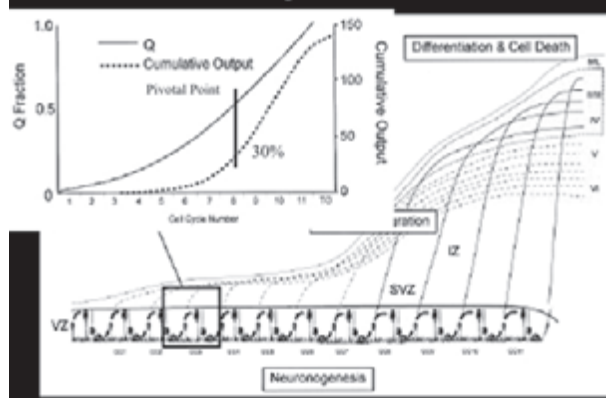
Cepeda et al., Epilepsy & Behavior, 2006: 9:219-235.

CD Pathogenesis:
A Hypothesis Based on Clinico-Pathologic Observations

Normal Corticoneurogenesis

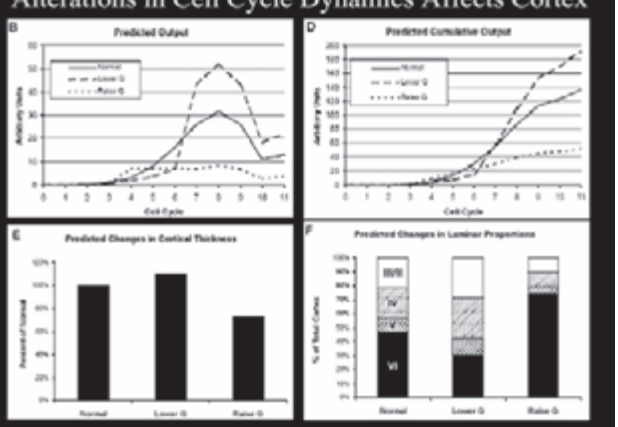


Corticoneurogenesis in the Mouse



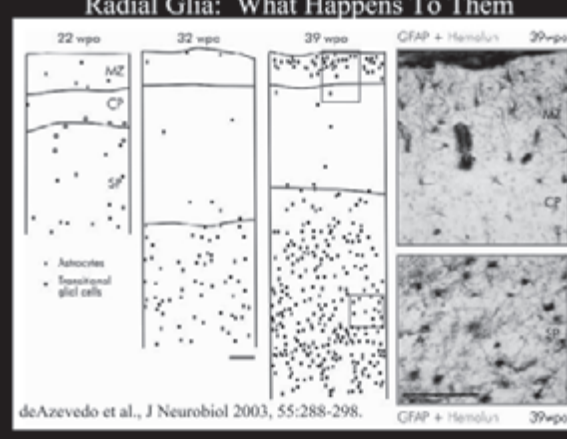
Caviness et al., Mental Retardation and Dev Disabilities Research Reviews 2000, 6:22-33.

Alterations in Cell Cycle Dynamics Affects Cortex



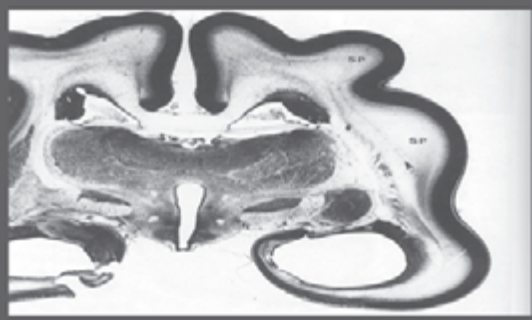
Caviness et al., Cerebral Cortex 2003, 13:592-598.

Radial Glia: What Happens To Them

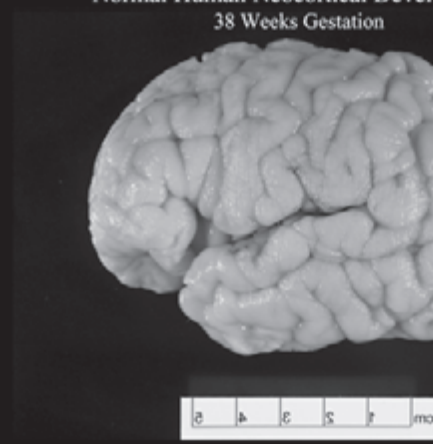


deAzevedo et al., J Neurobiol 2003, 55:288-298.

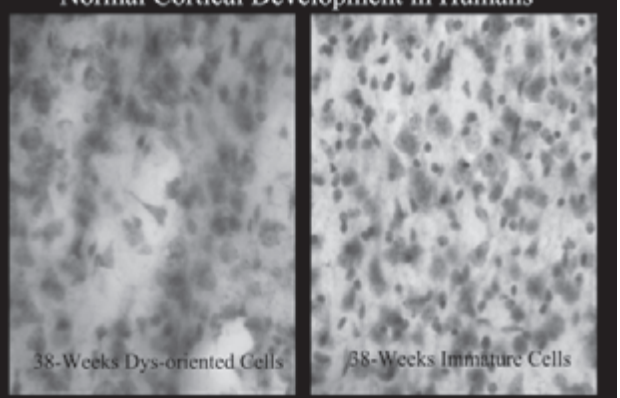
Variations of thickness of the subplate zone



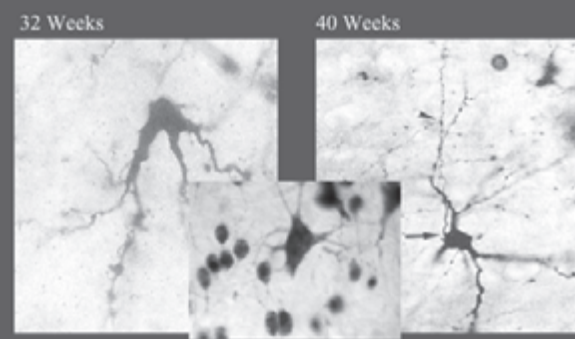
Normal Human Neocortical Development
38 Weeks Gestation



Normal Cortical Development in Humans



Human Subplate Neurons



Timing of CD Pathogenesis During Cortical Development

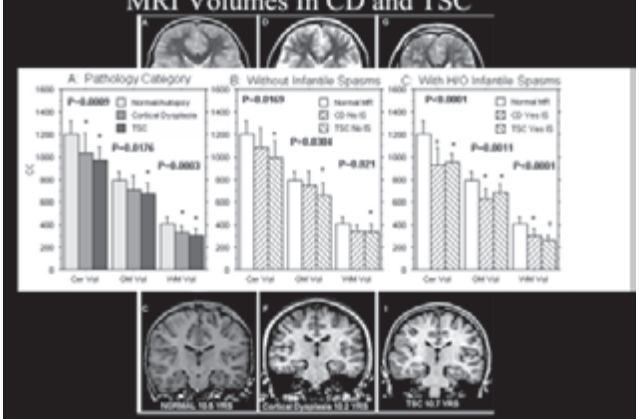
If from early abnormal periventricular neuroglial differentiation then there it should be early reduction of neuroblasts. This should reduce total cortical cell numbers and hemisphere size.

If from neuronal migration defects, then there should be reduced numbers of neurons in the cortex because they are stuck in the white matter.

If from late differentiation of too many neuroblasts, then there should be more neurons in the cortex, some being stuck in the white matter & normal size brains.

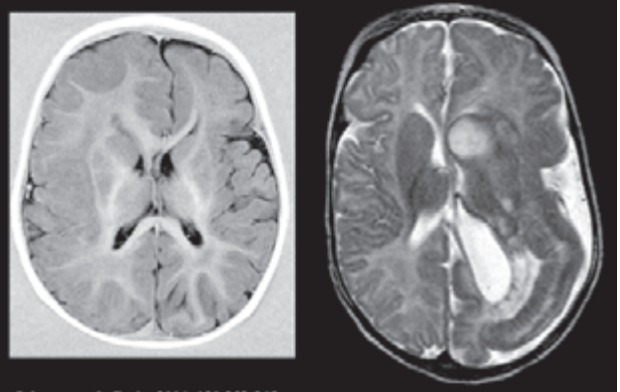
If from defects of programmed cell death later in corticoneurogenesis then prevent loss of subplate cells and failure of secondary gyral folding.

MRI Volumes In CD and TSC



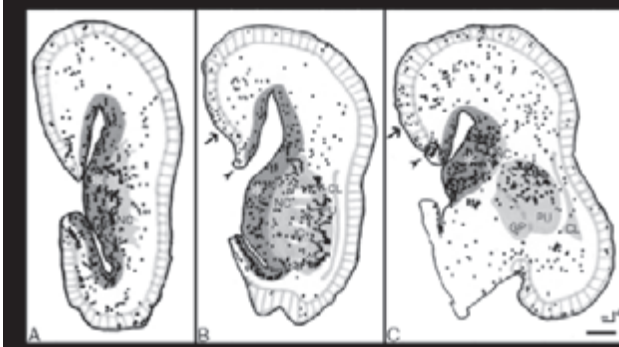
Chandra et al, Neurology 2007; 68:438-445.

Abnormal Deep Structures in Hemimegalencephaly



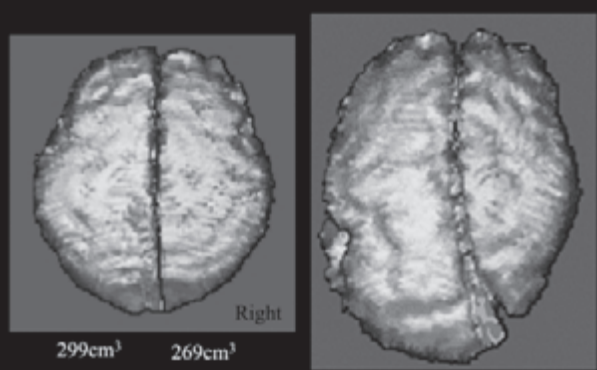
Salamon et al., Brain, 2006; 129:352-365.

Programmed Cell Death In Human Telencephalon at 17 WeeksGA



Rakic S and Zecevic N; Eur J Neurosci 12:2721-2734, 2000

Monozygotic Twins & Hemimegalencephaly

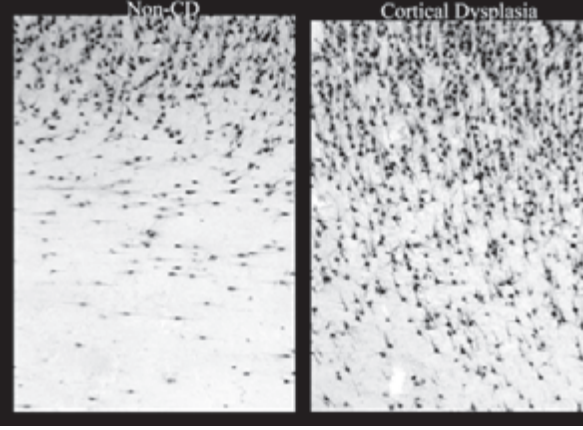


299cm³ 269cm³

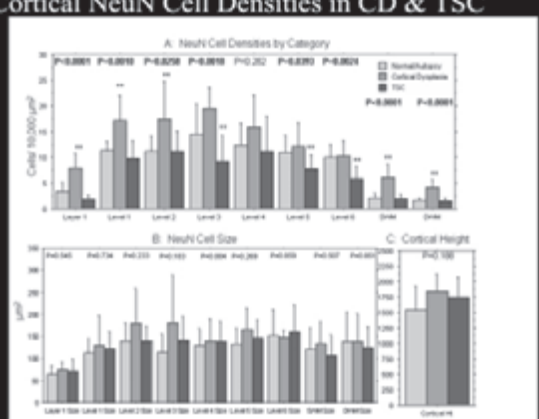
353cm³ 186cm³

Salamon et al., Brain, 2006; 129:352-365.

NeuN Neuronal Densities in Cortical Dysplasia



Cortical NeuN Cell Densities in CD & TSC



Chandra et al
Neurology 2007;68:438-445

Conclusions of MRI/Cell Density Studies:

Cerebral gray matter and total volumes are normal in children with cortical dysplasia without a history of infantile spasms.

In HME the affected side is larger and non-affected side smaller than expected. In TSC, brains are smaller.

Molecular layer, upper gray matter, and white matter neuron densities were increased in CD and decreased in TSC patients.

In CD, the pattern of abnormalities are consistent with a problem in late corticoneurogenesis involving: A) a greater production or lack of programmed cell death of neurons & B) preservation of a portion of pre-plate neurons.

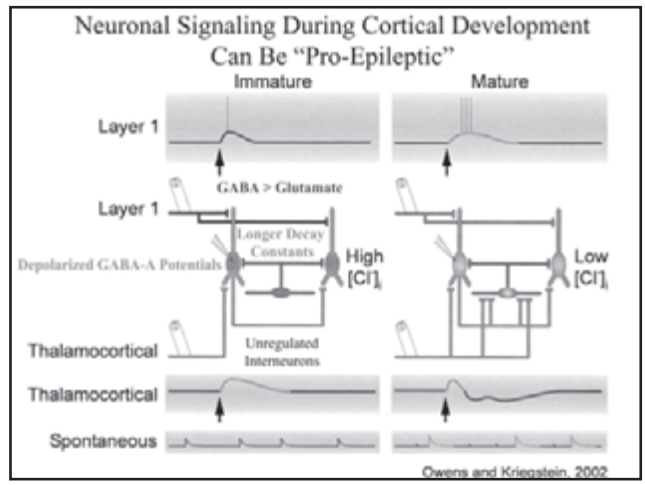
Epileptogenesis in Pediatric Cortical Dysplasia:
The Dysmature Cerebral Developmental Hypothesis

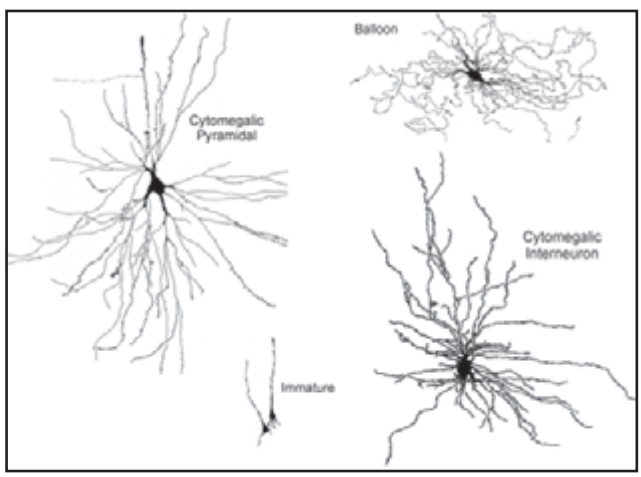
If CD pathogenesis involves processes that delay or prevent later stages of human corticogenesis, then what could be the consequence of these actions that explains seizure generation?

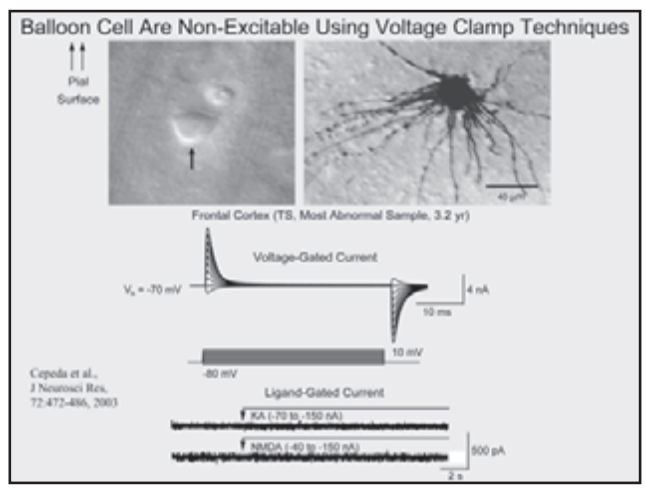
Delayed cortical maturation should result in CD tissue that contains prenatal-like meganeurons with electrophysiological features atypical for postnatal neurons

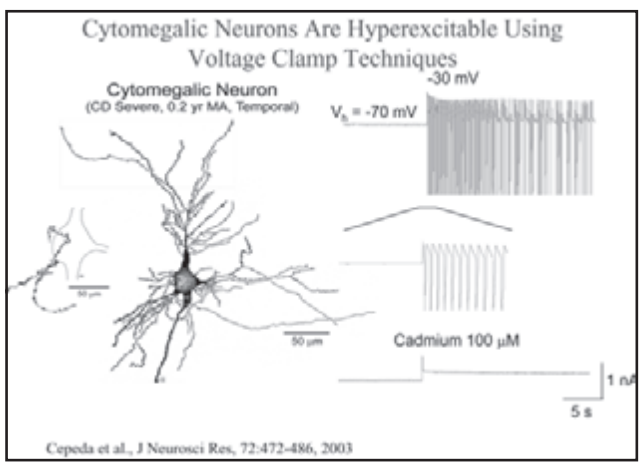
Normal appearing neurons with cellular and synaptic properties similar to those in immature developing cortex

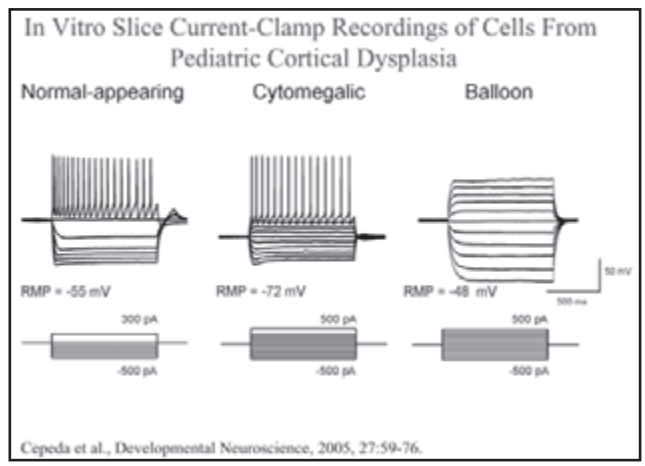
Seizures would occur because areas of CD contain cells and synaptic properties with immature electrophysiological characteristics that are hyperexcitable and "pro-epileptic compared with the normal postnatal brain.

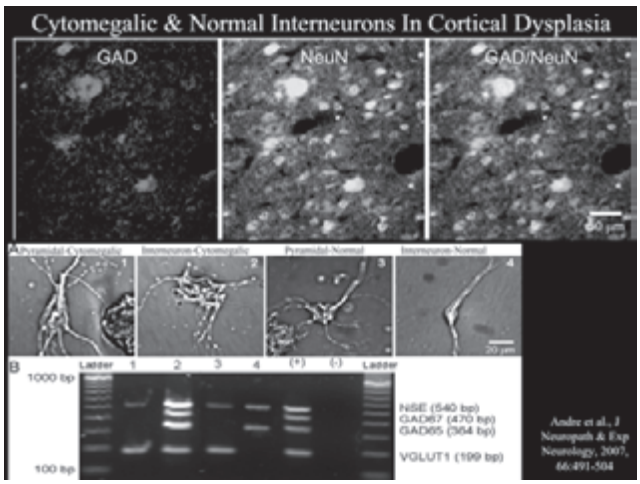


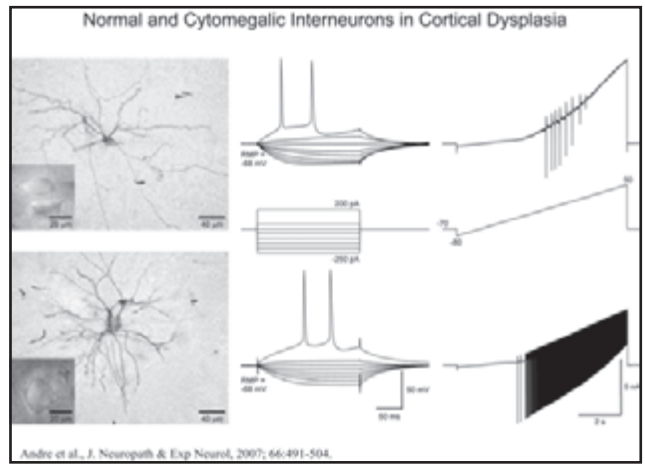


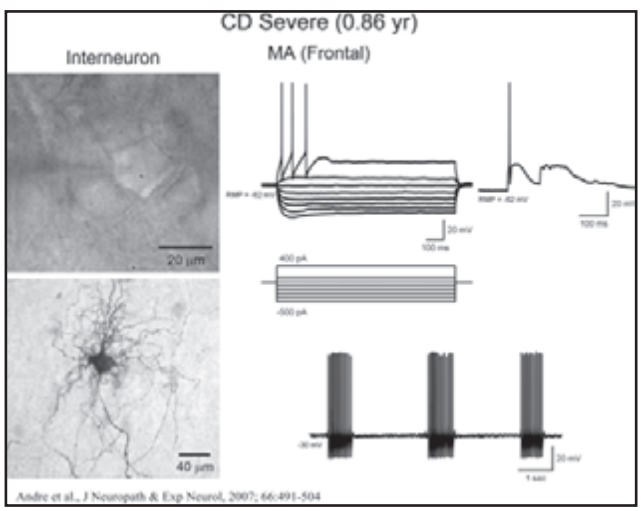


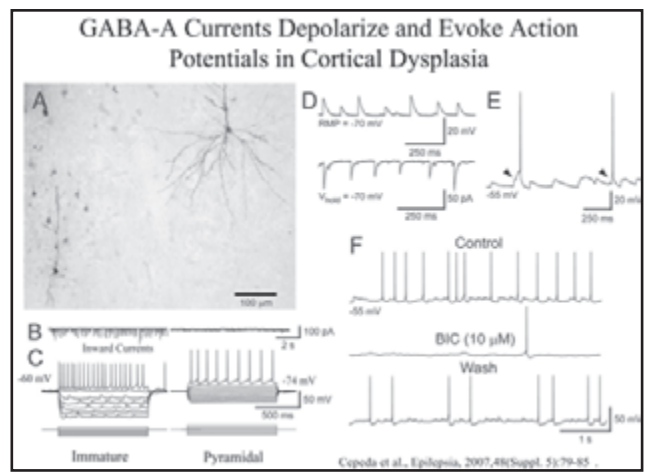


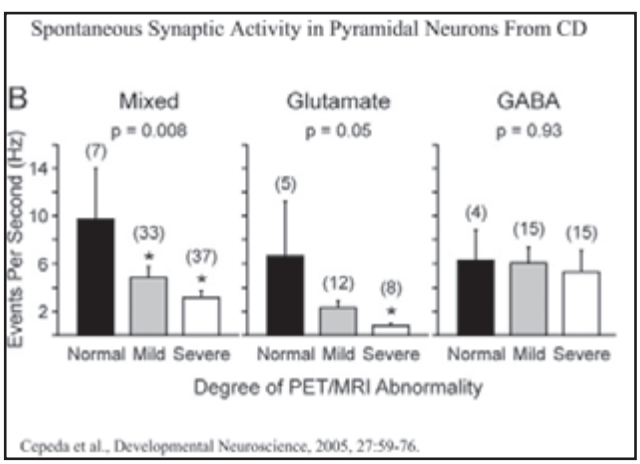


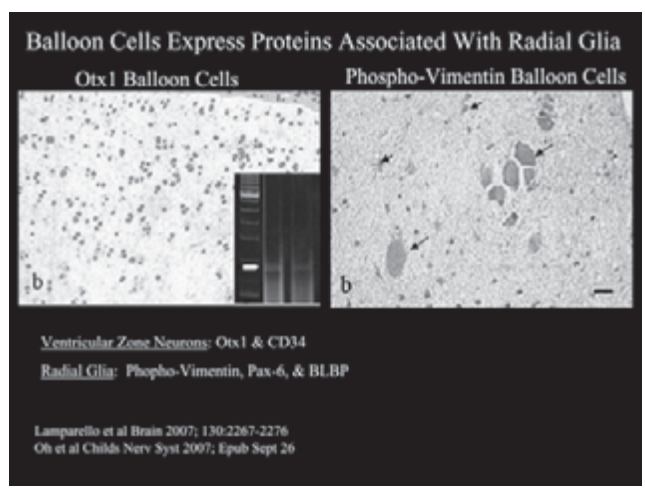

Cytomegalic & Normal Interneurons In Cortical Dysplasia
GAD
NeuN
GAD/NeuN
Pyramidal-Cytomegaly
Interneuron-Cytomegaly
Pyramidal-Normal
Interneuron-Normal
Ladder
1000 bp
100 bp
NSE (540 bp)
GAD67 (470 bp)
GAD65 (364 bp)
VGLUT1 (199 bp)
Andre et al., J Neuropath & Exp Neurology, 2007, 66:491-504

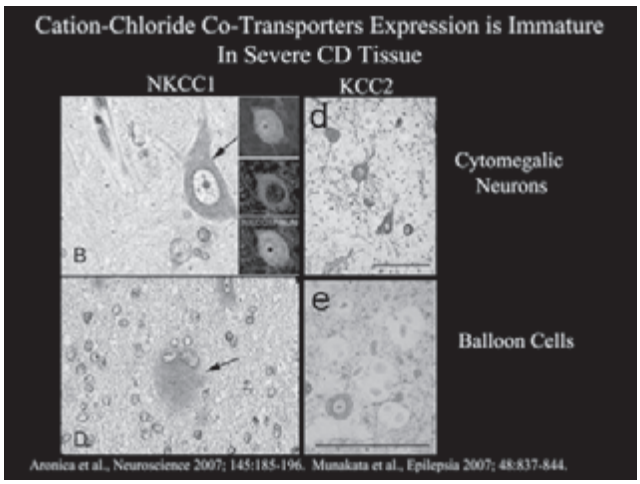

Normal and Cytomegalic Interneurons in Cortical Dysplasia
Andre et al., J. Neuropath & Exp Neurol, 2007; 66:491-504.

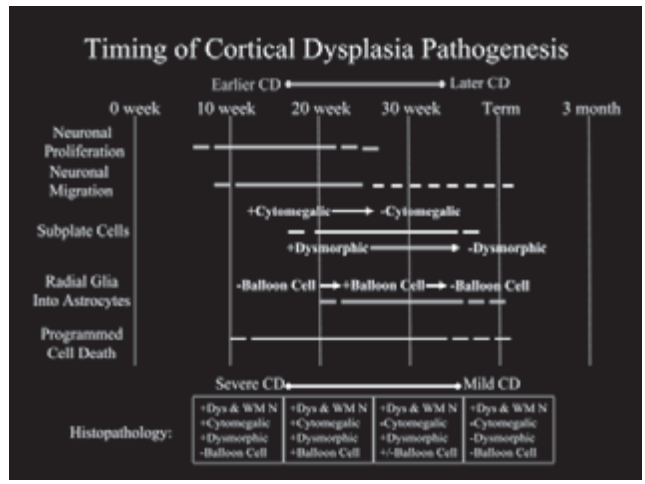

CD Severe (0.86 yr)
Interneuron
MA (Frontal)
20 µm
40 µm
Andre et al., J Neuropath & Exp Neurol, 2007; 66:491-504


GABA-A Currents Depolarize and Evoke Action Potentials in Cortical Dysplasia
Control
BIC (10 µM)
Wash
Immature
Pyramidal
Cepeda et al., Epilepsia, 2007,48(Suppl. 5):79-85


Spontaneous Synaptic Activity in Pyramidal Neurons From CD
Mixed
p = 0.008
Glutamate
p = 0.05
GABA
p = 0.93
Events Per Second (Hz)
Normal Mild Severe
Degree of PET/MRI Abnormality
Cepeda et al., Developmental Neuroscience, 2005, 27:59-76.


Balloon Cells Express Proteins Associated With Radial Glia
Otx1 Balloon Cells
Phospho-Vimentin Balloon Cells
Ventricular Zone Neurons: Otx1 & CD34
Radial Glia: Phopho-Vimentin, Pax-6, & BLBP
Lamparello et al Brain 2007; 130:2267-2276
Oh et al Childs Nerv Syst 2007; Epub Sept 26


Cation-Chloride Co-Transporters Expression is Immature
In Severe CD Tissue
NKCC1
KCC2
B
d
Cytomegalic
Neurons
D
e
Balloon Cells
Aronica et al., Neuroscience 2007; 145:185-196. Munakata et al., Epilepsia 2007; 48:837-844.


Timing of Cortical Dysplasia Pathogenesis
Earlier CD
Later CD
0 week
10 week
20 week
30 week
Term
3 month
Neuronal Proliferation
Neuronal Migration
Subplate Cells
+Cytomegalic
-Cytomegalic
+Dysmorphic
-Dysmorphic
Radial Glia Into Astrocytes
-Balloon Cell
+Balloon Cell
-Balloon Cell
Programmed Cell Death
Severe CD
Mild CD
Histopathology:
+Dys & WM N
+Cytomegalic
+Dysmorphic
-Balloon Cell
+Dys & WM N
+Cytomegalic
+Dysmorphic
+Balloon Cell
+Dys & WM N
-Cytomegalic
+Dysmorphic
+/-Balloon Cell
+Dys & WM N
-Cytomegalic
-Dysmorphic
-Balloon Cell

Surgical approach to adulthood epilepsies: temporal lobe

Ricardo Centeno (Brazil)

Cirurgia do Lobo Temporal

Ricardo S. Centeno

UNIFESP - EPM
Departamento de Neurologia e Neurocirurgia
Unidade de Pesquisa e Tratamento das Epilepsias

Objetivos da Apresentação

- Histórico
- Incidência
- Indicação/Tipos de cirurgia do lobo temporal
- Fatores Prognósticos/Resultados Cirúrgicos
- Complicações

História

✓Penfield W. and Baldwin M.;	1952
✓Falconer M. A. ;	1953
✓Penfield W. , Lende R. A. and Rasmussen T.;	1961
✓Crandal P.H., Walter R. D. and Rand R.W.;	1963
✓Walker, A. E. ;	1967
✓Kempe L. G. ;	1968

The New England Journal of Medicine

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

Tratamento clínico (40) x cirurgia (40)

– *Outcome* primário: freqüência de crises com perda de consciência

– *Outcomes* secundários: freqüência e gravidade de crises, qualidade de vida, incapacidade, morte

The New England Journal of Medicine

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

Após 1 ano:

– Grupo cirúrgico: 58% livres de crises incapacitantes

– Grupo clínico: 8% livres de crises incapacitantes

– Melhor qualidade de vida no grupo cirúrgico

Practice parameter: Temporal lobe and localized neocortical resections for epilepsy

American Academy of Neurology — Special Article

1 estudo classe I + 24 estudos classe IV

– Benefício obtido com ressecção anteromesial em pacientes com crises parciais complexas incapacitantes: maior do que aquele obtido com tratamento com DAES, com risco comparável

– Referir pacientes a centros de cirurgia de epilepsia deve ser fortemente considerado

Neurology 2003; 60: 538-547

Incidência

EPILEPSIA: doença neurológica grave mais comum

⇨ prevalência: 1%

EPILEPSIA DO LOBO TEMPORAL: epilepsia focal mais comum em adultos

⇨ 70%

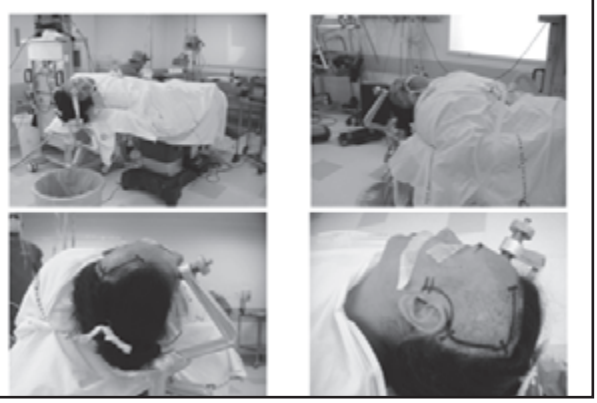
ESCLEROSE MESIAL TEMPORAL: substrato anátomo-patológico mais freqüente

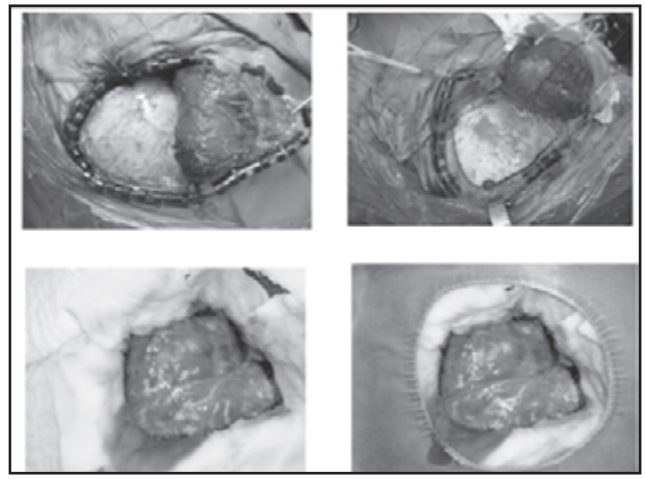
⇨ 70%

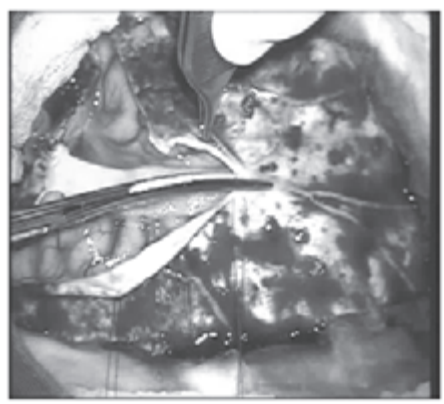
Técnicas Cirúrgicas Lobo Temporal

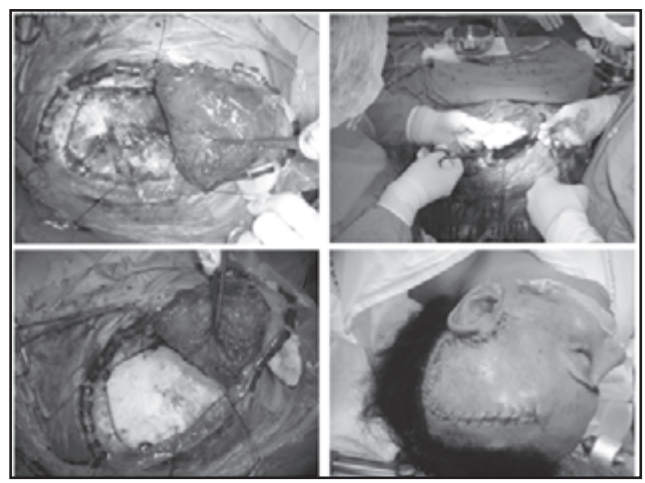
- Corticoamigdalohipocampectomia (CAH)
- Amigdalohipocampectomia Seletiva (AH Seletiva)
- Corticoamigdalectomia (CA)
- Ressecções Focais Neocorticais

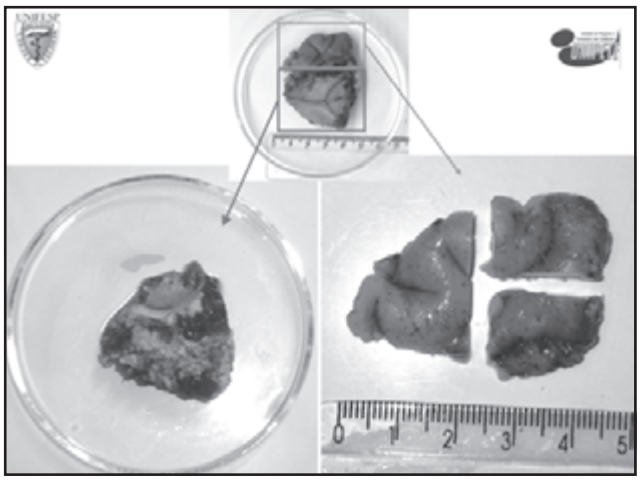
Corticoamigdalohipocampectomia

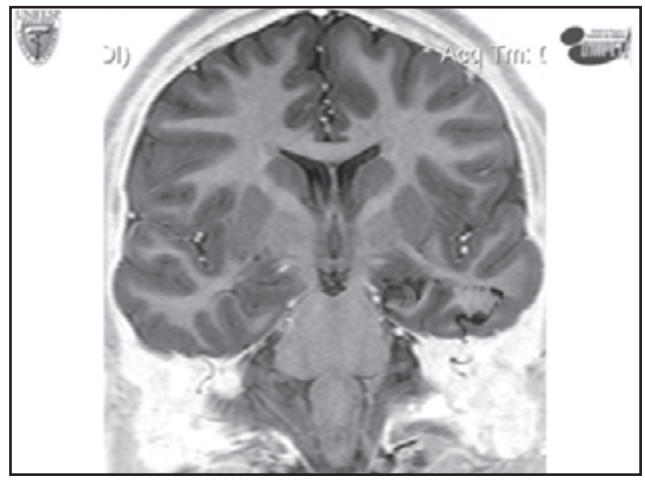


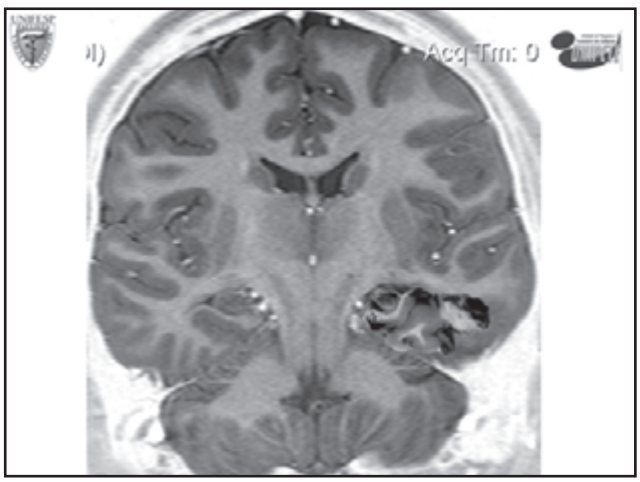


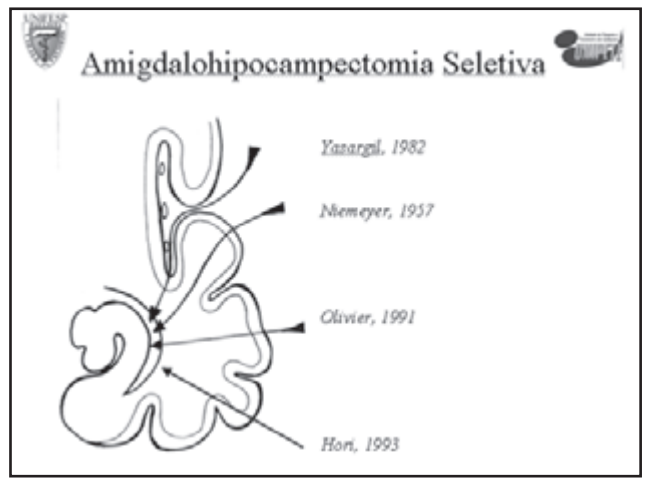


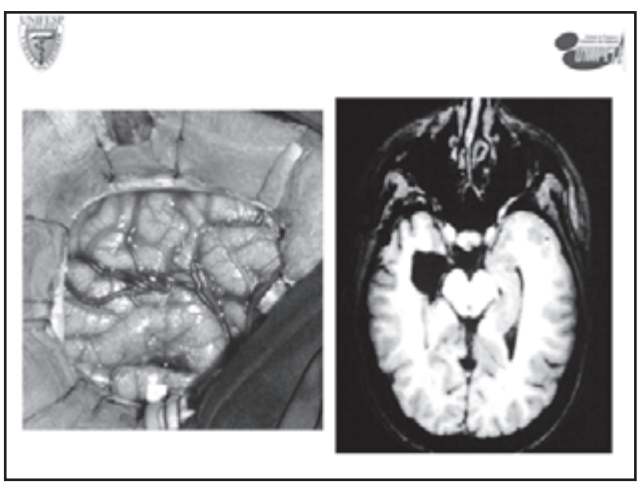


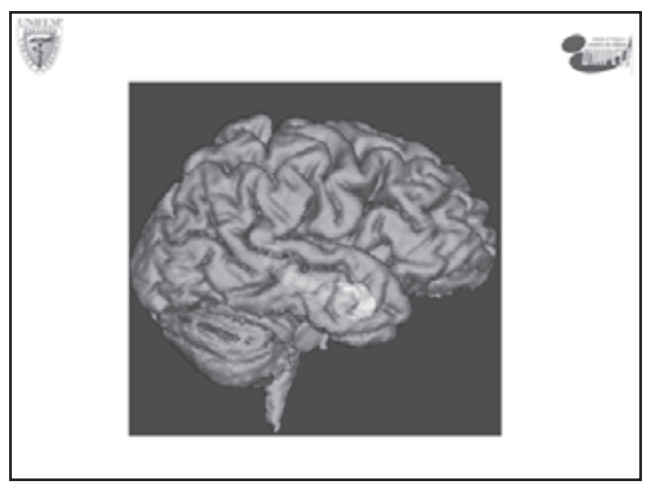


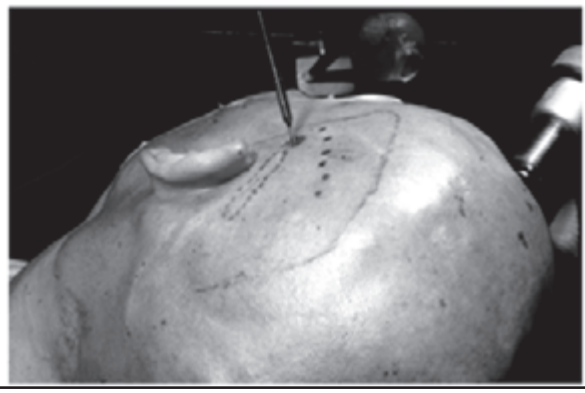


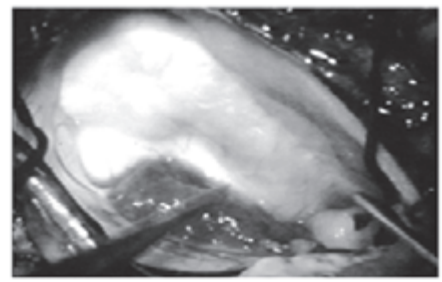



Amigdalohipocampectomia Seletiva
Yasargil, 1982
Niemeyer, 1957
Olivier, 1991
Hori, 1993



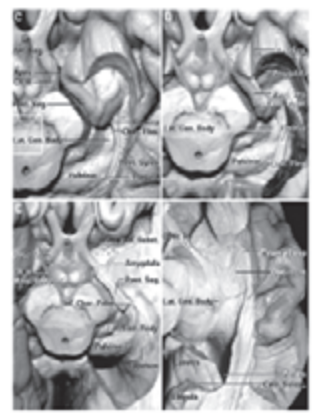






CAH *versus* AH seletiva

- Preservação das funções cognitivas
- Preservação do campo visual
- Resultado cirúrgico



Ressecções Neocorticais

- Ressecção zona lesional + zona irritativa
- "Dual Pathology"

Fatores Prognósticos relacionados à cirurgia do lobo temporal

- ✓Extensão da ressecção do hipocampo
- ✓Tipo de cirurgia (CAH vs AHSel)
- ✓Lesionectomia + área irritativa perilesional
- ✓"Dual pathology"
- ✓Tumores com resecção parcial

Resultado da cirurgia do lobo temporal

- Melhora da freqüência das crises
- Evitar déficits neurológicos adicionais

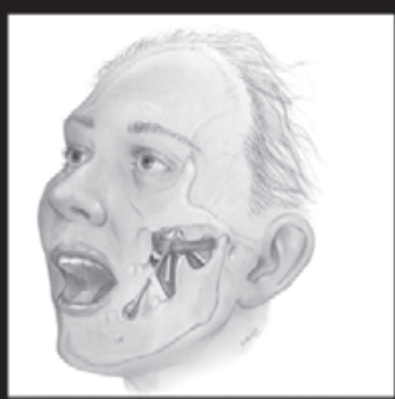
Resultado da cirurgia do lobo temporal

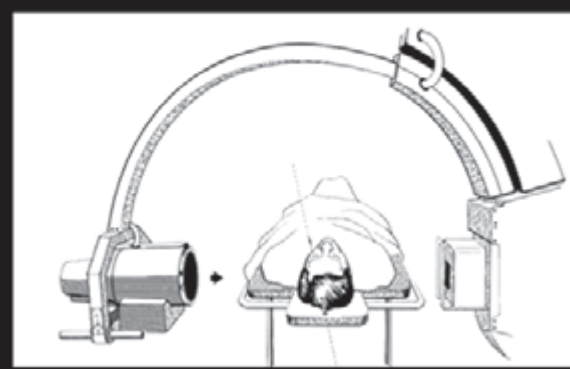
Diminuição da freqüência das crises

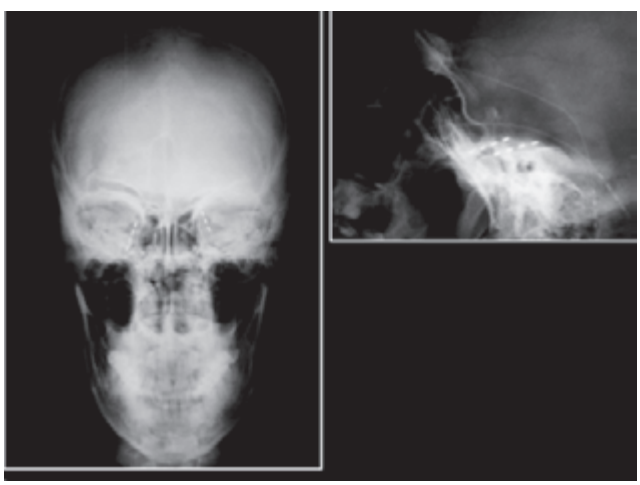
- Convergência dos dados da investigação

Clínica
Eletrofisiologia
Imagem

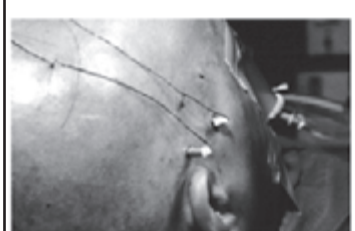
Eletrodos de Foramen Ovale

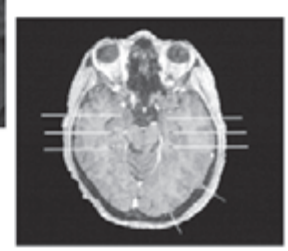




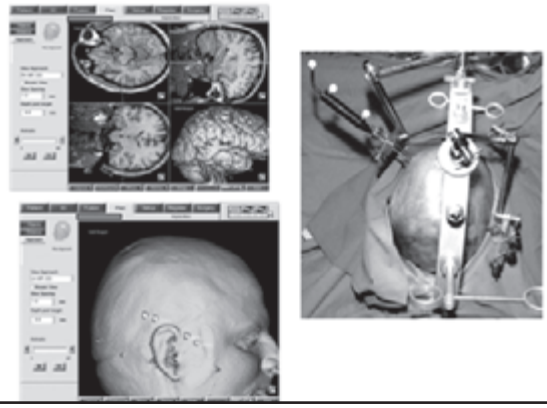


Implantação de eletrodos profundos

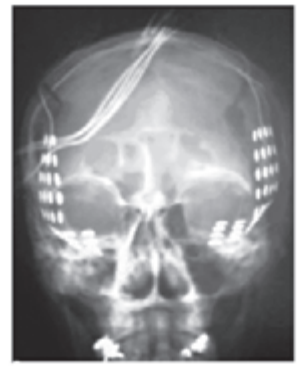




Implantação de eletrodos bilateral



Subdural "strips" and "grids"



Resultado da cirurgia do lobo temporal

Evitar déficits neurológicos adicionais

- Testes neuropsicológicos
- Teste de Wada
- RM funcional
- Mapeamento cortical funcional (intra ou extra-operatório)

Teste de Wada: amobarbital intracarotídeo

- **injeção de amobarbital em carótida interna esquerda e direita**
- **teste de memória e linguagem**
- **definição da capacidade funcional e da reserva funcional**

Teste de Wada: amobarbital intracarotídeo

	CAPACIDADE FUNCIONAL	RESERVA FUNCIONAL
MELHOR SITUAÇÃO	⇩ ⇩ ⇩	⇧ ⇧ ⇧
PIOR SITUAÇÃO	⇧ ⇧ ⇧	⇩ ⇩ ⇩

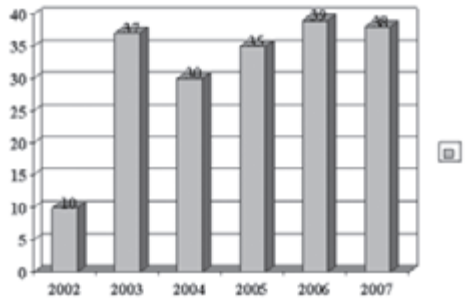
Complicações

- ✓ Mortalidade 0,5%
- ✓ Morbidade 2 a 12%

- Quadrantanopsia homônima superior
- Déficits de linguagem verbal
- Hemiparesia
- Infecção

Resultados

Número cirurgias/ano



Resultados

189 cirurgias

- 02 AH seletivas
- 01 Hemisferectomia funcional
- 04 Hemisferotomias
- 38 Lesionectomias/Lobectomias/Quadrantectomias
- 01 Calosotomia
- 143 Corticoamigdalohipocampectomias

Resultados

149 cirurgias do lobo temporal

- 02 AH seletivas
- 04 lesionectomias neocorticais
- 143 Corticoamigdalohipocampectomias

149/189 - 78% do total da casuística

Resultados

Classificação de Engel

Classe I: a) Pcte sem crises e sem auras
b) Pcte sem crises mas com auras
c) Pcte com crises no pós operatório, mas sem crises há pelo menos dois anos
d) Pcte que tiveram crises com abstinência de drogas e atualmente estão sem crises

Classe II: Pcte com até duas crises ao ano

Classe III: Pcte com mais de duas crises ao ano mas com melhora significativa em relação ao pré operatório

Classe IV: Pctes que mantiveram o mesmo número de crises ou que apresentaram mais crises que no pré-operatório

Resultados

149 cirurgias do lobo temporal

Engel I	104	(69,8%)	(78,5%)
Engel II	13	(8,7%)	
Engel III	26	(17,5%)	(21,5%)
Engel IV	6	(4%)	

Conclusão

- Em casos bem selecionados a cirurgia do lobo temporal é bastante eficaz e segura
- Muita discussão ainda existe quanto à extensão da área geradora de crises no lobo temporal e da possibilidade de preservação cognitiva nas AH seletivas. Portanto, mantém-se viva a discussão entre as vantagens das ressecções temporais mais seletivas (AH seletiva) com relação às ressecções mais amplas (CAH)

Surgical approach to adulthood epilepsies: extratemporal epilepsies

Ney Azambuja (Brazil)

Surgical approach to childhood epilepsies
Helio Machado (Brazil)

EPILEPSIA NA INFÂNCIA
tratamento neurocirúrgico

Hélio Rubens Machado
Prof.Titular de Neurocirurgia

Faculdade de Medicina de Ribeirão Preto
Universidade de São Paulo

LASSE 2008

Cirurgia da epilepsia na infância

PROGRAMA PEDIÁTRICO

CIREP – Ribeirão Preto, Brasil

Diretor: Américo Sakamoto

Neurocirurgia Pediátrica: Hélio R Machado

Epilepto / Neurofisiologia
Vera C Terra-Bustamante
Regina M F Fernandes

Neuro-imagem
David Araújo
Antonio C Santos

Medicina Nuclear
Lauro Wichert-Ana

Neuro-psicologia
Sara R Rosset

Assistente Social
Sandra Funayama

Hélio Rubens Machado

Cirurgia da epilepsia na infância

HISTÓRICO

BRITISH MEDICAL ASSOCIATION.

PROCEEDINGS OF SECTIONS

Horsley,V: Brain surgery.
-Maio 25, 1886- primeira operação para epilepsia em uma criança.

Hélio Rubens Machado

Cirurgia da epilepsia na infância

HISTÓRICO
Hemisferectomia
22 junho 1938 – Betty, 16 anos

K.G Mckenzie

Histórico

- McKenzie KC: The present status of a patient who had the right cerebral hemisphere removed. JAMA 111:168,1938
  - 16 a , epilepsia pós.traumática, hemiplegia esq e convulsões
- Krynauw RA:Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatry 13:243, 1950
  - 12 pac. Com hemiplegia infantil, epilepsia/ dist.comportamento

Hélio Rubens Machado

Cirurgia da epilepsia na infância

HISTÓRICO

Resultados da cirurgia de epilepsia em crianças

Autores	Nº pacientes	Idade	Cirurgia	Melhora
Davidson & Falconer, 1975	40	<15	Temporal	80%
Rasmussen, 1977	77	6-15	Temporal	73%
Jensen & Vaernet, 1980	12	3-15	Temporal	83%
Whittle, 1981	8	5-18	Temporal	62%
Green & Poolsakul	32	<18	Temporal Hemisdirect	81%
Lindsay,1984	13	7-16	Temporal Hemisdirect	100%
Drake,1987	16	6-16	Temporal	100%
Wyllie,1988	23	3-18	Temporal Extraresp	70%

Hélio Rubens Machado

Cirurgia da epilepsia na infância

- Peculiaridades da cirurgia na infância
- Casuística
  - Etiologia e tipos de cirurgias
- Monitorização invasiva em crianças
  - Indicações e resultados
- Cirurgia do lobo temporal
- Cirurgias hemisféricas
- Epilepsia e tumores cerebrais

Hélio Rubens Machado

Peculiaridades da cirurgia na infância

- A criança deve ser tratada com cirurgia?
  - Objetivos
  - Plasticidade cerebral
  - Epidemiologia
  - Epilepsia catastrófica
  - Idade na cirurgia

Objetivos

- Alívio da epilepsia catastrófica
- Desenvolvimento neurológico normalizado
- Melhora comportamental

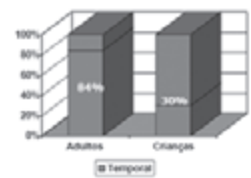
Plasticidade cerebral

- Crescimento e maturação cerebral - 90% até 5 anos
- Até 7 anos - sinaptogênese excessiva, conexões neuronais, maturação dendrítica

PERIODO DE MÁXIMA RECUPERAÇÃO

Epidemiologia

- Adultos x crianças



CIREP – Ribeirão Preto

•Adultos	606	
•Temp	511	
•EMT	446	(87%)
•Crianças	173	
•Temp	52	
•EMT	21	(41%)
•Total	779	

1994 a out 2005

Epilepsia catastrófica

- Síndrome Sturge Weber
- Hemimegalencefalia
- Encefalite Rasmussen
- Esclerose Tuberosa
- Displasia Cortical
- Porencefalia

Síndromes epilépticas catastróficas

Epilepsia Refratária

Média 666,9 crises/ mês
Status epilepticus 40,7%

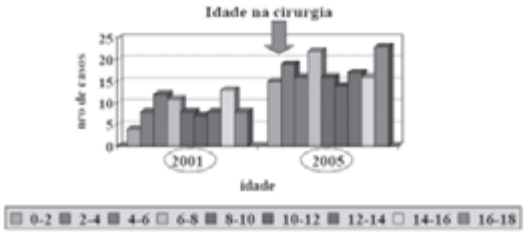
Deficit Neurológico Progressivo

hemiplegia espástica

Retardo Mental

Distúrbio de comportamento

- Idade na cirurgia



Questões

- A criança tem realmente epilepsia parcial intratável e incapacitante?
- **• New drugs have not altered the number of intractable cases in children (Holland, 2002).**
- O foco pode ser removido ou sua propagação interrompida?
- Qual o tipo de lesão que está provocando a epilepsia?
- Pode-se definir o prognóstico e o risco cirúrgico?

Nordli & Kelley, 01

CIREP Pediátrico – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

1996 a ago 2007 — Crianças 219, Cirurgias 232

Patologia	
Displasia Cortical	56
Tumor	36
Esclerose Mesial Temporal	33
Encefalite Rasmussen	17
Esclerose Tuberosa	10
Porencefalia	10
Gliosis	34
MR normal	8
Sturge-Weber	6
Atrofia Difusa	5
Malformação Arterio-venosa	3
(ignorada 1) Total	218.

CIREP Pediátrico – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

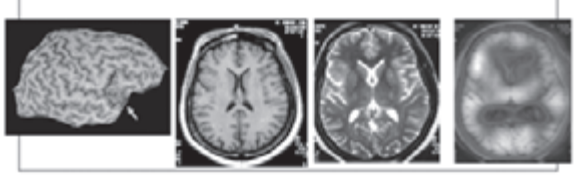
1996 a ago 2007 — Crianças 219, Cirurgias 232

Tipos de cirurgias (219 pacientes)	
Lobectomia Temporal	69
Hemisferotomia	56
Lesionectomia	41
Resecção Multilobar	22
Calosotomia	16
lobectomia Frontal	15
Corticectomia Focal	8
lobectomia Occipital	5
(reoperações 13)	
Total	232

Monitorização não invasiva

1. **Avaliação clínica – FASE I**

- EEG, Vídeo – EEG, avaliação neuro-psicológica, etc
- Spect ictal e inter-ictal, CT scan e Ressonância magnética



Polimicrogiria focal

Monitorização invasiva

2. Avaliação invasiva – FASE II

"MAPEAMENTO CORTICAL"

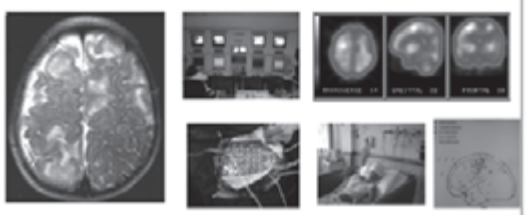
Placas ou estrias corticais

Estimulação cortical direta

Intra-operatório ou registro crônico estudo da zona epileptogênica e estimulação cortical

Questões relevantes

- A zona epileptogênica pode ser identificada?



MONITORIZAÇÃO INVASIVA EM CRIANÇAS

CIREP
Hospital das Clínicas da
Faculdade de Medicina de Ribeirão Preto
Universidade de São Paulo

- Monitorização Invasiva em Crianças
  - Indicações
    - Video EEG não oferece dados suficientes
    - Video EEG mostra dados discordantes com outros exames (RM)
    - Necessidade de mapas funcionais
      - MOTORES
      - SENSITIVOS
      - LINGUAGEM

- Monitorização Invasiva em Crianças
  - ECoG (registro agudo)
  - ECog + eletrodos subdurais (registro crônico)
  - Estimulação Motora
  - Estimulação Linguagem

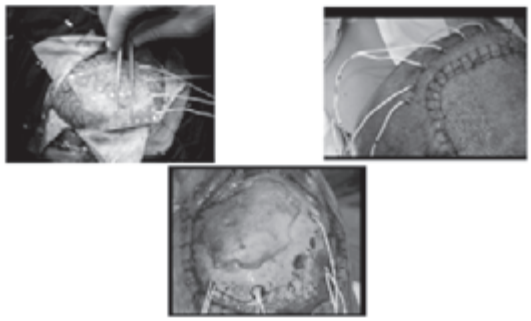
ECog – REGISTRO AGUDO

- VANTAGENS
  - Menor morbidade
  - Única cirurgia
  - Custo reduzido
  - Bom resultado em casos lesionais
- DESVANTAGENS
  - Raro registro de crises
  - Tempo cirúrgico prolongado
  - Decisão operatória deve ser rápida
  - Resultados piores em casos não lesionais

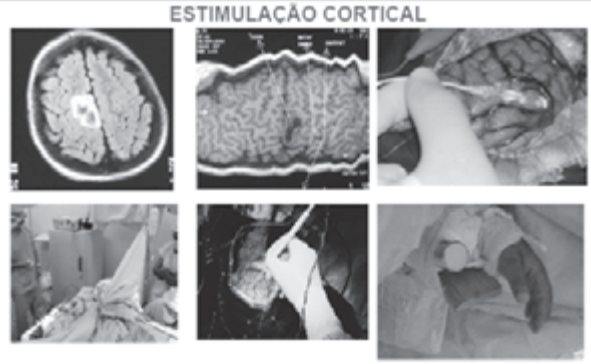
REGISTRO CRÔNICO

- VANTAGENS
  - Registro prolongado de crises
  - Mais tempo para decisão operatória
- MAS...
  - Evitar "fishing expedition"...
- DESVANTAGENS
  - Morbidade
  - Custo
  - 2 cirurgias

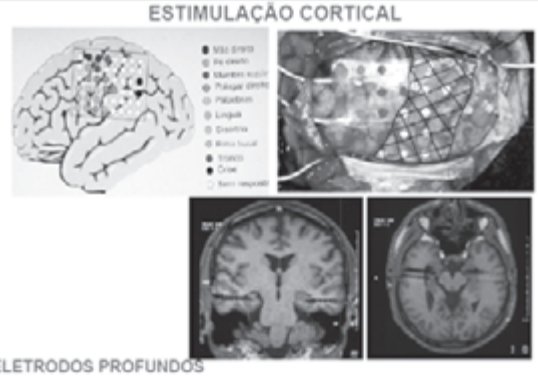
REGISTRO CRÔNICO



ESTIMULAÇÃO CORTICAL

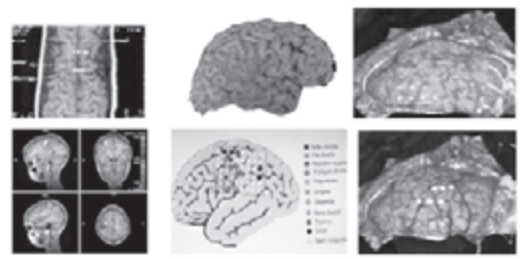


ESTIMULAÇÃO CORTICAL



ELETRODOS PROFUNDOS

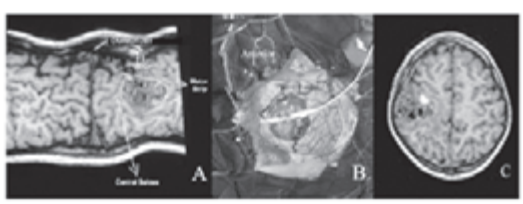
- Localização de áreas eloqüentes



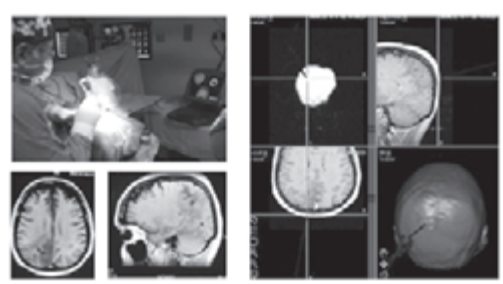
Araujo D, Machado HR et al. Brain surface reformatted imaging (BSRI) in surgical planning for resections around eloquent cortex. Childs Nerv Syst 22:1122-1126, 2006

PLANEJAMENTO CIRÚRGICO

Brain surface reformatted imaging (BSR) in surgical planning for resection around eloquent cortex



- Tática cirúrgica - Neuronavegação



CIREP Pediátrico – Ribeirão Preto

1996 a 2004

Cirurgias 142
Monitorização Invasiva 71

Monitorização Invasiva

- ECoG: 50 pacientes.
- ECoG + eletrodos subdurais: 21 pacientes.
- Estimulação Motora : 25 pacientes.
- Estimulação Linguagem : 1 paciente.

Monitorização Invasiva

Etiologia

MDC	47,6%
Tumor	15,9%
Esclerose Tuberosa	11,1%
Encefalite Rasmussen	6,3%
Gliosis	4,8%
MTS	4,8%
Síndrome Sturge-Weber	4,8%
MRI Normal	3,2%
Porencefalia	1,6%

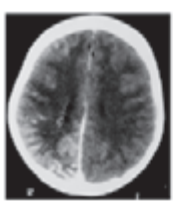
Cirurgia

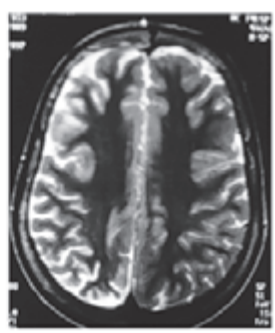
Lesionectomia	33.3%
Lobectomia Temporal	22.2%
Cirurgia Multilobar	17,5%
Lobectomia Frontal	12.7%
Cirurgia Hemisferica	7.9%
Lobectomia Occipital	4.8%
Calosotomia	1.6%

Monitorização Invasiva - resultados

- DECISIVA para o procedimento – 28,6 % dos casos
  - Cirurgia possível devido à monitorização
- CONTRIBUIU para a decisão cirúrgica – 68,2 % dos casos
  - Monitorização modificou o procedimento cirúrgico, mas não o lobo operado
- NÃO CONTRIBUIU para a decisão cirúrgica – 3,2 % dos casos

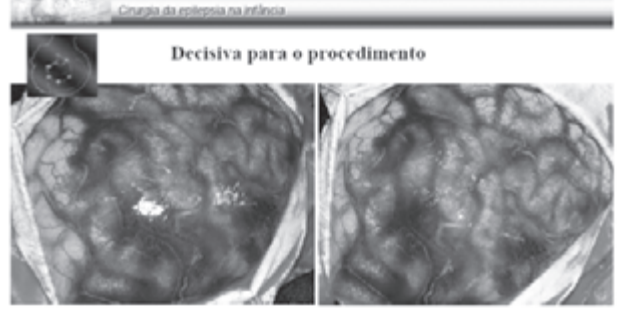
Decisiva para o procedimento





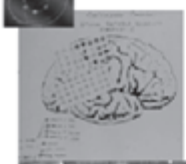
Bruna, 7 yo: Tonic seizures.
Sturge- Weber

Decisiva para o procedimento

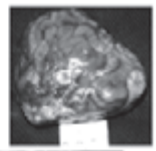


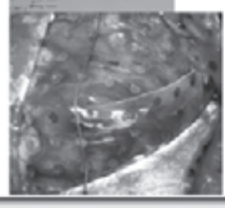
Bruna, 7 a:
Sturge- Weber

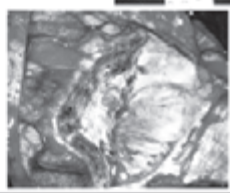
Decisiva para o procedimento



Bruna, 7 yo:
Sturge- Weber
Post-op ENGEL II







CIREP Pediátrico – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

1996 a ago 2007 — Crianças 219, Cirurgias 232

Tipos de cirurgias (219 pacientes)

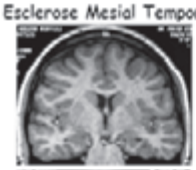
Lobectomia Temporal	69
Hemisferotomia	56
Lesionectomia	41
Resecção Multilobar	22
Calosotomia	16
lobectomia Frontal	15
Corticectomia Focal	8
lobectomia Occipital	5
(reoperações 13)	
Total	232

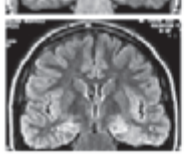
CIREP RIBEIRÃO PRETO

Patologia	N (%)
MTS	18 (39,1%)
MCD	10 (21,7%)
TUMOR	10 (21,7%)
MCD PLUS	5 (10,9%)
ESCLEROSE TUBEROSA	1 (2,2%)
AVM	1 (2,2%)
PORENCEFALIA	1 (2,2%)

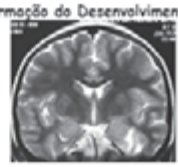
Avaliação Pré-op - MRI

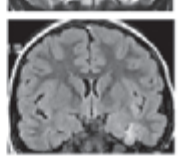
Esclerose Mesial Temporal





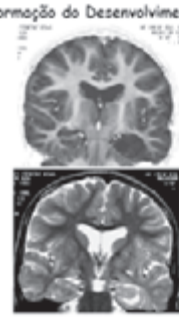
Malformação do Desenvolvimento Cortical



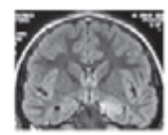


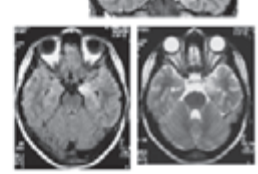
Avaliação Pré-op - MRI

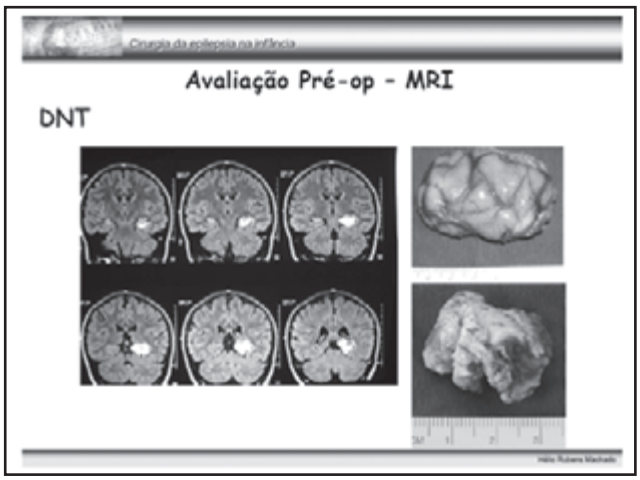
Malformação do Desenvolvimento Cortical



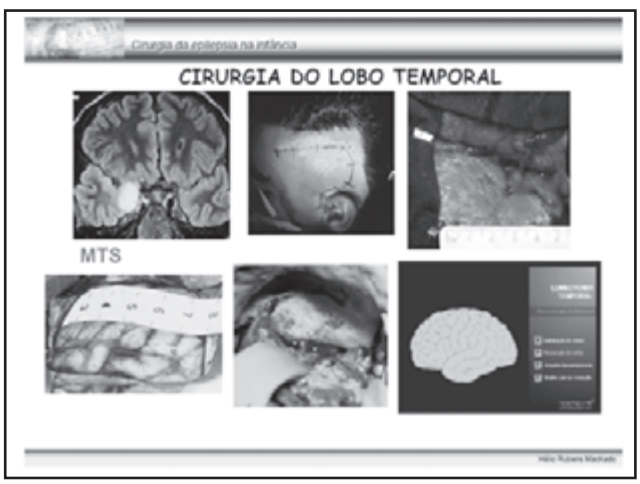
DNT



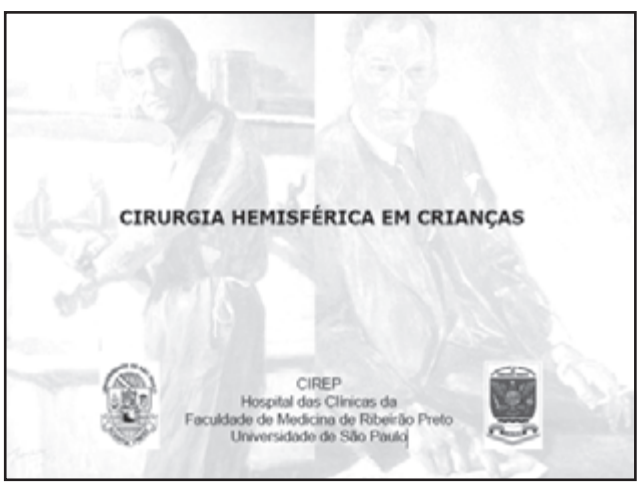


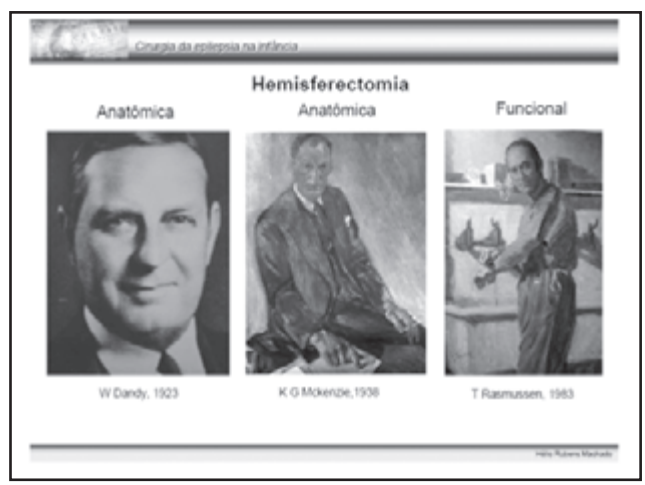

Cirurgia da epilepsia na infância
Avaliação Pré-op - MRI
DNT


Cirurgia da epilepsia na infância
CIREP RIBEIRÃO PRETO
LOBO TEMPORAL
46 / 140 cirurgias: 32,9 %
Jan 1995 a mar 2004
Idade 1 a 2 me até 18 anos
0 to 5
6 to 10
11 to 18
age (years)


Cirurgia da epilepsia na infância
CIRURGIA DO LOBO TEMPORAL
MTS


Cirurgia da epilepsia na infância
CIREP RIBEIRÃO PRETO
100%
80%
60%
40%
20%
0%
82 %
I
II
III
IV
Engel


CIRURGIA HEMISFÉRICA EM CRIANÇAS
CIREP
Hospital das Clínicas da
Faculdade de Medicina de Ribeirão Preto
Universidade de São Paulo


Cirurgia da epilepsia na infância
Hemisferectomia
Anatômica
Anatômica
Funcional
W Dandy, 1923
K G Mckenzie, 1938
T Rasmussen, 1983

CIREP Pediátrico – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

1996 a ago 2007

Crianças 219
Cirurgias 232

Tipos de cirurgias (219 pacientes)	
Lobectomia Temporal	69
Hemisferotomia	56
Lesionectomia	41
Resecção Multilobar	22
Calosotomia	16
lobectomia Frontal	15
Corticectomia Focal	8
lobectomia Occipital	5
(reoperações 13)	
Total	232

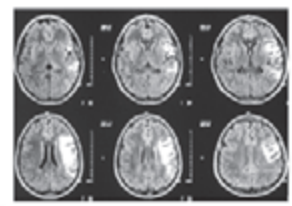
Síndromes epilépticas catastróficas

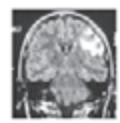
Etiologia	
Encefalite Rasmussen	17
Gliosis	13
Displasia Cortical	11
Porencefalia (encefaloclastica)	10
Sturge-Weber	4
Esclerose Tuberosa	1
Total	56

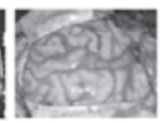
CIREP Pediátrico – Ribeirão Preto

Tipos de crises	
Tônicas	39,6 %
Epilepsia parcial continua	33,3 %
Focal motor	12,5 %
Espasmos Infantis	10,4 %
Parcial Complexa	4,2 %

Encefalite de Rasmussen



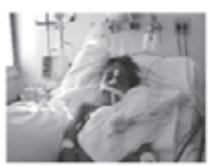


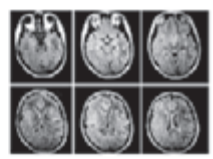


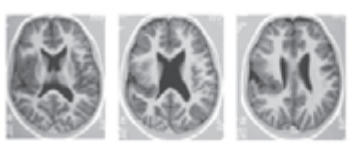
DSF, 13 a. Crises convulsivas evoluindo há 1 ano. Epilepsia parcial continua. Afasia e moderado rebaixamento mental.

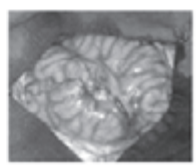
Resultado cirúrgico: Engel 1a

Displasia cortical hemisférica



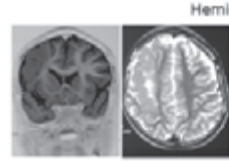


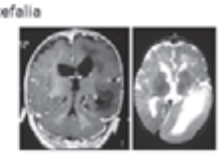


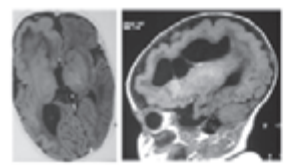


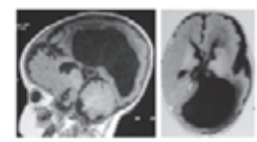
Polimicrogiria peri-silviana

Hemimegalencefalia

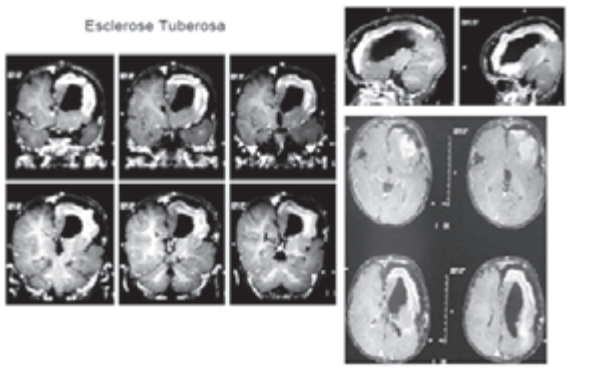




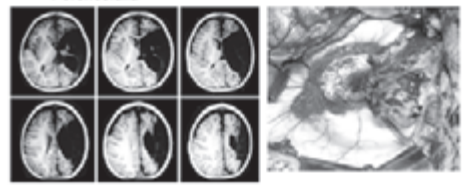




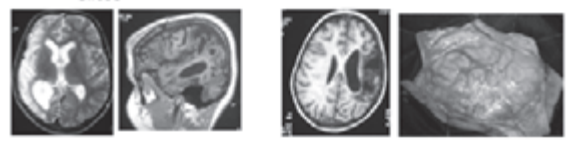
Esclerose Tuberosa



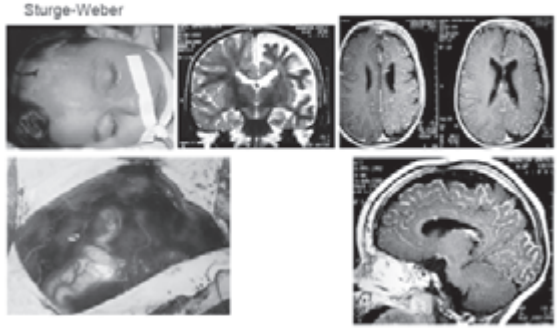
Porencefalia



Gliose



Sturge-Weber



CIREP Pediátrico – Ribeirão Preto

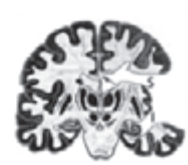
Técnica Cirúrgica

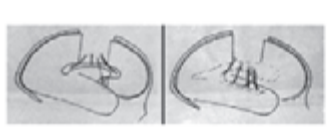
Hemisferotomia	48
Hemisferectomia Funcional	**6**
Hemidecorticação	**2**

Hemisferotomias

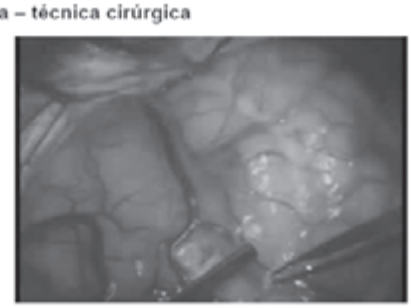
Delalande, 92
Villemure, 93
Schramm, 94

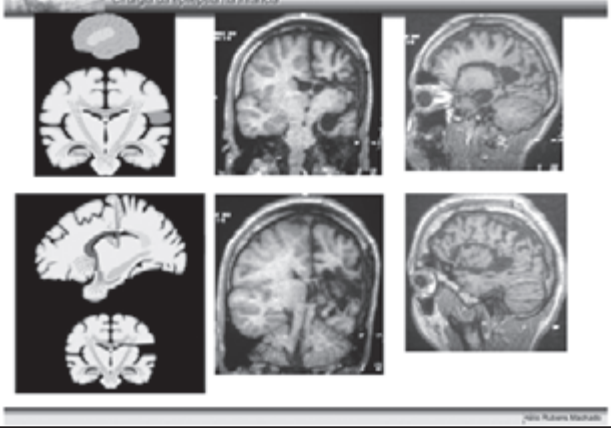
Shimizu, 00
Danielpour, 01



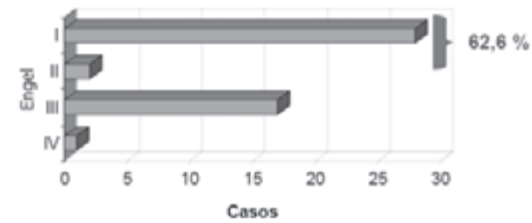


Hemisferotomia – técnica cirúrgica





Resultados



Engel

I Livre de crises II Raras crises III Considerável melhora IV Sem melhora

Epilepsia e Tumores do SNC
Tratamento Cirúrgico

CIREP
Hospital das Clínicas da
Faculdade de Medicina de Ribeirão Preto
Universidade de São Paulo

- Incidência de epilepsia em tumores cerebrais:
  - Le Blanc & Rasmussen, 74: 35%
    - Oligodendroglioma 92%
    - Astrocitoma/ Meningioma 70%
    - GBM 35%
  - Crianças:
    - Hirsch et al, 89: 76% (todos low grade)

- Epilepsia e tumores cerebrais (centros de cirurgia de epilepsia)
  - Spencer et al, 84 (Yale): 190 pac.- 10%
  - Theodore et al, 90 (NIH): 26 pac. – 11,5%
  - Morris et al, 96 (Cleveland Clinic): 39 pac. – 20%
  - Crianças:
    - Drake et al, 87: 25%
    - Bruner, 87: 46%

CIREP Pediátrico – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

1996 a ago 2007

Crianças 219
Cirurgias 232

Patologia	
Displasia Cortical	56
Tumor	36
Esclerose Mesial Temporal	33
Encefalite Rasmussen	17
Esclerose Tuberosa	10
Porencefalia	10
Gliosis	34
MR normal	8
Sturge-Weber	6
Atrofia Difusa	5
Malformação Arterio-venosa	3
(ignorada 1) Total	218.

Cirurgia da epilepsia na infância

Patients:

TUMOR
36 Patients

1. Refractory epilepsy
2.
3.
4.
5.

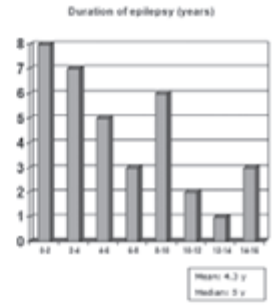
Hélio Rubens Machado

Cirurgia da epilepsia na infância

Patients:

TUMOR
36 Patients

1. Refractory epilepsy
2. Duration of epilepsy
3.
4.
5.



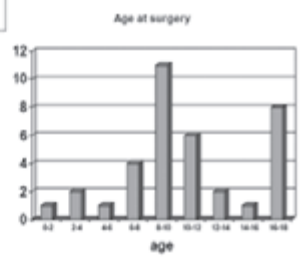
Hélio Rubens Machado

Cirurgia da epilepsia na infância

Patients:

TUMOR
36 Patients

1. Refractory epilepsy
2. Duration of epilepsy
3. Age at surgery
4.
5.



Hélio Rubens Machado

Cirurgia da epilepsia na infância

Patients:

TUMOR
36 Patients

1. Refractory epilepsy
2. Duration of epilepsy
3. Age at surgery
4. Pathology
5.

Pathology	
DNET	15
DNET + DC	3
Ganglioglioma	4
Astrocytoma	2
Pilocytic Astrocytoma	2
Oligodendroglioma	3
Glioma	1
Hamartoma	4
Dermoid	1
Cavernous angioma	1
TOTAL	36

Hélio Rubens Machado

Cirurgia da epilepsia na infância

Patients:

TUMOR
36 Patients

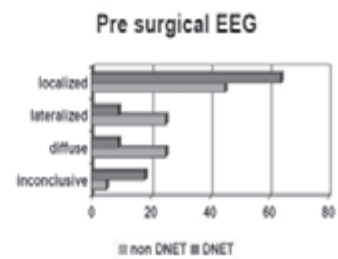
1. Refractory epilepsy
2. Duration of epilepsy
3. Age at surgery
4. Pathology
5. Location of the tumor

Location	
Temporal	18
Frontal	8
Parietal	4
Hypothalamus	2
Cerebelar peduncle	2
Occipital	2
Total	36

Hélio Rubens Machado

Cirurgia da epilepsia na infância

- Results
  1. Pre surgical monitoring
  2.
     1.
     2.
  3.
  4.



Hélio Rubens Machado

- Results
  1. Pre surgical monitoring
  2. Location x ECoG
     1. Temporal
     2. Extra-temporal
  3. Extension of surgery
  4.

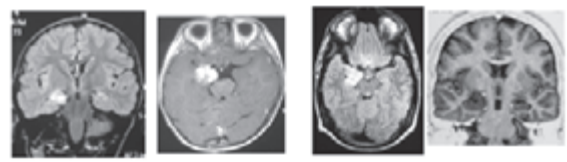
Temporal Type of surgery		ECog	
Lesionectomy	2	0	2
Temporal lobectomy + amygdalo hypocampectomy	10	6	16
Total	12	6	18

•Indications for ECoG:
•Limits of surgery – Extended

Temporal lobe surgery without use of ECoG

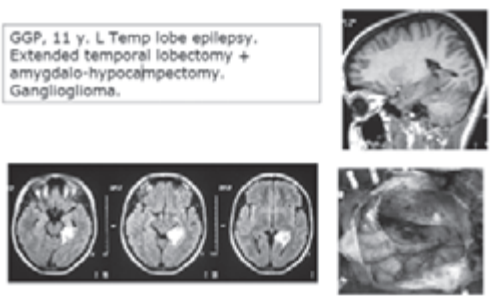
DROL, 3 y. R Temp lobe epilepsy. Temporal lobectomy + amygdalo-hypocampectomy. Ganglioglioma.

RRP, 16 y. R Temp lobe epilepsy. Temporal lobectomy + amygdalo-hypocampectomy. Ganglioglioma.



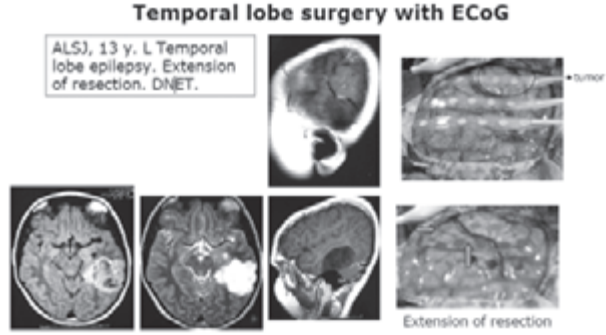
Temporal lobe surgery without use of ECoG

GGP, 11 y. L Temp lobe epilepsy. Extended temporal lobectomy + amygdalo-hypocampectomy. Ganglioglioma.



Temporal lobe surgery with ECoG

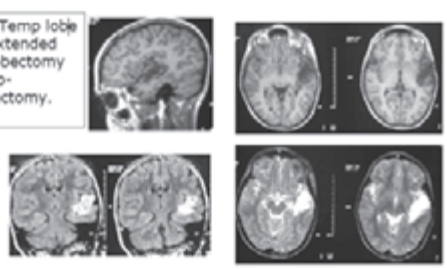
ALSJ, 13 y. L Temporal lobe epilepsy. Extension of resection. DNET.



Extension of resection

Temporal lobe surgery with ECoG

JAKG, 9 y. Temp lobe epilepsy. Extended temporal lobectomy + amygdalo-hypocampectomy. DNET.



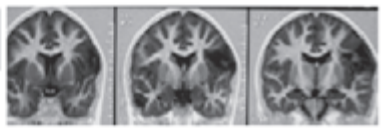
- Results
  1. Pre surgical monitoring
  2. Location x ECoG
     1. Temporal
     2. Extra-temporal
  3. Extension of surgery
  4.

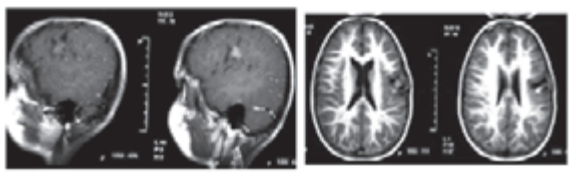
Extra-temporal		ECoG	
Frontal	1	7	8
Parietal	0	4	4
Occipital	1	1	2
Other	3	1	4
Total	5	13	18

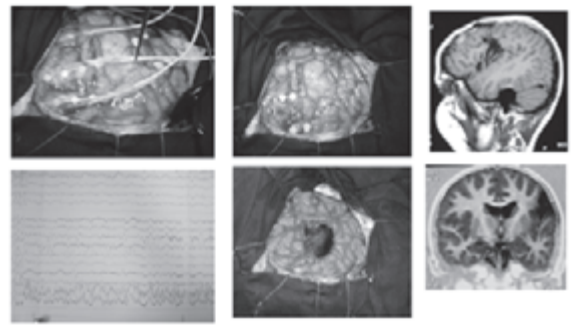
•Indications for ECoG:
•Limits of surgery – Extended
•Motor area – Frontal & Parietal

Extra-temporal surgery with ECoG

ACE, 7 y. Complex partial seizures. Extended resection. DNET.

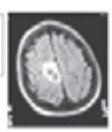


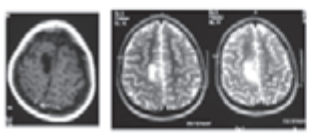


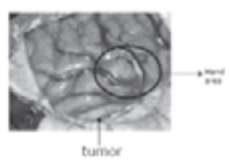


Extra-temporal surgery with ECoG

KRRM, 7 y. Motor focal seizure. Lesionectomy. Low grade astrocytoma.







tumor

- Results
  1. Pre surgical monitoring
  2. Location x ECoG
     1. Temporal
     2. Extra-temporal
  3. Extension of surgery
  4. Late results

Late results	
Recurrences	none
Focal deficits	none
Engel I – DNET (18)	all
Engel III / IV – Glioma (12)	3

CONCLUSÕES

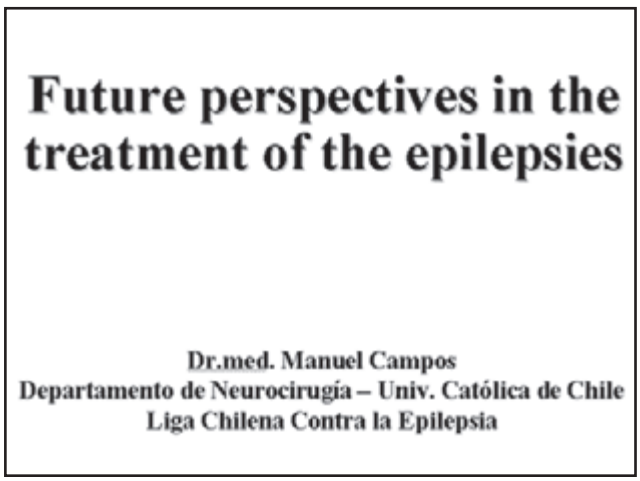
- **Cirurgia da epilepsia deve ser indicada o mais precocemente possível, antes do aparecimento de déficits irreversíveis.**
- **A criança deve ser atendida em ambiente especializado e por equipe treinada para este fim.**
- **Os resultados cirúrgicos são encorajadores apesar da complexidade da abordagem.**

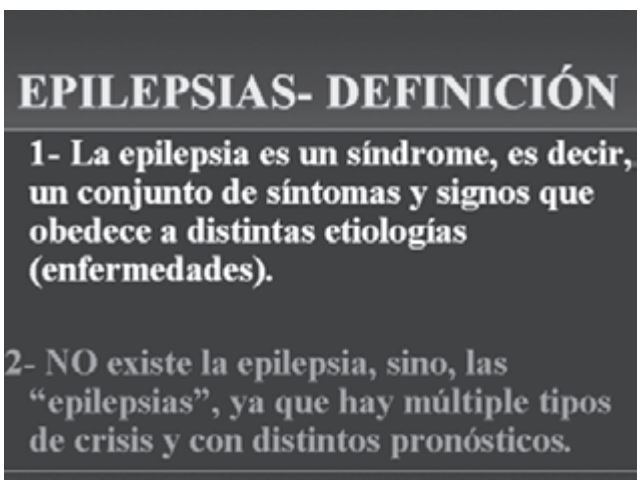
Vagus nerve stimulation

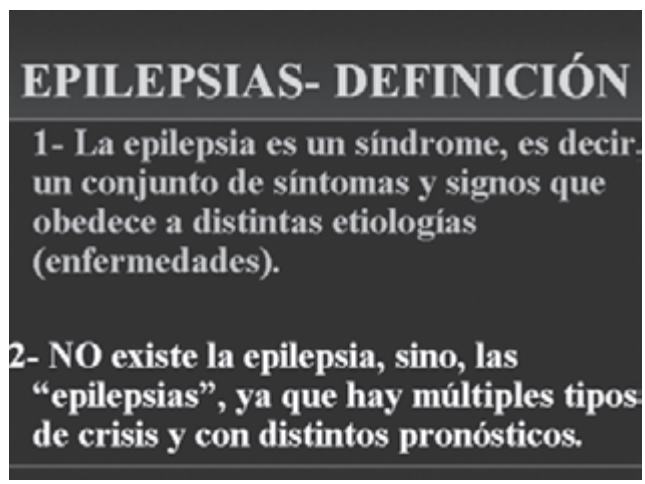
Mario Alonso Vanegas (México)

Future perspectives in the treatment of the epilepsies

Manuel Campos (Chile)







¿Qué es epilepsia fármaco resistente?

- **Crisis que persisten pese tratamiento farmacológico adecuado.**

Pero…..

- **¿Cuáles son y quien determina que FAEs son los adecuados?**

¿Qué es epilepsia fármaco resistente?

- **La definición de refractariedad varía:**
- -Falla > 2 FAEs con 1 o más crisis/mes últimos 18 meses.
- -Falla > 3 FAEs con 1 crisis/mes último año, etc.

- **Pero, el criterio de refractariedad involucra especialmente la calidad de vida.**

Tópicos	Evidencia
Porcentaje de refractariedad:	?
Ventana de tiempo para prevenir:	?
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	?
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

Tópicos	Evidencia
Porcentaje de refractariedad:	?
Ventana de tiempo para prevenir:	?
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	?
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

Factores predictores de epilepsias fármaco resistente
Control de Crisis

- 47% sin crisis con un fármaco en monoterapia
- 13% sin crisis con 2° fármaco en monoterapia.
- 4% libres con terapia bi o tri asociada.
- 36% de los pacientes persisten con a lo menos una crisis por año.

(Kwan and Brodie NEJM 2000)

Factores predictores de epilepsias:
Control Crisis Parciales reciente inicio
Estudio Prospectivo Ingles (N = 1721)
SANAD (Standard and New Antiepileptic Drugs)

CBZ en monoterapia.

VERSUS

Lamotrigina monoterapia.

Marson AG, et al. Lancet 2007;369:1000-15)

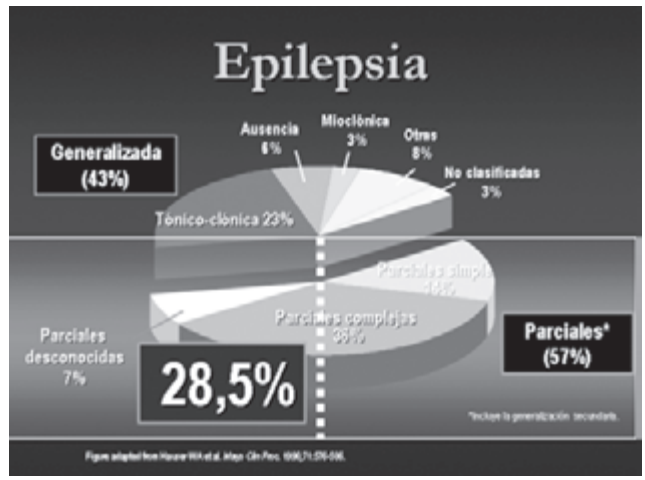
Factores predictores de epilepsias:
Control Crisis Parciales reciente inicio
RESULTADO
- Estudio Prospectivo Ingles -

50% sin crisis con CBZ en monoterapia.

VERSUS

55% sin crisis con Lamotrigina monoterapia.

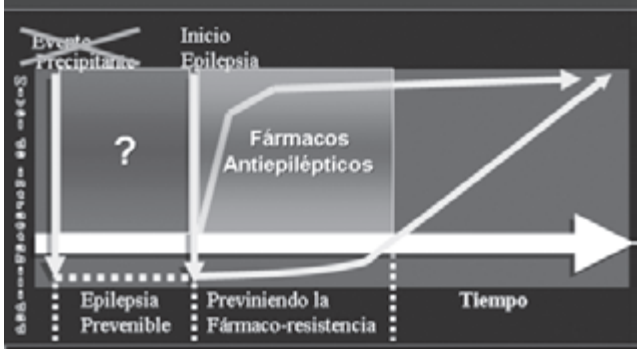
Marson AG, et al. Lancet 2007;369:1000-15



Tópicos	Evidencia
Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	?
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	?
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

Tópicos	Evidencia
Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	?
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	?
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

¿Existe una ventana de tiempo para prevenir la fármaco-resistencia?



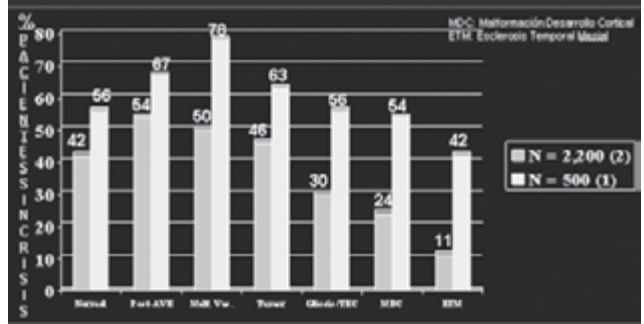
Tópicos	Evidencia
Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	?
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

Tópicos — Evidencia

Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	?
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

El 71% de los pacientes con CPC tienen una lesión en RM
(Semah, et al. Neurology 1998;51:1256-62)

libertad de crisis de diferentes causas



(1) Stephen LJ, et al. Epilepsia 2001;42:357-62 (70% Epilepsia recién diagnosticada)
(2) Semah F, et al. Neurology 1998;51:1256-62 (8% Epilepsia recién diagnosticada)

Hallazgos Neuropatológicos en Cirugía de la Epilepsia

- 30% Esclerosis del Hipocampo
- 25% Tumores cerebrales
- 11% Malformaciones del Desarrollo Cortical

Registro Neuropatológico (N = 2055)
Bonn-Bethel-Berlin-Erlangen-Freiburg
www.epilepsie-register.de
(Dr. Ingmar Blümcke)

Epilepsias fármaco resistente: Causas Prevenibles

IMPOSIBLES DE PREVENIR:	FACTIBLES DE PREVENIR:
- MDC	- Traumas de cráneo
- Tumores	- Lesiones del Parto
- Cavernomas	- Enfer. Infecciosas
- Esclerosis Hipocampal	-¿Accidente Cerebro-vascular?
- Alteraciones Genes	- Otras.
- Otras.	

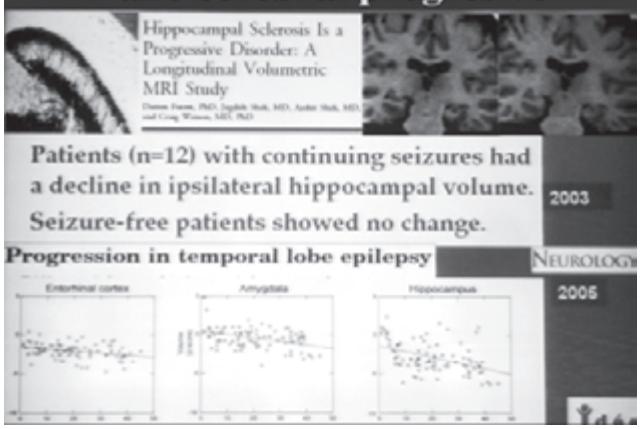
Tópicos — Evidencia

Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	Difícil de prevenir
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

Tópicos — Evidencia

Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	Difícil de prevenir
Neuro-degeneración progresiva:	?
Resistencia a FAEs:	?

Daño cerebral progresivo



Factor "Tiempo"

- En adultos Ud. se puede dar hasta 2 años de tiempo antes de declarar a un adulto "refractario a fármacos"
- pero, en niños Ud. NO puede darse más allá de un año para establecer la refractariedad, incluso hay autores quienes plantean 6 meses

Alexis Arzimanoglu, International Epilepsy Congress

ELT: Efecto Quirúrgico

Pacientes operados 147, follow-up 2-10 años

Helmstaedter C, et al. Ann Neurol 2003;54:425-432

Tópicos	Evidencia
Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	Difícil de prevenir
Neuro-degeneración progresiva:	Existe
Resistencia a FAEs:	?

Tópicos	Evidencia
Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	Difícil de prevenir
Neuro-degeneración progresiva:	Existe
Resistencia a FAEs:	?

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VOLUME 345 AUGUST 2, 2001 NUMBER 5

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*

N = 80

- Libres de crisis: 58% grupo quirúrgico P < 0.001
  8% grupo médico
- Mejor calidad de vida en grupo quirúrgico P < 0.001

Tópicos	Evidencia
Porcentaje de refractariedad:	20-30%
Ventana de tiempo para prevenir:	Incierta
• Potenciales blancos terapéuticos	
Etiología de la epilepsia:	Difícil de prevenir
Neuro-degeneración progresiva	Existe
Resistencia a FAEs:	Altamente Probable

¿Necesitamos nuevos fármacos antiepilépticos?

"SI"

¿Por qué necesitamos nuevos FAEs?

- Mejorar la eficacia
- Mejor tolerabilidad
- Mejor manejo de FAE
- Facil administración
- Mínima teratogenicidad
- Efecto antiepileptigénico

Respuesta* a los nuevos FAE

FAE	> 50% Reducción
VGB	45-50% (6000 mg/día)
LTG	25-35%
GBP	20-25%
TGB	20-30%
TPM	40-45%
LEV	40-45%
PGB	31-51%
PLACEBO	Hasta 18%

*Epilepsia farmaco resistente, con terapia agregada (add-on).

Libertad de crisis con nuevos FAE

FAE	Libertad de crisis*	
VGB	5%	12 semanas
LTG	2-4%	
GBP	?%	
TGB	?%	
TPM	10%	
LEV	8%	
PGB	5-17%	
CIRUGIA	58%	1 año

*Epilepsia farmaco resistente, con terapia agregada (add-on).

Ranking Alemán de FAEs en epilepsias focales

- 1° Elección : Lamotrigina, Oxcarbacepina, Carbamacepina.
- 2° Elección : A. Valproico, Levetiracetam, Pregabalina, Gabapentina.
- 3° Elección : Fenitoina, Topiramato
- Otros: Tiagabina, Vigabatrina, Clobazam, Fenobarbital.

¿SE PUEDE PREVENIR LA REFRACTARIEDAD EN EPILEPSIA CON FARMACOS?

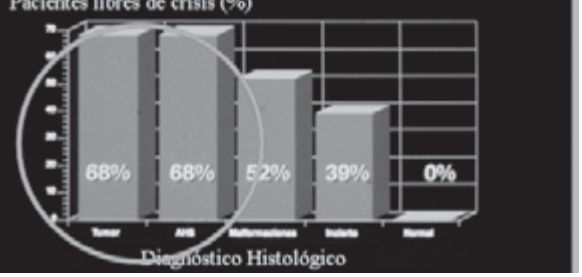
PERO...

¿SE PUEDE PREVENIR LA REFRACTARIEDAD EN EPILEPSIA CON CIRUGÍA?

?

Surgical treatment of temporal lobe epilepsy: clinical, radiological, and histopathological findings in 178 patients

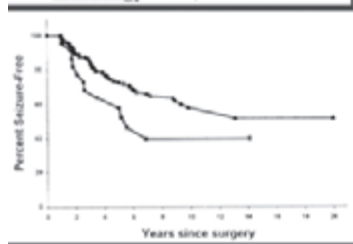
Josef Zentner, Andreas Hufnagel, Helmut K Wolf, Burkard Ostertun, Elga Behrens, Manuel G Campos, Laszlo Solymosi, Christian E Elger, Otmar D Wiestler, Johannes Schramm



CONTROL DE CRISIS POST-CIRUGIA RESECTIVA EN EPILEPSIAS

"Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery"
Yoon HH, et al.
Neurology 2003;61:445-450

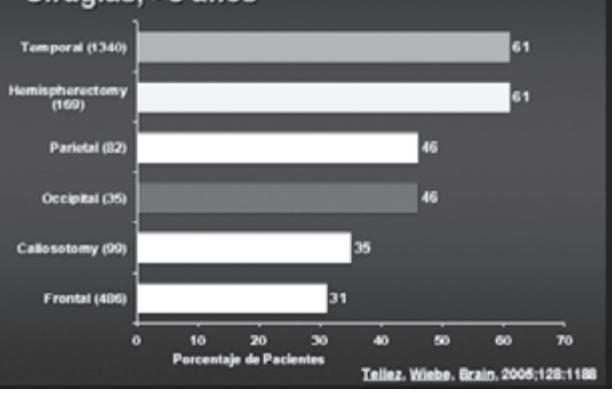
- N = 175
- 56% libres de crisis a 10 años.



- Factores Pronóstico
  - Más de 10 años de historia de crisis.
  - Histología normal del tejido resecado (extirpado).

Resultados a Largo Plazo

Cirugías, >5 años



Tellez, Wiebe, Brain, 2005;128:1188

¿SE PUEDE PREVENIR LA REFRACTARIEDAD EN EPILEPSIA CON CIRUGÍA?

"SI"

RESUMEN
¿Es prevenible la epilepsia refractaria?

- La ventana de tiempo para la prevención es incierta.
- La etiología de las epilepsias es difícil de prevenir.
- Los nuevos FAEs juegan un rol importante en el control de crisis.
- La cirugía de la epilepsia focal refractaria es una alternativa ahora ya!

CONCLUSIONES

- Existen las Epilepsias (plural) y no la Epilepsia (singular).

CONCLUSIONES

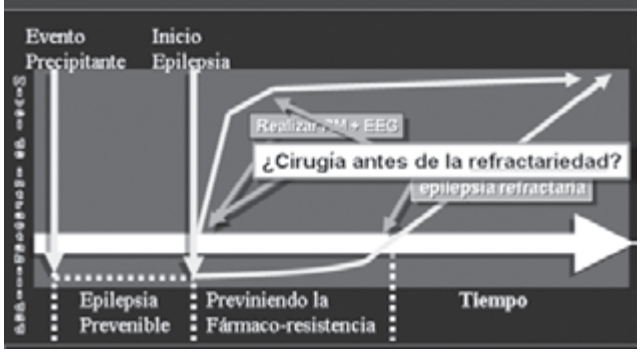
Es decir:

- Existen múltiples tipos de Síndromes Epilépticos, cada una con su propio pronóstico y tratamiento.

CONCLUSIONES

Actualmente la cirugía de la epilepsia refractaria esta solo indicada en casos de refractariedad. Pero puede que a futuro su indicación sea antes del inicio de la refractariedad, dependiendo de la etiología de la epilepsia.

¿Existe una ventana de tiempo para prevenir la fármaco-resistencia?



MUCHAS GRACIAS POR SU ATENCION

Programa – 16.02.2008

Presentation and discussion of research projects

Adjourn

Organização:

Apoio:

Universidade Federal de São Paulo
Escola Paulista de Medicina