There was no good evidence to guide optimum initial management of refractory status epilepticus.

**Clinical Problem:**
A 22 year-old man without a prior history of epilepsy is admitted to the intensive care unit with ongoing seizures resistant to treatment with lorazepam, followed by phenytoin loading and a bolus of phenobarbital. You are consulted with regards to acute management to stop his seizures.

**Clinical Question:**
What is the therapy most likely to achieve prompt and durable seizure control in an adult patient with refractory status epilepticus (RSE)?

**Search Strategy:**
- **Cochrane database:** one review of the acute management of tonic-clonic convulsions in children not focusing on refractory cases. [1]
- **Bandolier:** no relevant articles on status epilepticus
- **SumSearch:** (“Status Epilepticus” AND “Refractory”) Two DARE citations including a review of RSE in children and an article retrospectively examining propofol alone. [2] PubMed possible systematic reviews included a systematic review comparing different treatment options in adult patient with RSE [4] which was selected for further analysis, and the two DARE citations mentioned.
- **PubMed:** (Status Epilepticus/drug therapy [MeSH] AND [Refractory OR Resistant]) limited to meta-analysis yielded the pediatric review (#1). Limiting to ‘Randomized Controlled Trial’ yielded two articles, one of which was a relevant comparison of midazolam and diazepam in children. [5] The article chosen was only retrieved when limiting this search to ‘Review.’

**Clinical Bottom Lines:**
1. There are no randomized trials comparing different drugs in the management of refractory adult status epilepticus.
2. A systematic review of case series showed that a continuous Infusion of pentobarbital resulted in acute treatment failure in 8% of cases vs 20% for midazolam, 27% for propofol. Breakthrough seizures after six hours occurred in 51% of midazolam treated patients vs 15% for propofol, 12% for pentobarbital. However, patient populations were too different to enable meaningful comparisons and to determine which drug is most effective.
3. Pentobarbital caused hypotension requiring vasopressor support in 77% of cases vs 30-42% with the other 2 drugs.
4. There was no difference in mortality among the different drugs. Instead, mortality was determined largely by age, seizure duration, and etiology.

**The Evidence: Systematic Review**
The clinical question: was to compare impact of “PRO [propofol], MDL [midazolam], or PTB [pentobarbital] on treatment response, complications, and mortality in RSE patients.” Studies were identified through a literature search of MEDLINE and of the bibliographies of selected articles. Articles were selected using well-defined inclusion and exclusion criteria (included articles had to be peer-reviewed, include data on adult patients, use an appropriate definition of SE and RSE, and have treatment with one of the three regimens under investigation; they were excluded if seizures were simple partial or absence, intermittent doses not continuous infusions were used, or another agent was used for RSE prior to the three agents under study). Extraction of data was performed independently by two investigators and included type of SE (and convulsive versus non-convulsive), prior history of epilepsy, treatment goal, type of EEG monitoring and eventual
outcome. Main outcome measures examined were treatment failure, either early on, breakthrough (after six hours) or withdrawal seizures. Whether the agent needed to be changed to another was also recorded. Hypotension as an adverse effect of therapy was specifically looked for.

Data:
From 28 studies meeting the inclusion criteria, 198 patients treated for RSE were examined:

NO STATISTICAL ANALYSIS WAS PERFORMED / DATA FROM STUDIES IS POOLED

<table>
<thead>
<tr>
<th></th>
<th>Midazolam (n = 54)</th>
<th>Propofol (n = 33)</th>
<th>Pentobarbital (n = 106)</th>
<th>MDL NCSE (n = 47)</th>
<th>PRO NCSE (n = 25)</th>
<th>PTB NCSE (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Failure</td>
<td>20% (11/54)</td>
<td>27% (9/33)</td>
<td>8% (8/106)</td>
<td>23% (11/47)</td>
<td>32% (8/25)</td>
<td>20% (4/20)</td>
</tr>
<tr>
<td>Breakthrough Seizures</td>
<td>51% (23/45)</td>
<td>15% (2/13)</td>
<td>12% (11/92)</td>
<td>56% (22/39)</td>
<td>0 (0/6)</td>
<td>0 (0/11)</td>
</tr>
<tr>
<td>Withdrawal Seizures</td>
<td>63% (25/40)</td>
<td>46% (6/13)</td>
<td>43% (34/79)</td>
<td>66% (23/35)</td>
<td>50% (3/6)</td>
<td>33% (2/6)</td>
</tr>
<tr>
<td>Hypotension (requiring pressors)</td>
<td>30% (14/47)</td>
<td>42% (10/24)</td>
<td>77% (79/103)</td>
<td>30% (13/43)</td>
<td>39% (9/23)</td>
<td>45% (9/20)</td>
</tr>
<tr>
<td>Refractory Hypotension</td>
<td>2% (1/47)</td>
<td>8% (2/24)</td>
<td>3% (3/103)</td>
<td>2% (1/43)</td>
<td>9% (2/23)</td>
<td>0 (0/20)</td>
</tr>
<tr>
<td>Change of AED</td>
<td>21% (10/47)</td>
<td>20% (4/20)</td>
<td>3% (3/106)</td>
<td>20% (8/41)</td>
<td>25% (8/41)</td>
<td>10% (2/20)</td>
</tr>
<tr>
<td>Mortality</td>
<td>46% (25/54)</td>
<td>52% (16/31)</td>
<td>48% (49/102)</td>
<td>47% (22/47)</td>
<td>56% (14/25)</td>
<td>30% (6/20)</td>
</tr>
</tbody>
</table>

Comments:
1. There are no randomized trials comparing various drugs/approaches.
2. Data for the table above was combined without any statistical model to account for heterogeneity or study quality. The entire population of patients was treated as a single cohort which is methodologically questionable.
3. Given the number of individual comparisons performed, the finding of marginal statistical significance in a few comparisons has little meaning.
4. Multiple largely unknown possibilities for confounding bias exist in the combination of varied case series with different selection criteria and populations.
5. For example, a known difference is that midazolam was generally used later in the course of SE, more often for NCSE than pentobarbital, and only in recent series. This means that continuous EEG monitoring was used in most patients on midazolam and rarely for pentobarbital, making detection of breakthrough seizures variable. The goal in all patients on midazolam was seizure suppression, while in many patients on pentobarbital it was EEG suppression also. Patients and treatment approaches were likely different among groups, which confounds difference in outcomes.
6. Data were not available on how quickly seizures were brought under control with the various agents and whether the newer agents (MDL, PRO) terminated seizures more rapidly.
7. The secondary analysis revealed that those patients treated with a goal of EEG suppression had less breakthrough seizures than those with only seizure suppression as goal (4% vs 53%). They were more likely to suffer hypotension, however, and tended to be treated with PTB.
APPENDIX

RSE and the Use of Other Agents

Specific modalities in RSE (both convulsive and NCSE):

1. **Inhalational anesthetic agents**: few case series mostly utilizing isoflurane but recent use of desflurane also.  
   References: [6], [7], [8]

2. **Valproate**: no controlled trials, but IV formulation is available and used in number of series including a series of 41 children with RSE (various types) given IV VPA, 78% response (65% immediate!) and was well tolerated.  
   References: [9]

3. **Carbamazepine**: no trials in SE or RSE; concern that CBZ may induce absence status in certain populations.  
   References: [10]

4. **Topiramate**: small case series (n = 6) published recently showing effectiveness.  
   References: [11]

5. **Lamotrigine**: one case report in SE but one experimental study suggested it was not effective at all.  
   References: [12], [13]

6. **Oxcarbazepine**: no trials in SE or RSE.

7. **Tiagabine**: some felt may induce NCSE but systematic review not support this.  
   References: [14], [15]

8. **Vigabatrin**: no clinical studies but again some cases of it causing SE.  
   References: [16]

9. **Levetiracetam**: no clinical studies but again concern of inducing SE in some.  
   References: [17]

References:


**Key Words:** dementia, statin, prevention

**Appraiser:** Raj Dhar and the UWO Evidence Based Neurology Group

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