FENITOINA O LEVETIRACETAM?

Questo è il dilemma.....

Club a cura di:

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OLEDI' 20 NOVEMBRE ore 14, AULETTA 2° CR

ALCUNI DATI PER CAPIRE IL PERCHE'...

The incidence of seizures in the general ICUs ranges from 3.3% to 34.0%, depending on the ICU population and the detection method.

itted to the
ple, in an
vulsive seizures on continuous EEG, and 76% of them were in nonconv

Table Prognosis

Convulsive status epilepticus

Mortality

At hospital discharge: 9–21 % [19, 36–38]

At 30 days: 19–27 % [30, 39, 40]

days: 19 % [41]

lized 10-year mortality ratio: 2.8 in general population [42]

the mortality ranges from 3 to 11 % in retrospective series [43]. In a prospective study, the mortality

Morbi

Severe l or cognitive sequelae: 11–16 % [19, 44–46]

Deteriorati onal status 23–26 % [19, 36, 38]

At 90 days afte % had marked functional impairment (glasgow outcome scale score 2–4) a good recovery (glasgow outc core 5) [41]

Factors associated w tcome after GCSE

Underlying etiology, d velopment of SE in hospitalized patients, older age, impa consciousness, duration of seizures, at onset focal neurold , and the presence of medical complications [36, 3 7–49]

Mortality rate is higher (61 SE develops de novo in hospitalized patients

In patients with adequate therap lity rate may be as low as 8 % while i high as 45 % in those with insufficient therapy (insufficient dose given, wrong minustration, unnecessary delay eatments, inadequate ventilation, medical complications, or lack of EEG mor uide treatment) [47]. Adhe reatment protocol was associated with better seizure control and shorter ICU and hospita ay [50]

Nonconvulsive status epilepticus

Mortality

At hospital discharge: 18–52 % [51–53]

At 30 days: 65 % [30]

Factors associated with poor outcome after NCSE:

Underlying etiology, severe mental status impai duration [28, 51, 53, 54]

For patients diagnosed within 30 min of seizu ortali compared with 75 % for those patients diagnosed ≥24 h after seizure onset seizures [51]

Patients with NCSE treated and resolve h had 10 % mor % mortality if seizures continued longer than 20 h [51]

Mortality at hospital discharge in N 7 % vs. 3 % comparing ith vs. without known acute medical cause [53]

Refractory status epilepticus

Mortality

At hospital discharge: 23–6 , 38, 55–67]

At 3 months: 39 % in R ng propofol with barbiturate infusions [68]

In children with RSE lity rate was very low [69] to 32 % [70], but greatest in th ute symptomatic SE [70, 71]

In a meta-analysi children, the mortality rate was 20 % in symptomatic SE and 4 thic SE [72]

Morbidity

Return to fu eline is more likely for SE patients than for RSE patients [66] and was seen in 39 patients at 3 months [68]. At hosp ge among 13 survivors: 23 % vegetative state, 62 % severely disabled, 15 % indepen derately disabled [28, 73] lepsy may be seen more frequently in long-term survivors with RSE than in those with non SE (88 % vs. 22 %) [6

In ith RSE, a new deficit occurred in 36 and 32 % returned to baseline [70]. Motor and visual deficits may year after SE owever, no child with acute symptomatic RSE returned to baseline [71] and the morbidity and mortality is hose with ptomatic SE or a progressive encephalopathy [34, 74]

tors associated with poor outcome after RSE:

Underlying etiology, older age (e.g., >50 years), long seizure duration, and high Acute Physiology and Chronic Health Eva (APACHE-2) scale scores [51, 63, 67, 75]

Recently one study reported that after correcting for underlying etiology, coma, and type of SE seizure, duration was not associate outcome [64]

EEG electroencephalogram; *GCSE* generalized convulsive status epilepticus; *NCSE* nonconvulsive status epilepticus; *ICU* intensive care unit; *RCT* randomized clinical trial; *RSE* refractory status epilepticus; *SE* status epilepticus

EPILESSIA E CRISI EPILETTICHE

nt seizure disorders that have been classified in accordance with the location and ex

DEFINITIONS

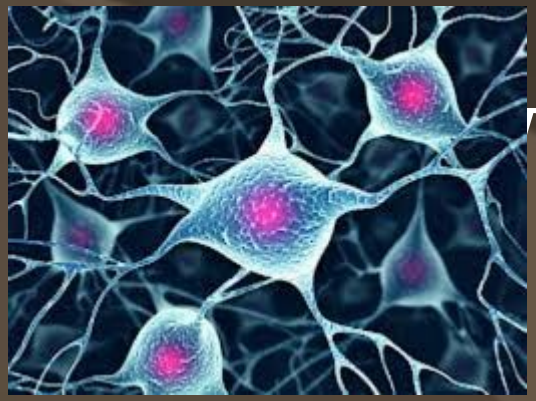
CONVULSIVE

- PARZIALI o FOCALI

CRISI EPILETTICHE

- NON CONVULSIVE

- GENERALIZZATE



TIONS

CONVULSIVO

STATO DI MALE EPILETTICO

→ 5 min or more of (i) continuous clinical and/or electro-graphic seizure activity or (ii) recurrent seizure activity without recovery (returning to baseline) between seizures.

NON CONVULSIVO

DEFINITIONS

STATO DI MALE EPILETTICO NON CONVULSIVO (NCSE)

In ICU il 5% to 10% dei pazienti in coma esaminati con EEG sonio in NCSE.

Definito come attività epilettica visibile all'EEG senza segni/sintomi visibili associati .

Nel paziente critico, il NCSE si può presentare con:

✔ *SINTOMI NEGATIVI: anoressia, afasia/mutismo, amnesia, catatonia, coma, confusione, letargia, sguardo fisso.*

✔ *SINTOMI POSITIVI: agitazione/aggressività, automatismo, ammiccamento, pianto, delirio, depressione, ecolalia, facial twitching, risata, nausea/vomito, nistagmo, deviazione dello sguardo, ripetitività, psicosi, tremori.*

DEFINITIONS

STATO DI MALE EPILETTICO REFRATTARIO

Si definisce come la persistenza di crisi epilettiche visibili clincamente o elettroencefalicamente nonostante la somministrazione di terapia con benzodiazepine seguita da una dose adeguata di farmaco antiepilettico (AED).

Box 1
Common causes of critical care seizures

Neurologic pathology
Neurovascular
- Ischemic stroke
- Hemorrhagic stroke
  - Subarachnoid hemorrhage
  - Intracerebral hemorrhage
- Arteriovenous malformation
- Cerebral sinus thrombosis
- Hyperperfusion syndrome

Tumor
- Primary
- Metastatic

Central nervous system (CNS) infection
- Abscess
- Meningitis
- Encephalitis

Encephalitis (noninfectious)
- Paraneoplastic limbic
  - N-methyl-d-aspartate–receptor antibodies
- Nonparaneoplastic limbic
  - Voltage–gated K+ channel antibodies (VGKC/LGI1)

Inflammatory disease
- Vasculitis
- Acute disseminated encephalomyelitis

Traumatic head injury
- Depressed skull fragments
- Cerebral contusion
- Extra-axial hemorrhage
  - Subdural hematoma
  - Epidural hematoma
  - Hygroma (?)

Primary epilepsy

Primary CNS metabolic disturbance (inherited)

Complications of critical illness

Hypoxia/ischemia

Drug/substance toxicity
- Antibiotics
- Antiviral agents
- Antidepressants
- Antipsychotics
- Bronchodilators
- Local anesthetics
- Immunosuppressives
- Cocaine
- Amphetamines
- Phencyclidine

Drug/substance withdrawal
- Barbiturates
- Benzodiazepines
- Opioids
- Alcohol

Infection (febrile seizures)

Metabolic abnormalities
- Hypophosphatemia
- Hyponatremia
- Hypoglycemia
- Renal/hepatic dysfunction

Data from Mirski MA, Varelas PN. Seizures and status epilepticus in the critically ill. Crit Care Clin 2008;24:115–47, ix.

CAUSE AND PATHOPHYSIOLOGY

Seizures in the NICU can be caused either by primary neurologic pathology or as a complication of critical illness (**Box 1**). Although in general ICUs the latter may be more common, in neurologic and neurosurgical patients, structural pathology may be the leading cause. In several patients, however, both can be present. In this case, it is difficult to decide which one of the two is the major contributor, but correcting the nonstructural disorder usually brings seizures under control.

The mechanisms by which nonstructural abnormalities induce seizures are, in many cases, unknown. Drugs precipitate seizures by either preventing γ-aminobutyric acid (GABA) binding to the $GABA_A$ receptor,[5] such as with antibiotics, or via antagonism at the Na^+ channels, such as with the local anesthetics. Depending on the level of potassium, hyperkalemia may depolarize the neuronal membranes or inactivate the Na^+ and Ca^{++} channels, leading to an increased threshold for membrane depolarization. Hyponatremia and low osmolarity, as a consequence of increased cellular edema and increased neuronal excitability, may also lead to seizures. During alkalosis, increased inward Na^+ and Ca^{++} channel currents and during hypomagnesemia decreased N-methyl-d-aspartate receptor antagonism promote cell depolarization.[6]

- ***MANAGEMENT DELL'EPILESSIA IN NICU***

Le convulsione si verificano più spesso in NICU che in terapia intensiva generale o altre specialità di terapia intensiva.

Perché?

- **Per la tipologia di pazienti**
- **Per il tipo di monitoraggio**

- ***EZIOLOGIA***

- **Causa neurologica primaria**
- **Cause non neurologiche**

- ***INCIDENZA***

Da 3.3% a 34% e sono più frequenti nelle emorragia che nelle ischemie e si dividono in:

- Precoci
- Tardive

EPILESSIA E IPH

- **Il rischio di avere convulsione è 2-3 volte> rispetto all'ischemia cerebrale**
- **28% può avere convulsione anche in caso di profilassi con AEDs**
- **Le linee guida attuali suggeriscono trattamento antiepilettico per un mese poi sospensione in caso di regressione**

- ***EPILESSIA E SAH***

Tutti i pz hanno manifestazioni motorie e perdita di coscienza all'insorgenza di SAH

- **Le crisi precoci si manifestano da 1.1% a 16%**
- **Le crisi tardive invece nel 5.1-14%**

- ***EPILESSIA E ICTUS ISCHEMICO***

- **L'incidenza varia da 0% a 28%**
- **Sono più frequenti con i pz oltre 60%**

- ***EPILESSIA E TROMBOSI VENOSA CEREBRALE***

- **L'incidenza è del 29-50%**
- **Crisi precoci in 34-44% dei pz**
- **Crisi tardive nel 9.5%**

EPILESSIA E RHS

- **RHS è una complicanza non comune nel:**
  - **TEA carotideo**
  - **Angioplastica e stenting carotideo**
- **Le crisi precoci si verificano immediatamente dopo la procedura chirurgica**
- **Le crisi tardive si verificano dopo 7 ore a 14 giorni**

EPILESSIA E TBI

- **L'incidenza varia ampiamente da 2-12% nella popolazione civile , e più del 52% nella popolazione militare**
- **Le crisi precoci (entro una settimana dal trauma con incidenza del 2.1-16.9%)**
- **Le crisi tardive con incidenza del 1.9->30%**
- **L'American Academy of Neurology e il Brain Trauma Foundation suggeriscono il trattamento profilattico con Fenitoina per i primi sette giorni**

- ***EPILESSIA E FARMACI***

- **Penicilline, cefalosporine, azetronam, fluorchinolonici, isoniazide, metronidazolo**
- **Baclofene**
- **Anestetitici locale in dose tossica**
- **Acido tranexamico**

DISORDINI ELETTROLITICI E METABOLICI

- **Circa il 18% dei pazienti ricoverati in ICU può avere insorgenza di nuovi crisi convulsivi per iponatremia acuta**
- **Sia l'ipo che l'iperglicemia sono in grado di causare convulsione**

- ***TRATTAMENTO***

Treatment of Seizures in the Neurologic Intensive Care Unit

Panayiotis N. Varelas, MD, PhD
Marek Mirski, MD, PhD

TRATTAMENTO

- **La gestione delle crisi convulsive in NICU segue sostanzialmente le stesse regole generali che guidano il trattamento dei paz non critici.**
- **La familiarità del personale medico-infermieristico nel processo diagnostico-terapeutico è essenziale**
- **Il trattamento deve essere urgente senza panico soprattutto in caso di crisi ricorrenti/male epilettico**

TRATTAMENTO

- **Crisi singola e breve (<60 secondi)**
  - **Eliminazione di cause scatenanti**
  - **Terapia cronica con fenitoina 15-20 mg/kg, fosfofenitoina 15-20 mg/kg seguite da 300-400 mg/die**
  - **Considerare l'acido valproico 600-3000 mg/die o carbamazepine 600-1200 mg/die in caso di intolleranza a fenitoina**

TRATTAMENTO

- **Crisi prolungata o >1**
  - **SpO2 e segni vitali**
  - **Somministrazione immediata di benzodiazepine ev: Lorazepam 1-2 mg, Diazepam 10-20 mg, Midazolam 2-5mg con carico contemporaneo di fenitoina 15-20 mg/kg o fosfofenitoina 15-20 mg/kg seguite da 300-400 mg/die**
  - **Considerare acido valproico 400-600 mg ogni 6 ore se intolleranza a fenitoina**

• *TRATTAMENTO*

- **Crisi ricorrenti >5 min o >2 crisi senza recupero di coscienza**
  - **Definizione dello stato epilettico**
  - **ABC. Considerare IOT**
  - **Controllo glicemia e somministrazione di Tiamina 100 mg ev e glucosio**
  - **Controllo emocromo, elettroliti, funzionalità epatica, CK, screening tossicologico, EAB, dosaggio AEDs**
  - **Somministrazione immediata di BDZ (LZP 5-10 mg, DZP 20-40mg, MDZ 5-20 mg)**
  - **Dose carico di Fenitoina 20 mg/kg o fosfofenitoina 20mg/kg**
  - **Considerare acido valproico (15-20 mg/kg) seguite da 400-600 mg ogni 6 ore in caso di intolleranza da fenitoina**
  - **Considerare levetiracetam 1000mg*2/die se intolleranza a fenitoina e valproato**
  - **EEG continuo se possibile**
  - **Se la crisi continua dose aggiuntiva di fenitoina 85-10 mg/kg)**
  - **Se la crisi prosegue oltre 60 minuti: diagnosi di stato refrattario e somministrazione farmacologica per ottenere suppressione EEG.**

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REVIEW

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

- ***TRATTAMENTO***

- Trattamento emergente e mirato
- Ridurre morbilità e mortalità

- ***TRATTAMENTO***

- **L’obiettivo principale è di bloccare l’attività epilettica sia clinica che EEGrafica**

Table 5 Critical care treatment outline for convulsive and non-convulsive SE that should be completed prior or upon arrival to the intensive care unit (Note: timing is merely a guide as all interventions should be done as soon as possible.)

Critical care treatment	Timing (minutes post seizure onset)	Goals	Rationale/references
Non-invasive airway protection and gas exchange with head positioning	Immediate (0–2 min)	Maintain airway patency, avoid snoring, administer O_2	[40, 76–79]
Intubation (if airway/gas exchange compromised or elevated ICP suspected)	Immediate (0–10 min)	Establish secure oxygenation and ventilation	Expert opinion
Vital signs: O_2 saturation, BP, HR	Immediate (0–2 min)	Establish and support baseline vital signs	[80–81]
Vasopressor support of BP if SBP <90 mmHg or MAP <70	Immediate (5–15 min)	Support CPP	Expert opinion
Finger stick blood glucose	Immediate (0–2 min)	Diagnose hypoglycemia	
Peripheral IV access	Immediate (0–5 min)	Establish medication route	[80–82]
1. Emergent initial AED therapy (i.e. benzodiazepine)		1. Stop seizure	
2. Fluid resuscitation		2. Establish euvolemia	
3. Nutrient resuscitation (thiamine given before dextrose; dextrose)		3. Reverse thiamine deficiency, treat hypoglycemia	
Urgent SE control therapy with AED	Immediate after initial AED given (5–10 min)	Stop seizure	[80–82]
Neurologic exam	Urgent (5–10 min)	Evaluate for mass lesion, acute intracranial process	Expert opinion
Triage lab test panel (see Table 2)	Immediate (5 min)	Diagnose life threatening metabolic condition	Expert opinion
Refractory SE treatment	Urgent (20–60 min after 2nd AED)	Stop seizures; treatment strategies based on individual patient response and AED concentrations (if applicable)	Expert opinion
Urinary catheter	Urgent (0–60 min)	Evaluate systemic circulation	Expert opinion
Continuous EEG	Urgent (15–60 min)	Evaluate for NCSE if not waking up after clinically obvious seizures cease	[50, 73, 75]
Diagnostic testing (selection depends on clinical presentation)	Urgent (0–60 min)	Evaluate for mass lesions, meningitis, encephalitis	Expert opinion
CT			
LP			
MRI			
Intracranial pressure monitoring (depending on clinical presentation)	Urgent (0–60 min of imaging diagnosis)	Measure and control ICP	Expert opinion

AED antiepileptic drug; *BP* blood pressure; *CPP* cerebral perfusion pressure; *CT* computed tomography; *EEG* electroencephalogram; *HR* heart rate; *ICP* intracranial pressure; *LP* lumbar puncture; *MAP* mean arterial pressure; *MRI* magnetic resonance imaging; *SBP* systolic blood pressure

TRATTAMENTO IN EMERGENZA

- **Il farmaco di scelta per la terapia iniziale: Benzodiazepine**
- **La via ev è da preferire**
- **Per la via ev la prima scelta è il Lorazepam**
- **Per la via im il Midazolam**
- **Per la via rettale il Diazepam**

Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class IIa, level A
Phenytoin/fosphenytoin	Class IIb, level A
Phenobarbital	Class IIb, level A
Valproate sodium	Class IIb, level A
Levetiracetam	Class IIb, level C
Urgent treatment	
Valproate sodium	Class IIa, level A
Phenytoin/fosphenytoin	Class IIa, level B
Midazolam (continuous infusion)	Class IIb, level B
Phenobarbital	Class IIb, level C
Levetiracetam	Class IIb, level C
Refractory treatment	
Midazolam	Class IIa, level B
Propofol	Class IIb, level B
Pentobarbital/thiopental	Class IIb, level B
Valproate sodium	Class IIa, level B
Levetiracetam	Class IIb, level C
Phenytoin/fosphenytoin	Class IIb, level C
Lacosamide	Class IIb, level C
Topiramate	Class IIb, level C
Phenobarbital	Class IIb, level C

Table 7 Intermittent drug dosing in SE

Drug	Initial dosing	Administration rates and alternative dosing recommendations	Serious adverse effects	Considerations
Diazepam	0.15 mg/kg IV up to 10 mg per dose, may repeat in 5 min	Up to 5 mg/min (IVP) Peds: 2–5 years, 0.5 mg/kg (PR); 6–11 years, 0.3 mg/kg (PR); greater than 12 years, 0.2 mg/kg (PR)	Hypotension Respiratory depression	Rapid redistribution (short duration), active metabolite, IV contains propylene glycol
Lorazepam	0.1 mg/kg IV up to 4 mg per dose, may repeat in 5–10 min	Up to 2 mg/min (IVP)	Hypotension Respiratory depression	Dilute 1:1 with saline IV contains propylene glycol
Midazolam	0.2 mg/kg IM up to maximum of 10 mg	Peds: 10 mg IM (>40 kg); 5 mg IM (13–40 kg); 0.2 mg/kg (intranasal); 0.5 mg/kg (buccal)	Respiratory depression Hypotension	Active metabolite, renal elimination, rapid redistribution (short duration)
Fosphenytoin	20 mg PE/kg IV, may give additional 5 mg/kg	Up to 150 mg PE/min; may give additional dose 10 min after loading infusion Peds: up to 3 mg/kg/min	Hypotension Arrhythmias	Compatible in saline, dextrose, and lactated ringers solutions
Lacosamide	200–400 mg IV	200 mg IV over 15 min No pediatric dosing established	PR prolongation Hypotension	Minimal drug interactions Limited experience in treatment of SE
Levetiracetam	1,000–3,000 mg IV Peds: 20–60 mg/kg IV	2–5 mg/kg/min IV		Minimal drug interactions Not hepatically metabolized
Phenobarbital	20 mg/kg IV, may give an additional 5–10 mg/kg	50–100 mg/min IV, may give additional dose 10 min after loading infusion	Hypotension Respiratory depression	IV contains propylene glycol
Phenytoin	20 mg/kg IV, may give an additional 5–10 mg/kg	Up to 50 mg/min IV; may give additional dose 10 min after loading infusion Peds: up to 1 mg/kg/min	Arrhythmias Hypotension Purple glove syndrome	Only compatible in saline IV contains propylene glycol
Topiramate	200–400 mg NG/PO	300–1,600 mg/day orally (divided 2–4 times daily) No pediatric dosing established	Metabolic acidosis	No IV formulation available
Valproate sodium	20–40 mg/kg IV, may give an additional 20 mg/kg	3–6 mg/kg/min, may give additional dose 10 min after loading infusion Peds: 1.5–3 mg/kg/min	Hyperammonemia Pancreatitis Thrombocytopenia Hepatotoxicity	Use with caution in patients with traumatic head injury; may be a preferred agent in patients with glioblastoma multiforme

IM intramuscular; *IV* intravenous; *IVP* intravenous push; *min* minute; *NG* nasogastric; *PE* phenytoin equivalents; *PEDs* pediatric; *PO* by mouth; *PR* rectal administration; *PRIS* propofol related infusion syndrome

- ***TRATTAMENTO URGENTE***

- **Tutti i pz vanno trattati con BDZ a breve durata d'azione a meno che non sia riconosciuta la causa scatenante**
- **2 sono le obiettivi**
  - **Rapido raggiungimento la dei livelli terapeutici di DAEs**
  - **Fermare la crisi in atto**

Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class IIa, level A
Phenytoin/fosphenytoin	Class IIb, level A
Phenobarbital	Class IIb, level A
Valproate sodium	Class IIb, level A
Levetiracetam	Class IIb, level C
Urgent treatment	
Valproate sodium	Class IIa, level A
Phenytoin/fosphenytoin	Class IIa, level B
Midazolam (continuous infusion)	Class IIb, level B
Phenobarbital	Class IIb, level C
Levetiracetam	Class IIb, level C
Refractory treatment	
Midazolam	Class IIa, level B
Propofol	Class IIb, level B
Pentobarbital/thiopental	Class IIb, level B
Valproate sodium	Class IIa, level B
Levetiracetam	Class IIb, level C
Phenytoin/fosphenytoin	Class IIb, level C
Lacosamide	Class IIb, level C
Topiramate	Class IIb, level C
Phenobarbital	Class IIb, level C

TRATTAMENTO DELLE CRISI REFRATTARIE

- **Bolo supplementare**
- **Aggiunta di un altro farmaco**
- **Infusione continua o boli?**

Table 8 RSE dosing recommendations

Drug	Initial dose	Continuous infusion dosing recommendations-titrated to EEG	Serious adverse effects	Considerations
Midazolam	0.2 mg/kg; administer at an infusion rate of 2 mg/min	0.05–2 mg/kg/hr CI Breakthrough SE: 0.1–0.2 mg/kg bolus, increase CI rate by 0.05–0.1 mg/kg/hr every 3–4 h	Respiratory depression Hypotension	Tachyphylaxis occurs after prolonged use Active metabolite, renally eliminated, rapid redistribution (short duration), does NOT contain propylene glycol
Pentobarbital	5–15 mg/kg, may give additional 5–10 mg/kg; administer at an infusion rate ≤50 mg/min	0.5–5 mg/kg/h CI Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h	Hypotension Respiratory depression Cardiac depression Paralytic ileus At high doses, complete loss of neurological function	Requires mechanical ventilation IV contains propylene glycol
Propofol	Start at 20 mcg/kg/min, with 1–2 mg/kg loading dose	30–200 mcg/kg/min CI Use caution when administering high doses (>80 mcg/kg/min) for extended periods of time (i.e., >48 h) Peds: Use caution with doses >65 mcg/kg/min; contraindicated in young children Breakthrough SE: Increase CI rate by 5–10 mcg/kg/min every 5 min or 1 mg/kg bolus plus CI titration	Hypotension (especially with loading dose in critically ill patients) Respiratory depression Cardiac failure Rhabdomyolysis Metabolic acidosis Renal failure (PRIS)	Requires mechanical ventilation Must adjust daily caloric intake (1.1 kcal/ml)
Thiopental	2–7 mg/kg, administer at an infusion rate ≤50 mg/min	0.5–5 mg/kg/h CI Breakthrough SE: 1–2 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h	Hypotension Respiratory depression Cardiac depression	Requires mechanical ventilation Metabolized to pentobarbital

CI continuous infusion; *EEG* electroencephalogram; *h* hour; *IM* intramuscular; *IV* intravenous; *IVP* intravenous push; *min* minute; *PRIS* propofol related infusion syndrome

- ***ALTERNATIVE***
  - **Il trattamento aggressivo va continuato finchè non si stabilisce l'esito della terapia**
  - **La terapia prolungata va proseguita in pz giovani con stato premorboso sano, in caso di malattia autolimitata e in assenza di lesioni intracraniche**
  - **L'uso di farmaci emergenti**

Table 9 Alternative therapies for RSE

	Number of articles related to treatment of RSE	Case series $n \geq 3$	Comments
Pharmacological			
Ketamine	9	2	Intravenous drip, potential neurotoxicity
Corticosteroids	16	2	Rasmussen's encephalitis, Hashimoto's encephalopathy
Inhaled anesthetics	19	2	High complication rate/morbidity
Immunomodulation (IVIG or PE)	3	1	Rasmussen's encephalitis, EPC
Non-pharmacological			
Vagus nerve stimulation	8	2	Catastrophic epilepsy in infants
Ketogenic diet	20	3	Landau-Kleffner syndrome, pediatrics
Hypothermia	4	2	Single or small case series only
Electroconvulsive therapy	5	1	Single or small case series only
Transcranial magnetic stimulation	9	1	EPC in most cases
Surgical management	13	4	Most often used and successful in pediatrics

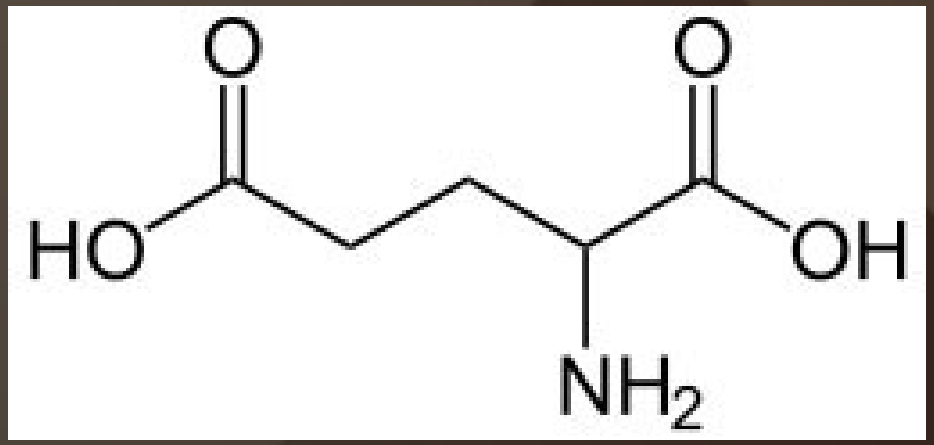
EPC epilepsia partialis continua

Levetiracetam?

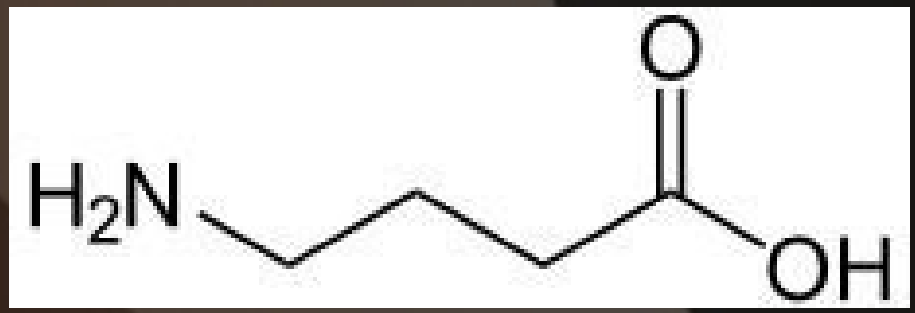

CENNI…
di FARMACOLOGIA…

NATURA e MECCANISMI delle CRISI COMIZIALI

- *aumento dell'attività sinaptica eccitatoria*
- *riduzione dell'attività sinaptica inibitoria*

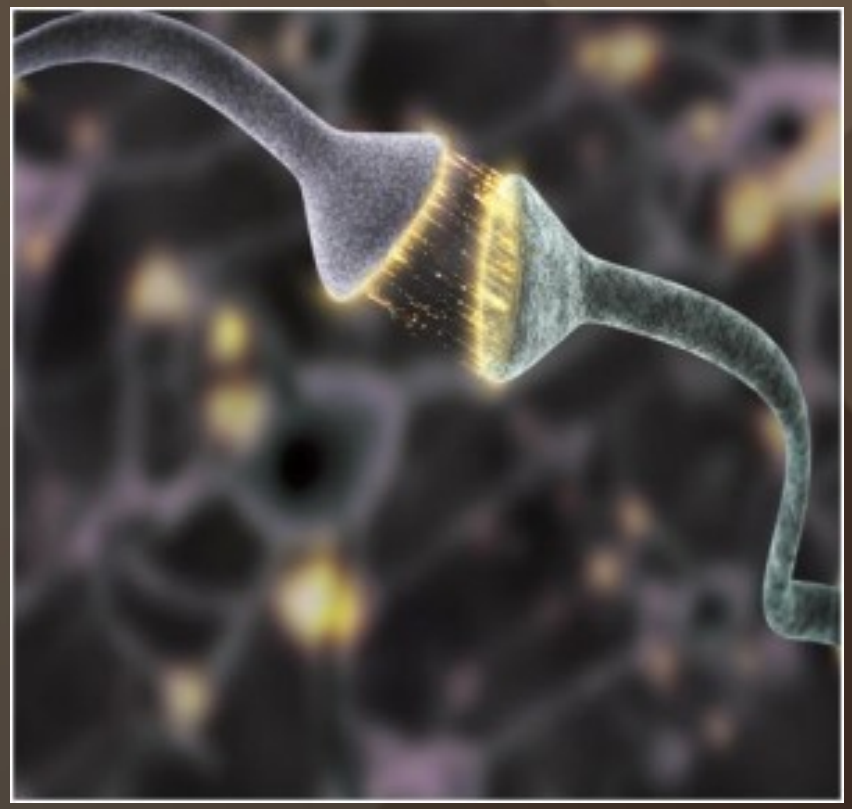


GLUTAMATO

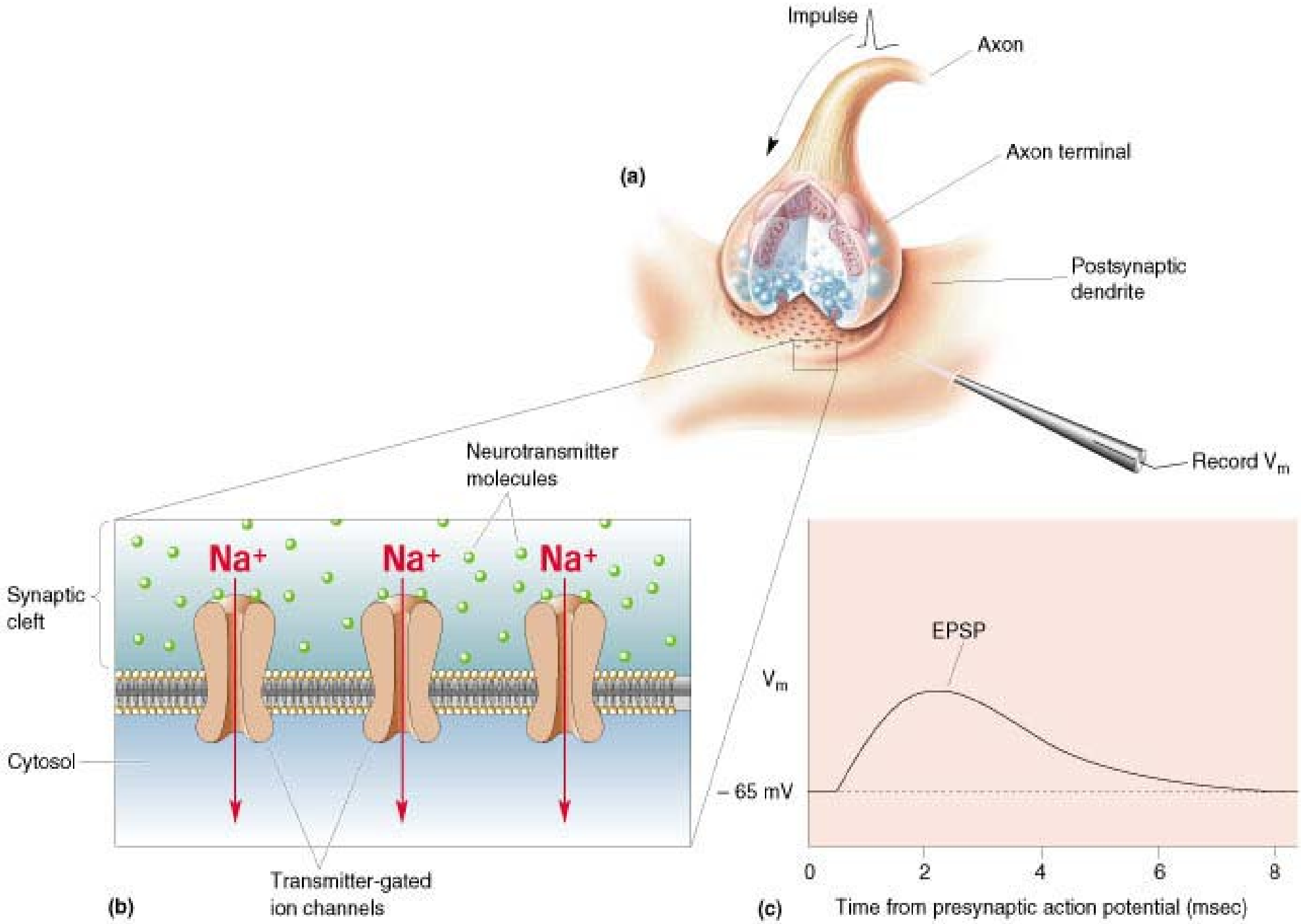


GABA

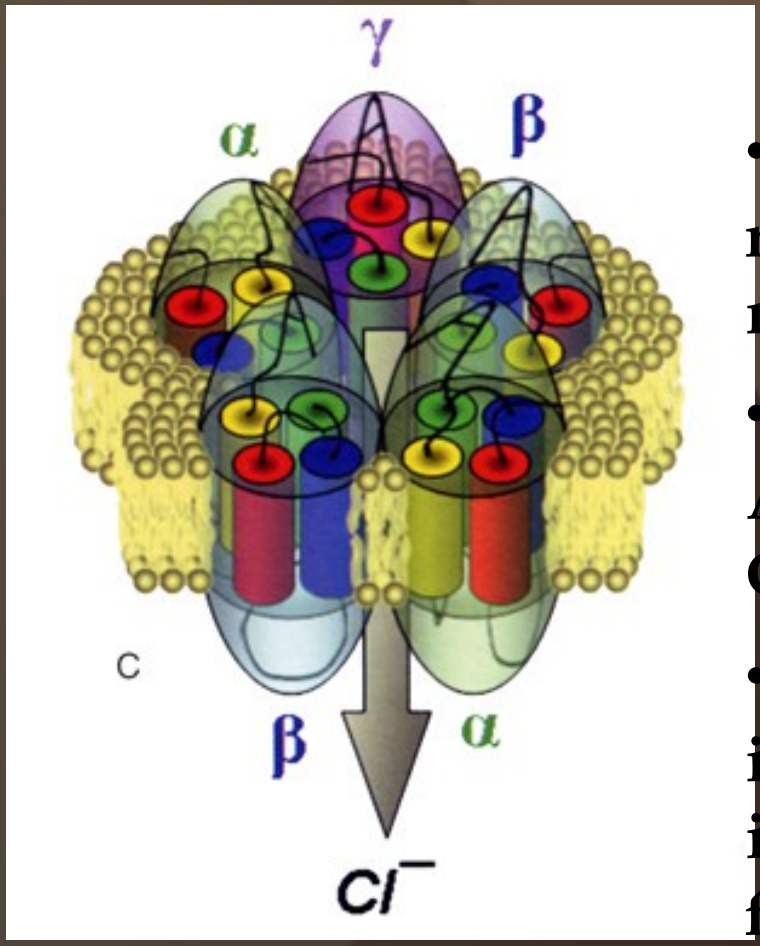
NATURA e MECCANISMI delle CRISI COMIZIALI



- L'impulso stimola il rilascio di neurotrasmettitore dal terminale presinaptico
- Il legame del neurotrasmettitore al canale sul versante postsinaptico modifica la conduttanza al sodio, che entra nella cellula
- La membrana si depolarizza


Impulse
Axon
Axon terminal
(a)
Postsynaptic dendrite
Record V_m
Neurotransmitter molecules
Na^+
Na^+
Na^+
Synaptic cleft
Cytosol
Transmitter-gated ion channels
(b)
V_m
EPSP
– 65 mV
0
2
4
6
8
(c)
Time from presynaptic action potential (msec)

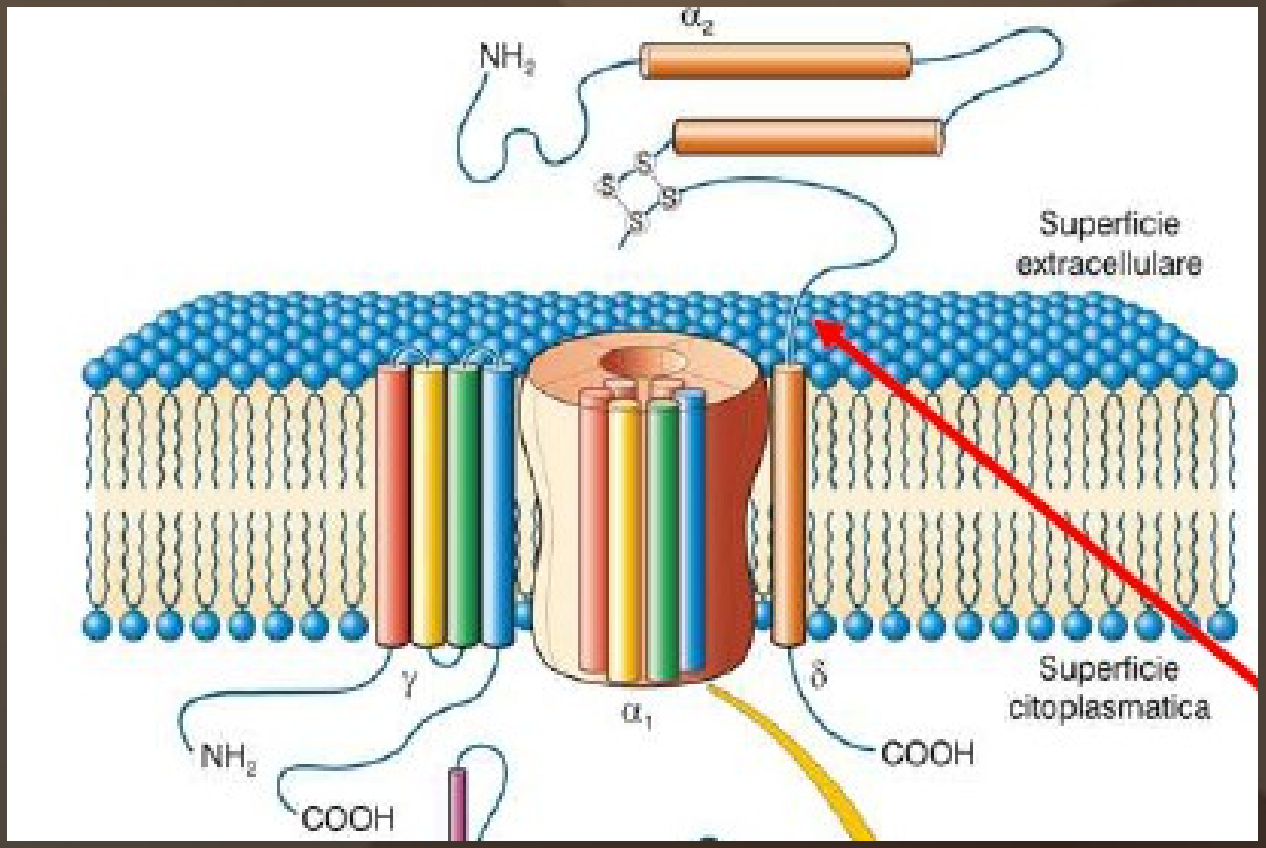
NATURA e MECCANISMI delle CRISI COMIZIALI



- In condizioni fisiologiche il canale è regolato da presenza intermittente di neurotrasmettitore
- In presenza di GABA, il recettore di tipo A si apre permettendo l'ingresso di ioni Cloro nella cellula postsinaptica
- Il Cloro in elevate concentrazioni iperpolarizza il neurone rendendolo insensibile a scariche di impulsi ad alta frequenza

NATURA e MECCANISMI delle CRISI COMIZIALI

Canali "T"



- **Canali del calcio a basso voltaggio**
- **Rapida cinetica di attivazione**
- **Si aprono in risposta a piccole e deboli variazioni d'impulso**

FARMACOLOGIA: FENITOINA

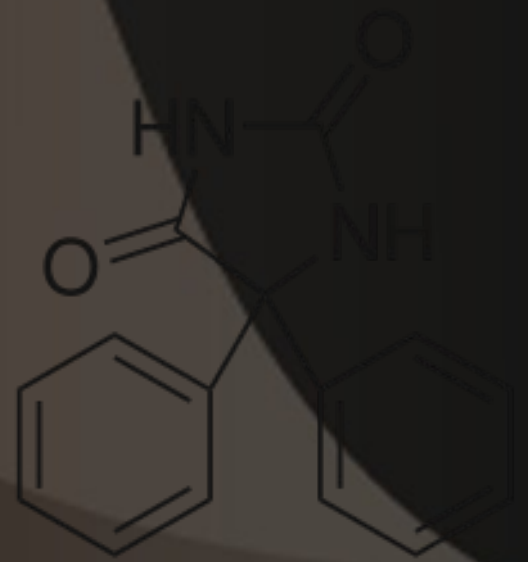
"Difenil – Idantoina"

Indicazioni:

- epilessia parziale, tonico-clonica ma non assenze

Proprietà:

- non depressione SNC
- a dosi tossiche: eccitazione
- a dosi letali: rigidità da decerebrazione



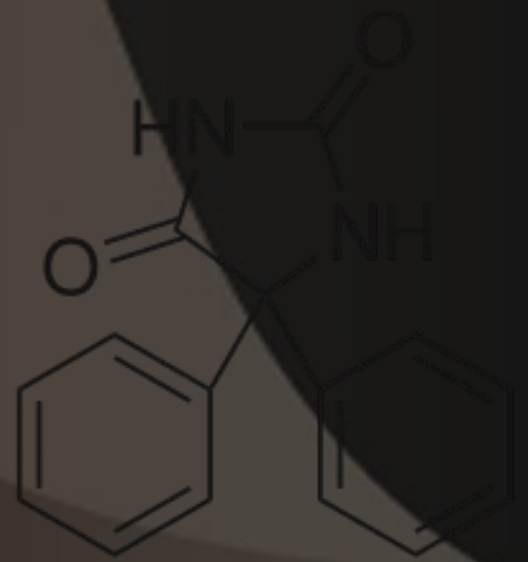
FARMACOLOGIA: FENITOINA

Meccanismo d'azione:

- **prolunga il periodo refrattario dei canali al Na+ voltaggio – dipendenti (in modo SELETTIVO*)**

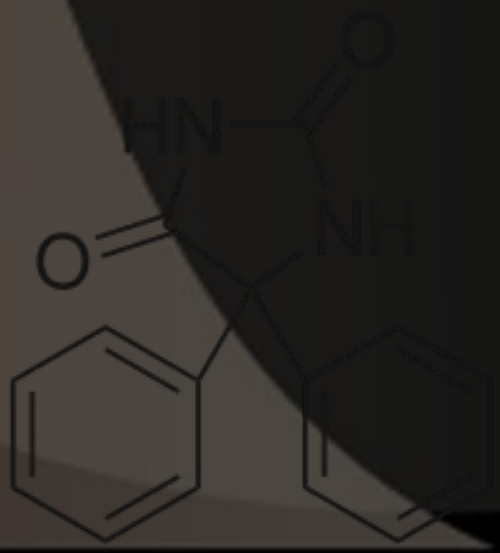
Farmacocinetica:

- **rilascio immediato**
- **rilascio prolungato**
- **90% legata alle proteine plasmatiche (ALB)**
- **il farmaco ATTIVO è la quota libera***
- **interferenze con altri antiepilettici***



FARMACOLOGIA: FENITOINA

- la velocità di eliminazione è concentrazione – dipendente
- l'emivita varia tra le 6-24 h se [f] < 10 µg/ml
- l'emivita aumenta all'aumentare della [f] plasmatica
- il metabolismo è epatico (95% CYP) con un meccanismo saturabile e ne deriva un metabolita inattivo (paraidrossifenilico)
- attenzione a WARFARIN
- aumentata degradazione di contraccetivi orali
- teratogenicità nota



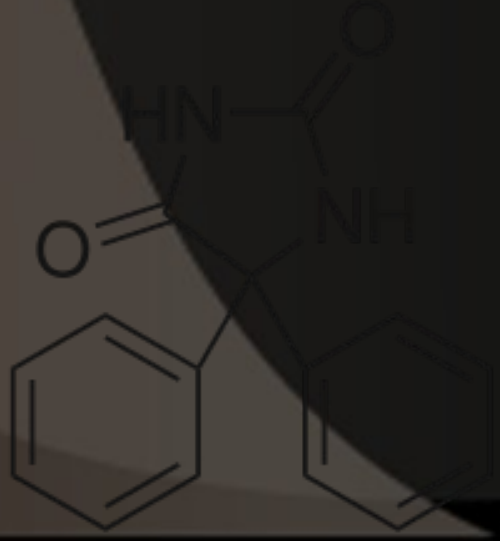
FARMACOLOGIA: FENITOINA

- **scarsa idrosolubilità**
- **FOSFENITOINA: profarmaco idrosolubile, convertito a Fenitoina da fosfatasi epatiche/eritrocitarie; si lega alle proteine plasmatiche competendo con la Fenitoina e quindi ne aumenta la quota libera**

Tossicità: (via di somministrazione, durata, dose)

- **e.v. rapida: aritmie, ↓PA , depressione SNC**

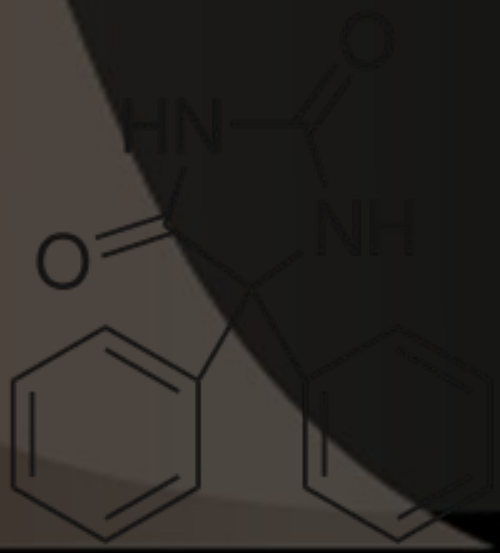
→ *Non superare l'equivalente di Fenitoina 150mg/min*



FARMACOLOGIA: FENITOINA

Tossicità: (via di somministrazione, durata, dose)

- **sovradosaggio x os: segni cerebellari, vestibolari, atrofia cerebellare**
- **in fase iniziale: ↑ transitorio transaminasi**
- **in cronico: modificazioni comportamentali, ↑ frequenza crisi, sintomi gastrointestinali, osteomalacia, anemia megaloblastica, irsutismo**
- **intolleranza: manifestazioni cutanee, alterata funzione epatica e midollare**



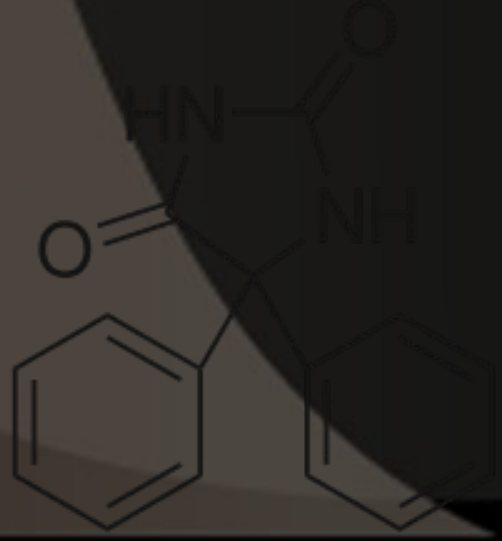
FARMACOLOGIA: FENITOINA

IPERPLASIA GENGIVALE

- alterazioni del metabolismo del collagene
- incidenza 20%; più comune nei bambini e adolescenti, nei soggetti con tratti somatici dismorfici del volto
- non richiede la sospensione del farmaco

EFFETTI ENDOCRINI

- alterata secrezione di vasopressina
- iperglicemia, glicosuria (↓ insulina)
- alterato metabolismo Vit. D (↓ assorb Ca+)
- ↑ metabolismo Vit. K



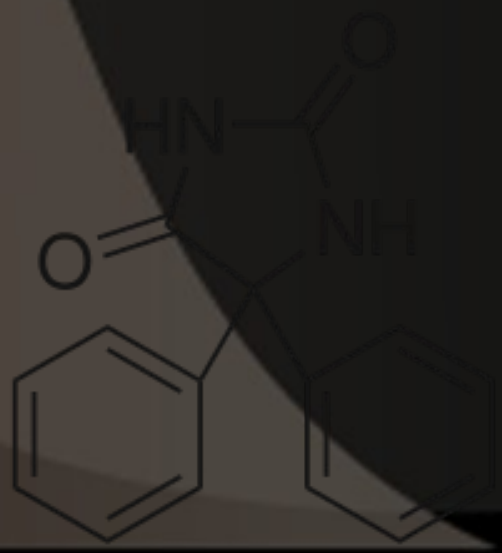
FARMACOLOGIA: FENITOINA

IPERSENSIBILITA'

- eruzioni cutanee morbilliformi
- Sdr di Steven Johnson (variante gene HLA-B * Asia)

REAZIONI EMATOLOGICHE

- neutropenia, leucopenia, anemia aplastica, agranulocitosi, trombocitopenia, ↓ sintesi IgA (linfoadenopatia)



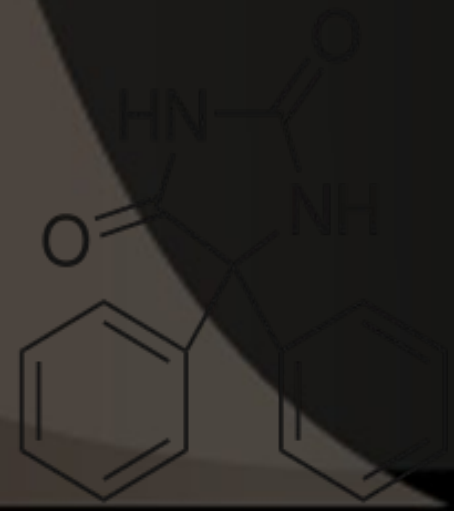
FARMACOLOGIA: FENITOINA

SINDROME da IPERSENSIBILITA' (AHS)

- sdr multiorgano rara ma potenzialmente fatale
- febbre, rash, linfoadenopatia, insufficienza epatica
- compare dopo 2-4 settimane dalla prima esposizione
- fattori di rischio: familiarità, immunodepressione, etnia

SINDROME da GUANTO COLOR PORPORA

- irritazione ed infiammazione dei tessuti molli al sito di iniezione, con o senza stravaso del farmaco
- edema, decolorazione, necrosi, desquamazione



FARMACOLOGIA: FENITOINA

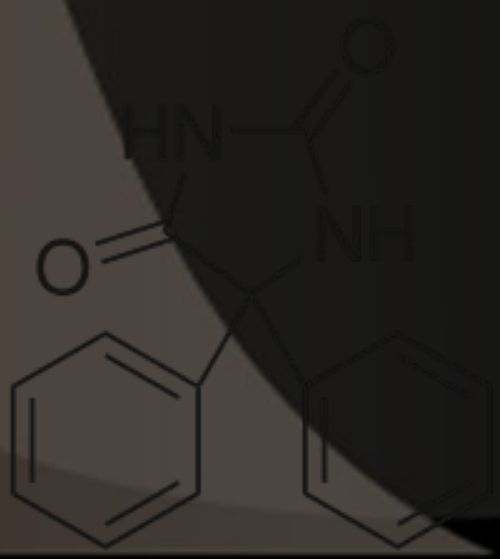
Concentrazione Plasmatica:

Range terapeutico: [f] > 10 µg/ml

Tossicità: [f] > 20 µg/ml

Interazioni generiche:

- **la somministrazione concomitante di qualsiasi farmaco metabolizzato da CYP2C9 o CYP2C10 può aumentare la concentrazione plasmatica di fenitoina**
- **i farmaci che inducono i CYP possono accelerare il metabolismo della fenitoina**



FARMACOLOGIA: FENITOINA

Altre indicazioni:

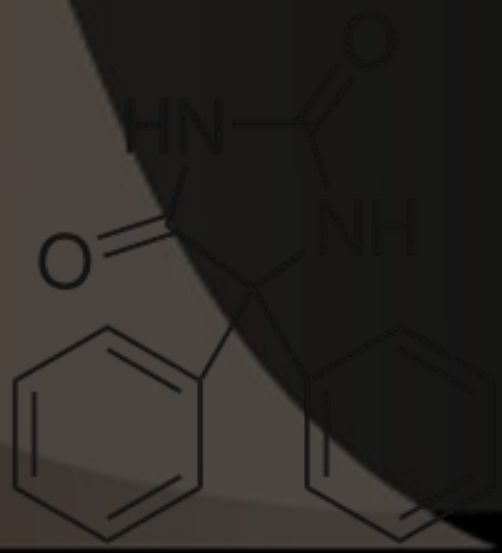
- **Trattamento di aritmie cardiache se terapia di prima scelta inefficace (spt se associate a digitale)**

Controindicazioni:

- **Bradicardia Sinusale, BAV 2^/3^, sdr di Adams-Stokes**

Adulto: infusione < 50 mg/min

Neonato e bambino: 1-3 mg/kg/min



FARMACOLOGIA: FENITOINA

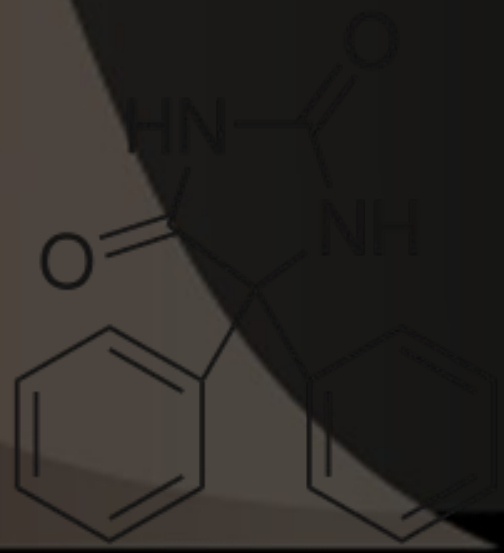
AUMENTO dei livelli sierici di Fenitoina
Cloramfenicolo, Dicumarolo, Ticlopidina, Alcool, Salicilati, Eritromicina, Isoniazide, Antifungini, Fluorouracile, Diazepam, Amiodarone, Diltiazem, Nefedipina, Cimtedina, Estrogeni, Omeprazolo, Fluoxetina, Sertralina
DIMINUZIONE dei livelli sierici di Fenitoina
Carbamazepina, Alcool (cronico), Acido Folico, Rifampicina, Ciprofloxacina, Vigabatrin, Teofillina, Iperglicemizzanti, Nelfinavir, preparazioni a base di ***Hypericum Perforatum***
Farmaci i cui livelli ematici possono essere alterati da Fenitoina
Broncodilatatori (Teofillina), Lamotrigina, Antifungini, Digitale, Nimodipina, Verapamil, Ciclosporina, Furosemide, Vecuronio, Clozapina, Paroxetina

FARMACOLOGIA: FENITOINA

DOSI:

- **Stato epilettico: <u>dose di attacco</u> pari a 10-15 mg/kg e.v. (vel < 50mg/min; circa 20 min in un soggetto di 70kg) seguita da <u>dosi di mantenimento</u> pari a 100 mg x os o e.v. ogn i 6-8 h.**
- **Nel neonato l'assorbimento orale è inattendibile: si mantiene la dose di attacco pari a 10-15 mg/kg e.v. (vel 1-3 mg/kg/min)**

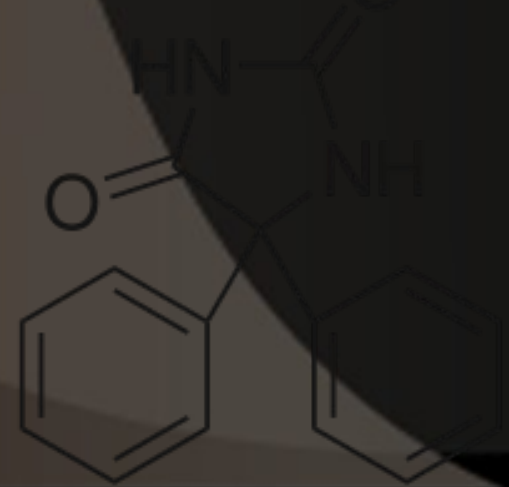
La determinazione dei livelli plasmatici (10-20 µg/ml è utile per la definizione del dosaggio di mantenimento



FARMACOLOGIA: FENITOINA

DOSI:

- **Aritmie Cardiache: 3,5-5 µg/kg e.v. con ripetizione se necessario (non superare i 50 mg/min)**



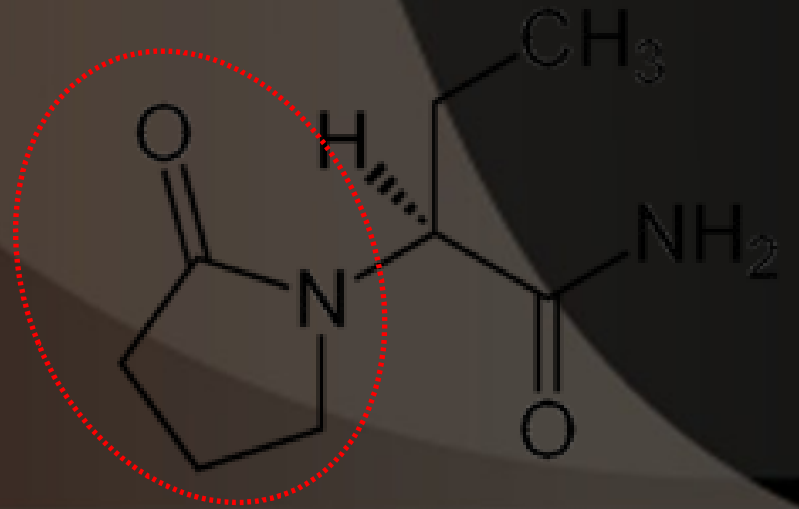
FARMACOLOGIA: LEVETIRACETAM

"S-enatiomero dell' α-etil-2-oxo-1-pirrolidinacetamide"

Indicazioni:

- **farmaco unico a partire dai 16 anni con epilessia di nuova diagnosi, per crisi ad esordio parziale con o senza generalizzazione secondaria**

- **in aggiunta ad altri farmaci per: crisi ad esordio parziale con o senza generalizzazione (dai 4 aa di età), epilessia mioclonica giovanile (12 aa), epilessia generalizzata idiopatica (12 aa)**



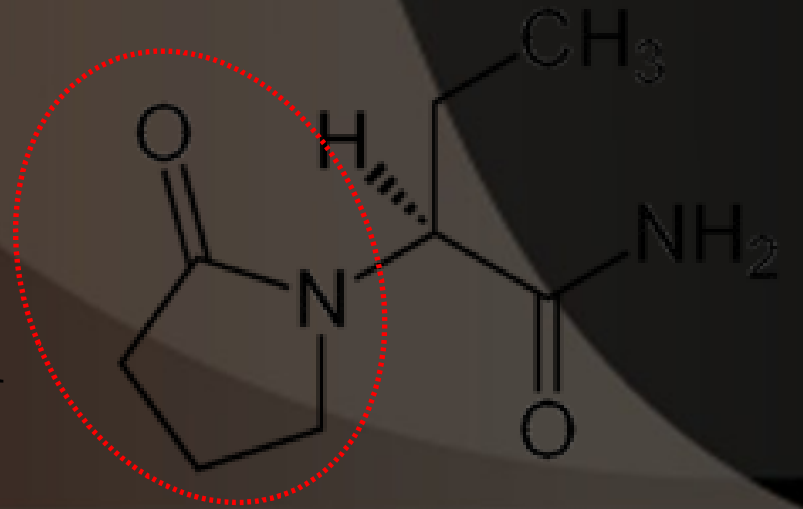
FARMACOLOGIA: LEVETIRACETAM

Meccanismo d'azione:

- **NON NOTO.** *"Agirebbe riducendo il rilascio di Calcio dai siti intraneuronali di deposito. Inoltre si legherebbe alla proteina 2A della vescicola sinaptica coinvolta nel rilascio di neurotrasmettitori dalle cellule nervose. L'inibizione dei canali del calcio presinaptici si ritiene impedisca la conduzione dell'impulso attraverso la sinapsi"*

Farmacocinetica:

- **rapidamente assorbito (x os)**
- **non si lega alle proteine plasmatiche**
- **95% del farmaco e del metabolita inattivo vengono escreti con le urine**



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Molecular Pharmacology
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Mol Pharmacol 82:199–208, 2012

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The Synaptic Vesicle Glycoprotein 2A Ligand Levetiracetam Inhibits Presynaptic Ca^{2+} Channels through an Intracellular Pathway[S]

Christian Vogl, Sumiko Mochida, Christian Wolff, Benjamin J. Whalley, and Gary J. Stephens

School of Pharmacy, University of Reading, Reading, United Kingdom (C.V., B.J.W., G.J.S.); Department of Physiology, Tokyo Medical University, Tokyo, Japan (S.M.); and UCB Centre for CNS Innovation, UCB Pharma, CNS Research, Braine-l'Alleud, Belgium (C.W.)

Received November 4, 2011; accepted May 3, 2012

LEV Inhibits Cholinergic Transmission. This study demonstrates that the prominent SV2A ligand LEV inhibits cholinergic transmission through actions on Ca_V channels in sympathetic neurons. We show that entry into the intracel-

LEV Reduces Synaptic Transmission and Inhibits Ca_V Channels through an Intracellular Pathway. We

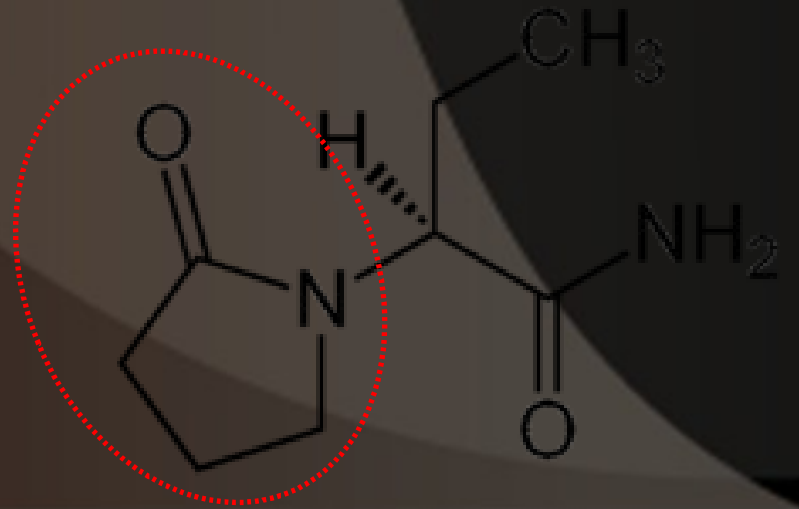
LEV Affects Membrane Properties under Physiological Conditions. LEV effects on SCGN intrinsic membrane properties were consistent with reduced Ca^{2+} influx through Ca_V channels. LEV reduced the amplitude of the AHP, a

FARMACOLOGIA: LEVETIRACETAM

Farmacocinetica:

- **65% del farmaco viene escreto immodificato**
- **24% metabolismo mediante idrolisi del gruppo acetamidico**

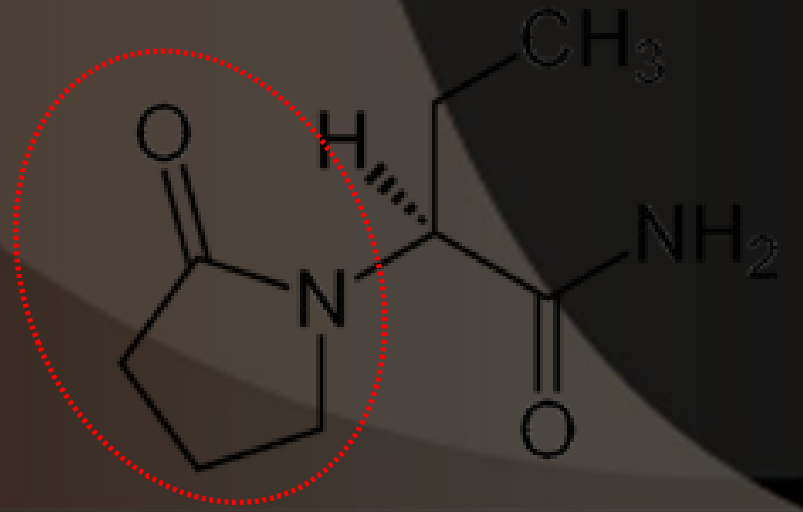
"...non induce né rappresenta un substrato ad alta affinità per i CYP o per le glucuronidasi ed è quindi privo di interazioni con altri antiepilettici, contraccettivi orali, o anticoagulanti..."



FARMACOLOGIA: LEVETIRACETAM

Tossicità, eventi avversi:

- **generalmente ben tollerato**
- **molto comuni (>1/10pz): sonnolenza, astenia, affaticamento**
- **comuni (1/10): nasofaringite, ↓ PLT, anoressia, ↑ peso, tosse, labilità emotiva, alterazioni del pensiero, capogiri, vertigini, diplopia, rash, prurito, mialgia**
- **frequenza non nota: eritropenia, leucopenia, comportamenti anomali, parestesie, pancreatite, insufficienza epatica, eruzioni cutanee**



FARMACOLOGIA: LEVETIRACETAM

DOSI:

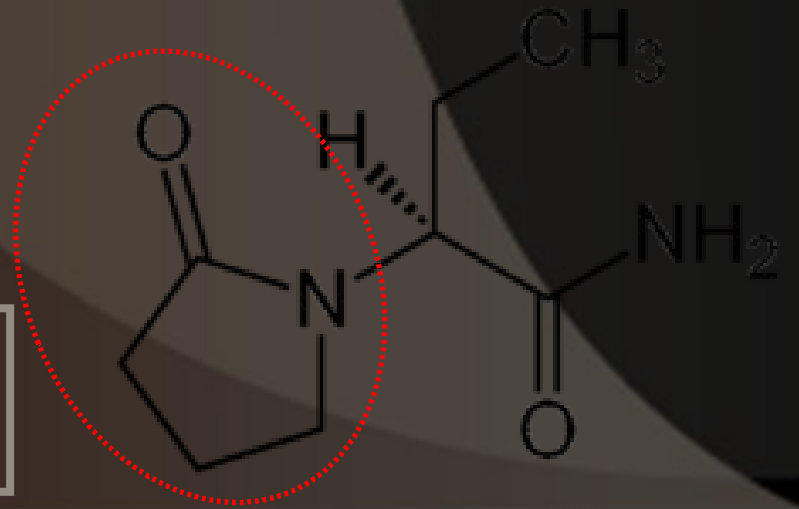
- **MONOTERAPIA (a partire dai 16 aa): dose tipica tra 1000-3000 mg/die**

*** Per le prime 2 settimane di terapia la dose è minima**

- **TERAPIA AGGIUNTIVA:**

*** Per adulti ed età > 16aa con peso ≥ 50kg: 1000-3000 mg/die**

*** Per bambini (4-11 aa) e dai 12-17aa con peso < 50 kg: dose tipica tra 20-60 mg/kg al giorno**



Diluito in 100ml e infuso in > 15 min

FENITOINA o LEVETIRACETAM?

- ✓ **Farmaci con profilo farmacocinetico diverso**
- ✓ **Meccanismo d'azione noto/non chiaramente noto**
- ✓ **Efficacia relativamente sovrapponibile**
- ✓ **Fenitoina € 29,92 (5 fl; 250mg/5ml)**
- ✓ **Levetiracetam € 396 (500mg/5ml; confezione 10fl)**

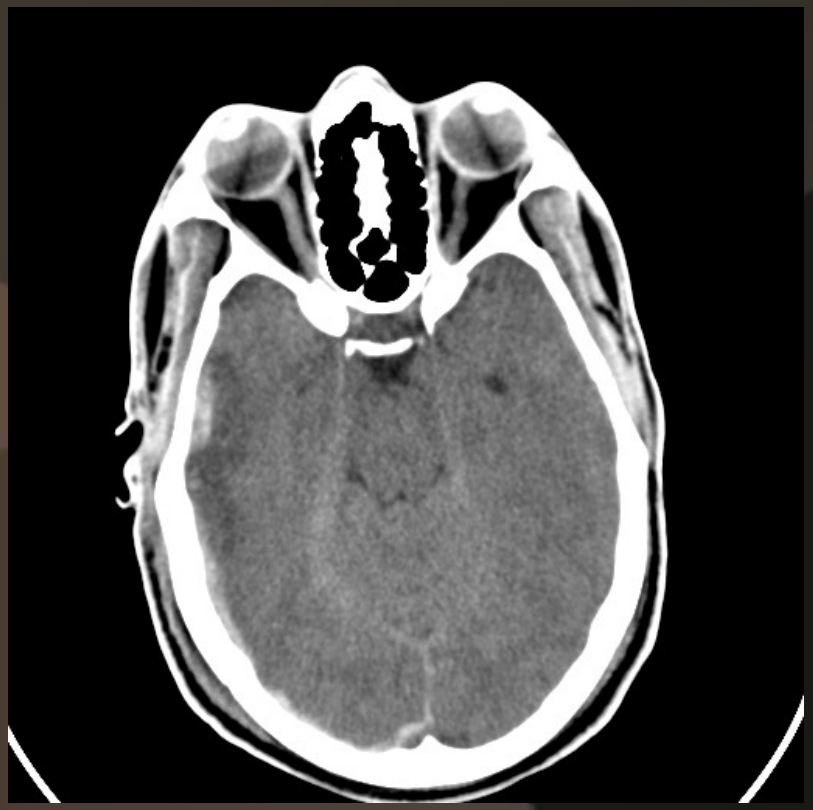
FENITOINA O LEVETIRACETAM?

Questo è il dilemma.....

Journal Club a cura di:
Dr.ssa Seghelini E., Dr.ssa Bertuetti R., Dr.ssa Volonté F., Dr. Darwish I.

MERCOLEDI' 20 NOVEMBRE
ore 14, AULETTA 2° CR

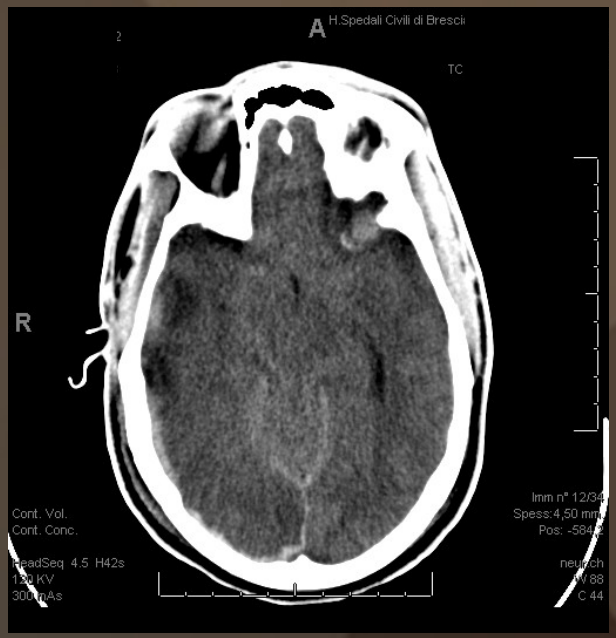
- uomo 40 anni
- anamnesi negativa
- trauma della strada, ciclista investito
- disorientato e agitato all'arrivo MSA
- intubato sul posto



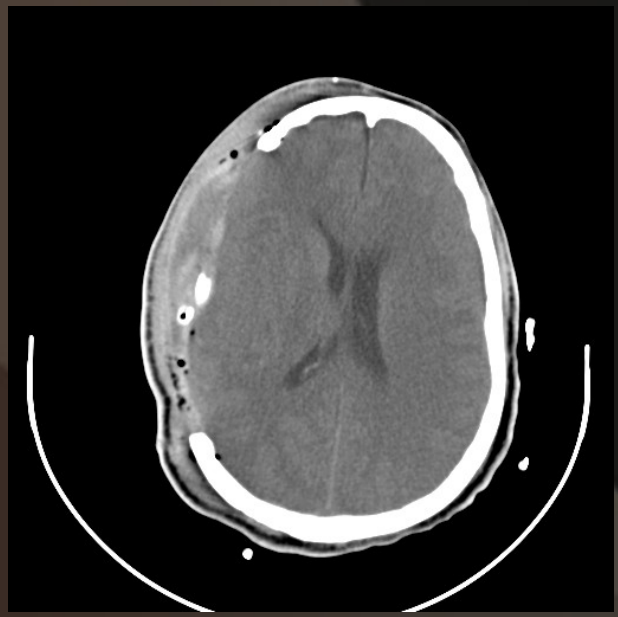
- sedato ed intubato per 4 gg
- PIC <15mmHg
- alla sospensione dei sedativi agitato a tratti
- crisi epilettica tonico-clonica, inizia levetiracetam 500mg x 2

- trasferito in NCH in 5° giornata
- stato di male in 6°
- aumenta il levetiracetam a 500mg x 3

- In 9° giornata crisi tonica con midriasi fissa, desaturazione e trisma
- IOT



- BO NCH : craniotomia- decompressiva temporale dx



Dott.ssa E. Seghelini II Servizio di Anestesia e Rianimazione

Zafar *et al. BMC Neurology* 2012, **12**:30
http://www.biomedcentral.com/1471-2377/12/30

BMC Neurology

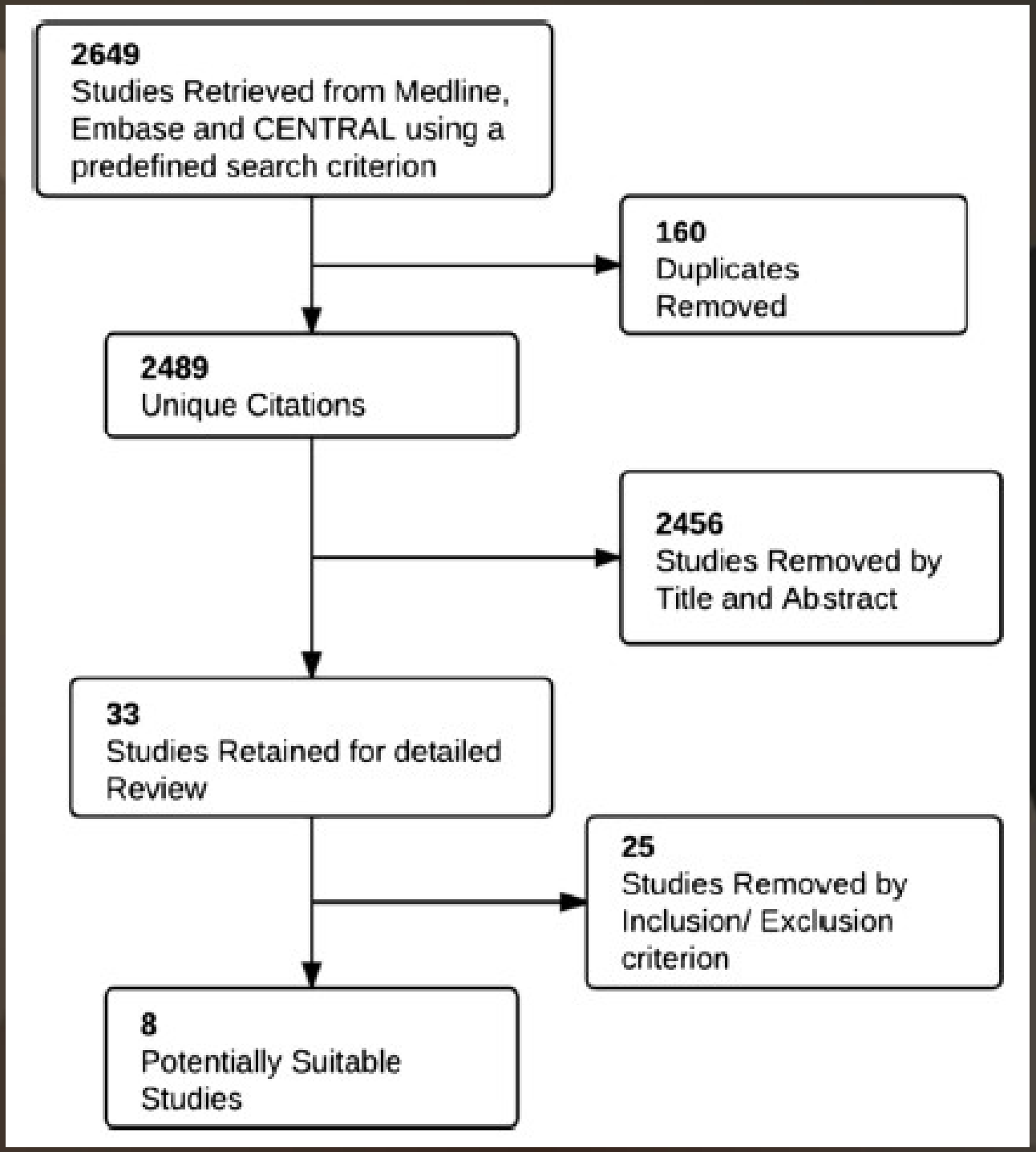
RESEARCH ARTICLE Open Access

Phenytoin versus Leviteracetam for Seizure Prophylaxis after brain injury – a meta analysis

Syed Nabeel Zafar[1], Abdul Ahad Khan[2], Asfar Ayaz Ghauri[2] and Muhammad Shahzad Shamim[1*]

Circa il 15% dei TBI sviluppa crisi epilettiche posttraumatiche.

Noto da tempo che l'utilizzo della fenitoina riduce del 73% il rischio di crisi (Temkin,1990)


2649
Studies Retrieved from Medline, Embase and CENTRAL using a predefined search criterion
160
Duplicates Removed
2489
Unique Citations
2456
Studies Removed by Title and Abstract
33
Studies Retained for detailed Review
25
Studies Removed by Inclusion/ Exclusion criterion
8
Potentially Suitable Studies

Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury

Kristen E. Jones, M.D.[1], Ava M. Puccio, R.N., Ph.D.[1], Kathy J. Harshman, R.N., B.S.N.[1], Bonnie Falcione, Pharm.D.[2], Neal Benedict, Pharm.D.[2], Brian T. Jankowitz, M.D.[1], Martina Stippler, M.D.[1], Michael Fischer, B.S.[1], Erin K. Sauber-Schatz, M.P.H.[1], Anthony Fabio, Ph.D., M.P.H.[1], Joseph M. Darby, M.D.[3], and David O. Okonkwo, M.D., Ph.D.[1]

[1]Department of Neurological Surgery, University of Pittsburgh Medical Center, Pennsylvania

[2]Department of Pharmacology, University of Pittsburgh, Pennsylvania

[3]Critical Care Medicine, University of Pittsburgh, Pennsylvania

- levetiracetam 500mg die dal 2006-2007, 32 pazienti
- fenitoina dal 2005 al 2006, 41 pazienti
- EEG se sospetta crisi, alterazioni coscienza o del comportamento,coma
- outcome: alterazioni EEG

Electroencephalographic findings stratified by cohort

	Phenytoin		Levetiracetam		
EEG Finding	**Yes**	**No**	**Yes**	**No**	**p Value**
seizure tendency*	0	12	7	8	0.007
seizure activity	0	12	**1**	**14**	0.556
abnormal EEG	0	12	8	7	0.003

Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery

- studio di coorte, retrospettivo
- monoterapia con levetiracetam o fenitoina
- monitoraggio crisi epilettica preoperatoria, dopo una settimana e dopo un mese
- ADR

- ✓ 305 : 105 pazienti in terapia con LEV e 210 con FEN
- ✓ epilessia preoperatoria: 33pz LEV e 45pz FEN, p = 0.07
- ✓ epilessia a una settimana: 1pz LEV e pz FEN, p = 0,17
- ✓ epilessia a 1 mese: 1,9%pz LEV e 5,6%pz FEN, p = 0,23
- ✓ ADR: 1pz LEV e 38pz FEN, p < 0,001

PARI EFFICACIA DEI DUE FARMACI
MINOR EFFETTI COLLATERALI LEVETIRACETAM

Tracey A. Milligan, MD
Shelley Hurwitz, PhD
Edward B. Bromfield, MD

- trial clinico randomizzato, 2:1 LEV: FEN
- TBI o ESA
  GCS 3-8
  TC patologica
- LEV 20mg/kg+200mg die, FEN 20mg/kg+5mg/kg/die per 7gg
- outomes: incidenza crisi epilettiche (EEG per 72h), ADR, long term outcomes

- ✓ 52 pz arruolati: 34 LEV e 18 FEN
- ✓ nessuna differenza per incidenza epilessia
- ✓ LEV minor episodi de deterioramento neurologico, p= 0,024
- ✓ LEV minor complicanze gastrointestinali, p= 0,043
- ✓ dei sopravvissuti GOSE alla dimissione, a 3 e 6 mesi migliore per LEV

MENO EFFETTI COLLATERALI
MIGLIOR OUTCOMES PER LEVETIRACETAM

Neurocrit Care (2010) 12:165–172
DOI 10.1007/s12028-009-9304-y

ORIGINAL ARTICLE

Prospective, Randomized, Single-Blinded Comparative Trial of Intravenous Levetiracetam Versus Phenytoin for Seizure Prophylaxis

Jerzy P. Szaflarski · Kiranpal S. Sangha · Christopher J. Lindsell · Lori A. Shutter

Neurocritical Care (2011) 15:80–84
DOI 10.1007/s12028-010-9341-6

ORIGINAL ARTICLE

Levetiracetam is Associated with Improved Cognitive Outcome for Patients with Intracranial Hemorrhage

Scott Taylor · Robin J. Heinrichs · Jeff M. Janzen · As'ad Ehtisham

- studio di coorte, retrospettivo
- ICH
- FEN 15-20mg/kg + concentrazine ematica di 1-2,5 microg/kg
  LEV 500-200mg/d

	Phenytoin ($n = 25$)	Levetiracetam ($n = 60$)	Significance
Discharge GCS	11 (8.8–15)	14 (11–15)	0.02
Discharge Level of consciousness	2 (1–3)	2 (1–3)	0.36
NCCU length of stay	9.24 ± 7	11 ± 7.5	0.31
Hospital length of stay	10.6 ± 8.4	12 ± 7.2	0.49
Seizure incidence	8%	0.0%	0.03
NCCU discharge destination (home)	16%	21.7%	0.04
Cognitive function (intact)	36%	56.7%	0.08

Zafar *et al. BMC Neurology* 2012, **12**:30
http://www.biomedcentral.com/1471-2377/12/30

BMC Neurology

RESEARCH ARTICLE Open Access

Phenytoin versus Leviteracetam for Seizure Prophylaxis after brain injury – a meta analysis

Syed Nabeel Zafar[1], Abdul Ahad Khan[2], Asfar Ayaz Ghauri[2] and Muhammad Shahzad Shamim[1*]

Conclusions

On the basis of our analysis of available literature, we conclude that there is no significant difference in seizure prophylaxis for either early or late seizures; for either Phenytoin or Levetiracetam. However, paucity of good quality evidence limits our conclusion. Better quality RCTs from centers in different parts of the world are recommended.

- studio di coorte, prospettico
- trauma cranico chiuso con ESA, SDH, EDH,DAI
- LEV 1000 mg x 2, FEN 20mg/kg+5mg/kg/die per 7gg

✓ 813 pz: 406 LEV , 407 FEN

AAST 2012 Plenary Paper

A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis

Kenji Inaba, MD, Jay Menaker, MD, Bernardino C. Branco, MD, Jonathan Gooch, Obi T. Okoye, MD, Joe Herrold, MD, Thomas M. Scalea, MD, Joseph DuBose, MD, *and* Demetrios Demetriades, MD, PhD, *Los Angeles, California*

TABLE 3. Outcomes

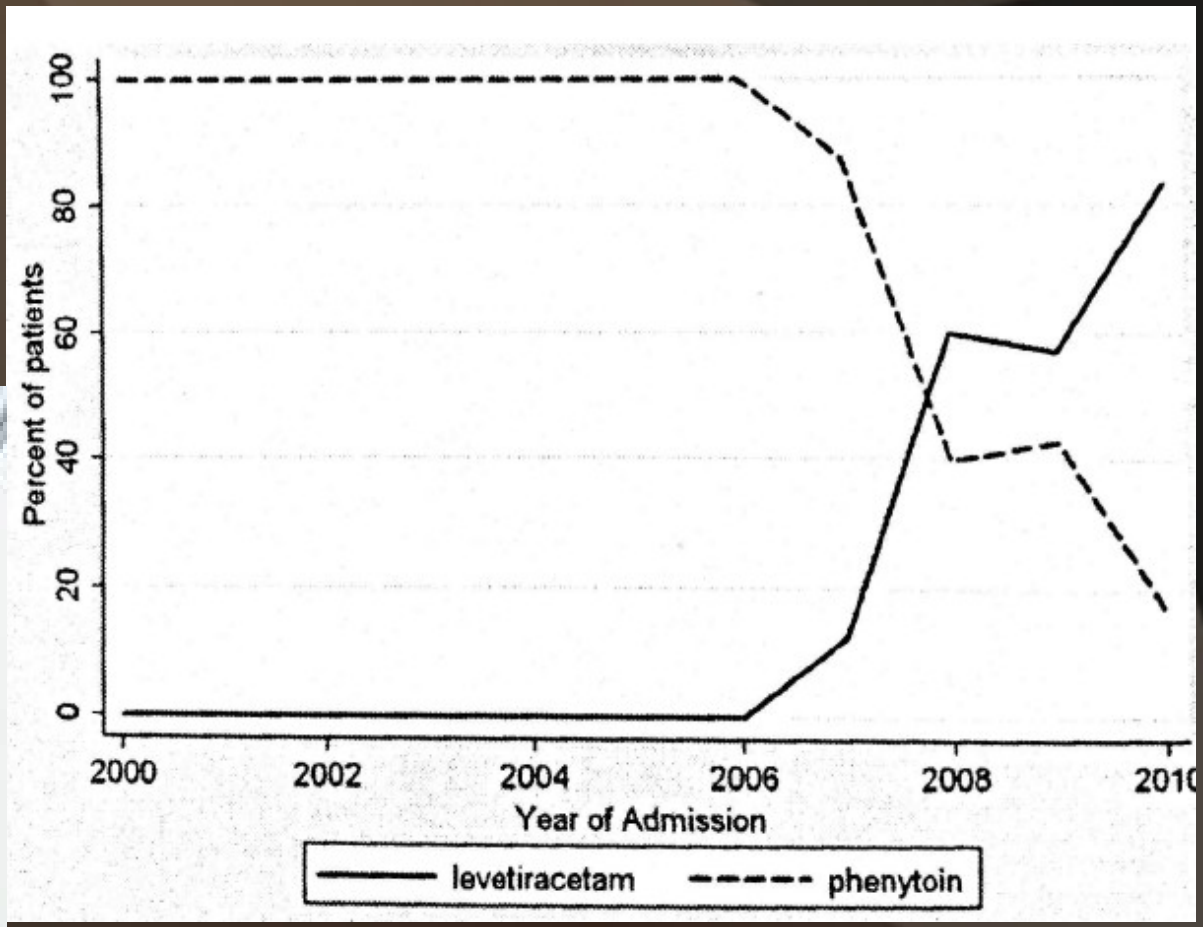
	Total (n = 813)	LEV (n = 406)	PHE (n = 407)	*p*
General				
Seizure, % (n)	1.5 (12)	1.5 (6)	1.5 (6)	0.997
Ventilation days, mean (SD) (range)	10.0 (10.1) (1–85)	10.0 (10.3) (1–85)	9.0 (3.5) (1–62)	0.548
ICU LOS, mean (SD) (range)	9.2 (10.7) (1–88)	8.8 (10.7) (1–88)	10.5 (10.9) (1–57)	0.038*
Hospital LOS, mean (SD) (range)	9.8 (11.4) (1–89)	11.8 (11.9) (1–89)	7.5 (10.2) (1–88)	<0.001*
Organ donors, % (n)	0.4 (3)	0.7 (3)	0.0 (0)	0.124
Mortality, % (n)	4.6 (37)	5.4 (22)	3.7 (15)	0.236
Adverse drug reactions, % (n)	9.1 (74)	7.9 (32)	10.3 (42)	0.227
Rash	0.2 (2)	0.2 (1)	0.2 (1)	1.000*
Leukocytosis	5.4 (44)	1.2 (5)	9.6 (39)	<0.001*
Hypotension	0.6 (5)	0.2 (1)	1.0 (4)	0.179
Drug discontinuation owing to adverse reaction	1.5 (12)	0.0 (0)	2.9 (12)	<0.001*
Complications, % (n)	27.7 (225)	28.3 (115)	27.0 (110)	0.679
Pulmonary edema	7.4 (60)	6.4 (26)	8.4 (34)	0.288
Pneumonia	2.0 (16)	2.5 (10)	1.5 (6)	0.310
ARDS	9.3 (76)	11.1 (45)	7.6 (31)	0.090
Meningitis	0.2 (2)	0.0 (0)	0.5 (2)	0.499
Other†	9.7 (79)	8.6 (35)	10.8 (44)	0.292

* *p* values are significantly different ($p < 0.05$).

†Other, diabetes insipidus, cerebral salt wasting syndrome, brain death, permanent cranial nerve deficit, thrombocytopenia, stroke, deep venous thrombosis, urinary tract infection, sepsis, and multiple-organ failure.

ARDS, adult respiratory distress syndrome.

Con il passare degli anni…



Changing trends in the use of seizure prophylaxiis after TBI: a shift from phenitoin to levetiracetam
Journals of Critical Care (2013) 28, 883.e9-e13

ORIGINAL ARTICLE

A cost-minimization analysis of phenytoin versus levetiracetam for early seizure pharmacoprophylaxis after traumatic brain injury

Fredric M. Pieracci, MD, MPH, Ernest E. Moore, MD, Kathryn Beauchamp, MD, Seth Tebockhorst, MD, Carlton C. Barnett, MD, Denis D. Bensard, MD, Clay C. Burlew, MD, Walter L. Biffl, MD, Robert T. Stoval, MD, *and* Jeffrey L. Johnson, MD, *Denver, Colorado*

- Calcolo dei costi per l'ospedale e per il paziente
- Profilassi per le crisi epilettiche
- 7 gg di trattamento
- ADR: deterioramento neurologico, anemizzazione

TABLE 1. Cost and Charge Data (USD)

Event	Cost to Institution	Charge to Patient
7-d course of LEV, 1,000 mg IV twice daily		
Medication	$370.16	$3,190.60
Total	$370.16	$3,190.60
7-d course of PHT 300 mg IV twice daily		
1,000 mg loading dose	$3.00	$120.00
Maintenance dose	$28.00	$1,008.00
Serum PHT concentration (determined twice)	$4.54	$282.98
Serum albumin concentration (determined twice)	$7.40	$90.52
Total	$40.67	$1501.50
Computed tomography of head	$218.69	$1,577.04
MRI of head	$593.15	$2,281.35
EEG	$145.42	$538.60
Complete blood count	$5.82	$59.82

The cost/charge of deterioration in mental status was approximated by the cost charge of computed tomography of the head; The cost/charge of anemia was approximated by the cost/charge of a complete blood count. All costs/charges are in 2011 USD.

COSTI OSPEDALIERI:

- ✓ 151 dollari per FEN vs 411 dollari per LEV
  (con dosaggio ematico bisettimanale per FEN)

- ✓ se deterioramento neurologico (più probabile nel gruppo della FEN) o anemizzazione (più frequente nel gruppo LEV)
  265 dollari per FEN vs 370 dollari per LEV se indagato con TC
  se indagato co RMN e EEG sempre più economico FEN

- ✓ se dosaggio ematico FEN e albumina quotidiano:
  183 dollari FEN vs 411 dollari LEV

CONCLUSIONI: *è difficile raccomandare l'utilizzo di una nuova strategia terapeutica che non è più efficace della precedente, ma che costa circa 3 volte di più.*

CONCLUDENDO

*Riservare **levetiracetam** per un sottogruppo di pazienti:*

- *Neurochirurgici d'elezione*
- *Pazienti già in terapia*
- *Epatopatici*
- *Importanti interazioni farmacologiche*
- *Instabilità emodinamica/alterazioni di ritmo*