Role of new antiepileptic medications in status epilepticus?''

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Status epilepticus

- Continuous or rapidly repeating seizures
  - Seizure that persists for a sufficient length of time
  - Repeated frequently enough that recovery between attacks does not occur.
- More recent publication
  - Seizures that persist for 20-30 min "neuronal injury"
  - Should begin Rx for status epilepticus
    - Before 20 minutes
    - Isolated GTC rarely last more than a few minutes

Gastaut H, 1967.
Coeytaux A, Neurology 2000
DeLorenzo RJ, Neurology 1996
Hesdorffer DC, neurology 1998
Knake S, Epilepsia 2001

Status epilepticus

- One of the most common neurologic emergencies
- New definition of status epilepticus should
  - Continuous seizures lasting > 5 min
  - ≥ 2 discrete seizures which incomplete recovery of consciousness

Status epilepticus

- Burden
  - 3 million people throughout the world per year
  - Estimates of the overall incidence ~ 10 to 60 per 100,000 person-years
  - A life-threatening condition
    - Associated with high morbidity and mortality (Overall mortality ~ 20%)
    - esp. generalized convulsive status epilepticus
- Cause of death
  - Underlying condition > status epilepticus
- Prognosis related to
  - Aetiology
  - Age (higher mortality in elderly)
- Controlled clinical trial: difficult to conduct

Definition

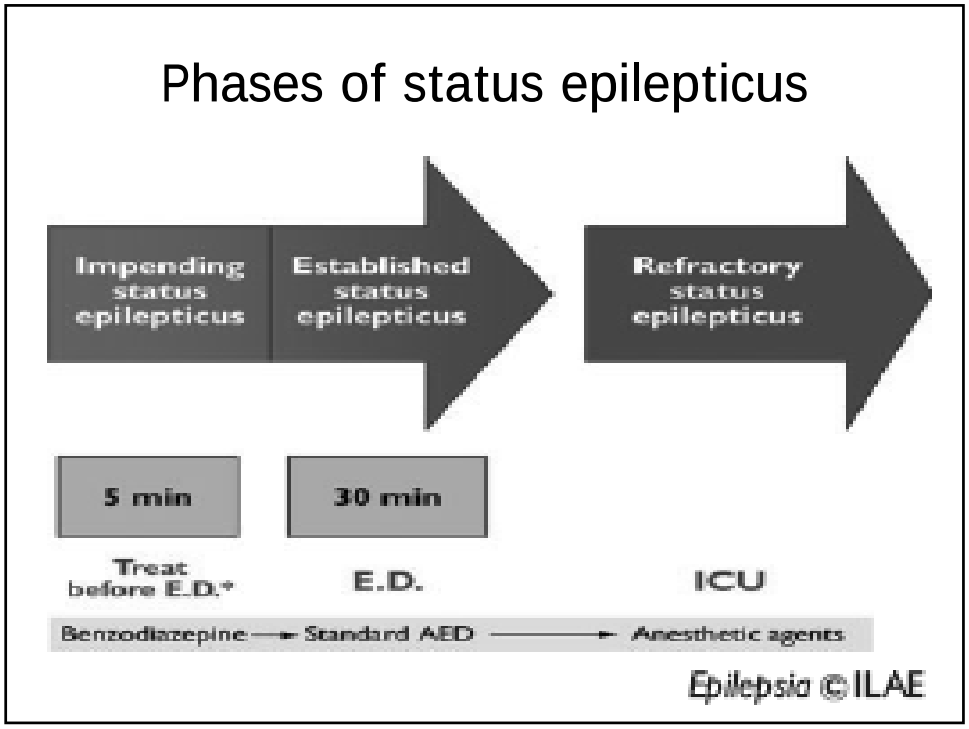
- Refractory status epilepticus
  - severe form of SE that does not respond to first (benzodiazepines) and second (phenytoin, phenobarbital) treatment efforts with antiepileptic drugs (AEDs)
  - Seizure continuing after 30 min of treatment above

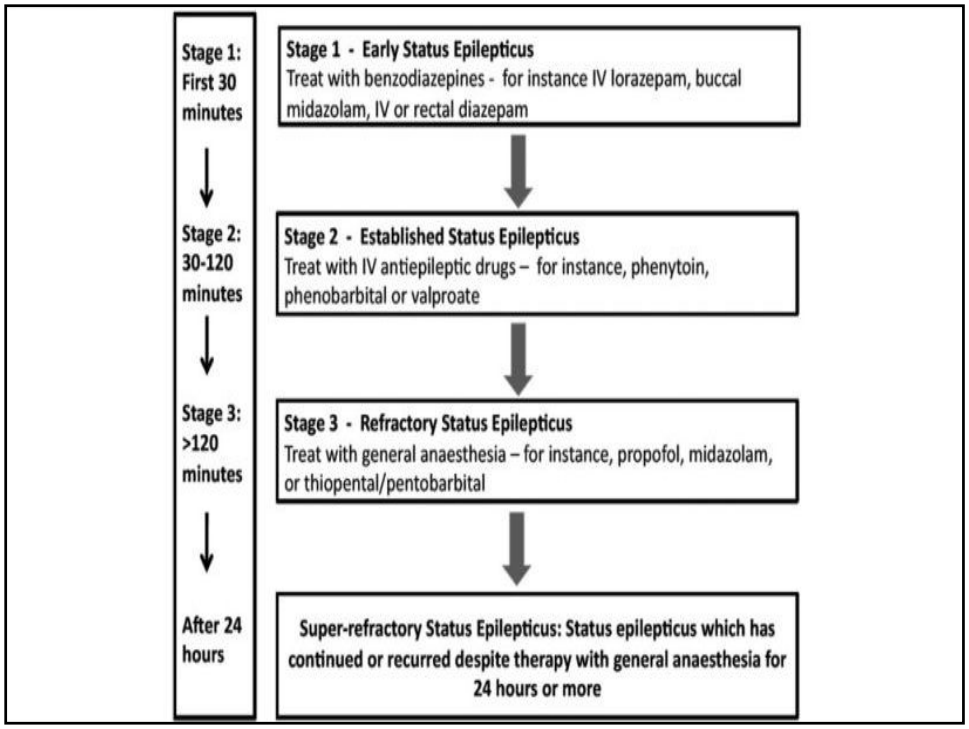
Ferlisi M et al. Brain 2012

Definition

- Super-refractory status epilepticus
  - status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia

Ferlisi M et al. Brain 2012


Phases of status epilepticus
Impending status epilepticus
Established status epilepticus
Refractory status epilepticus
5 min
30 min
Treat before E.D.*
E.D.
ICU
Benzodiazepine
Standard AED
Anesthetic agents
Epilepsia © ILAE


Stage 1: First 30 minutes
Stage 2: 30-120 minutes
Stage 3: >120 minutes
After 24 hours
Stage 1 - Early Status Epilepticus
Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam
Stage 2 - Established Status Epilepticus
Treat with IV antiepileptic drugs – for instance, phenytoin, phenobarbital or valproate
Stage 3 - Refractory Status Epilepticus
Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital
Super-refractory Status Epilepticus: Status epilepticus which has continued or recurred despite therapy with general anaesthesia for 24 hours or more

General concepts for status Rx

- Emergency treatment
  - Life support measures
  - Identification and treatment of the underlying cause
  - Rapid institution of intravenous antiepileptic drugs (AEDs)

Cause: acute process

- Metabolic disturbances
  - Electrolyte abnormalities
  - Renal failure
  - Sepsis
- Central nervous system
  - Infection
  - Stroke
  - Head trauma
  - Drug toxicity
  - Hypoxia

Acute process : CNS

- Often difficult to control
- Associated with a higher mortality
- Especially after hypoxia and in older patients
- Myoclonic status epilepticus after hypoxia
  - Grave prognosis

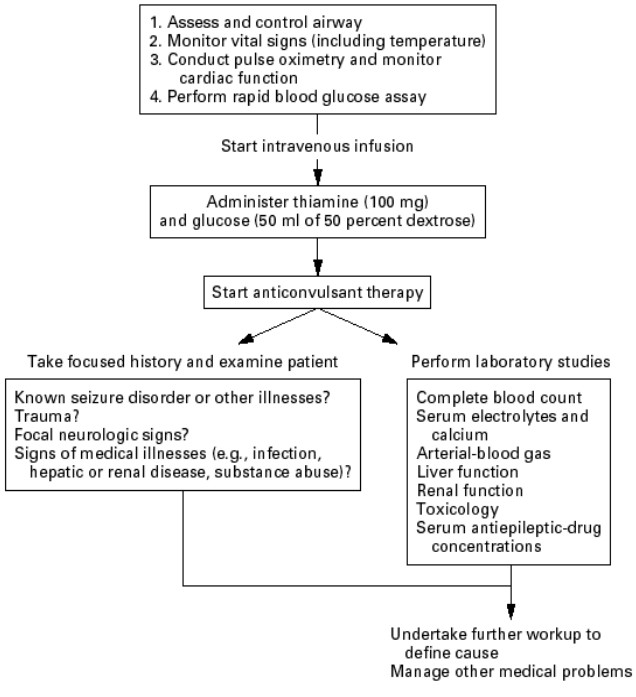
Cause: chronic process

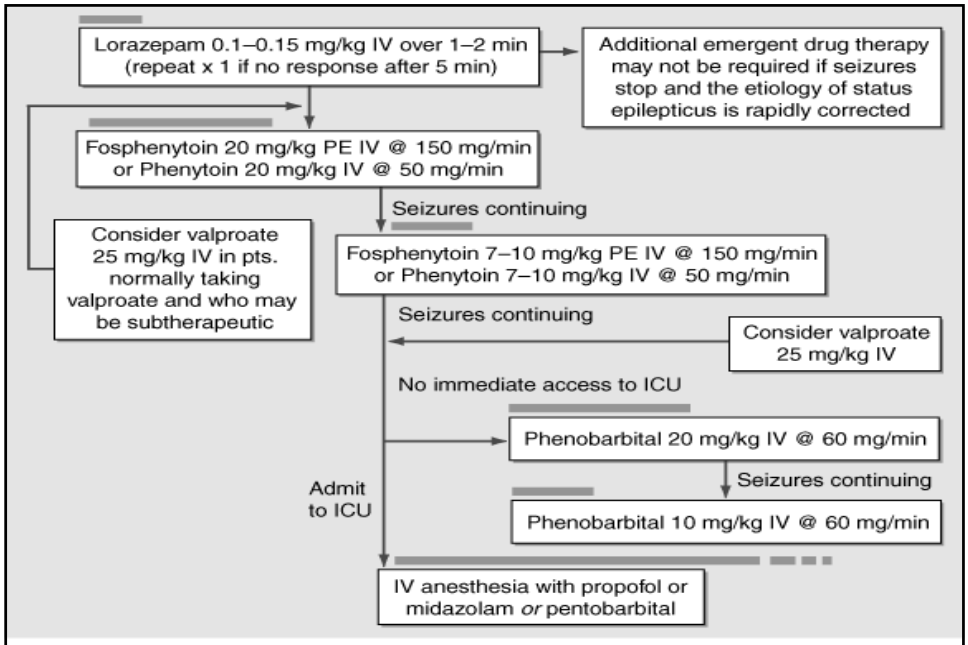
- Breakthrough seizures
- Discontinuation of antiepileptic drugs
- Chronic ethanol abuse
- CNS tumors or strokes

* Respond well to anticonvulsant Rx*

Principles of Drug Treatment

- Goal of Rx
  - Antiepileptic drugs
    - Easy to use
    - Immediate or rapid action
    - A long-lasting antiepileptic effect
    - Minimal cardiopulmonary and other side-effects
    - Prompt cessation of seizure activity





Refractory status epilepticus (RSE)

- An emergency
  - A risk of physiological compromise, neuronal damage
  - Progressive drug resistance, ICU for early anesthesia
- Prolonged ICU and hospital stays
- Requiring
  - neurointensive care
  - aggressive management (therapeutic coma)
  - multiple antiepileptic drugs (AEDs)
  - continuous infusions of propofol, midazolam, or pentobarbital, ketamine, inhalational anaesthetics (isoflurane, desflurane)
- Prognosis: poor, mortality 48%, morbidity 70%

Mechanism of drug resistance in status epilepticus

- From rat models SE>30 minutes
  - Progressive alterations of GABAA receptors, including reduced surface expression of these receptors by receptor trafficking, which would explain the loss of efficacy of benzodiazepines
  - SE-induced overexpression of drug efflux transporters, such as P-glycoprotein (Pgp), in the brain may be involved in the resistance to AEDs (including phenytoin and phenobarbital) that are Pgp substrates

Loscher W. Epilepsia 2007

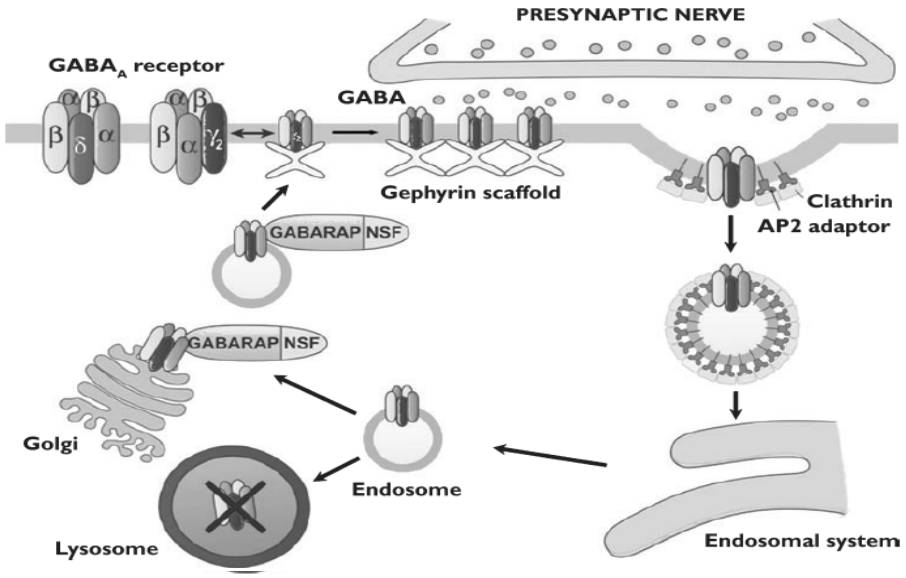


Figure 2.
Cartoon summarizing our model of the role of receptor trafficking in the transition from single seizures to status epilepticus (SE). After repeated seizures, and massive γ-aminobutyric acid (GABA) release, the synaptic membrane of $GABA_A$ receptors forms clathrin-coated pits (CI), which internalize. This inactivates the receptors, which are no longer within reach of the neurotransmitter. These vesicles evolve into endosomes (E), and reach a phosphorylation-dependent decision point where they are transported toward the soma to lysosomes (L) where the receptors are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane.

Traditional AEDs

- Current standard treatment of established status epilepticus after failure of benzodiazepines is intravenous phenytoin/fosphenytoin, phenobarbital, or valproate
- If RSE → cIV-AED: Pentobarbital, midazolam, propofol
  - titration goal "seizure suppression" or "EEG background suppression“
  - EEG background suppression, may be more effective but increase frequency of hypotension,
  - No effect on mortality

Claassen J, et al. Epilepsia 2002
Wasterlain CG, et al. Epilepsia 2008

Side effect of standard treatment

- Respiratory depression
- Hypotonia
- Cardiac arrhythmia
- Pharmacokinetic interactions
  - Inducer or inhibitor for hepatic enzymes

New antiepileptic drugs in status epilepticus

- Alternative treatment of refractory status epilepticus (RSE)
- No prospective randomized studies
- Levetiracetam, pregabalin, topiramate, lacosamide

Evidence-based
New antiepileptic drugs
in the treatment of status epilepticus

- Oral topiramate
- Oral and intravenous levetiracetam
- Intravenous lacosamide
- Pregabalin

Topiramate

Topiramate

- A potent broad-spectrum AED
- Several modes of action
  - Blockade of sodium channels
  - Enhancement of (GABA)ergic transmission
  - Antagonism of alpha amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors
- An adjunctive treatment in RSE
- no commercially available intravenous formulation

Selvitelli & Drislane, 2007

N	Bolus	Dose/d	Efficacy	Safety	Reference
1 RSE		300-1,600	good	Lethargy, no SAE	Towne AR. Neurology 2003
3 RSE children	2-3 mg/Kg	5-6 MKD	Terminate all in 24 hours		Kahriman M. Epilepsia 2003
3 RSE	500 mg BID for 2-5 d	200 mg BID	2/3		Bensalem MK. Epilepsy Behav 2003
3 RSE children	10 mg/Kg (x2d)	5 MKD	Aborted in 21 h after initial dose		Epilepsia. 2006
14 RSE children	5 mg/Kg	5 MKD (x2d)	5.5 h (2-48 h) 9 full responders 3 partial responders 2 non-responders	X3 mild metabolic acidosis	Akyildiz BN. Childs Nerv Syst 2011
6 GCSE, 7 NCSE With medical co-morbidity			100% in 3.7 days	No AE	Kim W. J Epilepsy Res 2011
35/113 RSE Rx in 2 days		Up to 800 mg/d	71% in 72 h 3rd-86% 4th+-67% Mortality 31% (~etiology)	No SAE	Hottinger A. CNS Drug 2012
35 RSE			11% in 1 d 29% in 2 days 40% in 3 days	No AE	Synowiec AS. Epilepsy Res 2012

Oral and intravenous levetiracetam in SE

Levetiracetam

- A wide spectrum of action
- Good tolerability and a favorable pharmacokinetic profile
- Easy to use and administration and limited side effects
- Effectiveness in the treatment of focal and generalized epilepsies
- LEV may safely be used in porphyria

Levetiracetam

- The mechanism of action of LEV is poorly Understood
  - Alters glutamatergic neurotransmission
  - Delayed rectifier channels and N- and P/Q-type calcium Channels
  - Reduces the calcium release from intraneuronal stores
  - The synaptic vesicle protein 2A (SV2A)
  - Inhibits HVA-Ca2 channels (N-type)
  - Reverses the inhibition of negative allosteric modulators such as zinc and beta-carbolines of c-aminobutyric acid (GABA)- and glycine-gated currents

Surges et al., 2008

LEV in status epilepticus

- Several reports of levetiracetam in animal models
  - Possible efficacy in experimental models of SE
- Human studies
  - Open-label experience in reported cases or retrospective case series are accumulating
  - No randomised controlled studies (class I or II) in this field
  - Firstly used the oral formulation
  - Most often applied via a nasogastric tube

Ramael S. Clin Ther 2006, Ramael S. Epilepsia 2006
Baulac M. Epilepsia 2005, Baulac M. Epilepsia 2007

Oral LEV in status epilepticus

- 58 patients reported in 13 case reports or case series
- Various forms of SE
- Oral LEV (500-9,000 mg/day)
  - The most often used effective dose was 2,000–3,000 mg/day.
- Responder rates of 69% (43–100%) within 12 hours to 4 days after onset
- Adverse events (n = 3)
  - Somnolence, dizziness

Ramael S. Clin Ther 2006, Ramael S. Epilepsia 2006
Baulac M. Epilepsia 2005, Baulac M. Epilepsia 2007

Intravenous levetiracetam

- Available 2006, approval for the treatment of patients with epileptic seizures who are temporary unable to swallow
  - It has been widely used since its availability to treat all forms of acute seizures and status epilepticus
  - Bioequivalent to the oral preparation
- IV levetiracetam was administered over a period of 15-30 minutes; each 500 mg of levetiracetam was diluted in 100 mL of normal saline
- Well tolerated even at higher doses and/or at faster infusion rates
- Non-randomised, uncontrolled open-label experience in retrospective case series is accumulating.

Ramael et al., 2006

N	Bolus	Dose/d	Efficacy	Safety	Reference
6 RSE		500 - 3000	Good control in 12-96 h	No SAE	Patel NCl. Seizure 2006
16 (focal +/- sec gen)			Good	No SAE	JNNP 2008
156	2,000–3,000 in 15 minutes		65.4	Adverse events 7.1%, (mild and transient)	Goraya 2008; Ruegg. 2008; Knake 2007, Schulze-Bonhage A. JNNP 2007, Knake S. JNNP 2008
34 RSE (82% focal)	1,000	2,000 (1,000-3,000)	71%	No AE	Gamez-Leyva G. CNS Drugs 2009
32 (20 NCSE) Rx in 6 h	2,000	3,500	Good 23/32 Not improve 7/32	1 n, v 1 abn LFT (on VPA)	Berning S. J Neurol 2009
11 RSE children	30 mg/Kg	40 mg/kg/day	45% (5/11) in 1.5 days (1-8 days)	No SAE	Gallentine WB. Epilepsy Behav 2009
36	500-2000 in 1 h	3000 (1000-9000)	69% responder (assoc with loading dose) Mortality 17% (Responder 4%, non-responder 45%)	No SAE	Moddel G. JNNP 2009
40 (90% partial sz)			57.5% in 14.4 h	Mild AE 15%	Aiguabella M. Seizure 2011
707	2,000-3,000 in 15 minute		70%	<10% (mild and transient)	Eugen Trinka. Epilepsia, 2011
34 Thai*			61.8% (~ co-morbidity)		Thongplew S. Neurology Asia 2013

Levetiracetam versus lorazepam in SE

- A randomized, open labeled pilot study, N 79 patients
- Comparing the efficacy and safety of LEV and LOR in convulsive or subtle convulsive SE
- IV LEV 20 mg/kg IV over 15 min or LOR 0.1 mg/kg over 2-4 min
- Failure to control SE within 10 min of administration of one study drug was treated by the other study drug.
- Primary endpoint was clinical seizure cessation
- Secondary endpoints were 24 h freedom from seizure, hospital mortality, and adverse events

Misra UK, et al. J Neurol 2012

Levetiracetam versus lorazepam in SE

- Result
- LEV and LOR were equally effective
  - SE was controlled
    - LEV in 76.3% (29/38)
    - LOR in 75.6% (31/41)
  - In those resistant to the above regimen, controlled SE
    - LEV in 70.0% (7/10)
    - LOR in 88.9% (8/9) patients.
  - The 24-h freedom from seizure was also comparable
    - LEV in 79.3% (23/29)
    - LOR in 67.7% (21/31)

Misra UK, et al. J Neurol 2012

Levetiracetam versus lorazepam in SE

- Side effect
  - LOR was associated with significantly higher need of artificial ventilation and insignificantly higher frequency of hypotension
- Conclusion
  - For the treatment of SE, LEV is an alternative to LOR and may be preferred in patients with respiratory compromise and hypotension.

Misra UK, et al. J Neurol 2012

Lacosamide

Lacosamide

- A functionalized amino acid with anticonvulsant properties
- Mechanism of action
  - A novel dual mechanism of action
    - Selective enhancement of sodium channel slow inactivation
    - Modulation of collapsin response mediator protein (CRMP)-2 activity
- Available 2008, for adjunctive treatment of partial onset epilepsies

Beyreuther et al., 2007

Lacosamide

- Approval from the European Medicines Agency (EMEA) as adjunctive treatment for refractory partial-onset seizures
- IV bioequivalence to the oral formulation
- No sedating effects
- A potent treatment option for RSE
- intravenous (i.v., (10 mg/ml) LCM as an add-on treatment in adult RSE patients

Beyreuther et al., 2007

N	Bolus	Dose/d	Efficacy	Safety	Reference
126 SE+other	400	200-400	67%		Beyreuther. 2007
9 RSE Initiate in 0-14 d (X 2 d)	200	200 mg q 12 h	No	2 angioedema 3 withdrawn	Goodwin H. Neurocriti Care 2011
7 RSE			100% in 24 hours	No AE	Alber JM. Seizure 2011
31/48 SE	200 (200–400)		88% 1st or 2nd -100% 3rd – 81%, 4th+ - 75%	No serious AE 2 skin rash and pruritus	Hofler J. Epilepsia 2011
39 RSE	400 (200-400)		1st-2nd – 3/5 3rd – 11/19 4th+ - 3/15 5 RSE not terminated	No SAE	Kellinghaus C. Acta Neurol Scand 2011
4 NCSE			Good	No AE	Koubeissi MZ,. Acta Neurol Scand 2011
9 RSE		50-100	20% (~ age)		Rantsch K. Seizure 2011
53% of 111 RSE			Good (OR 2.34) Mortality 30% Reduce (OR0.34)	No serious AE	Sutter Rl. NS Drugs2013
136 RSE	200-400 in 3-5 min		56% (76/136)	25% Mild sedation 1 angioedema 1 arrhythmia	Hofler J. Epilepsia 2013

Pregabalin

Pregabalin

- 21 patients with non-convulsive seizures and non-convulsive status epilepticus
- Criteria
  - Effective = terminate seizure within 24h of initiation of PGB without the addition of another antiepileptic agent
- via a nasogastric tube, the 2nd to 4th agent used
- The average initial dose and total daily dose of PGB 342mg

Swisher CB et al. Seizure 2013

Pregabalin

- 11/21 (52%) were responders
  - aborting NCS (9 patients, 82%)
  - Aborting NCSE (2 patients, 18%)
- All patients with hypoxic injury (4) did not respond to PGB
- The responders were noted to have better clinical outcome (64% vs. 9% discharged home)
- Side effect: 2 dizziness and sedation

Swisher CB et al. Seizure 2013

Pregabalin

- 11 SE episodes (10 patients) treated with PGB
- Mostly had refractory, partial SE
- A definite electroclinical response in 5 of 11, already evident 24 h after PGB introduction
  - NB: a possible response (concomitantly with other AEDs) in 3 of 11 of the episodes
- 3/11 did not respond
- Well tolerated

Novy J et al. Epilepsia 2010

Summary (1)

- Identify causes of status epilepticus and address them
- Standard Rx
  - lorazepam, phenytonin, fosphenytoin, valproic acid, phenobarbital
- Anaesthetic agents
  - thiopental, pentobarbital, midazolam, propofol
  - inhalational anaesthetics (isoflurane, desflurane)
- Anti-epileptic drugs
    - topiramate, lacosamide,pregabalin, levetiracetam

Summary (2)

- Other options
  - ketamine: blocks NMDA receptor, which is over-expressed in prolonged SE
  - hypothermia, ketogenic diet
  - magnesium infusion, pyridoxine, steroids and immunotherapy,
  - emergency resective neurosurgery and multiple subpial transection
  - transcranial magnetic stimulation, electroconvulsive therapy
  - vagal nerve stimulation, deep brain stimulation
  - trigeminal nerve stimulation, drainage of the cerebrospinal fluid

Summary (3)
New AEDs in status epilepticus

- Enteral or parenteral
  - Improve outcome, low or non-related side effect
- Evidence based: NO RCT with some publication biases
  - Case reports
  - Case series
  - Retrospective chart review
  - Non randomized open label head-to-head study
  - Randomized open label label head to head (pilot) study
- Third line treatment (add-on treatment), ? 2nd line
- Future direction: ??large control (head-to-head) study

Thank You