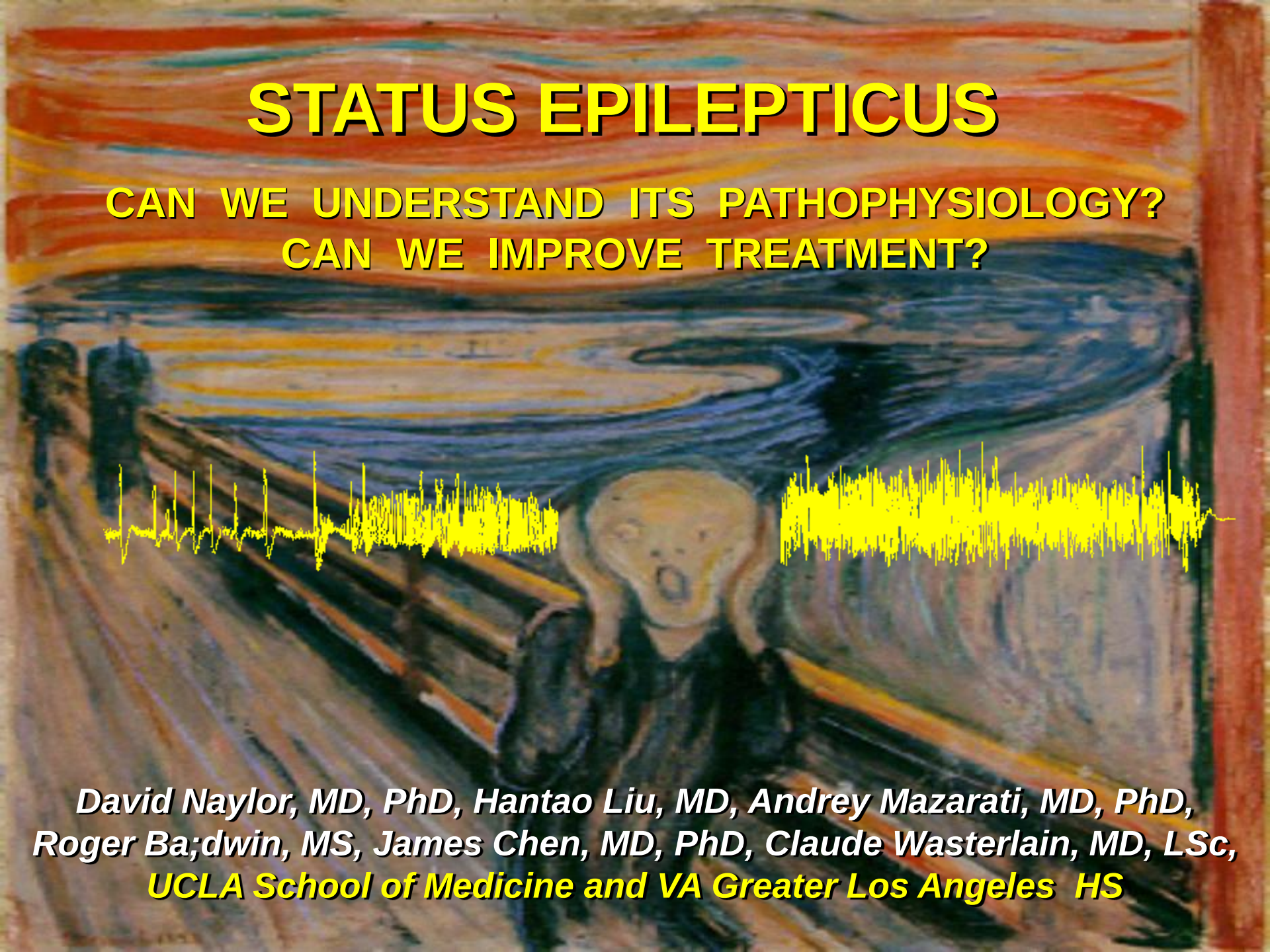
STATUS EPILEPTICUS

CAN WE UNDERSTAND ITS PATHOPHYSIOLOGY?
CAN WE IMPROVE TREATMENT?



David Naylor, MD, PhD, Hantao Liu, MD, Andrey Mazarati, MD, PhD,
Roger Ba;dwin, MS, James Chen, MD, PhD, Claude Wasterlain, MD, LSc,
UCLA School of Medicine and VA Greater Los Angeles HS

STATUS EPILEPTICUS: THE CURRENT STATE OF AFFAIRS

- ABOUT 150,000 CASES/YEAR IN THE USA
- MORTALITY (Richmond study): age, etiology, duration

Children: 3%

Young adults:14%

Elderly: 38%

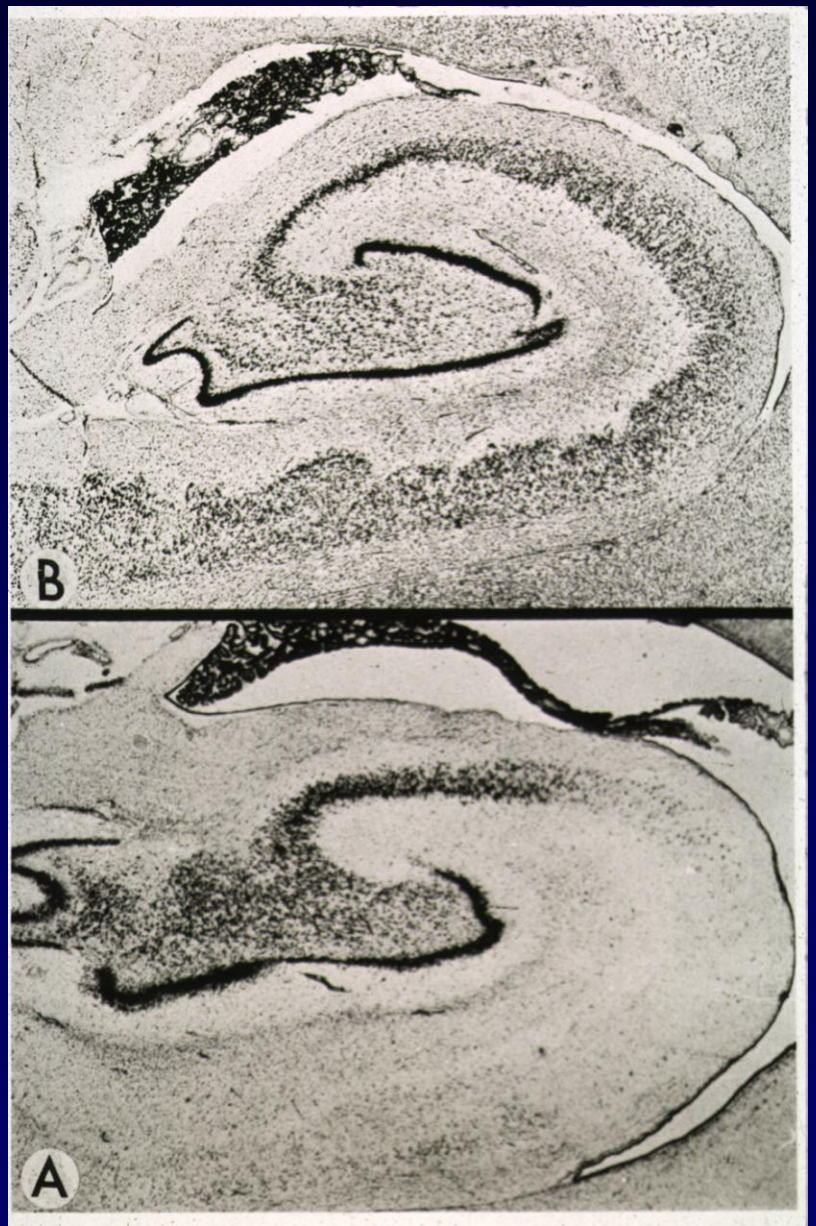
VA Cooperative Study 55%

- ONLY 3 DOUBLE-BLIND STUDIES OF TREATMENT OF SE
- NO TREATMENT OF SE HAS EVER INTRODUCED WITH TYPE 1 EVIDENCE OF EFFICACY
- MOST NEWER AEDs ARE NOT AVAILABLE BY IV ROUTE OR ARE NOT INDICATED FOR TREATMENT OF SE (FDA)

CONSEQUENCES OF SE

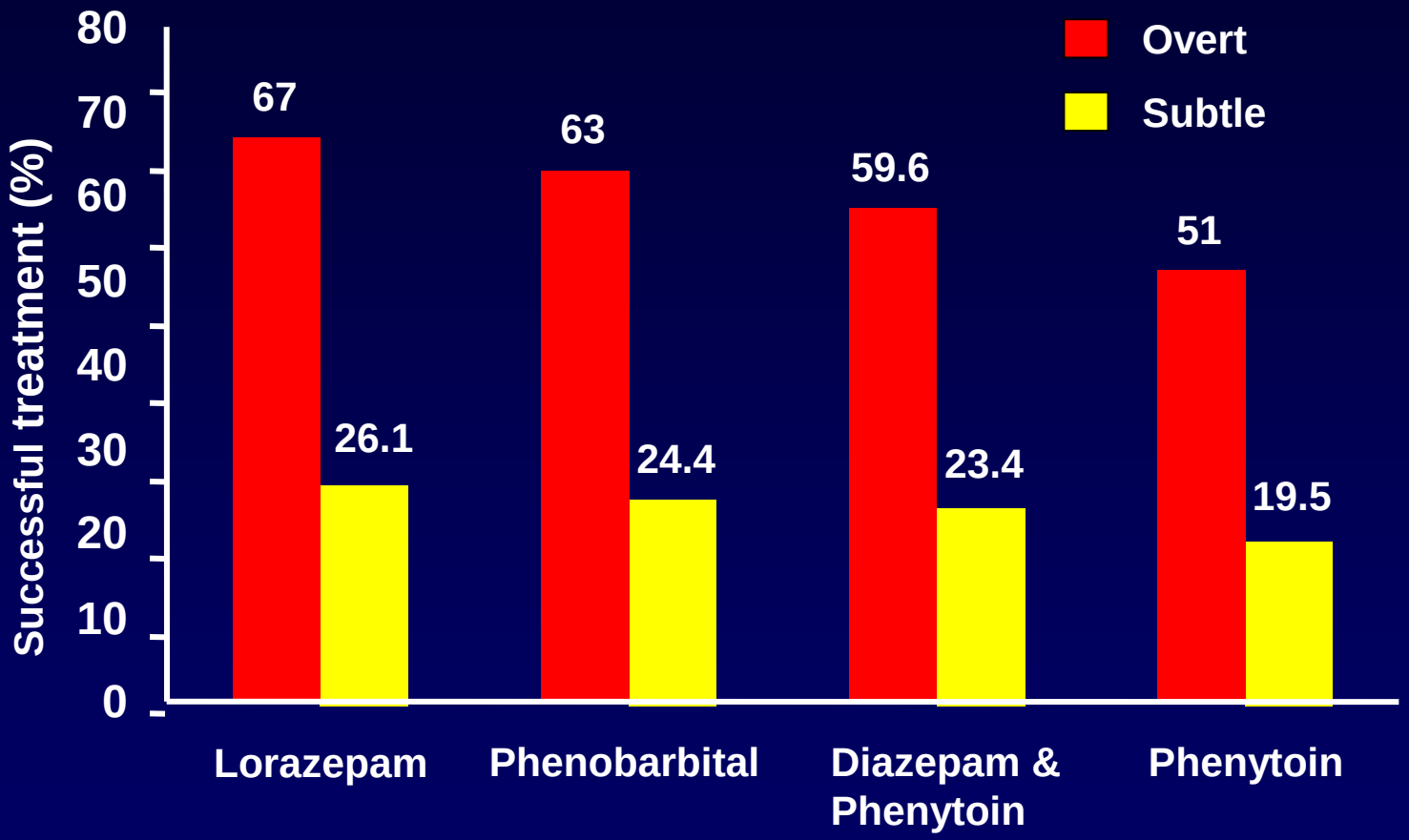
CONTROL

STATUS EPILEPTICUS



Time-dependent pharmacoresistance in SE

- Early treatment more effective than late treatment



- Good response to first drug used: 53%
- Good response to third drug used: 2%
- Regardless of which drug was used

Treiman et al, NEJM 1998

STATUS EPILEPTICUS

WE HAVE VERY EFFECTIVE MECHANISMS FOR STOPPING SEIZURES, YET IN SE THEY FAIL

SEIZURES TEND TO BECOME SELF-SUSTAINING

TIME-DEPENDENT PHARMACORESISTANCE

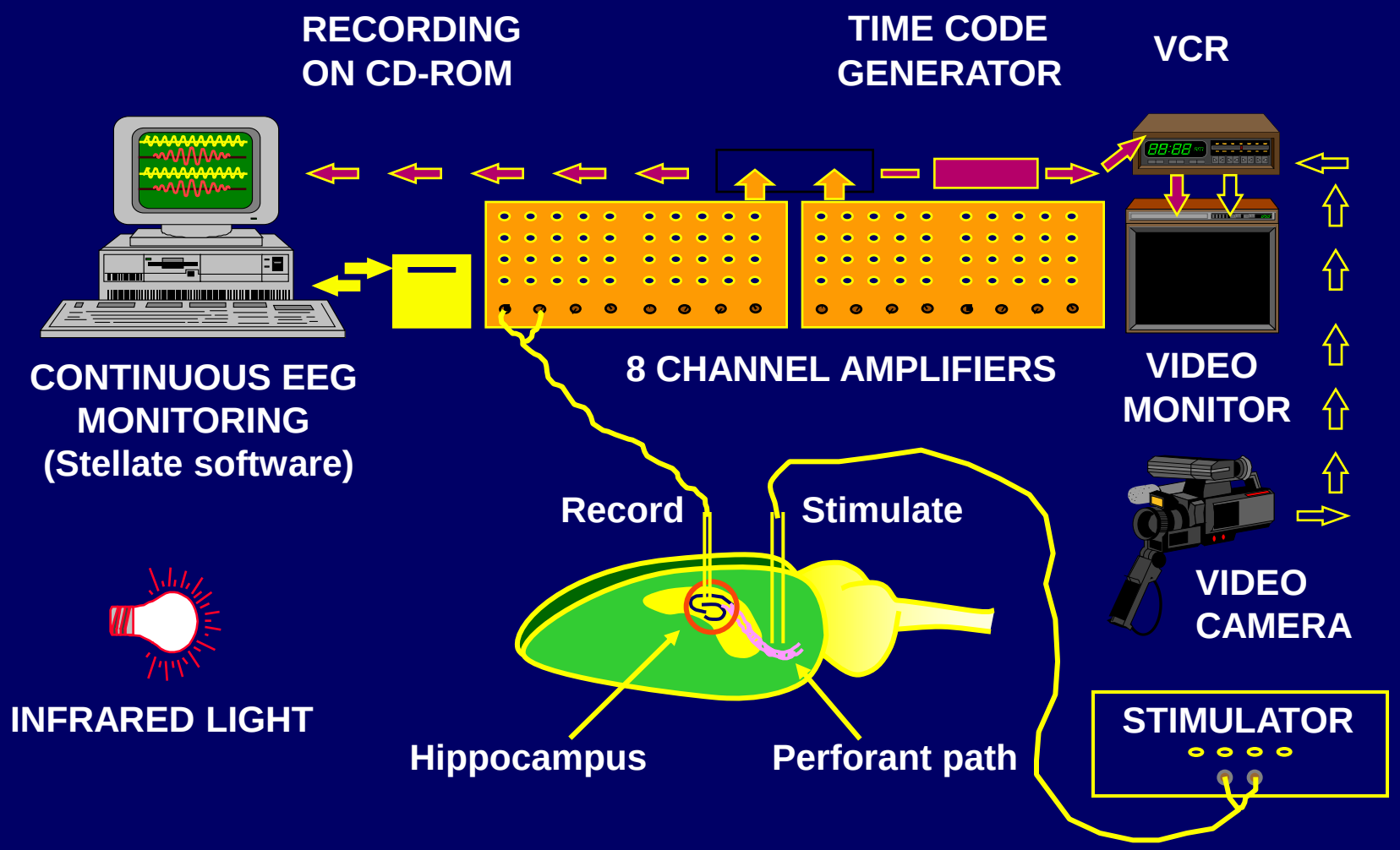
HIPPOCAMPAL SWELLING THEN ATROPHY

Experimental SE: Pharmacoresistance, neuronal injury in 30 min.

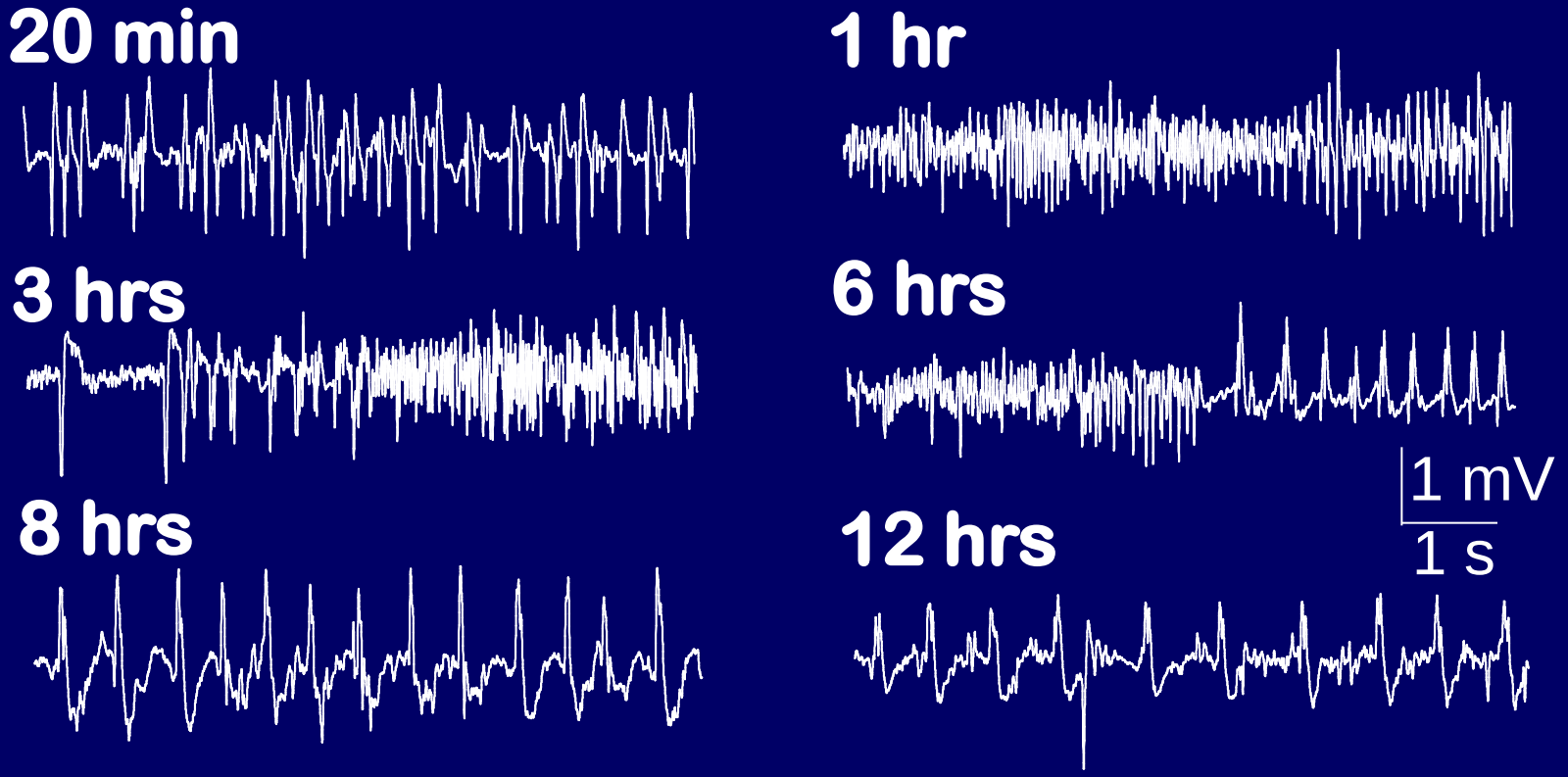
SELF-SUSTAINING STATUS EPILEPTICUS

- What mechanism accounts for the transition from single seizures to status epilepticus?
- What mechanism accounts for the time-dependent development of pharmacoresistance? (seizure-induced tachyphylaxis)

Video-EEG seizure monitoring in rodents

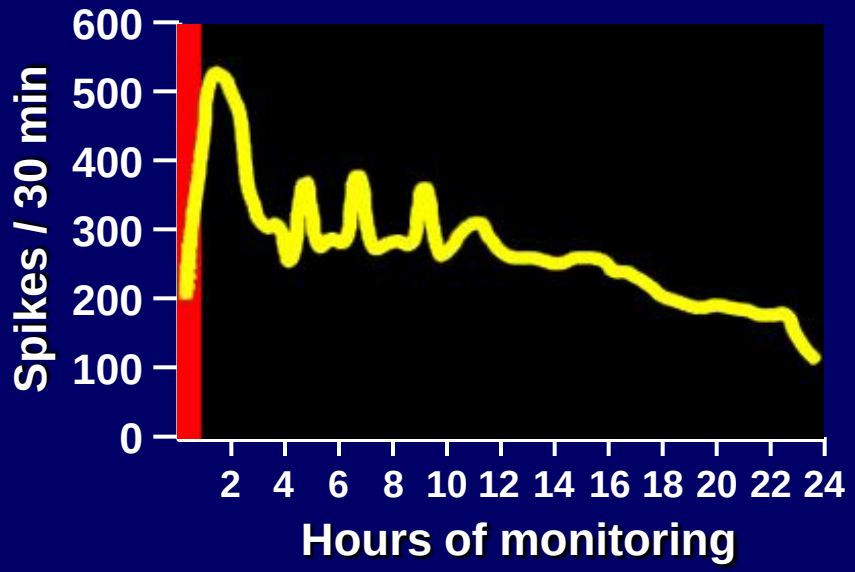


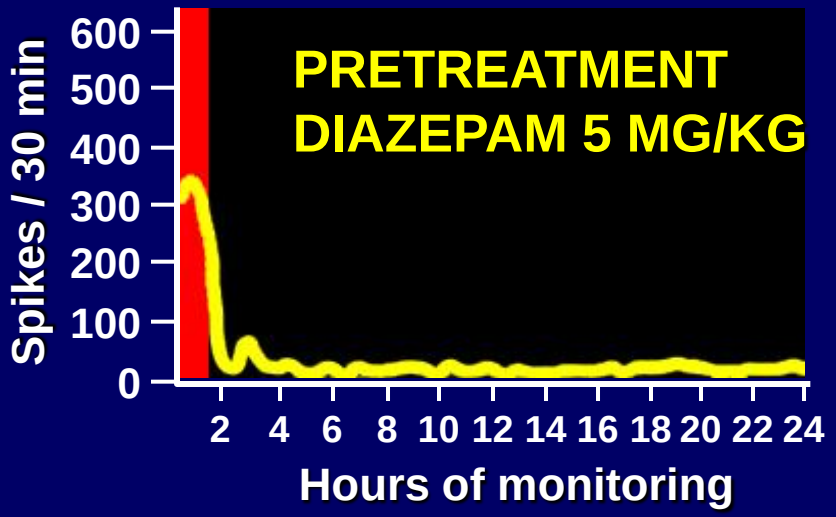
SELF-SUSTAINING STATUS EPILEPTICUS

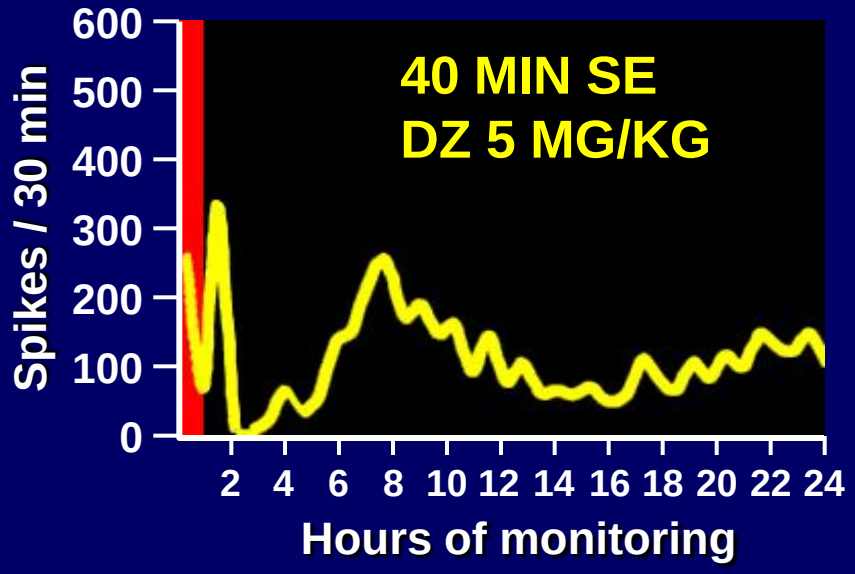


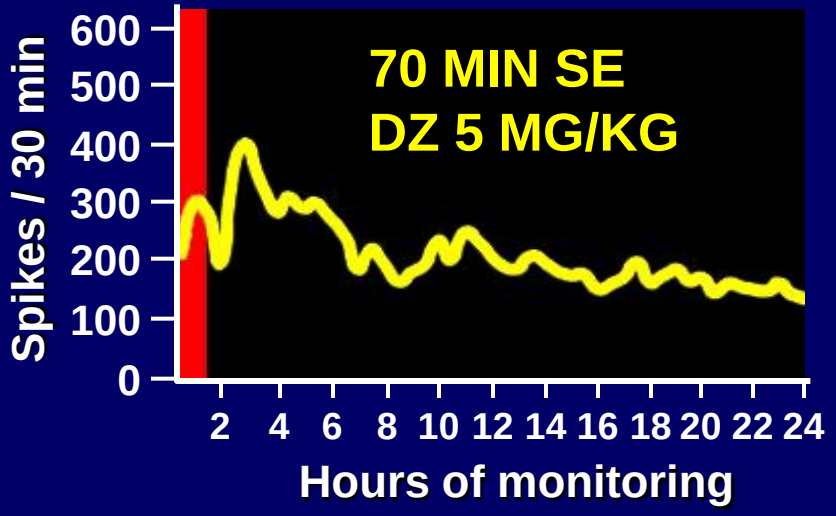
Bars: M±SEM;
Numbers: Median (min-max)

TIME-DEPENDENT PHARMACORESISTANCE IN SE





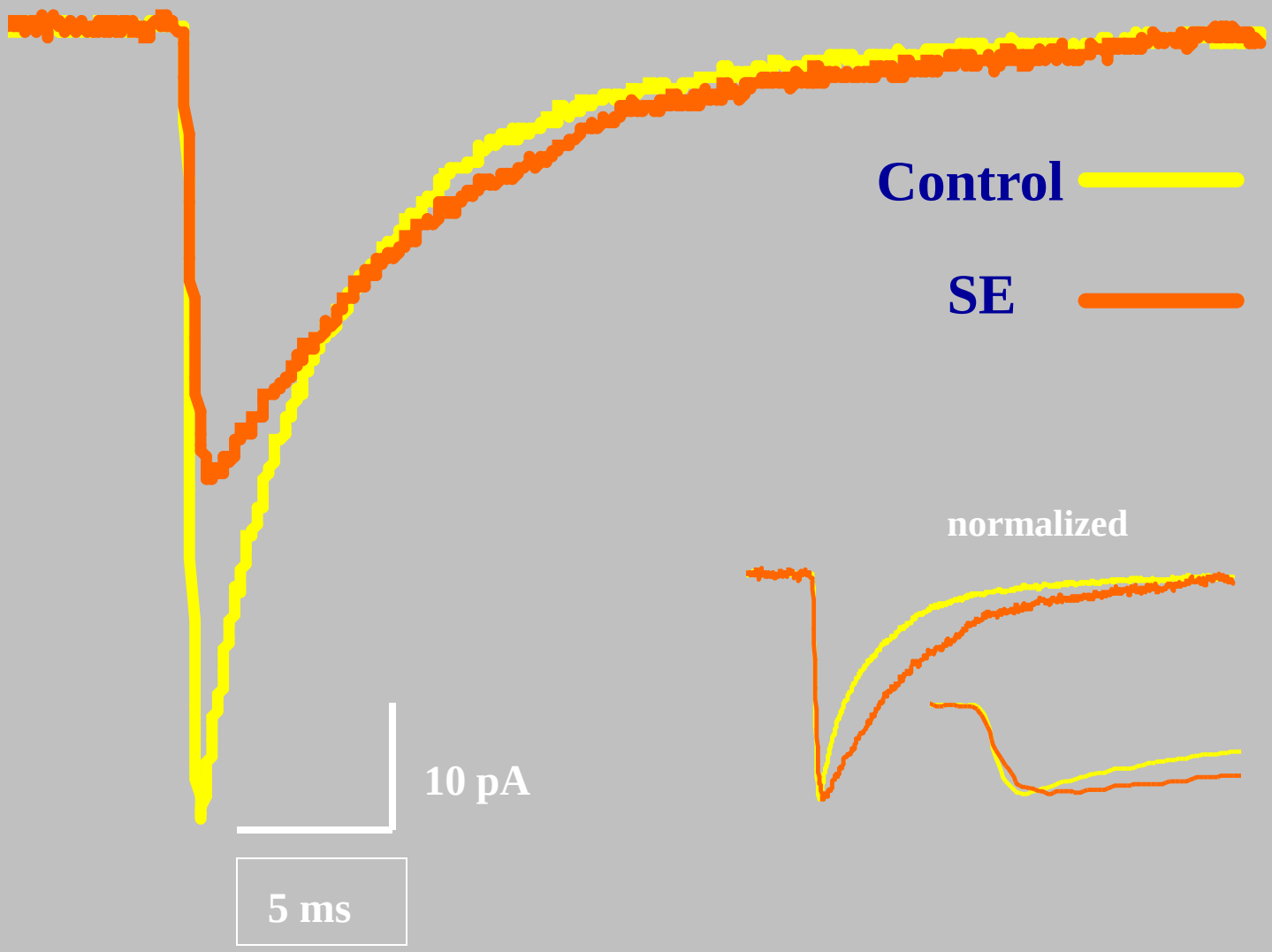




GABA AND STATUS EPILEPTICUS

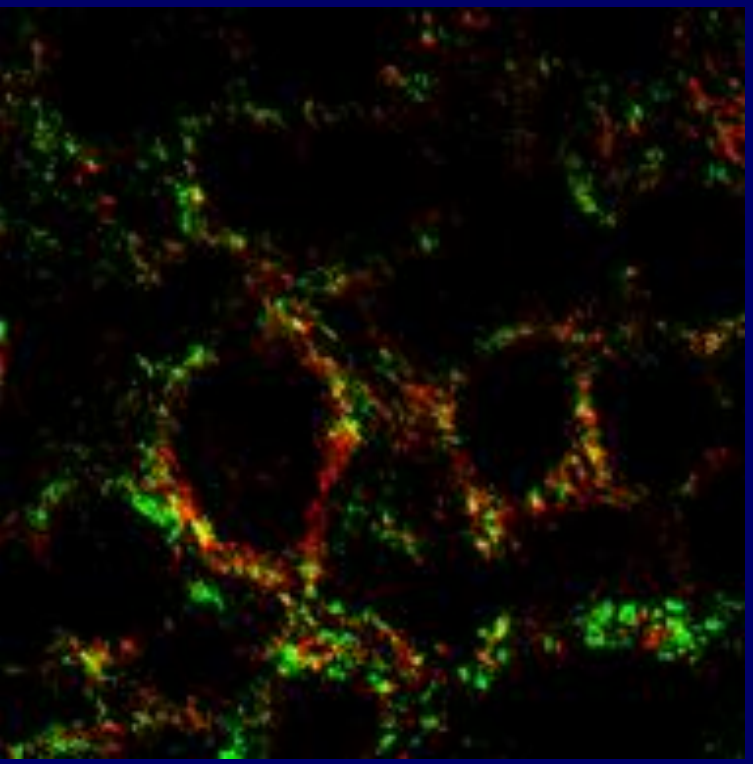
- GABA is the primary CNS inhibitor
- Many convulsants are GABA antagonists (e.g. bicuculline, picrotoxin, penicillin, PTZ)
- Decreased GABA receptors in SE (Kapur, ‘94)
- Decreased BZD response during SE (Kapur & MacDonald, ‘97)
- Increased failure of BZDs to terminate SE as it progresses (Mazarati et al, ‘98; Treiman et al., ‘98)

Effect of SE on mIPSCs

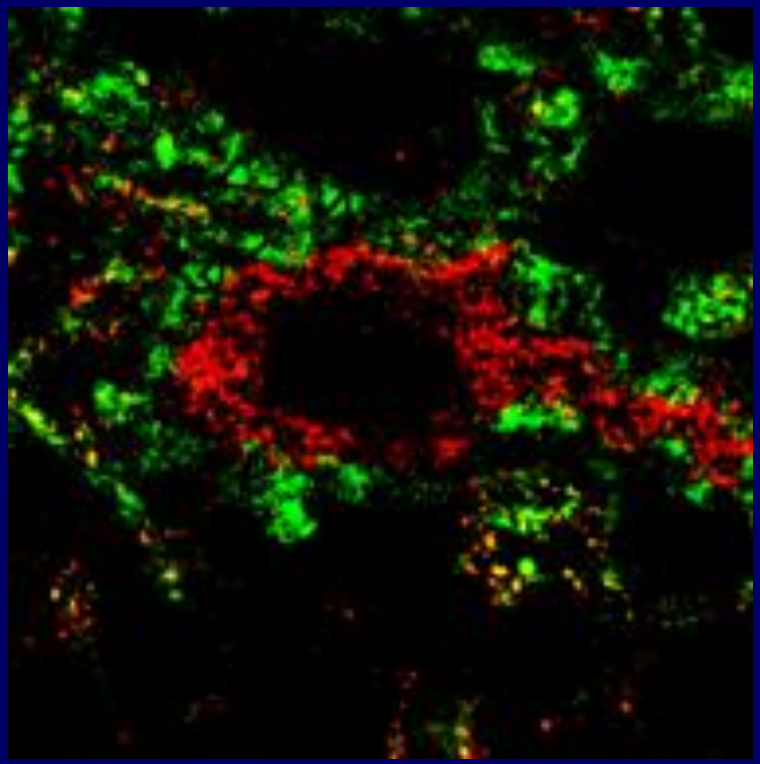


$GABA_A$ Receptor Trafficking

C



SE



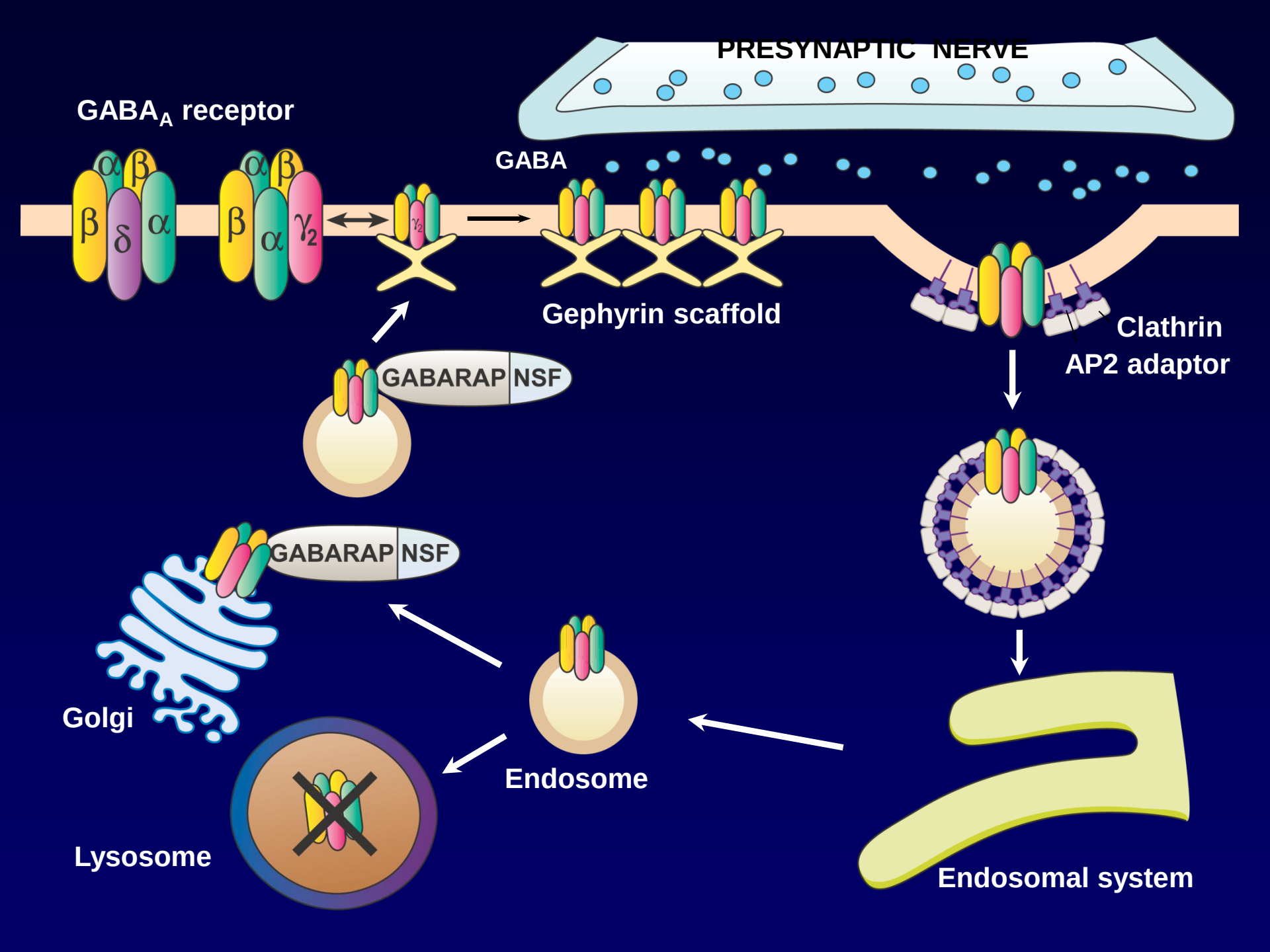
CONTROL OF SYNAPTIC FUNCTION

- Milliseconds to sec.:
  protein phosphorylation, allosteric changes

- Minutes to hours:
  Trafficking of receptors, other proteins

- Minutes to weeks:
  Gene expression

Example: physiology of short-term memory


PRESYNAPTIC NERVE
GABA$_A$ receptor
GABA
Gephyrin scaffold
Clathrin
AP2 adaptor
GABARAP
NSF
GABARAP
NSF
Golgi
Endosome
Lysosome
Endosomal system

GABA RECEPTOR TRAFFICKING IN SE

- Internalized receptors are no longer functional

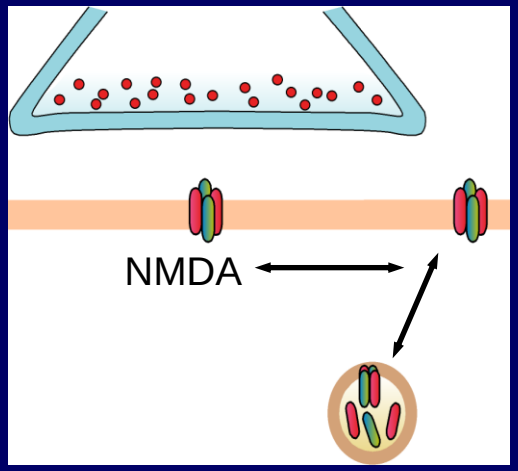
- Fewer GABA receptors at the synapse means loss of inhibition

- Benzodiazepines and other drugs have fewer receptors to work on: development of pharmacoresistance

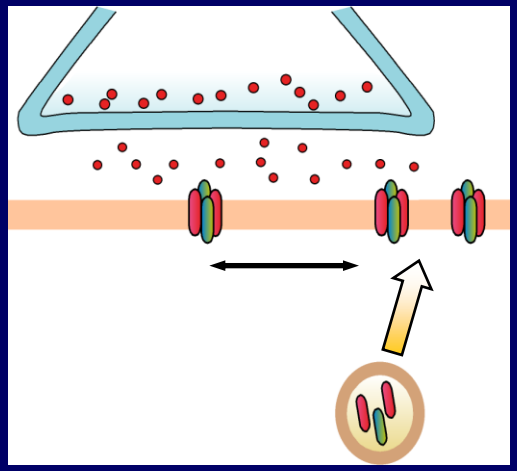
- There is less defense against seizures: development of self-sustaining seizures.

NMDA synapses during SE

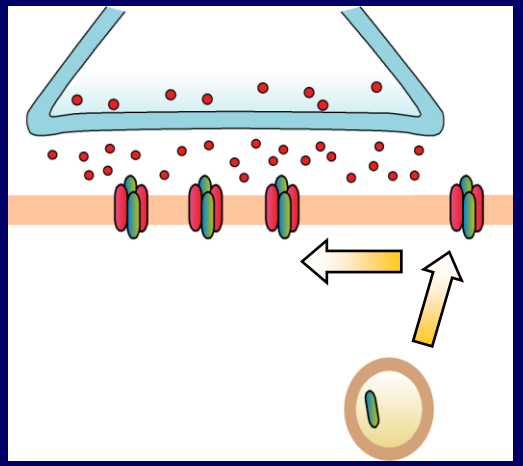
Resting



Stimulation



SE



RECEPTOR TRAFFICKING IN SE: CLINICAL IMPLICATIONS

- Time is of the essence (TIME IS BRAIN)
- Pre-hospital treatment should help avoid pharmacoresistance
- Start with high dose
- Combine benzodiazepines with a non-GABAergic agent

PRE-HOSPITAL TREATMENT OF SE

- Rectal diazepam is effective
- Lorazepam (LZ) and Diazepam (DZ) given i.v. are equally effective *(Alldredge, Lowenstein)*
- Complication rates are similar for LZ and DZ and are lower than placebo.
- Buccal/nasal midazolam is effective in children, should be evaluated in adults.

A trial of IM midazolam is under way.

WHERE CAN WE SAVE TIME = BRAIN?

TIME TO TREATMENT IN STATUS EPILEPTICUS

Retrospective review of treatment access time of 30 patients with SE admitted to the emergency department of St. Bernardino Medical Center

Onset of SE to arrival of EMT 30 min (15-40 min)

Arrival of EMT to arrival at ED 20 min (10-40 min)

Arrival at ED to initiation of treatment 35 min (15-83 min)

Jordan KG. Status epilepticus: a perspective from the Neuroscience Care Unit. Neurosurg. Clin N Am. 1994;5:671-696

IN THE ER, WHEN SHOULD WE TREAT?

1. The concept of impending SE

Duration of tonic-clonic seizures (*Theodore et al 1984*)

Patients	Mean duration	Range
120	62 sec	8-118 sec

Five min. of continuous GC seizures is a rare event, the risk that SE is present or impending is high

2. SE lasting over 30 min. causes neuronal loss

3. SE lasting over 15 min. becomes self-sustaining and pharmacoresistant

CONCLUSION: TREAT WITH HIGH DOSES OF INTRAVENOUS DRUGS AFTER 5 MINUTES OF REPEATED SEIZURES WITHOUT RECOVERY OF CONSCIOUSNESS BETWEEN SEIZURES

INITIAL TREATMENT OF GCSE

- **RESTORE HOMEOSTASIS:**
- maintain airway and blood pressure,
- start an IV line and draw blood
- inject 50ml of 50% DW and 100 mg thiamine. Take hx of allergy if possible, then

- **INJECT ANTICONVULSANTS** :
- IV fosphenytoin 20 mg/kg PE
- IV midazolam 0.2 mg/kg bolus followed by 10 μg/kg/hr for 1 hr.

EMERGENCY EVALUATION OF SE

- Accucheck
- CBC
- Chemistries
- Monitoring EKG, EEG
- Pulse oxymetry, ABGs
- CXR
- Toxicology screen

EVIDENCE-BASED MEDICINE:
WHICH AEDS ARE EFFICACIOUS FOR TC SEIZURES LASTING > 10 MIN IN ADULTS?

One vs two drugs? No difference between Lorazepam (LZ) and Diazepam (DZ) + Phenytoin (PHT).

But: LZ 0.1 mg/kg vs DZ 0.15 mg/kg. Doses were not equivalent.

Best regimen? No difference in efficacy or toxicity between LZ, DZ + PHT, Phenobarbital (PB).
PHT alone less efficacious than LZ.

Best benzodiazepine? No difference between LZ, DZ.

Currently available IV formulations of AEDs

- **Benzodiazepines**
  - diazepam
  - lorazepam
  - clonazepam
  - midazolam
- **Barbiturates**
  - phenobarbital
  - thiopental
  - pentobarbital
- **Hydantoins**
  - fosphenytoin
  - phenytoin
- **Valproate sodium**
- **Levetiracetam**
- **Lacosamide**

IV = intravenous

GCSE: CHOICE OF BENZODIAZEPINES

DIAZEPAM	LORAZEPAM	MIDAZOLAM
Peak brain concentr. 1 min.	Peak brain concentr. 5 min.	Peak brain concentr. 5 min
Redistributes to general body fat, [brain] falls after 15 min.	Little secondary fall.	Little secondary fall.
Elimination ½ life 48-60 hrs.	Elimination ½ life 20 hrs.	Elimination ½ life 1½ hr+

CGSE: INITIAL TREATMENT

PHENYTOIN

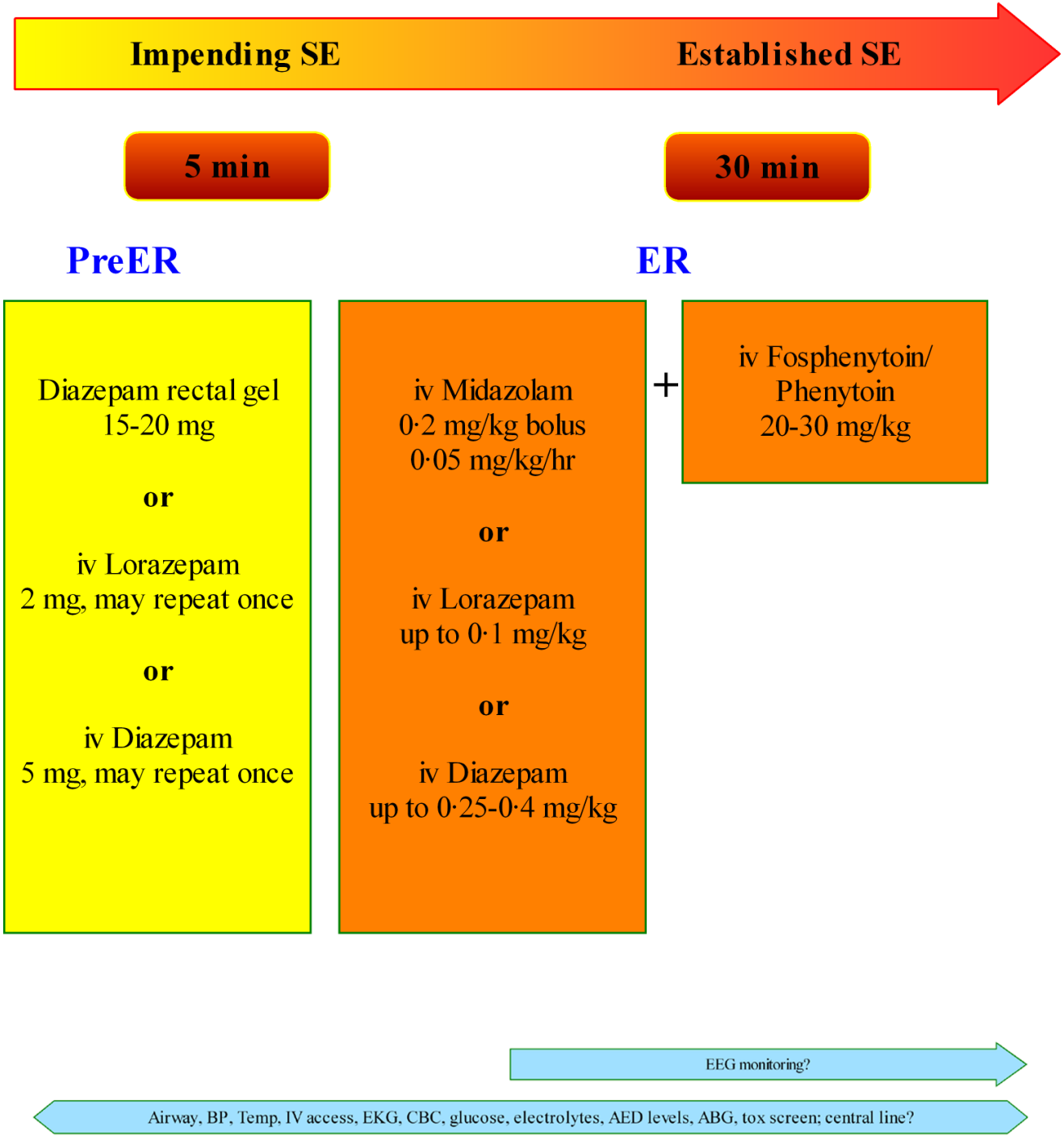
- Solvent propylene glycol, PH 12
- Purple glove syndrome
- Cardiac arrhythmias
- Max IV infusion rate 50 mg/m

FOSPHENITOIN

- Water-soluble, few local complications
- Fewer cardiac complications reported
- Max rate 150 mg/m
- Free [phenytoin] increases faster

INITIAL TREATMENT OF GCSE: EXCEPTIONS

- **Hx of drug intolerance:** avoid specific antigen
- **GCSE associated with PME or JME:** replace hydantoins by IV valproate 40-50 mg/kg, 3 mg/kg/min.
- **GCSE with hepatic encephalopathy:** lorazepam may deepen coma, phenytoin may damage liver; replace by IV levetiracetam 50 mg/kg, 250 mg/min.
- **Acute intermittent porphyria:** avoid all P450 inducers. IV levetiracetam


Impending SE
Established SE
5 min
30 min
PreER
ER
Diazepam rectal gel
15-20 mg
or
iv Lorazepam
2 mg, may repeat once
or
iv Diazepam
5 mg, may repeat once
iv Midazolam
0·2 mg/kg bolus
0·05 mg/kg/hr
or
iv Lorazepam
up to 0·1 mg/kg
or
iv Diazepam
up to 0·25-0·4 mg/kg
+
iv Fosphenytoin/
Phenytoin
20-30 mg/kg
EEG monitoring?
Airway, BP, Temp, IV access, EKG, CBC, glucose, electrolytes, AED levels, ABG, tox screen; central line?

DEFINITION OF REFRACTORY SE

- We define refractory SE by the failure of seizures to stop after intravenous injection of adequate amounts of 2 appropriate anticonvulsants.
- Adequate treatment = high therapeutic serum levels of anticonvulsants.
- Treatment should start IMMEDIATELY after the end of the previous injection. No waiting!

THERAPEUTIC ALGORITHM FOR REFRACTORY SE

- Intubate, maintain BP>90
- First maximize anticonvulsant dosage. Add IV fosphenytoin up to 30mg/kg PE
- Complete diagnostic work-up
- After failure of 2 drugs, consider anesthesia
- The place of new drugs is unclear

EMERGENCY EVALUATION OF SE

- Accucheck
- CBC
- Chemistries
- Monitoring EKG, EEG
- Pulse oxymetry, Arterial Blood Gazes
- CXR
- Toxicology screen

- Detailed history from chart and family
- Physical examination
- Anticonvulsant plasma levels
- Consider lumbar puncture and other tests

I.V. levetiracetam for status epilepticus

- **Maximal rate of i.v. administration: 4000 mg in 15 minutes well tolerated by healthy volunteers (*Ramael et al 2007)*.**
- **Lack of hepatic metabolism: drug of choice in acute intermittent porphyria, liver disease, for patients on chemotherapy, the elderly ? *Fattouch et al Acta Neurol Sc 2010*.**
- **Little effect on vital signs or level of consciousness (*Zaatreh, Clin Neuropharmacol, 2005; Baulac et al Epilepsia, 2007; Schulze-Bonhage et al JNNP 2007; Ruppert at al Epilepsy Res 2007).***
- **No hemato- or hepatotoxicity, no reported psychiatric side-effects to date.**
- **Synergistic with benzodiazepines in animal models .**
- **Too little experience to know its place, looks promising.**

I.V. LEVETIRACETAM FOR GCSE/NCSE: a meta-analysis

	case reports:	Abstracts:
• Patients with SE:	87	65
• Dose:	500-7500 mg	500-5000 mg
• Seizure control:	31-80%	80%
• Seizure type:	CPSE>GCSE	CPSE>GCSE
•Specific sz types:	AIP (acute intermittent porphyria)	Myoclonic 2 (1 Lafora)
• Complications:	somnolence 6	intubation 2, aggresssivity 1

I.V. valproate for status epilepticus

- Maximal rate of infusion 3 mg/kg/min
- Aim: serum levels of 150 µg/ml usually achieved with a dose of 40 mg/kg
- Little effect on vital signs or level of consciousness (Cattrell et al, Epilepsia, 2000, 41: 253)
-  Mitochondrial myopath., liver dis.

I.V. VALPROATE FOR SE: meta-analysis

3 randomized unblinded studies:

- **Misra 2006: valproate 30 mg/kg vs phenytoin 18 mg/kg (n= 35 V, 33 Ph). Success: V 1st tr. 66%, 2d tr. 79%; Ph 1st 42%, 2d 25%.**
- **Mehta 2007: valproate vs diazepam in children (n=20+20). V 80% success, sz stop 5 min., Dz 85%, sz stop 17 min.**
- **Agarwal 2007: valproate vs phenytoin (n = 50+50, benzo-refractory) Success: V 88%, Ph 84%.**

Case series: 139 pts, V 15-31.5 mg/kg, success SE 63-77%, serial sz 85%. Success w. treatment < 3 hrs 95%, 3-24 hrs 62%, > 24 hrs 40% (Olsen et al 2007). Complications: few but beware of publication bias.

THERAPEUTIC ALGORITHM FOR REFRACTORY SE: GENERAL ANESTHESIA

- **Option 1:** **Propofol** 1.5 mg/kg followed by continuous IV drip at 5-10 µg/kg/hr.
- If still seizing after 1 hr: option 5

- **Option 2:** **Midazolam** bolus 0.2 mg/kg followed by continuous iv infusion up to 0.05 mg/kg/hour

THERAPEUTIC ALGORITHM FOR REFRACTORY SE

- **Option 3: Phenobarbital** 20 mg/kg IV (100 mg/min).
- **Option 4: Pentobarbital :** loading dose 15 mg/kg
  - maintenance ≥ 1.5 mg/kg/hr
- **Option 5: Ketamine** bolus 1.5 mg/kg, then continuous iv 0.01-0.05 mg/kg/hour.
  Does not raise intracranial pressure*.
  Neuroprotective in experimental SE **
  Safety in neonates is uncertain ***

* *Himmelseher Anesth Analg 101:524-34, 2005 ** Fujikawa, Epilepsia 36:186-95, 1995; Mazarati Neurosci Lett 265:187, 1999 *** Ikonomidou et al, Science 283:70-4, 1999*

THERAPEUTIC ALGORITHM FOR REFRACTORY SE: ANESTHESIA

- Adjust to burst supression pattern
- Stop IV every morning and monitor seizures
- If recurrence, another 22 hrs of anesthesia

Management of GCSE in adults

Impending SE / Frank SE → **Refractory SE / Subtle SE**

5 min — **Pre-emergency room**

- Diazepam rectal gel 15–20 mg
- or
- IV lorazepam 2 mg, repeat x1
- or
- IV diazepam 5 mg repeat x1
- or
- Buccal midazolam in children

30 min — **Emergency room**

- midazolam 0.2 mg/kg bolus 0.05 mg/kg/h + fosphenytoin/ phenytoin 20–30 mg/kg
- or
- lorazepam up to 0.1 mg/kg
- or
- diazepam up to 0.25–0.4 mg/kg

Intensive care unit

- valproate 40–60 mg/kg 3 mg/kg/min
- Levetiracetam 50 mg/kg 250 mg/min.
- Lacosamide

- Propofol loading 2–5 mg/kg civ 2–10 mg/kg/h
- or
- Midazolam loading 0.2 mg/kg civ 0.1–2 mg/kg/h
- or
- Pentobarbital loading up to 10 mg/kg ≤25 mg/min civ 0.5–2 mg/kg/h
- or
- Phenobarbital 20 mg/kg 50–100 mg/min

- Ketamine bolus 1.5 mg/kg civ 0.01–0.05 mg/kg/h
- Others

EEG monitoring?

Airway, BP, temp, IV access, EKG, CBC, glucose, electrolytes, AED levels, ABG, tox screen, central line?

GCSE = generalised convulsive status epilepticus

Chen & Wasterlain, 2006

COMPLEX PARTIAL STATUS EPILEPTICUS

- Two forms: cyclic or continuous
- Partial responsiveness with reactive automatisms ⟷ total unresponsiveness with reactive automatisms
- May be distinguished from absence SE by EEG or presence of complex automatisms
- Response to benzos, interictal focus help dx

COMPLEX PARTIAL SE: PRINCIPLES OF TREATMENT

- Causes brain damage,
- Treat like CGSE
- Two drugs IV (benzo+ fosphenytoin)
- Time is of the essence
- Refractory CPSE: EFNS guidelines* levetiracetam or valproate
- general anesthesia if necessary

Meierkord et al EJN 2010

ABSENCE STATUS

- Distinguish from partial complex status
- Most common in children
- Not responsive to phenytoin or fosphenytoin
- Responsive to benzodiazepines

ELECTROGRAPHIC SE

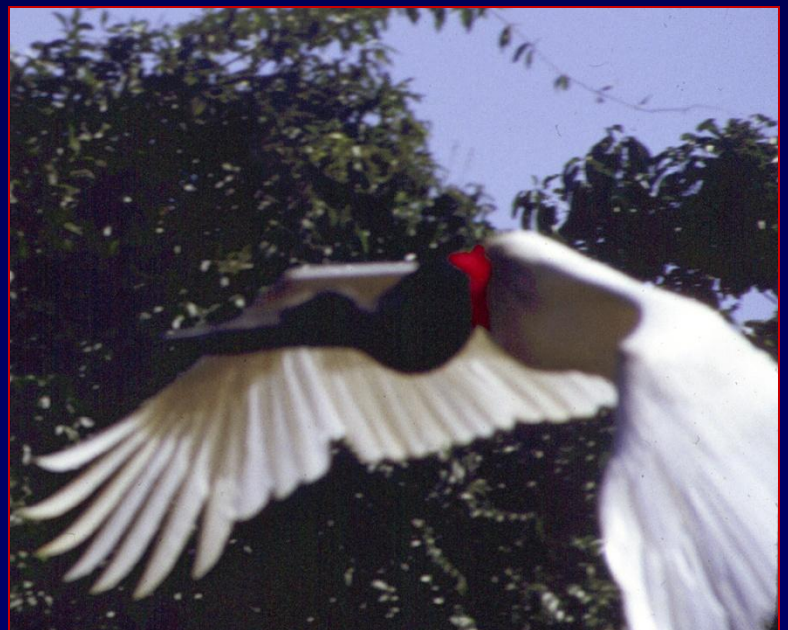
- **With impaired consciousness:**
  IV fosphenytoin and midazolam

- **Without impairment of consciousness:**
  - No need for IV treatment
  - Load p.o. or rectally

- **During sleep:**
  - No need for IV treatment

Conclusions:
don't be "too low, too slow"

- SE should be treated early, vigorously, in ICU.
- Pre-hospital treatment should be used.
- Refractory SE should quickly lead to general anesthesia
- Indications of valproate & levetiracetam uncertain



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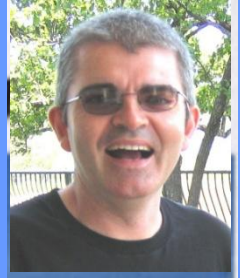

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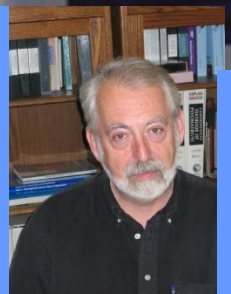

R BALDWIN

UCLA School of Medicine
West Los Angeles VAMC

C WASTERLAIN