Future Perspectives in the Management of Refractory Status Epilepticus

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Paracelsus Medical University
Disclosure

• E Trinka has acted as a paid consultant to Eisai, Medtronics, Bial, and UCB.
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• speakers’ honoraria from Bial, Cyberonics, Desitin Pharma, Eisai, Gerot, Böhringer-Ingelheim, Sanofi, Medis, and UCB.
Disclaimer

• This presentation may discuss unlicensed indications and/or use and/or products, including off-label use for the treatment of different forms of status epilepticus
• Licensed information may vary by country
• Always refer to the prescribing information in your country before prescribing any drug
Learning Objectives

• To learn the emerging treatment options in refractory SE and to understand their mechanism of action.
• To learn tailoring treatment along algorithms in refractory SE
Outline

• Outcomes of refractory SE (RSE) with current treatments
• Future strategies
  – Earlier treatment with established drugs
  – Rational polytherapy in SE
  – Emerging treatment options with new drugs
  – New drugs on the horizon
• Treatment algorithm for superrefractory SE
• Conclusion
Clinical course of convulsive status epilepticus

Stage 1
- Early phase
- Premonitory SE, impending SE

Stage 2
- Established SE

Stage 3
- Refractory SE: SE, that continues despite stage 1/2 treatment
- Subtle SE, stuporous SE\(^1,2\)

Stage 4
- Super-refractory SE\(^1\): SE, that continues despite treatment with anaesthetics > 24 hours

Unmet needs in the treatment of status epilepticus

• Current standard IV AEDs fail to control
  – 40% of patients in early status, and
  – 80% of patients in advanced status
• High degree of toxicity:
  – Hypotension, idiosyncratic adverse reactions
  – Non-linear pharmacokinetics of some standard AEDs
• Limited knowledge on pharmacokinetic properties of AEDs
  – With intact or disrupted blood-brain barrier
• No disease modification
  – Antiepileptogenesis?

Alldredge BK et al. NEJM 2001;345:631-7
Treiman DM et al. NEJM 1998;339:792-8
Trinka E and Shorvon S. Epilepsia 2009;50 Suppl 12:1-2
Trinka E. Epilepsia 2011
Staged approach to the treatment of Status epilepticus

Stage 1
- **Lorazepam**
  - $0.1\text{mg/Kg}$, $2\text{mg/min}$

Stage 2
- **Phenytoin**
  - $15-20\text{mg/Kg}$, $50\text{mg/min}$
- **Valproate***
  - $20-30\text{mg/Kg}$, $10\text{mg/Kg/min}$
- **Levetiracetam***
  - $30-70\text{mg/Kg}$? $500\text{mg/min}$?
- **Phenobarbital**
  - $20\text{mg/Kg}$, $100\text{mg/min}$
- **Lacosamide***
  - $5-6\text{mg/Kg}$? $40-80\text{mg/min}$?

Stage 3
- **Midazolam**
  - $0.2\text{mg/Kg Bolus}$, $0.1-0.4\text{mg/Kg/h}$
- **Propofol**
  - $3-5\text{mg/Kg Bolus}$, $5-10\text{mg/Kg/h}$
- **Thiopental**
  - $2-3\text{mg/Kg Bolus}$, $3-5\text{mg/Kg/h}$

**Modification after:**
- Trinka Nervenheilkunde 2007, Shorvon, Baulac, Cross, Trinka and Walker for the ILAE Task force on SE, Epilepsia 2008
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Mortality in status epilepticus by duration

Survival curves for prolonged and non-prolonged seizure duration. Data are presented as percent survival based on a 30-day follow-up period.

Length of Seizure
- >1 h
- <1 h

% Survival

Days

N=253

Towne et al. Epilepsia 1994;35:27-34
Randomized, doubleblind, phase 3, noninferiority clinical trial
N=883
IM MDZ (5-10mg) vs IV LZP (2-4mg)

Silbergleit et al. NEJM 2012
Randomized, doubleblind, phase 3, noninferiority clinical trial N=883
IM MDZ (5-10mg) vs IV LZP (2-4mg)

Time to active treatment
IM 1.2 min vs IV 4.8 min

Onset of action
IM 3.3 min vs. IV 1.6 min

Earlier treatment improves prognosis of early SE

Does earlier treatment prevent the development of RSE?
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Trousseau, 1867: “In the status epilepticus, when the convulsive condition is almost continuous, something special takes place which requires an explanation”
GABAergic AEDs in the early phase of SE: BDZ, PB

After GABAergic failure and maladaptive changes:

Antiglutamatergic AEDs: KET, TPM, NS-1209, PER², TAL³, GYKI 52466⁵

AEDs with other modes of action: LEV, LCM, PHT, VPA

Experimental evidence: LEV

Effects of LEV on self-sustaining status epilepticus (perforant path stimulation)\(^1\)

- Pretreatment with LEV IV reduced (30mg/kg) or prevented (50–100mg/kg) the development of SSSE
- 200mg/kg diminished and 500mg/kg or above aborted established SSSE

Mono- versus polytherapy in the treatment of status epilepticus

- Preclinical data are in favor of rational polytherapy in SE → translational gap
- Clinical trials in add on design e.g.:
  - BDZ+PBO vs BDZ+AED
  - BDZ+AED1 vs BDZ+AED2
- Choice of drugs: LEV, LCM, VPA, PHT, KET, PER, ...
- Proof of principal trials are needed
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Lacosamide$^{1,2}$

- Functionalized amino acid structurally related to D-serine
- Enhances slow inactivation of VGSC
- No effect on fast acting VGSC (unlike PHT)

- LCM has a broad spectrum of activity profile in animal models$^2$
  - focal seizures: Hc and Am kindling, 6Hz psychomotor seizures, MES
  - generalized seizures: WAG/Rij rats
  - Status epilepticus: SSSE and cobalt homocysteine model
- Water soluble
- Linear PK and low potential for interactions

Experimental evidence: LCM

Effects of IP LCM on self sustaining status epilepticus (perforant path stimulation)\(^1\)

- LCM 3, 10, 30, or 50mg/kg 10 min (early) or 40min (late) after PP stimulation
- Early treatment significantly reduced acute seizures
- Reduced the number of spontaneous seizures after 6 wks by 70% at 50mg/kg
- Reduction of spikes and time spent in seizures

1: Wasterlain et al. Epilepsy Res 2004
Experimental evidence: LCM

Effects of IP LCM on self sustaining status epilepticus (perforant path stimulation)\(^1\)

- LCM 3, 10, 30, or 50mg/kg 10 min (early) or 40min (late) after PP stimulation
- early treatment significantly reduced acute seizures and
- reduced the number of spontaneous seizures after 6 wks by 70% at 50mg/kg
- Reduction of spikes and time spent in seizures

LCM is efficaceous in the SSSE, but loses when administered late

\textit{“its potential for disease modification in this rat model of SSSE will require further studies”}

1: Wasterlain et al. Epilepsy Res 2004
IV Lacosamide: safety studies

1. PBO controlled safety trial with patients with focal epilepsy → switch from oral to IV LCM for 2 days using 60- and 30-min infusions at doses of 200–600 mg/day

2. 160 pts. with epilepsy and LCM treatment 200-800mg over 10, 15 and 30 min
• progressively increased infusion rates → 800mg over 15 min (@53.3 mg/min)
• Well tolerated; no increase of AEs with faster infusion rates, no EKG changes

BUT: data in the 700-800mg over 15 min group are restricted to n=7

IV Lacosamide: safety studies

Open label multicenter trial
Patients with 1-2 AEDs (n=100, 16-60yrs)
IV loading with 200mg, 300mg, 400mg LCM over 15 min followed 12h later by PO LCM (50% of loading dose)

→ 400mg less well tolerated (TEAEs) than 300mg and 400mg
→ Small increase of PR from baseline at end of infusion (6.1, 8.6, 10.6ms)
→ No prolongation of QTcF interval

<table>
<thead>
<tr>
<th>Assessment time</th>
<th>Statistics</th>
<th>LCM 200 mg (n = 25)</th>
<th>Combined LCM 300 mg (n = 50)</th>
<th>LCM 400 mg (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) (µg/ml)</td>
<td>3.193 12.130</td>
<td>0.683 16.017</td>
<td>4.779 23.133</td>
</tr>
<tr>
<td></td>
<td>Min, Max (µg/ml)</td>
<td>2.927 1.276</td>
<td>3.243 1.162</td>
<td>4.500 1.625</td>
</tr>
<tr>
<td>Day 1/Evening predose</td>
<td>n=23</td>
<td>1.612 7.674</td>
<td>1.108 8.154</td>
<td>2.843 8.794</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) (µg/ml)</td>
<td>2.247 1.276</td>
<td>3.844 1.730</td>
<td>4.917 1.499</td>
</tr>
<tr>
<td></td>
<td>Min, Max (µg/ml)</td>
<td>1.794 9.091</td>
<td>1.610 11.067</td>
<td>3.384 9.026</td>
</tr>
</tbody>
</table>

*Pharmacokinetic set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned cohort.

*Combined cohort = cohort 2 and repeat cohort (300-mg LCM).

1: Fountain et al. Epilepsia 2012
IV Lacosamide adverse events

• Studies for approval of LCM for treatment of painful neuropathy\(^2\)
  → 1 report of atrial fibrillation correlate with LCM administration

• 1 Case report\(^3\) : 89-year-old woman –
  Medical history: heart insufficiency, arterial hypertension, hypothyroidism.
  NCSE: → LCM 400 mg within 6 hours
  Normal PQ interval before and after the first dose of LCM
  → reversible complete AV block approximately 30 minutes after the second bolus
  → caution when using high doses of LCM in patients with significant cardiac diseases

IV Lacosamide in Status Epilepticus$^{1-3}$

- Overall **126 patients** with different types of SE treated with LCM
- Success rate 84/126: **66.7% [95%CI 58.4-74.9]**
- Most often used bolus: **400mg** (range 50-400mg)@ 40-80mg/min
- No obvious CNS depressant effect, no hypotension, no ECG changes
- Angioedema (n=2), skin rash (n=1)

Open issues:
- Optimal bolus dose and rate not explored → safety in high dose/high rate
- EEG response not well determined
- Relationship serum concentration and CSF/brain unknown
- Clear order effect
- → Place in the treatment algorithm stage II or add on stage I
- → RCT is needed

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  – New drugs on the horizon

• Treatment algorithm for superrefractory SE

• Conclusion
Translation of laboratory findings to clinic in the treatment of SE – a mission impossible?\textsuperscript{1,3}

- How to get first a compound from experimental laboratory to clinic?
- “Novel” drugs are those AEDs for which an IV formulation becomes available?
- CounterAct: preclinical trials in primates and safety data
- Validation of preclinical SE models with currently available drugs\textsuperscript{2,3}
- Disease modifying treatments after a brain insult\textsuperscript{3}
- Biomarkers and surrogate endpoints\textsuperscript{3}

\textsuperscript{1}: Pitkänen and Wasterlain Epilepsia 2009; \textsuperscript{2}: Baulac and Pitkänen Epilepsia 2009; \textsuperscript{3}: Galanopoulou et al. Epilepsia 2012
New drugs on the horizon

- SPD
- Stiripentol
- Perampanel
- GYKI 52466
- NS 1209
New drugs on the horizon

- SPD is a one-carbon homolog of valnoctamide (VCD)
- Benzodiazepine-resistant SE induced by pilocarpine (rats) and soman (rats and guinea pigs)

Table 1. SPD anticonvulsant activity (in comparison to valnoctamide-VCD) in various mouse (ip) and rat (po) models for epilepsy

<table>
<thead>
<tr>
<th>Anticonvulsant test</th>
<th>SPD-ED$_{50}$ (mg/kg)</th>
<th>95% confidence interval (mg/kg)</th>
<th>VCD-ED$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frings audiogenic seizures</td>
<td>20</td>
<td>18–22</td>
<td>–</td>
</tr>
<tr>
<td>Maximal electroshock seizure (mice-MES)</td>
<td>71</td>
<td>55–90</td>
<td>58</td>
</tr>
<tr>
<td>Maximal electroshock seizure (rats-MES)</td>
<td>ip: 20</td>
<td>15–27</td>
<td>po: 29</td>
</tr>
<tr>
<td></td>
<td>po: 29</td>
<td>1–53</td>
<td></td>
</tr>
<tr>
<td>Metrazol-induced seizure (mice-scMet)</td>
<td>62</td>
<td>47–71</td>
<td>32</td>
</tr>
<tr>
<td>Metrazol-induced seizure (rats-scMet)</td>
<td>18</td>
<td>13–25</td>
<td>54</td>
</tr>
<tr>
<td>Picrotoxin-induced seizure (mice-Pic)</td>
<td>17</td>
<td>9–28</td>
<td>–</td>
</tr>
<tr>
<td>Bicuculline-induced seizure (mice-Bic)</td>
<td>94</td>
<td>87–103</td>
<td>–</td>
</tr>
<tr>
<td>Corneal kindled mouse</td>
<td>39</td>
<td>31–45</td>
<td>–</td>
</tr>
<tr>
<td>Hippocampal kindled rats</td>
<td>19</td>
<td>13–28</td>
<td>~40</td>
</tr>
<tr>
<td>6 Hz-32 mA (mice)</td>
<td>27</td>
<td>24–30</td>
<td>37</td>
</tr>
<tr>
<td>Mice-neurotoxicity (TD$_{50}$)</td>
<td>88</td>
<td>81–95</td>
<td>77</td>
</tr>
<tr>
<td>Rat-neurotoxicity (TD$_{50}$)</td>
<td>ip: 49</td>
<td>43–55</td>
<td>po: 58</td>
</tr>
<tr>
<td></td>
<td>po: 131</td>
<td>94–175</td>
<td></td>
</tr>
</tbody>
</table>

–, not tested. [Correction added after online publication 9-Dec-2011: Columns in Table 1 have been reordered.]
New drugs on the horizon

- SPD is a one-carbon homolog of valnoctamide (VCD)
- Benzodiazepine-resistant SE induced by pilocarpine (rats):
  Highly efficacious ED$_{50}$ 84mg/kg

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>ED$_{50}$ - mg/kg (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min post SE onset</td>
</tr>
<tr>
<td>clonazepam</td>
<td>1.3 (0.6 - 2.5)</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>4.5 (38 - 52)</td>
</tr>
<tr>
<td>diazepam</td>
<td>3.0 (1.6 - 4.4)</td>
</tr>
<tr>
<td>valproic acid</td>
<td>366 (230 - 575)</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>31 (18 - 46)</td>
</tr>
<tr>
<td>VCD</td>
<td>8/8 protected at 65 mg/kg</td>
</tr>
<tr>
<td>SPD</td>
<td>8/8 protected at 65 mg/kg</td>
</tr>
</tbody>
</table>

1: White et al. Epilepsia 2012
New drugs on the horizon

- SPD is a one-carbon homolog of valnoctamide (VCD)
- **SPD**
  - Benzodiazepine-resistant SE induced by soman (rats and guinea pigs):

### Table 3. Number of animals and degree of neuropathology (mean neuropathology score) as a function of soman-induced seizure control by SPD in rats

<table>
<thead>
<tr>
<th>Seizure controlled</th>
<th>Seizure not controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuropathy</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>38 (X = 0)</td>
<td>2 (X = 11.5)</td>
</tr>
<tr>
<td>2 (X = 0)</td>
<td>29 (X = 17.5)</td>
</tr>
</tbody>
</table>

$\chi^2 = 55.67, \text{d.f.} = 3, p < 0.0001$.
New drugs on the horizon

- **SPD**
- **Stiripentol**
- **Perampanel**
- **GYKI 52466**
- **NS 1209**

Stiripentol (STP) is a $\alpha_3$ preferring allosteric modulator of GABA-R$^{1,2,4}$

- STP potentiates tonic and phasic inhibition in hippocampal slice preparations$^3$
- Potentiation of $\alpha_4$ and $\delta$ containing receptors suggest that STP may work in refractory SE$^2$
- STP but not DZP continues to potentiate miniature IPSPs following prolonged SE suggesting also a presynaptic action on GABA release$^{2,3}$

New drugs on the horizon

- SPD
- Stiripentol
- Perampanel
- GYKI 52466
- NS 1209

STP in BDZ refractory SE in the Lithium-Pilocarpine Model

Juvenile rats (15-23d)

Adult rats (57-63d)

1: Grosenbaugh and Mott Neuropharmacology 2012 in press
New drugs on the horizon

- Orally active, noncompetitive and highly selective AMPA-type glutamate (GLU) receptor antagonist
- Licensed in EU since 8/2012 for adjunctive treatment in refractory focal epilepsy

- Perampanel

- GLU is the principal excitatory neurotransmitter$^1$
- AMPA receptor $\rightarrow$ fast excitatory effects of GLU$^1$
  - Important in normal CNS activity and in the pathophysiology of epilepsy$^2$
- AMPA receptor antagonists block increased neuronal transmission during hyperexcitable states
  - Competitive $\rightarrow$ Less effective in the presence of high glutamate concentrations
  - Non-competitive $\rightarrow$ Inhibit AMPA receptors even in the presence of high glutamate concentrations

$^{1}$ Wilcox et al. Excitatory synaptic transmission. In: Epilepsy: A comprehensive textbook. 2008
$^{2}$ Meldrum BS, Rogawski MA. Neurotherapeutics 2007;4:18–61
New drugs on the horizon

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**Perampanel**

<table>
<thead>
<tr>
<th></th>
<th>Maximal Electroshock</th>
<th>Audiogenic seizures</th>
<th>PTZ- seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perampanel</td>
<td>1.6 (1.3, 1.9)</td>
<td>0.47 (-1.0)</td>
<td>0.94 (ND)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>21 (16, 45)</td>
<td>6.1 (4.1, 9.0)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>460 (290, 600)</td>
<td>160 (93, 260)</td>
<td>350 (260, 470)</td>
</tr>
</tbody>
</table>

$ED_{50}$ values: mg/kg, po (95% confidence interval [CI])
ND = not determined

Hashizume et al. Neurology 2008; 70: suppl (poster P02.113)
New drugs on the horizon

- SPD
- Stiripentol
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- GYKI 52466
- NS 1209

- GYKI 52466, a 2.3-BDZ is a highly selective non-competitive AMPA receptor antagonist\(^1\)
- Highly lipophilic with good BBB penetration\(^2\)
- Kainic acid induced SE: early (5min) and late (25min) treatment with GYKI 52466 vs. DZP\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>GYKI 52466</th>
<th>Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early SZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min pre treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min post treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h post treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epidural EEG recordings

New drugs on the horizon

- **NS 1209** competitive AMPA receptor antagonist with high Glu-R5 affinity\(^1,2\)
  - Neuroprotective and fast acting in MES and audiogenic seizures\(^3\)
  - Highly effective in self sustaining SE\(^4\)
  - Phase II clinical trial in refractory convulsive SE and NCSE was stopped due to low recruitment rate\(^5\)

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• Conclusion
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- Early phase
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Stage 2
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Stage 3
- Refractory SE\(^1,2\): SE, that continues despite stage 1/2 treatment
- Subtle SE, stuporous SE

Stage 4
- Super-refractory SE\(^1\): SE, that continues despite treatment with anaesthetics > 24 hours

Super-refractory Status epilepticus

<table>
<thead>
<tr>
<th></th>
<th>patients in controlled or randomised studies</th>
<th>patients in uncontrolled case series</th>
<th>publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0</td>
<td>661</td>
<td>29</td>
</tr>
<tr>
<td>Propofol</td>
<td>14*</td>
<td>183</td>
<td>34</td>
</tr>
<tr>
<td>Thiopental/Pentobarb</td>
<td>9*</td>
<td>377</td>
<td>32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>RSE with Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsieh</td>
<td>Clin Neuropharmacol</td>
<td>2010</td>
<td>1</td>
</tr>
<tr>
<td>Pruss</td>
<td>Epilepsy Res</td>
<td>2008</td>
<td>1</td>
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<tr>
<td>Ubogu</td>
<td>Epilepsy and Behaviour</td>
<td>2003</td>
<td>1</td>
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<tr>
<td>Mewasing</td>
<td>Seizure</td>
<td>2003</td>
<td>5</td>
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<tr>
<td>Bleck</td>
<td>Epilepsia</td>
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<td>Nathan</td>
<td>Neurology</td>
<td>2002</td>
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<td>Sheth</td>
<td>Neurology</td>
<td>1998</td>
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<td>Walker</td>
<td>Q J Med</td>
<td>1996</td>
<td>1</td>
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Shorvon and Ferlisi Brain 2011
### Super-refractory Status epilepticus

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Publications</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Inhalation narcotics</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Immunosuppressants/Steroids</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>6</td>
<td>20</td>
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<td>VNS</td>
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<td>Epilepsy surgery</td>
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<td>8</td>
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<td>CSF drainage</td>
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<td>Mozart</td>
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*Shorvon and Ferlisi Brain 2011*
Superrefractory Status epilepticus

General anaesthesia (including consideration of ketamine), antiepileptic drugs and full ITU support; and investigate urgently to identify the cause

Cause not identified

IV magnesium bolus 4g; Infusion 2-6g/h (and IV pyridoxine in children 30mg/Kg)

Steroids +/- IVIG +/- PEx

Consider hypothermia 32-35°C <48h

Consider ketogenic diet (1:1 to 1:4)

Consider ECT, CSF drainage and others

Cause identified

Treat cause if possible

Consider surgery in lesional cases

Shorvon and Ferlisi Brain 2011
Conclusions

• 40% of early and 80% of refractory SE are not controlled

• Excitotoxicity $\rightarrow$ neuronal loss and long term consequences

• Early treatment improved prognosis $\rightarrow$ public health measures

• Better understanding of basic mechanism led to new treatment concepts:
  – Therapeutic opportunities for early and refractory SE are different
  – GABA-ergic drugs in stage I and anti-glutamatergic in later stages

• Lack of translation due to
  – Challenges in clinical trial design
  – Ethical issues
  – Lack of industry interest (small market and high cost)

• Trials in patients with de novo SE $\rightarrow$ Antiepileptogenesis
The 4th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures.
4-6 April 2013
Salzburg, Austria

First Announcement
www.statusepilepticus2013.eu
AET symposium
Management of Refractory Status Epilepticus
December 1, 2012

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## Disclosure

<table>
<thead>
<tr>
<th>Research Funding</th>
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Several medications discussed in this presentation are not FDA approved for treatment of status epilepticus
Recognize and initiate appropriate treatment algorithms for RSE for adults and pediatric patient populations.

Learn current theories on the basic mechanisms of RSE and apply this information in patient care.

Recognize when autoimmune and inflammatory pathogenic processes may underlie RSE and implement etiology-specific treatment protocols in patient care.

Recognize when emerging treatments for RSE may be helpful in the management of RSE patients.
Adult Treatment Algorithm

- Target underlying etiology if possible
  - recognize immunological/inflammatory etiologies
- Initiate aggressive care quickly if convulsive, deferred care if CPS, never if absence
- Agent – MDZ > PRO > BBT
- EEG target – suppression/burst (1/10 seconds)
- Duration – 24 hours, then wean over 12-24 hours (repeat PRN)
- Consider carefully before giving up
Adult SE Treatment

Rossetti & Lowenstein  *Lancet Neurol* 2011
Pediatric Treatment Algorithm

- Target underlying etiology if possible
  - Recognize immunological/inflammatory etiologies (infectious, autoimmune, Rasmussen’s, FIRES)
  - Recognize other etiologies (hypoxic, metabolic, genetic)
  - Don’t forget pyridoxine, especially neonates and infants
- Initiate aggressive care quickly if convulsive, deferred care if CPS, never if absence
- Treat hyperthermia aggressively, maintain euglycemia
- Duration – 24 hours, then wean over 12-24 hours (repeat PRN)
- Consider carefully before giving up
Pediatric Treatment Algorithm

First AED: Lorazepam 0.1 mg/kg iv (Max 5 mg over 1-4 min)
If no iv: Diazepam 0.3-0.5 mg/kg/dose pr (Max. 20 mg/dose)

Second AED: Fosphenytoin 20-30 mg PE/kg iv
(If no Fosphenytoin: Phenytoin 20-30 mg/kg iv)
If < 2 years: Consider Pyridoxine 100 mg iv

Third AED: Phenobarbital 20-30 mg/kg iv
Or: Levetiracetam, Valproic acid, and others

Burst Suppression: Midazolam 0.2 mg/kg bolus; 0.1-3mg/kg/h
Or: Pentobarbital 3-5 mg/kg bolus; 0.3-10 mg/kg/h

Modified after: Children’s Hospital Boston Pharmacy and Therapeutics Committee
Overall Learning Objectives

✔ Recognize and initiate appropriate treatment algorithms for RSE for adults and pediatric patient populations.

✔ Learn current theories on the basic mechanisms of RSE and apply this information in patient care.

➢ Recognize when autoimmune and inflammatory pathogenic processes may underlie RSE and implement etiology-specific treatment protocols in patient care.

➢ Recognize when emerging treatments for RSE may be helpful in the management of RSE patients.
Basic Mechanisms of RSE

- Lessons from animal models in the management of RSE:
  - Early treatment of SE may be more effective
  - Early polytherapy may reduce or prevent the development of pharmaco-resistance of SE
  - Some drug combinations may have synergistic effects
  - Based upon receptor trafficking in SE, it may be beneficial to enhance inhibition AND reduce excitation very early in the course of treatment
Overall Learning Objectives

- Recognize and initiate appropriate treatment algorithms for RSE for adults and pediatric patient populations.
- Learn current theories on the basic mechanisms of RSE and apply this information in patient care.
- Recognize when autoimmune and inflammatory pathogenic processes may underlie RSE and implement etiology-specific treatment protocols in patient care.
- Recognize when emerging treatments for RSE may be helpful in the management of RSE patients.
Autoimmunity & Inflammation

- Multiple antibodies have been identified in RSE cases
  - Paraneoplastic (adults) or nonparaneoplastic (children)
  - ABs to intraneuronal proteins or to cell surface/synaptic proteins
  - Targeted oncologic and/or immunologic therapy specific to etiology

- SE induces/perpetuates inflammatory pathways in the brain
  - IL1R/TLR signaling important, along with cytokines, chemokines, mTOR, complement cascade, cell adhesion molecules, metalloproteases, COX-2
  - BBB damage, cell loss
  - Immunomodulatory therapies may improve outcome in RSE with immune/inflammatory etiologies
Overall Learning Objectives

✓ Recognize and initiate appropriate treatment algorithms for RSE for adults and pediatric patient populations.

✓ Learn current theories on the basic mechanisms of RSE and apply this information in patient care.

✓ Recognize when autoimmune and inflammatory pathogenic processes may underlie RSE and implement etiology-specific treatment protocols in patient care.

✓ Recognize when emerging treatments for RSE may be helpful in the management of RSE patients.
Emerging Treatments

- The future for our patients and their families is bright!
- Limited but emerging data on some of the newer currently available AEDs
  - levetiracetam, lacosamide, topiramate, perampanel
- Pipeline with a number of new AEDs with novel MOA
  - stiripentol, SPD, GYKI 52466, NS 1209
- Consider immunomodulatory therapies
- Consider resective surgery if lesional
- Consider additional therapies (hypothermia, ketogenic diet, neurostimulation)
Needs for RSE Management

- Infrastructure to accelerate access to effective therapies for SE
- Biomarkers and surrogate endpoints:
  - for earlier diagnosis of patients likely to progress to RSE
  - to predict outcomes after RSE
  - to effectively translate laboratory findings to patient care
- Treatments with better efficacy/tolerability for RSE
- IV formulations of novel drugs with different MOAs and better efficacy/tolerability needed
- Disease modifying treatments after CNS insults of varying etiologies

American Epilepsy Society | Annual Meeting 2012
Case 1

30 year old man (70kg) with no prior history of illness or seizures:

- **6 pm**: noted to have generalized tonic clonic seizure (GTC) activity, EMS was called
- **6:10 pm**: EMS arrival: afebrile, normal BP, unresponsive with continuous seizure activity → 4 mg lorazepam IV given → no effect
- **6:25 pm**: arrival to the ER, continuous seizure activity → repeat 4 mg lorazepam IV given → no effect
- **6:30 pm**: fosphenytoin 20 mg PE/kg IV infusion started
- **6:50 pm**: still unresponsive, normal BP, with persisting seizure activity
Case 2

18 year old girl:

- **2 weeks prior to admission**: fever, headache and upper respiratory symptoms
- **1 week later**: progressive anxiety, insomnia, delusions and paranoia, and episodes of catatonia
- **On admission**: temperature of 39°C, oro-lingual-facial dyskinesias and right hand twitching were noted
- **EEG**: continuous seizure activity maximal at the left hemisphere
- **CSF**: lymphocytic pleocytosis, mildly increased protein, and negative bacterial cultures
- Benzodiazepines and phenytoin load did not have any effect on abnormal movements and seizures
Thank You!