Meta-Analysis of Retention Rates of Post-Marketing Trials to Compare Effectiveness of Second Generation Antiepileptic Drugs

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Introduction

• Epilepsy is a severe CNS disorder with recurrent seizures affecting about 1% of the worldwide population
• About 30% of the patients, especially those with partial onset seizures (POS), are refractory or partial responders to antiepileptic drug (AED) medication and will continue to have seizures requiring long term treatment with 1 or more AEDs
• The efficacy of novel AEDs in clinical trials is usually evaluated in refractory patients with POS who receive a baseline therapy of 1 to 3 AEDs to which a novel compound or placebo is added for several months
• The primary endpoints of regulatory studies are
  • Median percent reduction in monthly seizure rate compared to baseline
  • Responder rate defined as the percent of study subjects achieving at least a 50% reduction in seizure frequency
• These standard designs have the downside of not measuring the overall effectiveness of the novel treatments not their long term benefits and risks due to the relatively short trial duration
• Novel long term effectiveness endpoints are crucial to compare the utility of novel AEDs in epilepsy
Motivation

• Both the International League Against Epilepsy (ILAE) and the European Medicines Agency (EMEA) have suggested to collect long term retention data as relevant endpoint for clinical trials of AEDs
• Retention is the duration of time a patient stays on treatment; it is calculated as the time to treatment failure/study withdrawal for any reason
• Retention/Treatment discontinuation can potentially be used as a long term effectiveness endpoint or Clinical Utility (CU) parameter since patients are only willing stay on medication if the benefits (seizure reduction) outweighs the risk (tolerability and safety issues) of a drug

Hypothesis:
• We hypothesized that newer AEDs (introduced after 1990), when used to treat patients with POS adjunctively, have a distinct characteristic retention profile
• This retention profile might be a useful parameter for comparative effectiveness evaluations
Objectives of the analysis, and purpose of this presentation

• To perform a meta-analysis and to develop a retention model from clinical trial publications of newer, so called “second-generation” AEDs in patients with POS treated adjunctively

• To describe the challenges of performing a meta-analysis of time-to-event data extracted from the literature, and our approach to solving this issue
Characteristics of trials and patients included in the meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin</th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
<th>Tiagabine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>3,680</td>
<td>3,149</td>
<td>5,187</td>
<td>1,563</td>
<td>3,246</td>
</tr>
<tr>
<td>Trials, N*</td>
<td>7</td>
<td>9</td>
<td>14</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Mean (range) baseline AEDs, N</td>
<td>1.9 (1.0-2.3)</td>
<td>1.7 (1.1-2.7)</td>
<td>1.8 (1.1-2.9)</td>
<td>2.1 (1.1-2.8)</td>
<td>1.7 (1.1-3.0)</td>
</tr>
<tr>
<td>Median (range) study duration, mo</td>
<td>6 (4-36)</td>
<td>36 (4-60)</td>
<td>18 (4-60)</td>
<td>4 (3-36)</td>
<td>14 (5-60)</td>
</tr>
<tr>
<td>Mean dose (range), mg</td>
<td>1,721 (1,575-2,582)</td>
<td>292 (226-392)</td>
<td>1,794 (1,650-2,373)</td>
<td>32.4 (29.1-39.1)</td>
<td>293 (233-355)</td>
</tr>
</tbody>
</table>

AED: antiepileptic drug.
*Some studies reported more than 1 drug.
Example of retention data – methodological challenges of the “survival” analysis

- In general retention can only be adequately compared within a certain study or across studies if the patient population and the study set up is similar
- The curves monotonically decline to a steady-state level
  - Most patients, who discontinue a 2nd generation AED by 3 years, will have already done so by 2 years
  - A simple constant hazard model for discontinuation will not be appropriate
- Information within a single curve is highly correlated
  - Cumulative retention over time
  - Any modeling methodology needs to appropriately account for this correlation.
- The retention rate is not just a function of the patient discontinuations
  - Presence of censoring, effectively decreases the number patients available to discontinue.
  - The calculated retention rate using the Kaplan-Meier (KM) estimator is less than the observed retention rate
- The information in the curves may become less reliable with increasing time
  - The number of patients still on treatment is gradually decreasing (discontinuation/loss to follow-up)
  - The precise numbers of patients (N, retention/discontinuation/loss to follow-up) from the curve may be unknown
- Substantial between-study variability in retention requires an appropriate mixed-effects structure

Peltola et al., 2009
Validation of our proposed approximate method of analysis

- Time to probability of retention was estimated with a 2-component constant hazard model
  - Steady-state retention level: the stable retention level typically reached over 3-5 years
  - Retention rate: speed of loss of retention (i.e., percent retention per unit of time)

- Simulation
  - Discontinuation profiles (raw data)
  - Construct KM curves from raw data
  - Sampled data from KM curves

- Analysis
  - Raw data: exact method
  - Sampled data: approximate method
  - Parameters were estimated with nonlinear mixed-effects regression in SPLUS 6.1 (nlme)

- Compare results
  - Precision
  - Bias
Analytical approaches—
exact method for survival (raw data)

\[ S_t = P_{SS} + (1 - P_{SS}) \cdot e^{-h \cdot t} \]

\[ L_i = (1 - X_i) \cdot S_t + X_i \cdot (1 - P_{SS}) \cdot h \cdot e^{-h \cdot t} \]

and

\[ L(h, P_{SS}) = \prod_i L_i \]

Where

– \( P_{SS} \) and \( h \) are the steady-state retention and first-order rate at which subjects discontinue, respectively

– \( X_i \) is a censor variable \( X_i \), where \( X_i = 1 \) if the subject has discontinued and \( X_i = 0 \) if the subject does not have a discontinuation time
Analytical approaches - approximate method for KM samples

\[ \Pr_i = \text{Prob}(\text{Discontinue in } [T_i, T_{i+1}] | h, P_{SS}) \]

\[ = \frac{\text{Prob}(\text{In Study at } T_i | h, P_{SS}) - \text{Prob}(\text{In Study at } T_{i+1} | h, P_{SS})}{\text{Prob}(\text{In Study at } T_i | h, P_{SS})} \]

\[ \text{Prob}(\text{In Study at } T_i | h, P_{SS}) = P_{SS} + (1 - P_{SS}) \cdot e^{-h \cdot t} \]

\[ \Pr_{\text{obs}} = \frac{(N_i - N_{i+1})}{N_i} \]

\[ \text{Obj}(h, P_{SS}) = \Sigma_i \left( \Pr_{\text{obs}} - \Pr_i(h, P_{SS}) \right)^2 \]
Validation of our proposed approximate method of analysis - results

- Estimated model fit using raw data (red) match with fit from sampled data (blue)
- 90% confidence intervals are also in agreement between the two methods
- Thus, sampled data contains all relevant information and correctly accounts for correlation between time points

<table>
<thead>
<tr>
<th>Description</th>
<th>Variable</th>
<th>Metric</th>
<th>Raw Data</th>
<th>Digitized Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state retention</td>
<td>$P_{ss}$ (%)</td>
<td>Range [10th, 50th, 90th %iles]</td>
<td>[40%, 50%, 57%]</td>
<td>[40%, 50%, 58%]</td>
</tr>
<tr>
<td>Steady-state retention</td>
<td>$P_{ss}$ (%)</td>
<td>Coverage 90% CI</td>
<td>67%</td>
<td>71%</td>
</tr>
<tr>
<td>Discontinuation hazard</td>
<td>$h$ (mo$^{-1}$)</td>
<td>Range [10th, 50th, 90th %iles]</td>
<td>[0.16, 0.20, 0.27]</td>
<td>[0.16, 0.21, 0.27]</td>
</tr>
<tr>
<td>Discontinuation hazard</td>
<td>$h$ (mo$^{-1}$)</td>
<td>Coverage 90% CI</td>
<td>79%</td>
<td>76%</td>
</tr>
</tbody>
</table>
Variability between trials in retention data

- Emphasize the need for a mixed effects model (MEM)
- Simulations further validate the approximate method using MEM

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<th>Metric</th>
<th>Digitized Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state retention</td>
<td>P&lt;sub&gt;ss&lt;/sub&gt; (%)</td>
<td>Range [10&lt;sup&gt;th&lt;/sup&gt;, 50&lt;sup&gt;th&lt;/sup&gt;, 90&lt;sup&gt;th&lt;/sup&gt; %iles]</td>
<td>[45%, 49%, 52%]</td>
</tr>
<tr>
<td>Steady-state retention</td>
<td>P&lt;sub&gt;ss&lt;/sub&gt; (%)</td>
<td>Coverage 90% CI</td>
<td>83%</td>
</tr>
<tr>
<td>Discontinuation hazard</td>
<td>h (mo&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>Range [10&lt;sup&gt;th&lt;/sup&gt;, 50&lt;sup&gt;th&lt;/sup&gt;, 90&lt;sup&gt;th&lt;/sup&gt; %iles]</td>
<td>[0.18, 0.20, 0.22]</td>
</tr>
<tr>
<td>Discontinuation hazard</td>
<td>h (mo&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>Coverage 90% CI</td>
<td>83%</td>
</tr>
<tr>
<td>Steady-state retention variability</td>
<td>σ&lt;sub&gt;Pss&lt;/sub&gt;</td>
<td>Range [10&lt;sup&gt;th&lt;/sup&gt;, 50&lt;sup&gt;th&lt;/sup&gt;, 90&lt;sup&gt;th&lt;/sup&gt; %iles]</td>
<td>[0.25, 0.37, 0.53]</td>
</tr>
<tr>
<td>Discontinuation variability</td>
<td>σ&lt;sub&gt;h&lt;/sub&gt;</td>
<td>Range [10&lt;sup&gt;th&lt;/sup&gt;, 50&lt;sup&gt;th&lt;/sup&gt;, 90&lt;sup&gt;th&lt;/sup&gt; %iles]</td>
<td>[0.08, 0.21, 0.30]</td>
</tr>
</tbody>
</table>
Model-predicted versus observed retention rates (lamotrigine)
Modeled-predicted retention rates for five AEDs in the database

<table>
<thead>
<tr>
<th>AED</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>84 (79-88)</td>
<td>74 (68-80)</td>
<td>64 (58-71)</td>
<td>61 (53-68)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>83 (78-86)</td>
<td>70 (64-76)</td>
<td>56 (49-62)*</td>
<td>49 (42-55)*</td>
</tr>
<tr>
<td>Topiramate</td>
<td>78 (72-83)**</td>
<td>63 (56-70)**</td>
<td>47 (40-55)**</td>
<td>40 (33-47)**</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>69 (60-76)**#</td>
<td>49 (39-59)**#</td>
<td>29 (21-39)**#</td>
<td>22 (15-31)**#</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>66 (54-78)**#</td>
<td>48 (36-64)**#</td>
<td>34 (22-55)**#</td>
<td>30 (17-53)*</td>
</tr>
</tbody>
</table>

*P<0.05 vs. lamotrigine.
**P<0.05 vs. levetiracetam.
#P<0.05 vs. topiramate.

![Graph showing retention rates over time for different AEDs](Image)
Model-based Findings

• At 6 months, there was an 18% difference between the best- and the worst-performing drug; this difference widened to 35% at the end of Year 2
• Modeled retention rates for the selected drugs were in the same order for all time points, with the exception of gabapentin and tiagabine, which crossed over after Year 1
• Significant differences in retention occurred as early as 3 to 6 months; however, lamotrigine did not become superior to levetiracetam until the end of Year 2
• Retention rates in double-blind studies (data not shown here)
  – Same rank order as for open-label/retrospective studies
  – However, for gabapentin, retention rate was higher
    • Much lower dose (900 mg/1200 mg) in double-blind studies than in post-marketing studies (1,575 mg to 2,582 mg).
• The effects of baseline AED, publication date, and sample size on retention were not significant
Conclusions/Comments

• We believe that this method is novel, and can be applied in general to parametric meta-analysis of survival curves
• Therefore, it has general applicability to time-to-event data
• We tried some more exact methods, but in general the calculations/programming took much longer
• Work in progress
  – Better characterization of the reason for discontinuation, which might give insights into the clinical differences in the drug profiles and their utility
  – Impact of various rates of loss-to-follow-up
• The methodology provided here can be used to
  – Plan future comparative effectiveness studies using retention as a primary endpoint and
  – Allow sample size calculation powered for the expected differences among compounds
Acknowledgements

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