Seizure Prophylaxis in Traumatic Brain Injury

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Pharmacotherapy Rounds
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Objectives

• Describe the pathophysiology of seizures in traumatic brain injury
• Review the mechanism of action and adverse effects associated with phenytoin and levetiracetam
• Compare and contrast outcomes associated with antiepileptic use in traumatic brain injury
• Develop a recommendation for seizure prophylaxis in traumatic brain injury patients
Introduction

I. Epidemiology of Traumatic Brain Injury

Figure 1. Epidemiology of Traumatic Brain Injury

- Definition: Any blunt force trauma to the brain
- Leading Causes
  a. Falls
  b. MVA
  c. Assaults
  d. Gunshot wounds
  e. Explosions
- Demographic Incidence
  a. Male
  b. Children 0-4yo, Adolescents 15-19yo, Elderly >65yo

II. Post-Traumatic Seizures (PTS)

- Pathophysiology – Sudden, abnormal electrical disturbance in the brain
  i. Inhibitory - GABA
     1. Cl⁻ Influx
  ii. Excitatory
     1. Na⁺ influx
     2. Ca²⁺ influx
     3. K⁺ efflux
  iii. Etiology
     1. Physical insult
     2. Neural tissue damage
     3. Cortical lesions

Figure 2. Seizure Pathophysiology
II. Post-Traumatic Seizures (cont.)

b. Incidence\textsuperscript{5,6}
   i. Early PTS 4-25%
      1. 50% within the first 24 hours
      2. 25% within the first hour
      3. 29-fold increased risk of developing epilepsy
   ii. Late PTS 9-42%
      1. 25% of patients with early PTS will have another seizure
      2. No benefit of PHE to prevent late PTS

III. Detection of Early Seizures\textsuperscript{4}
   a. Clinical
      i. Within 24 hours
         1. Tonic - Jerking, shaking
         2. Clonic - Muscle rigidity, loss of motor control
      ii. 24h - 7days
         1. Focal - Staring spells
   b. Electrical
      i. Electroencephalograph\textsuperscript{7}
         1. Shows abnormality in over 80% of epileptic patients
         2. Does not predict the risk of epilepsy or type of seizure
   c. TBI and Neuromuscular blockers can mask clinical signs & symptoms of early PTS
      i. Incidence of clinical seizures around 10%, can increase to 50% when diagnosed by EEG\textsuperscript{8}

IV. TBI Assessment
   a. Glasgow Coma Scale(See Appendix A)\textsuperscript{9}
      i. 15 point scale used to describe a patients level of consciousness
      ii. Scoring Categories
         1. Eye
         2. Verbal
         3. Motor
      iii. Severity of TBI
         1. Mild: 13-15 points
         2. Moderate: 9-12 points
         3. Severe: 3-8 points
   b. Glasgow Outcome Scale\textsuperscript{10}
      i. 5 (GOS) or 8 (GOS-E) point scoring system to assess how injury has affected functioning
c. Glasgow Outcome Scale (cont.)

i. Categories
   1. Consciousness
   2. Independence inside and outside the home
   3. Work
   4. Social/Leisure Activity
   5. Family and Friendships
   6. Return to normal life

ii. Scoring System
   1. Death
   2. Vegetative State
   3. Severe Disability
   4. Moderate Disability
   5. Good Recovery

Further classified into upper and lower on Extended GOS

V. Risk Factors for PTS\textsuperscript{11}
   a. Early
      i. Amnesia >30-24h minutes
      ii. Age <65
   b. Late
      i. Amnesia >24h
      ii. Age <65
   c. Early and Late
      i. Depressed skull fractures
      ii. Intracerebral or subdural hematoma
      iii. Penetrating head injury
      iv. GCS 3-8
      v. No/brief unconsciousness

VI. Current Guidelines
   a. American Academy of Neurology (AAN) 2003\textsuperscript{1}
      i. Prophylactic treatment with phenytoin as soon as possible
      ii. Prophylaxis NOT routinely used after 7 days
   b. Brian Trauma Foundation 2007\textsuperscript{7}
      i. Phenytoin shown to reduce incidence of early PTS
      ii. Valproate has comparable effects but higher mortality
      iii. Seizure prophylaxis >1 week after TBI not recommended
Early Post-traumatic Seizure Prophylaxis Timeline

VII. Early PTS Prophylaxis
   a. Carbamazepine

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glotzner et. al 1983(^{12})</td>
<td>CAR (n=75): 100mg TID titrated to therapeutic level of 300-600mcg/mL for 1.5-2 years</td>
<td>Placebo (n=76)</td>
<td>Early PTS, p&lt;0.05, RR = 0.37</td>
</tr>
</tbody>
</table>

   i. Bottom Line
   1. Significantly lower incidence of early; No difference in late seizures
   2. Patients were initially treated with PHE 750mg LD then 250-500mg daily until they could receive PO carbamazepine

b. Phenytoin

<table>
<thead>
<tr>
<th>Population</th>
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<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et. al 1983(^{13})</td>
<td>PHE (n=136): 11 mg/kg LD 13 mg/kg IM daily x 7 days</td>
<td>Placebo (n=108)</td>
<td>Early PTS, 5 (3.7%) vs. 5 (3.7%) p=0.75</td>
</tr>
<tr>
<td>Temkin et. al 1990(^{14})</td>
<td>PHE (n=208): 20mg/kg LD IV or PO MD adjusted to achieve level of 10-20</td>
<td>Placebo (n=198)</td>
<td>Early PTS, 3.6% vs. 14.2% p&lt;0.001, RR=0.27 [95% CI 0.12-0.62]</td>
</tr>
<tr>
<td>Haltiner et. al 1999(^{15})</td>
<td>PHE 20mg/kg LD IV or PO MD adjusted to achieve level of 10-20 x 12 mo</td>
<td>Placebo</td>
<td>Mortality p=0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity p=1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality in early PTS p=0.03</td>
</tr>
</tbody>
</table>

   i. Bottom Line
   1. Significantly lower risk of ePTS with PHE use (37% Risk reduction)
   2. No difference in hypersensitivity or mortality with PHE compared to placebo
   a. Significantly higher mortality in patients that suffered ePTS
   3. Monitoring
   a. 97% of PHE patients had levels in or above therapeutic range on the first day after injury, and 57% were maintained at 1 week in pooled analysis of Temkin and Haltiner studies\(^{1}\)
VII. Early PTS Prophylaxis (cont)

c. Valproate

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<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 14 yo, TBI, LD administered w/in 24 hours of admission (n=379)</td>
<td>PHE: 20mg/kg LD, 5mg/kg/d MD x 1 wk VPA: 20mg/kg LD, 15mg/kg/d x 1 mo VPA: 20mg/kg LD, 15mg/kg/d x 6 mo</td>
<td>Occurrence of late seizures</td>
<td>p=0.27, RR = 1.4 [95% CI 0.8-2.4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occurrence of early seizures</td>
<td>p=0.14, RR = 2.9 [95% CI 0.7-13.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>p=0.07, RR=2.0 [95% CI 0.9-2.8]</td>
</tr>
<tr>
<td>Dimken et. al 2000^{17}</td>
<td></td>
<td>Neuropsych capability at 1, 6, and 12 months</td>
<td>p values: 0.551-0.812</td>
</tr>
</tbody>
</table>

i. Bottom Line
1. No significant difference in rates of early PTS between VPA and PHE
2. No difference in long-term neuropsychological or cognitive measures
3. Trend towards greater mortality with VPA
   a. VPA not recommended due to limited data

Phenytoin and Levetiracetam

VIII. Phenytoin^{18}

a. Mechanism of Action
   i. Promotes sodium efflux from neurons; stabilizes threshold

b. Dosing
   i. LD: 15-20mg/kg, md: 300-600mg/day, divided in 3 doses

c. Monitoring^{21}
   i. Goal: 10-20mcg/mL
      1. Draw level 2-3 after LD; Can draw 2 hours after IV LD to aid dosing
      2. Need to adjust for low serum albumin: \( \text{AdjPHE} = \text{TotalPHE}/([0.2 \times \text{alb}) + 0.1] \)
   ii. Slow absorption, peaks usually reached in 4-8 hours
   iii. Steady State reached in 5-10 days
      1. Best trial data monitored levels 3x/week
   iv. Factors that can alter levels: CYP inducers and inhibitors, age, albumin, alcohol use, liver disease, uremia, drug displacement^{22,23}

d. Adverse Effects
   i. Hypersensitivity reactions (DRESS)
   ii. Stevens-Johnson syndrome
iii. Hepatotoxicity
iv. Hematopoietic complications
v. Purple glove syndrome
vi. IV Administration
   1. 50mg/min
   2. Cardiovascular complications

IX. Levetiracetam
    a. Mechanism of Action
       i. Exact mechanism unknown; Possible involvement of Ca$^{2+}$ channels and SV2A protein
    b. Dosing
       i. LD: 1,500-2,000mg IV infused over 15 minutes (off-label)
       ii. MD: 500mg daily, titrate to 1,500mg BID
    c. Monitoring
       i. Not required in acute treatment
    d. Adverse Effects
       i. Behavioral problems
       ii. Coordination Difficulties

Figure 3. Phenytoin and levetiracetam mechanism of action

X. Physician Preference (See Appendix B)
   a. Q-PULSE panel
      i. Epilepsy specialists from National Association of Epilepsy Centers (NAEC)
   b. Medication preference
      i. 74% Levetiracetam
      ii. 10% Phenytoin
   c. Impact on decision
      i. 86% of physicians report scientific data as having substantial impact on decision
      ii. 86% of physicians report personal experience having substantial impact on decision
Phenytoin vs. Levetiracetam - Literature Review


<table>
<thead>
<tr>
<th>Purpose</th>
<th>Evaluate the occurrence of early posttraumatic seizure activity based on EEG findings in patients receiving phenytoin versus those receiving levetiracetam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective cohort, single-center, double-blind</td>
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</tbody>
</table>
| Population        | Inclusion: Severe TBI, defined as GCS 3-8, administration of AED within 24 hours of admission, patient had an EEG examination, prophylaxis for 7 days  
                   | Exclusion: Not defined                                                                                                               |
| Intervention      | **LEV:** LD 500mg IV Q12H x 7 days                                                                                                    |
|                   | **PHE:** Not defined – cases pulled from severe TBI data base                                                                        |
|                   | • cEEG initiated and continued for 72 hours                                                                                           |
|                   | • PHE levels check on days 2 & 7, doses adjusted by one designated study pharmacist to maintain level between 10-20 mcg/dL         |
|                   | • Patients with seizures on MAX dose of treatment would receive opposite therapy in addition to original AED assigned          |
|                   |   o Max MD doses defined as 1500mg BID LEV or 20mcg/dL level of PHE                                                               |
| Outcomes          | **Primary**                                                                                                                        |
|                   | • Abnormal EEG findings                                                                                                              |
|                   |   o Status epilepticus                                                                                                               |
|                   |   o Seizure activity                                                                                                                 |
|                   | • Seizure tendency                                                                                                                   |
|                   | **Secondary**                                                                                                                        |
|                   | • Glasgow Outcome Scale at 3 and 6 months                                                                                           |
| Statistical       |                                                                                                                                  |
| Analyses          | • Fisher’s exact tests for comparison of categorical variables                                                                     |
|                   | • Chi-squared and Mann-Whitney U-tests for comparison of continuous variables                                                        |
| Results           | **Total** (n = 27); **LEV** (n = 15), **PHE** (n = 12)                                                                                  |
| Demographics      |                                                                                                                                  |
|                   | • No significant difference baseline characteristics or GCS score                                                                     |
| Primary Outcome   |                                                                                                                                  |
|                   | • Significant difference between occurrence of abnormal EEG findings in LEV vs PHE (53% vs 0%, p=0.003) and seizure tendency (47% vs. 0%, p=0.007) |
|                   | • No difference in seizure activity (1% vs 0%, p=0.556)                                                                                 |
| Secondary Outcomes|                                                                                                                                  |
|                   | • No difference in GOSE scores at 3 or 6 months (p=0.825, p=0.734)                                                                  |
| Conclusions       |                                                                                                                                  |
|                   | • No significant difference in occurrence of early seizures                                                                        |
|                   | • Further prospective studies should include EEG monitoring to obtain the most accurate results                                        |
| Critique          |                                                                                                                                  |
|                   | • Small sample size - Study not powered to detect outcome differences                                                               |
|                   | • Higher percentage of LEV patients required EEG monitoring due to coma, change in mental status, or clinical seizure activity     |
|                   | • Unclear if EEGs were assessed by the same neurologist – potential for bias                                                        |
|                   | • No information on PHE dosing or serum levels                                                                                       |

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<th>Purpose</th>
<th>Compare the safety of LEV in critically ill patients to the safety of PHE</th>
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<td>Design</td>
<td>Prospective, randomized, single-center, single-blinded</td>
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</table>
| Population | **Inclusion:** ≥17 years old, TBI or SAH admitted less than 24 hours prior to randomization, GCS Score 3-8 or GCS motor score <5 and abnormal CT scan, hemodynamically stable, at least one reactive pupil, signed informed consent  
**Exclusion:** Spinal cord injury, no IV access, history of or CT confirmation of previous brain injury, hemodynamically unstable, suspected anoxic events, peripheral trauma likely to result in liver failure, known hypersensitivity to any AED, contraindication to LEV or PHE |
| Intervention | **LEV:** LD 20mg/kg IV (rounded to the nearest 250mg) given over 60 minutes, then 1000mg IV Q12H given over 15 minutes x 7 days  
**PHE:** LD 20mg/kg IV (MAX 2000mg) given over 60 minutes, then MD 5mg/kg/dose (rounded to the nearest 100mg) IV Q12H given over 15 minutes x 7 days  
- Randomization at a 2:1 ratio of LEV:PHE  
- EEG initiated and continued for 72 hours  
- PHE levels check on days 2 & 7, doses adjusted by one designated study pharmacist to maintain level between 10-20 mcg/Dl  
- Patients with seizures on MAX dose of treatment would receive opposite therapy in addition to original AED assigned  
  - Max MD doses defined as 1500mg BID LEV or 20mcg/Dl level of PHE |
| Outcomes | **Primary**  
  - Incidence of clinical adverse events  
**Secondary**  
  - Seizure frequency  
  - Long term outcomes (GOSE, DRS) at 3 and 6 months |
| Statistical Analyses |  
- Fisher’s exact tests for comparison of categorical variables  
- Mann-Whitney U-tests for comparison of continuous variables  
- Generalized linear models to test for differences between groups |
| Results | Total (n = 52); LEV (n = 34), PHE (n = 18)  
**Demographics**  
  - No significant difference baseline characteristics or GCS score  
**Primary Outcome**  
  - No significant difference in early seizure occurrence (16.6% vs 14.7%, p=1.0) or death (22.2% vs. 41.1% p=0.227) between PHE and LEV  
  - Less worsening neurological status (p=0.024) and less GI problems (p=0.043) with LEV  
  - Lower incidence of anemia (p=0.076) with PHE  
**Secondary Outcomes**  
  - Significantly lower DRS at 3 (11 vs 5, p=0.006) & 6 (6 vs 3, p=0.037) months, and higher GOSE (5 vs 3, p=0.016) at 6 months in surviving patients receiving LEV vs PHE |
| Conclusions |  
- No difference in seizure rate or death with levetiracetam compared to phenytoin |
Conclusions (cont)

- Levetiracetam results in less side effects and better long term outcomes than phenytoin

Critique

- Subjective report of only one physician for EEG, only 1 pharmacist dosing PHE
  - Physicians managing the patients were not blinded to the treatments
- Statistical analyses not adjusted for multiple comparisons
- Secondary outcomes reported as significant were after adjustments for surviving patients.


<table>
<thead>
<tr>
<th>Purpose</th>
<th>Compare the efficacy of PHE with that of LEV for preventing early PTS.</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>Prospective, multicenter (two Level 1 trauma centers)</td>
</tr>
<tr>
<td>Population</td>
<td>Inclusion: ≥18 years old, severe blunt TBI (GCS Score ≤8 or &gt; 8 in the presence of CT imaging findings consistent with SAH, SDH, EDH, ICH, or DAI. Exclusion: Pregnancy, expected or confirmed brain death within 48 hours of admission, prehospital use of anticonvulsants, development of seizures before enrollment in study</td>
</tr>
<tr>
<td>Intervention</td>
<td>LEV 1000mg IV Q12H given over 15 minutes x 7 days</td>
</tr>
<tr>
<td></td>
<td>PHE LD 20mg/kg IV (MAX 2000mg) given at 50mg/min then MD 5mg/kg/dose (rounded to the nearest 100mg) IV Q8H given over 15 minutes x 7 days</td>
</tr>
<tr>
<td></td>
<td>- PHE levels checked daily and dosing was adjusted by a pharmacist to maintain a therapeutic level of 10-20 mcg/dL.</td>
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<td>- Medications switch to oral dosage forms once patient was tolerating diet</td>
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<tr>
<td></td>
<td>- In the event of a seizure, it was at the institutions’ neurosurgery team’s discretion to individualized anti-seizure medication</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: Early PTSs, defined as seizure occurring within the first 7 days of injury</td>
</tr>
<tr>
<td></td>
<td>Secondary: Clinical Adverse events, Mortality, Complications, Length of stay</td>
</tr>
<tr>
<td>Statistical Analyses</td>
<td>Shapiro-Wilk test to determine normality of distribution</td>
</tr>
<tr>
<td></td>
<td>Chi-squared or Fisher’s exact tests to compare proportions</td>
</tr>
<tr>
<td></td>
<td>Unpaired student’s t-tests or Mann-Whitney U-tests to compare means</td>
</tr>
</tbody>
</table>

Results

Total (n = 813); LEV (n = 406), PHE (n = 407)

Demographics

- No significant difference in age, sex, injury severity score, intubation rates, GCS score
  - SAH = 60% (n=488), SDH = 50.9% (n=414), ICH = 27.9% (n=227)

Primary Outcome

- No significant difference in seizure rate (1.5% vs. 1.5%, p=0.997)

Secondary Outcomes

- No significant difference in adverse drug reactions, complications, or mortality
- Lower incidence of leukocytosis in LEV group (1.2% vs. 9.6%, p < 0.001)
More discontinuation of AED in PHE group (0% vs. 2.9%, p < 0.001)
Increased hospital LOS in LEV group (11.8 vs 7.5, p < 0.001)

Levetiracetam was not superior to phenytoin for early post-traumatic seizure prevention
Cost and need for serum monitoring should be considered in guiding the choice of agent

EEG monitoring not performed, only clinical seizures were studied
- No report of PHE levels
- Patients were not randomized
  - LEV preferred at LAC+USC, PHE preferred at R. Adams Cowley Center
- Patients who switched from PHE to LEV were still analyzed as PHE patients
- Difference in LOS could be due to non-medication related factors around disposition

XI. Levetiracetam vs. Phenytoin Meta-Analysis

a. Methods
   i. MEDLINE, EMBASE, Clintrials.gov, and Cochrane
      1. Search Criteria: LEV, PHE, and TBI
   ii. Inclusion Criteria
      1. Comparative study
      2. Patients with brain injury
      3. LEV to PHE comparison, and
      4. Primary outcome of or side effects
b. Results (See Appendix C.)
   i. Early Seizures (as defined by author)
      1. OR 1.12 (95% CI = 0.34,3.46)
b. Results (cont.)
   ii. Early Seizures (within 7 days)
      1. OR 0.96 (95% CI = 0.34, 2.76)

c. Bottom Line
   i. No difference in early and late seizures
   ii. Risk of early PTS may depend on type of brain injury

XII. Long Term Outcomes
   a. Summary
      i. Jones et al. – No difference in GOS-E at 3 or 6 months
      ii. Szaflarski et al. - 2 point higher GOS-E score at 6 months for patients who received LEV

b. Methods
   i. Primary investigator contacted patients and caregiver by telephone up to 3 times
   ii. Blinded second investigator scored the GOS-E questionnaire

| Table 7. Comparison of GOS-E Outcome Scores in Patients Who Have Received PHE vs. LEV |
|----------------------------------------|----------------------------------------|----------------------------------------|
| Population                             | Intervention                          | Outcome (PHE vs. LEV)                  |
| Patients who received LEV or PHE >48h and ICD-9 code for TBI | 32 PHE patients                       | GOS-E scores                           |
|                                       | 14 respondents                         | 5.07 vs. 5.60                           |
| Gabriel et. al 2014<sup>28</sup>      | 14 LEV patients                        | p=0.58                                 |
|                                       | 5 respondents                          | Early seizures                         |
|                                       |                                        | 3 vs 0                                 |
|                                       |                                        | p=0.53                                 |
|                                        | Medication-related Complications       | p=0.038, OR =0.07                       |
|                                        |                                        | (95% CI = 0.01-0.86)                   |

c. Bottom Line
   i. No difference in GOS-E scores 6 months or more after TBI
   ii. Patients who received LEV had less medication-related complications

Cost

XIII. Cost Minimization Analysis
   a. Methods
      i. Compared studies by Jones and Szaflarski
      ii. Decision tree built based upon costs, charges, and probability estimates

b. Costs and charges estimations (See Appendix D)
   i. Deterioration in mental status = CT of head
   ii. Anemia = CBC
   iii. Gastrointestinal Upset = Marginal (not included)

c. Model Assumptions
   i. No difference in early seizure rate
   ii. Difference in adverse event rates
XIII. Cost Minimization Analysis (cont.)

d. Results
   i. Institutional Costs - PHE: $151.24, LEV: $411.85
   ii. Patient Charge - PHE: $2,302.50, LEV: $3498.40

e. Bottom Line
   i. PHE remained the less costly strategy even in most extreme scenario, where probabilities of deteriorating mental status and anemia were increased to 1.
   ii. LEV replaced PHE as less costly strategy only when cost of treating deteriorating mental status was > $1,100 (average cost: $218.69 - See Appendix D)

XIV. Cost Utility Analysis

a. Base Assumptions
   i. All TBI patients receive prophylaxis
   ii. PHE dosing: 1g fosPHE LD, followed by 100mg PHE IV Q8H
      1. Level drawn on day 3
      2. Therapeutic patients continue 100mg Q8H days 4-7
      3. Subtherapeutic patients receive 200mg Q8H days 4-7
   iii. LEV dosing: 500mg IV LD, followed by 500mg IV Q12H

b. Outcomes parameters
   i. 50% Poor Outcome (GOS = 2-3)
   ii. 40% Good Outcome (GOS = 4-5)
   iii. 10% Die (GOS = 1)

c. Results
   i. PHE = $1.58/QALY
   ii. LEV = $ 20.72 QALY

d. Bottom Line
   i. LEV would only be considered more effective than PHE if it cost <$400/day
   ii. Study did not account for costs related to PHE monitoring or side effects

XV. Take Home Points (See Appendix E)

a. Prophylaxis effective for early seizures only
   i. Treatment only for 7 days
b. No difference in long-term outcomes
c. Majority trial recommendations: LEV as effective as PHE
   i. Must assess clinical picture
d. Dosing strategies remain a question
XVI. References

Appendix A. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Glasgow Coma Scale</th>
<th>Scale</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Eye Opening Response</td>
<td>Eyes open spontaneously</td>
<td>4 Points</td>
</tr>
<tr>
<td></td>
<td>Eyes open to verbal command, speech, or shout</td>
<td>3 Points</td>
</tr>
<tr>
<td></td>
<td>Eyes open to pain (not applied to face)</td>
<td>2 Points</td>
</tr>
<tr>
<td></td>
<td>No eye opening</td>
<td>1 Point</td>
</tr>
<tr>
<td>Verbal Response</td>
<td>Oriented</td>
<td>5 Points</td>
</tr>
<tr>
<td></td>
<td>Confused conversation, but able to answer questions</td>
<td>4 Points</td>
</tr>
<tr>
<td></td>
<td>Inappropriate responses, words discernible</td>
<td>3 Points</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds or speech</td>
<td>2 Points</td>
</tr>
<tr>
<td></td>
<td>No verbal response</td>
<td>1 Point</td>
</tr>
<tr>
<td>Motor Response</td>
<td>Obey commands for movement</td>
<td>6 Points</td>
</tr>
<tr>
<td></td>
<td>Purposeful movement to painful stimulus</td>
<td>5 Points</td>
</tr>
<tr>
<td></td>
<td>Withdraws from pain</td>
<td>4 Points</td>
</tr>
<tr>
<td></td>
<td>Abnormal (spastic) flexion, decorticate posture</td>
<td>3 Points</td>
</tr>
<tr>
<td></td>
<td>Extensor (rigid) response, decerebrate posture</td>
<td>2 Points</td>
</tr>
<tr>
<td></td>
<td>No motor response</td>
<td>1 Point</td>
</tr>
</tbody>
</table>

Minor Brain Injury = 13-15 points; Moderate Brain Injury = 9-12 points; Severe Brain Injury = 5-8 points

Appendix B. Physician Prescribing Preference

![Graph showing prescribing preferences]
## Appendix C. 2012 Meta-Analysis Results

### Forrest Plot of Studies Reporting Early Seizures

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Seizure Incidence</th>
<th>Odds Ratio (95 CI%)</th>
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</thead>
<tbody>
<tr>
<td>Jones 2008</td>
<td>0/41 1/32</td>
<td>0.253 (0.010 - 6.421)</td>
</tr>
<tr>
<td>Milligan 2008</td>
<td>11/210 2/105</td>
<td>2.847 (0.619 - 13.085)</td>
</tr>
<tr>
<td>Szafarski 2010</td>
<td>3/18 5/34</td>
<td>1.160 (0.243 - 5.527)</td>
</tr>
<tr>
<td>Taylor 2010</td>
<td>2/25 0/60</td>
<td>12.872 (0.585 - 278.270)</td>
</tr>
<tr>
<td>Murphey-Human 2011</td>
<td>10/297 12/145</td>
<td>0.386 (0.163 - 0.916)</td>
</tr>
<tr>
<td>POOLED</td>
<td>26/591 20/376</td>
<td>1.118 (0.343 - 3.636)</td>
</tr>
</tbody>
</table>

(I- squared = 56.6 % p = 0.056)

### Forrest Plot of Studies Reporting Early Seizures Within 7 Days

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Seizure Incidence</th>
<th>Odds Ratio (95 CI%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones 2008</td>
<td>0/41 1/32</td>
<td>0.253 (0.010 - 6.421)</td>
</tr>
<tr>
<td>Milligan 2008</td>
<td>9/210 1/105</td>
<td>4.657 (0.582 - 37.256)</td>
</tr>
<tr>
<td>Szafarski 2010</td>
<td>3/18 5/34</td>
<td>1.160 (0.243 - 5.527)</td>
</tr>
<tr>
<td>Murphy-Human 2011</td>
<td>4/297 4/145</td>
<td>0.481 (0.119 - 1.952)</td>
</tr>
<tr>
<td>POOLED</td>
<td>16/566 11/316</td>
<td>0.962 (0.338 - 2.756)</td>
</tr>
</tbody>
</table>

(I- squared = 22.2 % p = 0.278)
## Appendix D. Cost Minimization Analysis

### Probability Estimates for Baseline Events

<table>
<thead>
<tr>
<th>Event</th>
<th>PHE</th>
<th>LEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Seizure</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Deteriorating Mental Status</td>
<td>0.50</td>
<td>0.18</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.21</td>
<td>0.40</td>
</tr>
<tr>
<td>Gastrointestinal Upset</td>
<td>0.22</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Appendix E. Dosing Algorithm

Phenytoin
15-20mg/kg IV LD
100mg IV Q8H MD x 7 days

Check level by day 3
Consider free PHE in organ failure

<65
Age
>65

Normal
LFTs
Elevated

CrCl >10
CKD
CrCl <10

No
Hx liver disease or alcohol abuse
Yes

Levetiracetam
1000mg IV LD
500mg Q12H MD x 7 days

Shortage

Phenytoin

No organ failure
Normal Dosing

Organ failure
No Bolus