Approach to the management of Status Epilepticus

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Definition of SE

- **Epilepsy Foundation of America's Working Group:** a seizure lasting 30 minutes or 2 or more seizures without full recovery of consciousness between episodes
- **Lowenstein et al**: 5 minutes or more of either a continuous seizure or 2 or more discrete seizures between which there is incomplete recovery of consciousness
- **Pre-Hospital Treatment of SE (PHTSE) study:** seizure activity continuing longer than 5 minutes
- **VA Cooperative Trial on Treatment of GCSE:** continuous seizure activity of greater than 10 minutes, or more than 2 seizures without full recovery of consciousness between seizures

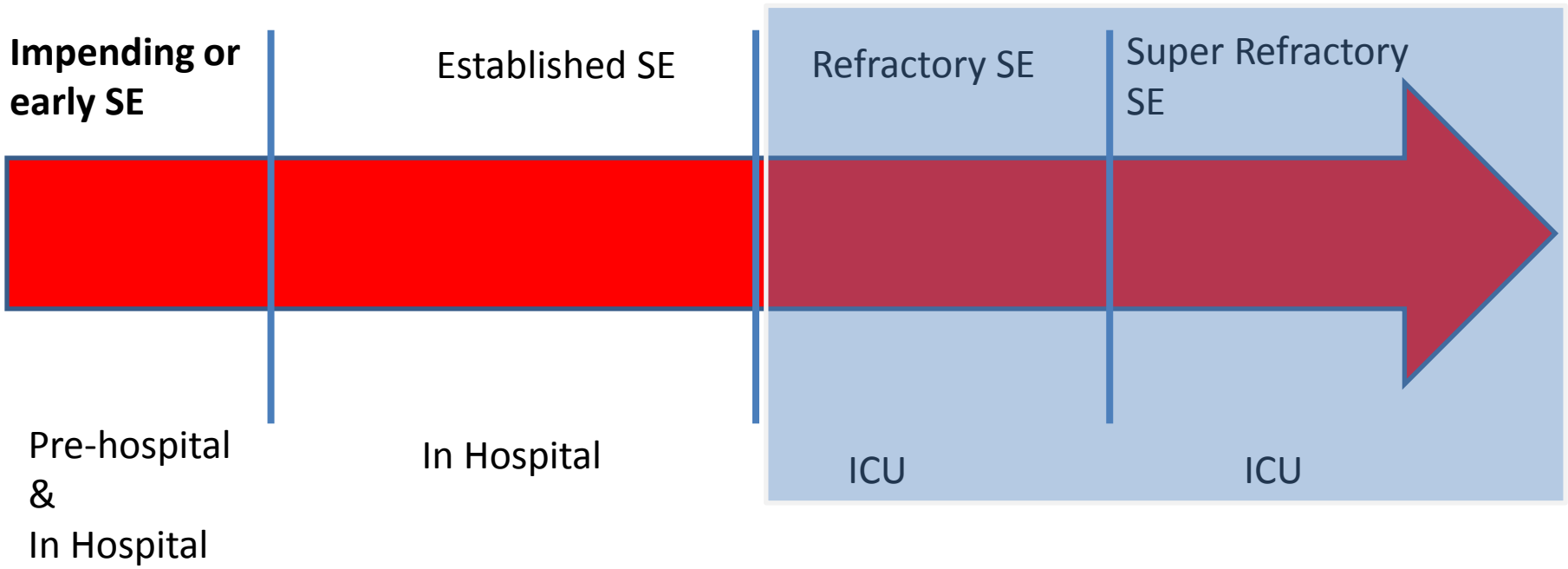
Antiepileptic drugs used in status epilepticus

Drugs	Dose	Side effects
Short acting		
Lorazepam	0.1 mg/kg @ 2 mg/min (adult) rate	Respiratory depression, hypotension, decreased level of consciousness
Midazolam	0.2 mg/kg at 0.2-5 mg/kg	Hypotension, respiratory depression, decreased level of consciousness
Diazepam	0.2 mg/kg at 5 mg/min	Sedation, respiratory depression
Propofol	2 mg/kg at 2-10 mg/kg/h (up to 200 mg/kg/min)	Sedation, hypotension, respiratory depression Infusion syndrome
Ketamine	1.5 mg/kg IV every 5 min maximum dose 4.5 mg/kg	Hypertension, possible raise in intracranial pressure
Paraldehyde	0.8 ml/kg deep IM	Muscle necrosis
Long acting		
Phenytoin	20 mg/kg IV, maximum 50 mg/min	Hypotension, QT prolongation, purple glove syndrome
Phosphenytoin	20 mg/kg at 150 mg/min	Hypotension, cardiac arrhythmia
Phenobarbitone	15-20 mg/kg at 100 mg/min	Hypotension, respiratory depression
Levetiracetam	Up to 20 mg/kg (usually 2 g) over 5-15 min	Mild sedation
Valproate	25-45 mg/kg up to 6 mg/kg/min	Severe encephalopathy if a patient has hyperammonemia or mitochondrial disorder
Lacosamide	400 mg IV over 5 min	No major adverse reaction, but may prolong PR interval

SE = Status epilepticus

Misra et al, AIAN, 2014

Phases of SE


Impending or early SE
Established SE
Refractory SE
Super Refractory SE
Pre-hospital & In Hospital
In Hospital
ICU
ICU

Pre hospital management of SE

- Duration of SE correlate with the refractoriness to treatment
- Treatment of SE: to be initiated as early as possible even before shifting to hospital
- **Midazolam**
  - **Intramuscular**: 5–10 mg adults, 0.15–0.3 mg/kg in children, can be repeated once
  - **Buccal**: instillation of 10 mg can be done by catheter and syringe in children and adults
  - **Intranasal**: 0.2–0.3 mg/kg in a 5 mg/mL ampoule dripped directly into the nostrils, over 3 min in children, over 5 min in adults
- **Non-IV therapy:** may be used where facilities for resuscitation do not exist
  - Options: rectal diazepam, buccal midazolam, or intranasal midazolam

First London colloquium on SE

Midazolam vs. diazepam as Pre hospital Rx

Study	Type	No of patients	Conclusions
McIntyre et al (2005)	Randomised controlled Buccal midazolam (0.5 mg/kg) vs Rectal diazepam (0.5 mg/kg)	177	56% (61 of 109) for buccal midazolam compared with only 27% (30 of 110) for rectal diazepam
Mpimbaza et al (2008)	single-blind randomized trial	330	Buccal midazolam was as well tolerated as and more effective than rectal diazepam in children without malaria.

'Evidence supports the use of buccal midazolam as the first-line treatment of acute tonic–clonic seizures in childhood including convulsive status epilepticus in which intravenous access is unavailable' **2008 cochrane review**

Summary of guidelines – pre hospital management

London colloquium	NICE guidelines
Buccal / nasal midazolam, rectal diazepam	Buccal midazolam – 1st line
	Rectal diazepam if buccal midazolam is unavailable
	Iv lorazepam if i.v. access is established

Initial Management: General measures

- **ABC** of emergency medicine
- **Investigations**
  - Blood gases, glucose, renal and hepatic function, electrolytes
  - ECG
  - AED levels and save serum for future analyses
- **Emergency Rx**
  - Emergency intravenous AEDs
  - IV thiamine/glucose if patient is alcoholic
  - IV glucose if hypoglycaemia is present
  - Maintenance AED
  - Correct metabolic abnormalities if present
  - Pressor support if hypotension is present
  - Correction of respiratory or cardiac failure
- Establish **etiology**: CT etc

Critical care guideline of what should be done in patients with SE

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

Initial management - guidelines

Initial management	EFNS	NICE
Airway	+	+
ABG monitoring	+	+
ECG & BP monitoring	+	+
RBS & biochemical tests	+	+
i.v glucose & thiamine	+	+

Treatment of early tonic-clonic status epilepticus

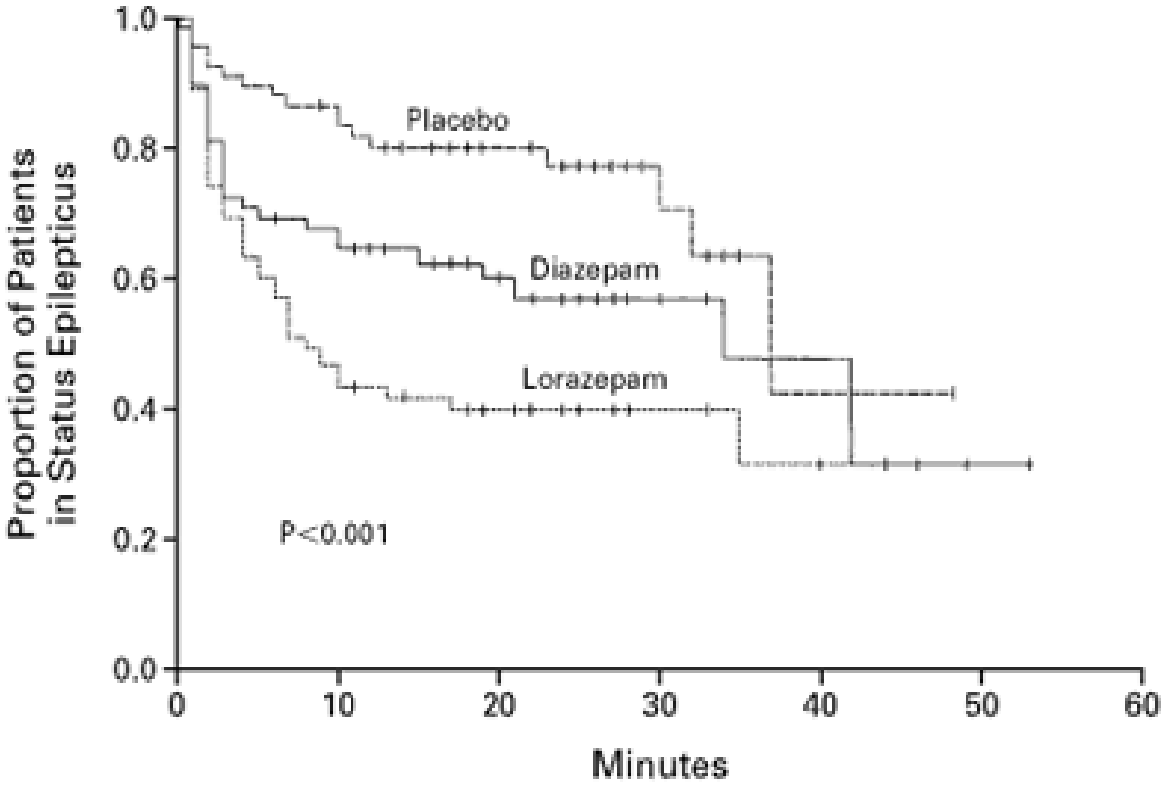
- **Early status epilepticus**
  - defined as the first 5 to 10 minutes of SE
  - initiate treatment with a fast acting benzodiazepine-intravenous lorazepam is the drug of choice
  - The advantage of LZP over DZP or midazolam is its long-lasting clinical effect

Table 1 Drugs used in first stage of tonic–clonic status epilepticus (stage of early status epilepticus: from the consensus document of the workshop of European epileptologists)

	Route of administration	Adult dose	Pediatric dose
Diazepam	i.v. bolus (not exceeding 2–5 mg/min)	10–20 mg	0.25–0.5 mg/kg
	Rectal administration	10–30 mg	0.5–0.75 mg/kg[a]
Clonazepam	i.v. bolus (not exceeding 2 mg/min)	1–2 mg at 2 mg/min[a]	200–500 µg
Lorazepam	i.v. bolus	0.007 mg/kg (usually 4 mg)[a]	0.1 mg/kg
Midazolam	Buccal or intranasal	5–10 mg[a]	0.15–0.3 mg/kg[a]

Stage of early SE: In-hospital IV therapy

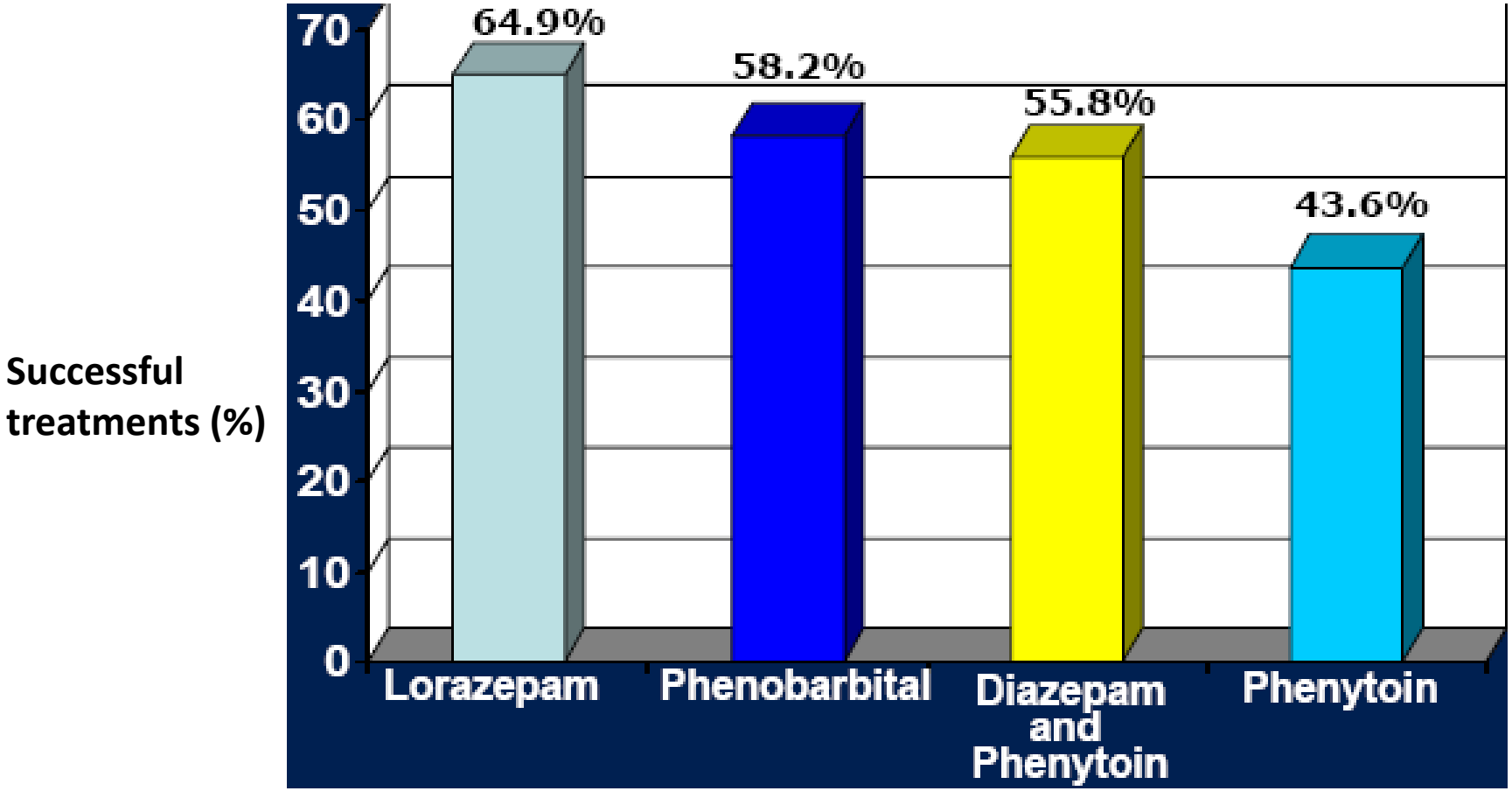
- **The slight advantage of lorazepam over diazepam is well established**



No. at Risk						
Diazepam	68	41	21	8	2	1
Lorazepam	65	29	15	8	2	0
Placebo	67	53	26	10	1	0

Alldredge et al. NEJM 2001 345: 631

Treatment of convulsive SE: VA study



We recommend Lorazepam for the initial treatment,--- although it was no more efficacious than Phenobarbital or than diazepam+phenytoin, it is easier to use

Trieman et al, NEJM, 1998

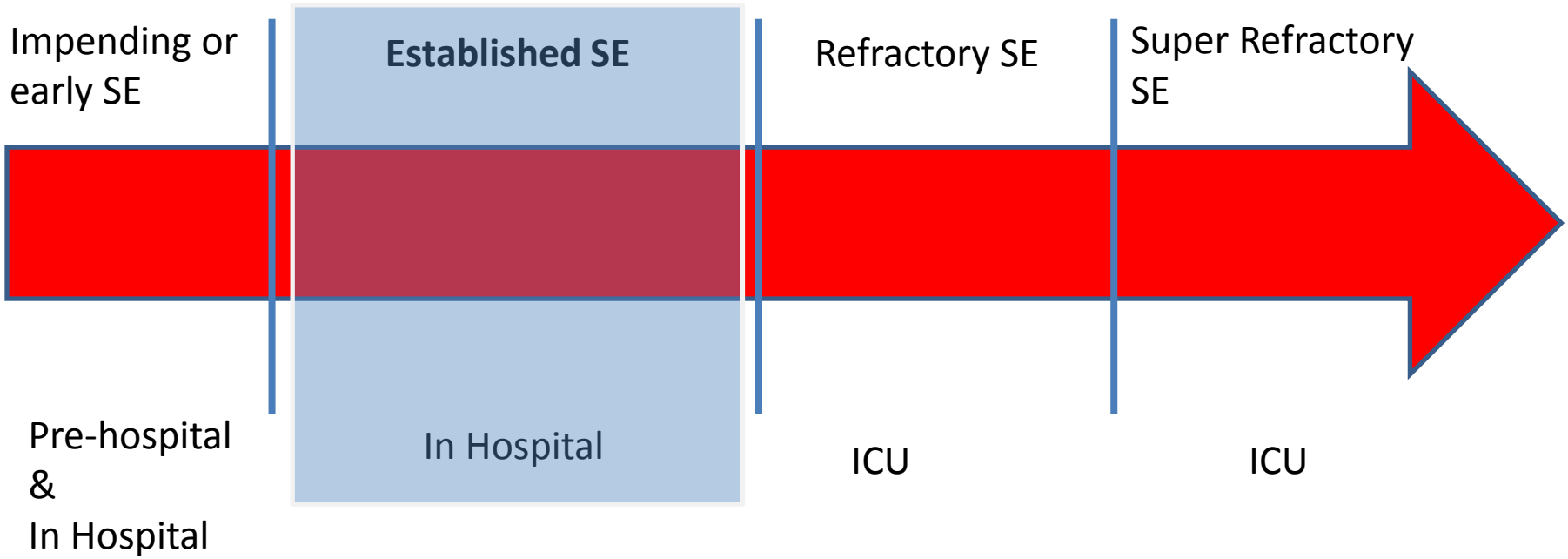
In-hospital IV therapy in early SE

- **In-hospital IV therapy in early SE**
  - Lorazepam vs diazepam — 3 RCTs (n=289)
  - Lorazepam vs placebo — 1 RCT (n=137)
  - Lorazepam vs diazepam/phenytoin — 1 RCT (n=192)
  - Lorazepam vs phenobarbital — 1 RCT (n=188)
  - Lorazepam vs phenytoin — 1 RCT (n=198)
  - Midazolam vs lorazepam — 1 RCT (n=27)
  - Midazolam vs diazepam — 1 RCT (n=40)
  - Diazepam vs placebo — 1 RCT (n=139)
- **Conclusions of related 10 RCTs:**
  - DZP and LZP are better than placebo
  - LZP is better than phenytoin
  - LZP may be better than DZP (2/3 measures)

Summary of guidelines – In hospital treatment

London colloquium	**EFNS**	**NICE**
IV lorazepam – 1st line	IV lorazepam – 1st line	IV lorazepam – 1st line
Diazepam/ clonazepam can be used	Diazepam followed by phenytoin / fosphenytoin	IV Diazepam if lorazepam is unavailable

Phases of SE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Established status epilepticus (30-120 min)

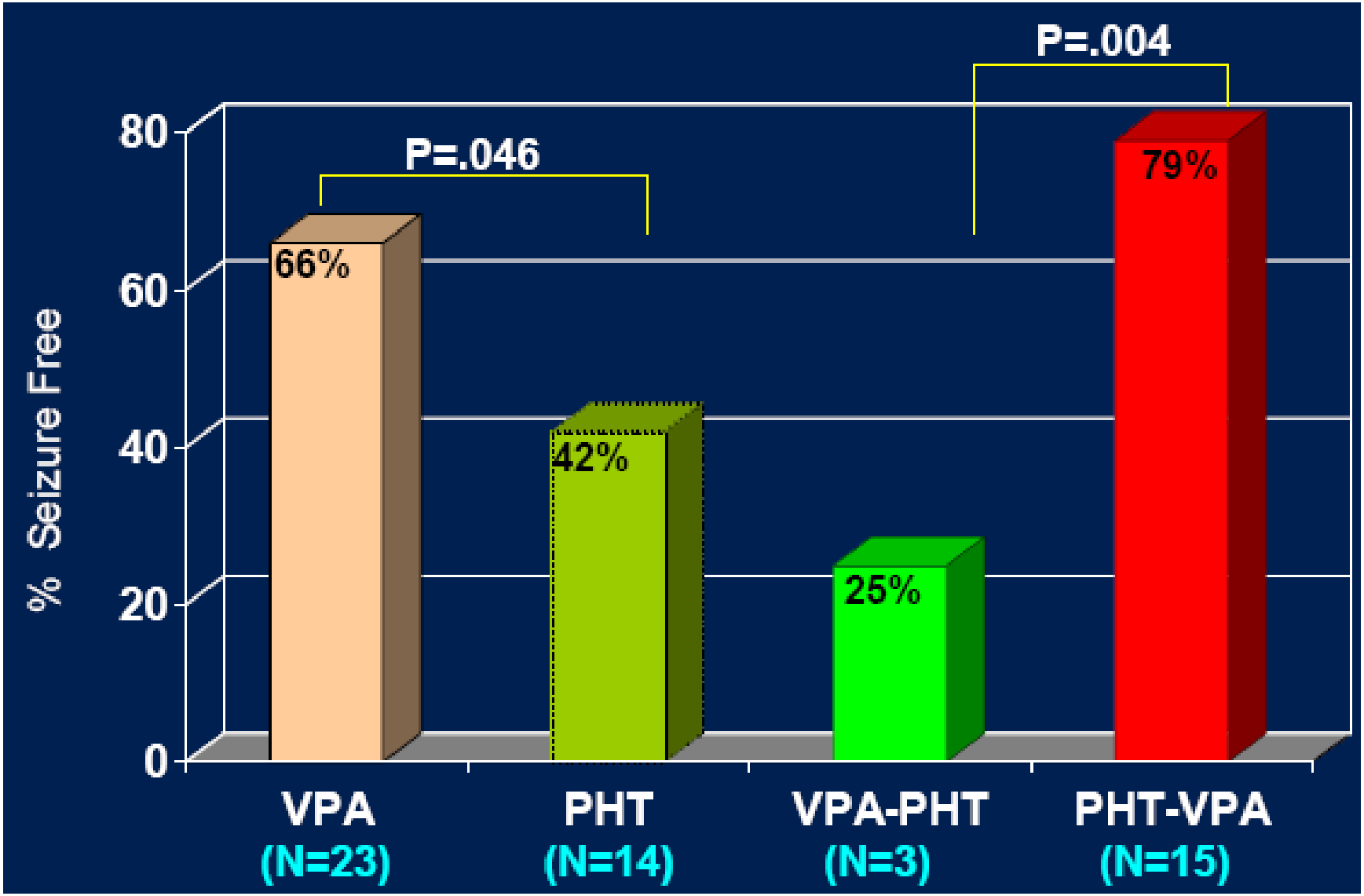
- No adequate studies available that compare different treatment regimens in established status after benzodiazepines (BZPs) have failed
- Conventional AEDs:
  - Phenytoin
  - Fosphenytoin
  - Phenobarbital
- Recent AEDs:
  - Valproate
  - Levetiracetam
  - Lacosamide

Established status epilepticus

Table 2 Drugs used in the second stage of tonic-clonic status epilepticus (stage of established status epilepticus: from the consensus document of the workshop of European epileptologists)

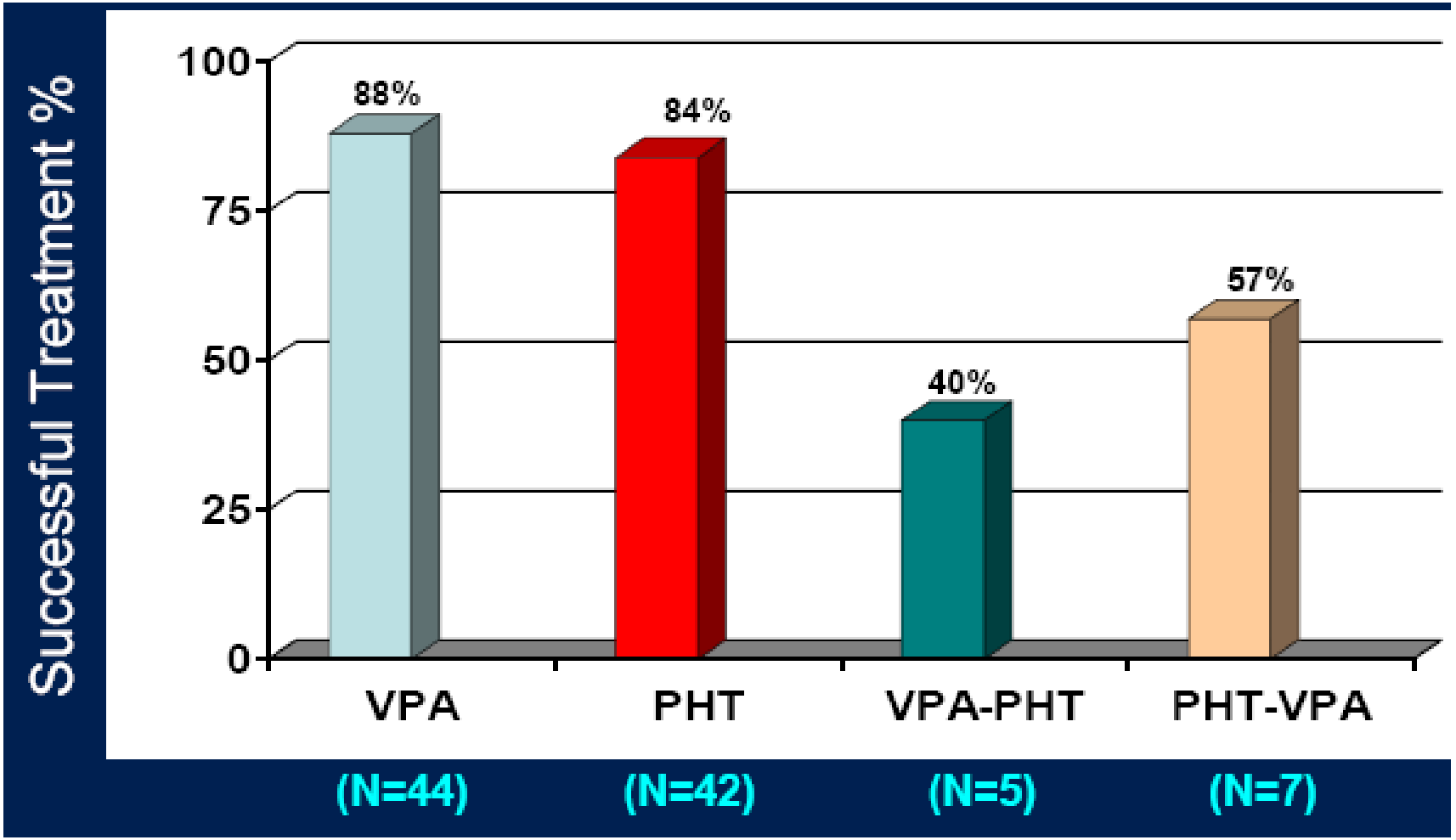
	Route of administration	Adult dose	Pediatric dose
Fosphenytoin	i.v. bolus (not exceeding 100 mg PE/min)	15–20 mg PE/kg	n/a
Levetiracetam	i.v. bolus	Optimal dose not known, most often used 2000–4000 mg	n/a
Phenytoin	i.v. bolus/infusion (not exceeding 50 mg/min)	15–20 mg/kg	20 mg/kg at 25 mg/min
Phenobarbital	i.v. bolus (not exceeding 100 mg/min)	10–20 mg/kg	15–20 mg/kg
Valproate	i.v. bolus	15–30 mg/kg	20–40 mg/kg

Treatment of SE: Valproate vs. Phenytoin



Misra et al, Neurology, 2006

Treatment of SE: Valproate vs. Phenytoin

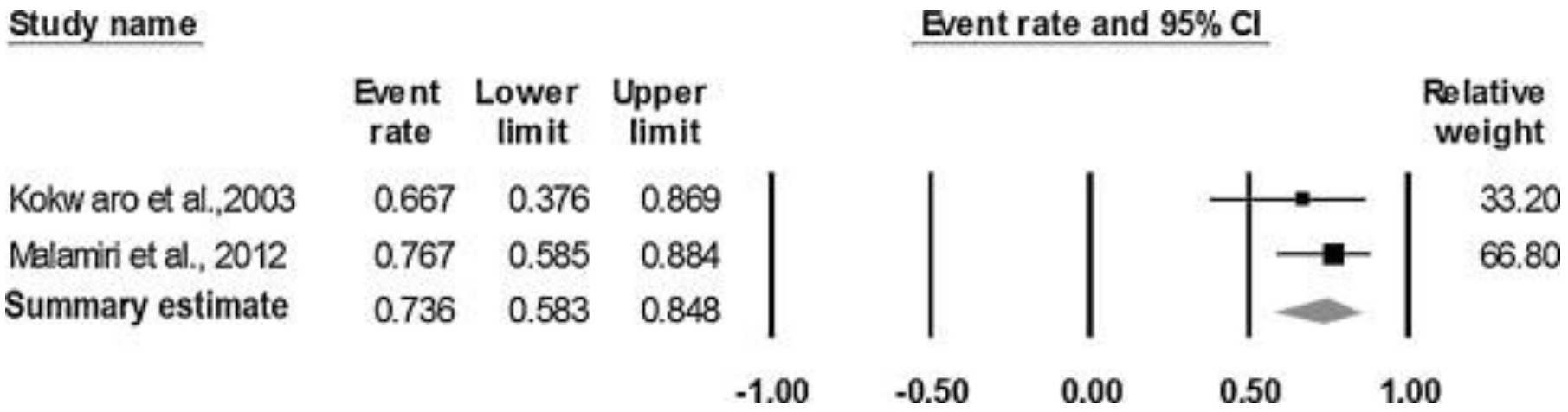


Agrawal et al, Seizure, 2007

Studies of Rx in established SE

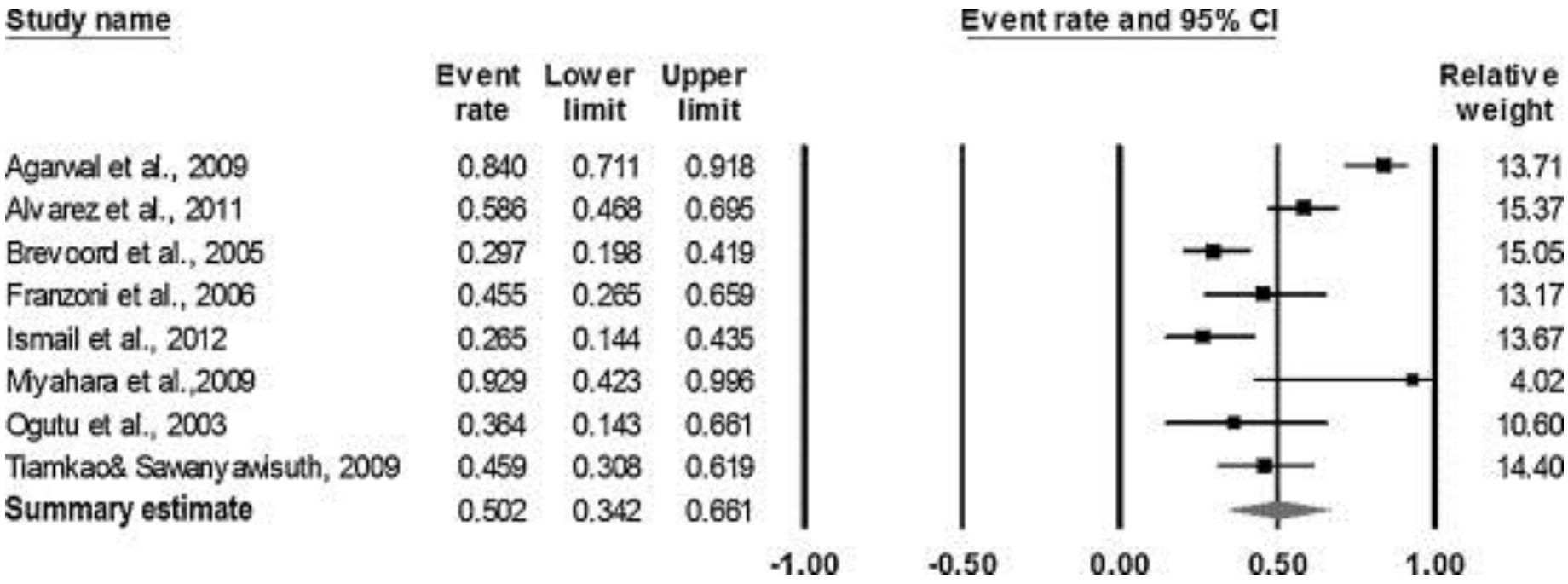
Study	Study design	n	Comments
Misra et al, 2006	RCT to compare the efficacy of VPA and PHT in convulsive SE	68	Seizures were aborted in 66% in the VPA group and 42% in the PHT group.
Misra et al, 2012	open labeled pilot study	79	LEV controlled SE in 76.3% compared to 75.6% with lorazepam with 24 hours seizure freedom
Agrawal et al 2007	Randomized study	98	iv SVA was successful in 88% and IV phenytoin in 84% of patients of benzodiazepine resistant SE
Alvarez et al 2011	Retrospective	70	SVA controlled SE in 74.5%, PHT in 59.6%, and LEV in 51.7% of episodes. LEV was possibly less efficient than VPA to control SE after benzodiazepines

Phenobarbital in established SE



Yasiry & Shorvon. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies. Seizure, Volume 23, Issue 3, 2014, 167 - 174

Phenytoin in established SE



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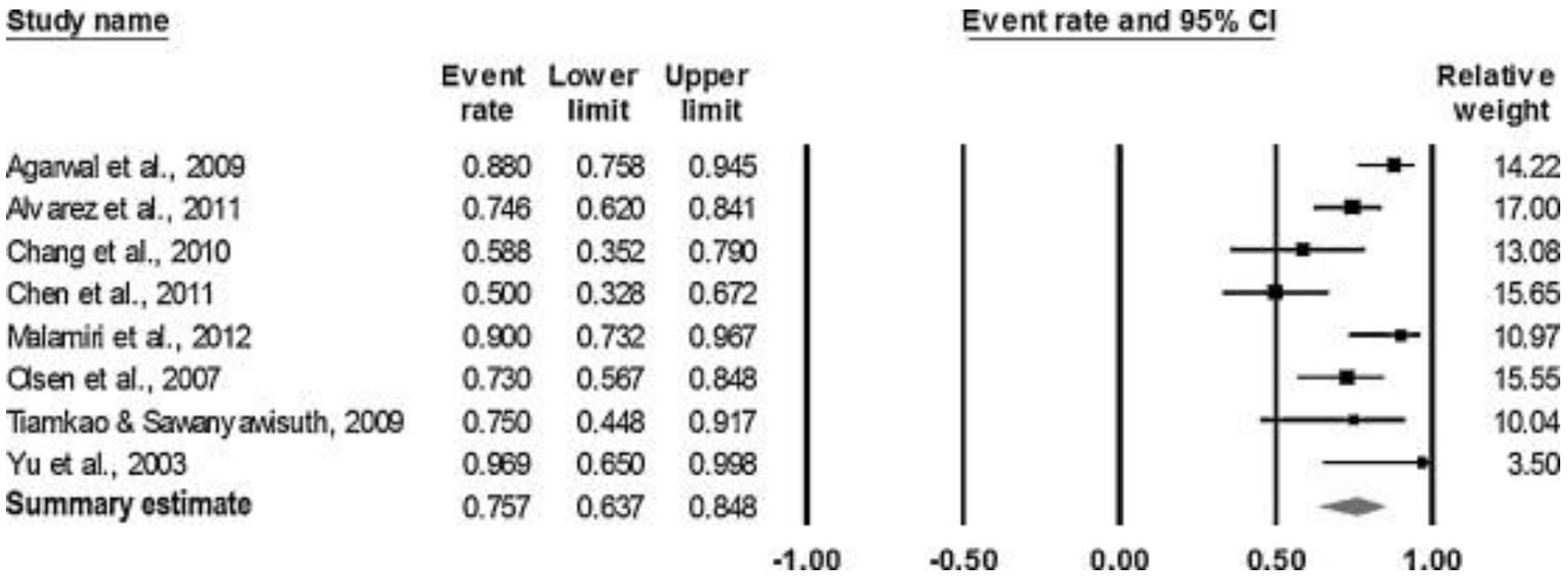
Valproate and SE

- Nine prospective or retrospective series and three randomized open trials published including 633 adults or children
- These studies suggest that intravenous VPA is as effective as PHE/fPHE in resolving SE in patients who have previously failed conventional first-line therapies such as BZPs.
- Success rate between 60% and 83% have been reported
- Intravenous VPA with intravenous PHE as first-line treatment: favor intravenous VPA (66% vs. 42%) (Misra et al., 2006)

Valproate in established SE



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Levetiracetam and SE

- Several studies: nonrandomised, uncontrolled retrospective case series
- Comparison of phenytoin, valproate, and levetiracetam (Alvarez et al, 2011)
  - Retrospective study
  - LEV seems less efficient than VPA/PHT to control SE after benzodiazepine
- Overall success rate in these studies was 81.6%
- First London Colloquium on Status Epilepticus, is listed intravenous LEV as a ‘‘treatment option for the stage of established SE’’(Shorvon et al., 2008)
- Somnolence, rash, thrombocytopenia, and paradoxical agitation have been noted with levetiracetam, but respiratory depression and hypotension are not present
- An additional advantage of levetiracetam is the presence of very limited drug-drug interactions owing to its lack of CYP450 metabolism

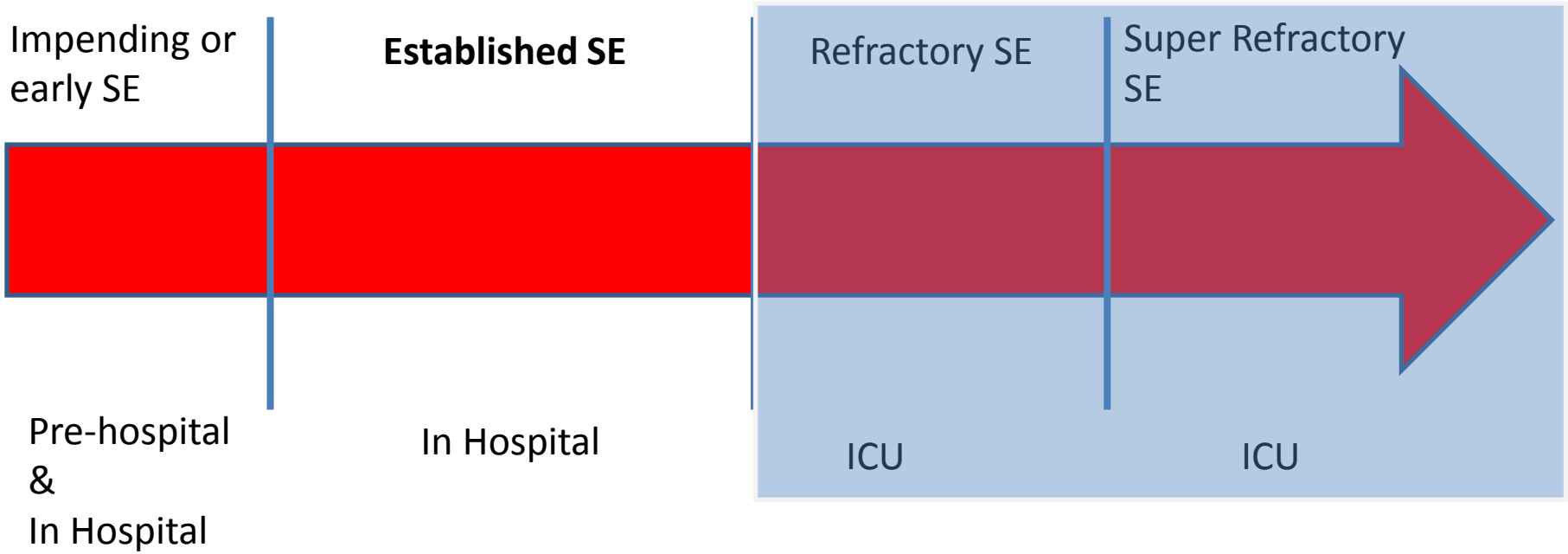
Lacosamide and SE

- Inactivation of voltage-dependent sodium channels
- Eleven reports (5 case reports and 6 case series)
- Successful termination of status epilepticus in a majority of these reports
- Two recent studies had success rates of 44% to 100%
- Santamarina et al (2013): 67% (n=92) of patients with focal motor or non-convulsive SE responded to lacosamide

Summary of guidelines – In hospital treatment

London colloquium	EFNS	NICE
IV phenytoin/ fosphenytoin – 1st line	IV phenytoin / fosphenytoin – 1st line	IV phenytoin/ fosphenytoin – 1st line
IV phenobarbital	IV phenobarbital	IV phenobarbital
IV valproate/ levetirecetam - alternatives		

Phases of SE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Stage of refractory status epilepticus

- Defined as SE that continues despite treatment with benzodiazepines and one AED: 23–43% of patients with SE
- Mortality after RSE is about three times higher than for non-refractory SE
- The conventional choice (as described in the European consensus document) is between thiopental (or pentobarbital), propofol and midazolam.
- There are no published controlled data on their effectiveness

Stage of refractory status epilepticus

- Before starting coma-inducing therapy rule out
  - NEAD/pseudoseizures
  - Movement disorders
- The overall aggressiveness of treatment depends on the type of SE
- GCSE should be treated aggressively in view of the danger of systemic and neurological injury with ongoing seizures
- NCSE without noticeable impairment of consciousness can usually be treated more conservatively

Drugs and dosages in RSE

	Loading dose	Maintenance dose	Comments
Midazolam	0·2 mg/kg	0·2–0·6 mg/kg per h	Increasing doses needed with time
Propofol	2 mg/kg	2–5 mg/kg per h, in some cases can be raised to 10 mg/kg per h	Attention to PRIS, especially in young children; combine with benzodiazepines
Barbiturates	Thiopental: 1–2 mg/kg Pentobarbital: 5 mg/kg	Thiopental: 1–5 mg/kg per h Pentobarbital: 1–5 mg/kg per h	Both need loading with repetitive boluses and have long wash-out times

PRIS=propofol infusion syndrome.

Table 1: **Anaesthetic agents for refractory status epilepticus**[5,53,56]

Choice of anaesthetic agents

- Midazolam is mostly used initially
  - Advantages- short half life, antidote available for reversal
  - Disadvantage: tachyphylaxis
- Propofol
  - Advantages: short half-life, allows rapid titration and withdrawal, broad spectrum
  - Disadvantages:
    - propofol infusion syndrome
      - due to impairment of mitochondrial activity
      - fatal cardiocirculatory collapse with lactic acidosis, hypertriglyceridaemia, and rhabdomyolysis
      - In RSE as 7% (fatal) and 38% (non-fatal)

Choice of anaesthetic agents

- Thiopentol: long half life
- A meta-analysis of the use of barbiturates, propofol, or midazolam in RSE
  - did not show any significant difference in short-term mortality,
  - immediate effectiveness (favouring barbiturates)
  - tolerability (favouring midazolam and propofol).

EEG Monitoring

- Initial course targeting EEG burst suppression patterns with an inter burst interval of about 10 s for 24 h, followed by progressive tapering over 6–12 h

- Triphasic waves are often recorded during anaesthetic tapering, and not every sharply contoured EEG transient should be a cause for concern, but rather the focus should be on definite seizure patterns

Other treatments

	Advantages	Disadvantages/comments
Isoflurane[71]	Fast acting	Possible neurotoxicity Needs closed system, ie, gas recovery
Ketamine[72–75]	NMDA receptor antagonist	Possible neurotoxicity; combine with benzodiazepines
Lidocaine[76,77]	Can rescue phenytoin-resistant refractory status epilepticus	Cardiac monitoring needed; possible seizure induction
Verapamil[78,79]	Safe	Does not have antiepileptic drug action; might improve availability of antiepileptic drugs in CNS
Magnesium[80]	Can enhance NMDA receptor blockade	Possible induction of neuromuscular blockade
Ketogenic diet[81,82]	Safe	Need skilled dietician; check for ketonuria
Immunological treatments[83]	Can act causally	Formal exclusion of infection needed before treatment

Table 2: **Other pharmacological and nutritional treatments for refractory status epilepticus**

Non pharmacological treatments in RSE

	Advantages	Disadvantages/comments
Resective surgery[101]	Can act causally	Not appropriate in multifocal status epilepticus; need for skilled interdisciplinary team; surgical risks
Vagal nerve stimulation[102]	Appropriate for long-term use	Invasive procedure; cardiac arrhythmias rarely reported
Repetitive transcranial magnetic stimulation[103]	Non-invasive procedure	Possible seizure induction; need for sustained treatment
Electroconvulsive treatment[104,105,106]	Non-invasive procedure	Need for skilled interdisciplinary team; possible seizure induction
Mild hypothermia[107]	Acts on several pathophysiological mechanisms	Usually only transitory control; avoid barbiturates (ileus)
Classical music[108]	No known side-effects	Based on one case series

Table 3: **Non-pharmacological options for refractory status epilepticus**

Super refractory status epilepticus

- Definition: SE that continues or recurs 24 h or more after the onset of anaesthetic therapy, or recurs on the reduction or withdrawal of anaesthesia
- 15% of all the cases with status epilepticus admitted to hospital will become super-refractory
- Establish the cause of the status epilepticus
- Common: a severe brain insult (e.g. trauma, infection and stroke),
- Uncommon
  - immunological disorders;
  - mitochondrial disorders;
  - uncommon infectious diseases;
  - drugs or toxins;
  - uncommon genetic diseases
  - NORSE

Common reasons for treatment failure

- Inadequate drug treatment
- Failure to initiate or continue maintenance antiepileptic drug therapy.
- Medical factors can exacerbate seizures
- Failure to treat (or identify) the underlying cause
- Misdiagnosis common problem is to fail to diagnose pseudostatus
- **Failure recognize NCSE**

Non Convulsive SE – diagnostic criteria

- Any pattern that last at least 10 s that satisfy any one of the following three **Primary criteria**:
- Repetitive generalized or focal spikes, sharp waves, spike-and-slow-wave or sharp-and-slow-wave at > 3/s
- Repetitive generalized or focal spikes, sharp waves, spike-and-slow-wave or sharp-and-slow-waves at <3/s along with secondary criterion
- Sequential rhythmic, periodic, or quasi-periodic waves at >1/s and unequivocal evolution in frequency, morphology, or location

  (Change in amplitude alone or change in contour of sharpness alone without change in other features of morphology is not sufficient)

Consensus document – First London colloquium on SE
- Pediatric SE

- *Stage of early status (stage 1)*
- There is universal consensus that a benzodiazepine should be used as a drug of choice in treatment of a prolonged seizure or in early SE in children (including febrile SE)
- The therapy follows similar lines to that in adults

IV sodium valproate is not preferred in children under age 2 or children with metabolic disorders at any age

Consensus document – First London colloquium on SE

- Pediatric SE

- *Stage of established SE (stage 2)*
- Insufficient evidence on the relative advantages and disadvantages of different therapies in children
- IV valproate is unlikely to be used in the de novo acute situation in view of the risk of metabolic disease
- In addition, due to possibility of extravasation injury, phenytoin is not preferred
- There is no evidence of superiority of fosphenytoin against phenobarbitone or levetiracetam
- All 3 can be used

Consensus document – First London colloquium on SE

- Pediatric SE

- *Stage of refractory SE (stage 3)*
- As in adults, there is a clear need to decide when to proceed to anesthesia and which anesthetic to use
- This will again depend on experience and tradition
- There is also a need for statement with regard to EEG monitoring.

IV propofol is avoided because of the risk of multi organ failure and the propofol infusion syndrome

SE liver disease

- Seizures and SE usually develop in stages III to IV
- Increase in ammonia levels / excitatory neurotransmitters deriving from intestinal amines and by-passing the liver
- **Wilson's disease** rarely causes seizures- gliosis, B6 deficiency
- **Porphyria**: Gabapentin or levetiracetam may be helpful
- **HELLP sydrome:** Termination of pregnancy and use of magnesium sulfate to prevent seizures are indicated
- AED serum levels altered - due to impaired metabolism/ decreased serum protein binding
- Important to know the inductor/inhibitor profile of each AED

SE & liver disease

Treatment

- low protein diet and lactulose or neomicin
- Raised ICP - hyperventilation & mannitol
- Barbiturate sedation and hypothermia can be employed
- Phenytoin/benzodiazepines - ineffective & to be avoided
- Avoid valproate - hepatic encephalopathy and Reye's syndrome
- Preferred AEDs – levetiracetam, gabapentin, lacosamide

SE & Renal failure

- **Reasons:**
  - Due to accumulation of toxic organic acids
  - Malignant hypertension
  - Reversible posterior leukoencephalopathy syndrome
  - Subdural and intracranial haemorrhage
  - Sepsis
  - Glucose, electrolytic and acid-basic disturbances
- **Rx:** Adequate renal failure management, including hypertension control, volume control and renal replacement therapy
- **AEDs of choice**:
  - More lipophylic high protein bound AEDs like **carbamazepine, phenytoin, lamotrigine, benzodiazepines and valproate** - little affected by renal disease
  - Benzodiazepines for myoclonic seizures, convulsive and non-convulsive partial complex or absence status epilepticus
  - Ethosuximide for absence status epilepticus
  - Phenytoin and phenobarbital for convulsive status epilepticus
  - Acute tubular necrosis & Fanconi's syndrome following sodium valproate use rarely reported

Status epilepticus in patients with HIV

- Protocol for management of SE is same as per usual protocol
- Newer AEDs such as levetirecetam and Lacosamide and clobazam that do not induce the hepatic cytochrome P450 oxidase system are preferable

Status epilepticus & Neurosurgery

- No specific guideline
- Head Injury: Like SE in adults
- Post-operative: De novo SE vs. on AEDs
- ICU: non-convulsive SE
- Raised ICP due to mass and SE: Herniation

Guidelines for status epilepticus in India

- Premonitory stage
- Rectal diazepam (10 mg) or buccal midazolam (10 mg)
- 1st stage
- Lorazepam (0.1mg/kg) or diazepam (0.2 mg/kg) iv – can repeat once after 5 min
- Established GCSE
- Phenytoin 15 – 20 mg/kg or fosphenytoin 15 – 18 mg/kg iv

IES

Guidelines for status epilepticus in India

- If seizures continue even after 10 min of phenytoin loading
- Phenytoin 5-10 mg/kg or fosphenytoin 5 mg/kg iv
- If seizures still continue
- Option 1 – sodium valproate 25 – 35 mg/kg iv at rate of 6 mg/kg/hr
- Option 2 – phenobarbital 20 mg/kg iv at 60 mg/min

IES

WFN guidelines for management of SE in resource poor countries

- Ensure ABC; quick physical examination for causes & comorbidities
- If a patient is already receiving AED that should be restarted through NG tube unless contraindicated because of frequent seizures
- IV line is maintained with NS & rapidly acting AED (diazepam, **lorazepam** or midazolam) may be administered. 25% glucose (1 ml/kg with 100 mg thiamine) is administered. If the seizures continue after 5-10 min, repeat it
- Blood is collected after the IV line for cell counts, malarial parasite and serum chemistry.
- Respiratory rate is 8 bpm (10 bpm in children): 3rd dose of short acting AED is administered and is prepared to administer a long acting AED.
- Respiratory rate is <8 bpm (10 bpm in children): administer long-acting AED
- Respiratory rate is <4 bpm: delay administration of long-acting AED for 30 min and provide supplementary oxygen and artificial manual breathing unit ventilation
- Pregnant females with eclampsia: MgSO4 2 g IV & continuous infusion of 2 g/h in 5% dextrose. Tendon reflexes - to monitor magnesium dosage - maximum dose of MgSO4 is 40 g/24 h.
- Investigate for possible cause: malaria, meningoencephalitis, alcohol or AED withdrawal.
- Quinolones, 3rd generation cephalosporins, cefepime and carbapenem can result in seizure

Engel J, Birbeck GL, Diop AG, Jain S, Palmini A, editors. Epilepsy: Status Epilepticus Global Issues for the Practicing Neurologist WFN Seminars in Clinical Neurology. Vol. 2. New York: Demos; 2005. p. 77-82.

Cochrane Review

Anticonvulsant therapy for status epilepticus

Prasad et al, Cochrane Database of Systematic Reviews 2005, Issue 4

- Eleven studies with 2017 participants were included
- **Lorazepam is better than diazepam or phenytoin alone** for cessation of seizures and carries a lower risk of continuation of status epilepticus requiring a different drug or general anaesthesia. Both lorazepam and diazepam are better than placebo for the same outcomes
- Treatment of premonitory seizures: diazepam 30 mg in an intrarectal gel is better than 20 mg for cessation of seizures without a statistically significant increase in adverse effects.
- Universally accepted definitions of premonitory, early, established and refractory status epilepticus are required.

Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children

Appleton et al. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews 2008, Issue 3

- The conclusions of this update have changed to suggest that intravenous lorazepam is at least as effective as intravenous diazepam and is associated with fewer adverse events in the treatment of acute tonic-clonic convulsions.
- Where intravenous access is unavailable there is evidence from one trial that buccal midazolam is the treatment of choice

SE: an approach

Buccal/nasal midazolam or rectal diazepam ← Pre-hospital management

iv Lorazepam (0.1 mg/kg) ← Impending SE

iv Phenytoin (20 mg/kg)
or
iv fosphenytoin (15-20 mg/kg)

iv Valproate (20-30 mg/kg)

iv Levetiracetam (20 -30 mg/kg)

Lacosamide? ← Established SE

Early Refractory SE

ICU, Anesthetics etc ← Refractory & Super-refractory SE

iv BZD f/b others ← NCSE

Special Situations and SE

Pregnancy
Eclampsia - MgSO4

Elderly
Avoid Phenytoin

Liver
Levetiracetam/Lacosamide

Neonates
Phenobarbitone

Children
BZD followed by Fosphenytoin, phenobarbitone, levetiracetam

HIV
Levetiracetam
Lacosamide