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

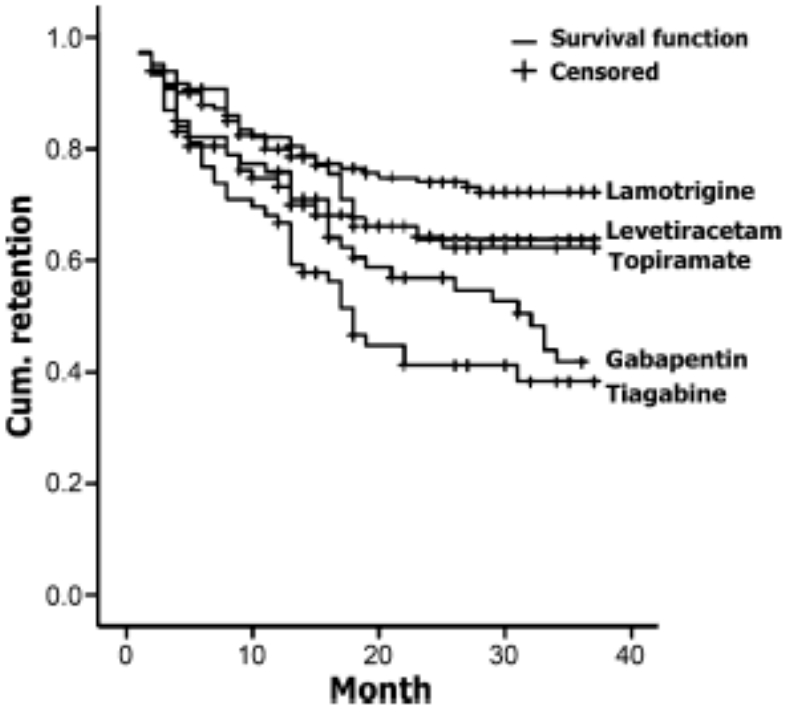
- To perform a meta-analysis and to develop a retention model from clinical trial publications of newer, so called “second-generation” AEDs in patients with POS treated adjunctively
- To describe the challenges of performing a meta-analysis of time-to-event data extracted from the literature, and our approach to solving this issue

Characteristics of trials and patients included in the meta-analysis

	Gabapentin	Lamotrigine	Levetiracetam	Tiagabine	Topiramate
Patients, N	3,680	3,149	5,187	1,563	3,246
Trials, N*	7	9	14	7	11
Mean (range) baseline AEDs, N	1.9 (1.0-2.3)	1.7 (1.1-2.7)	1.8 (1.1-2.9)	2.1 (1.1-2.8)	1.7 (1.1-3.0)
Median (range) study duration, mo	6 (4-36)	36 (4-60)	18 (4-60)	4 (3-36)	14 (5-60)
Mean dose (range), mg	1,721 (1,575-2,582)	292 (226-392)	1,794 (1,650-2,373)	32.4 (29.1-39.1)	293 (233-355)
Median (range) publication year	2005 (1996-2009)	2005 (1996-2009)	2006 (2003-2009)	2005 (2001-2009)	2005 (1999-2009)
Year first available	1993	1990	1999	1996	1995

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

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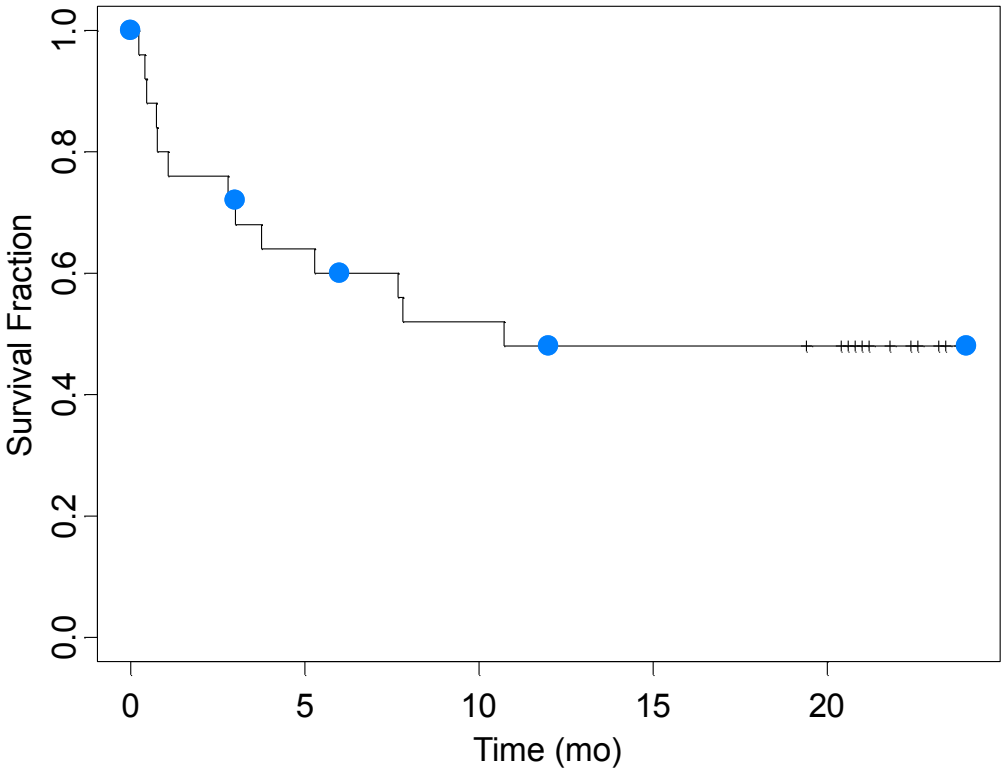
Validation of our proposed approximate method of analysis



- 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 (ie, 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)

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

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

$$and$$

$$L(h, P_{SS}) = \Pi_i \; L_i$$

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

$$\mathrm{Pr}_i = \mathrm{Prob}(Discontinue\ in\ [Ti, Ti+1] \mid h, P_{SS})$$

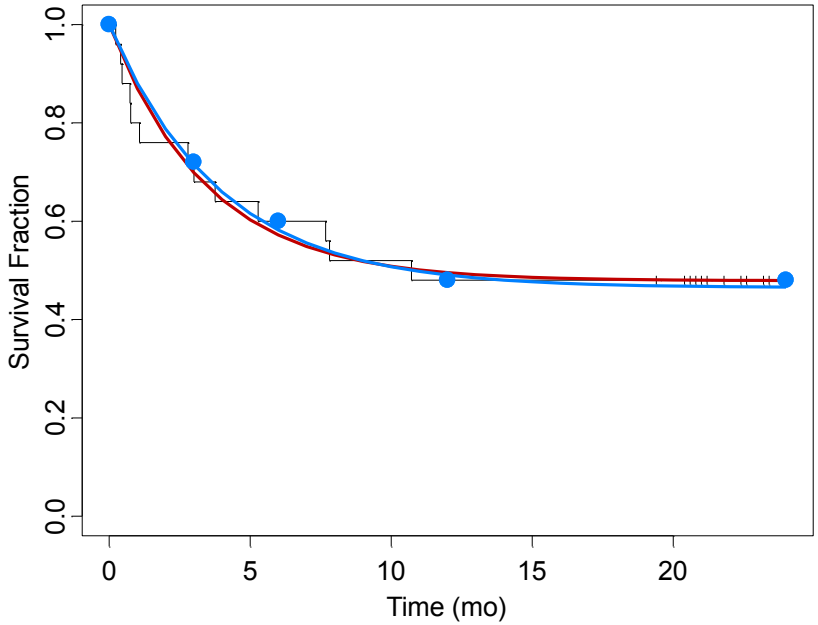
$$= \frac{\mathrm{Prob}(In\ Study\ at\ T_i \mid h, P_{SS}) - \mathrm{Prob}(In\ Study\ at\ T_{i+1} \mid h, P_{SS})}{\mathrm{Prob}(In\ Study\ at\ T_i \mid h, P_{SS})}$$

$$\mathrm{Prob}(In\ Study\ at\ T_i \mid h, P_{SS}) = P_{SS} + (1 - P_{SS}) \cdot e^{-h \cdot t}$$

$$\mathrm{Pr}_{obs} = \frac{(N_i - N_{i+1})}{N_i}$$

$$Obj(h, P_{SS}) = \Sigma_i \left(\mathrm{Pr}_{obs} - \mathrm{Pr}_i(h, P_{SS})\right)^2$$

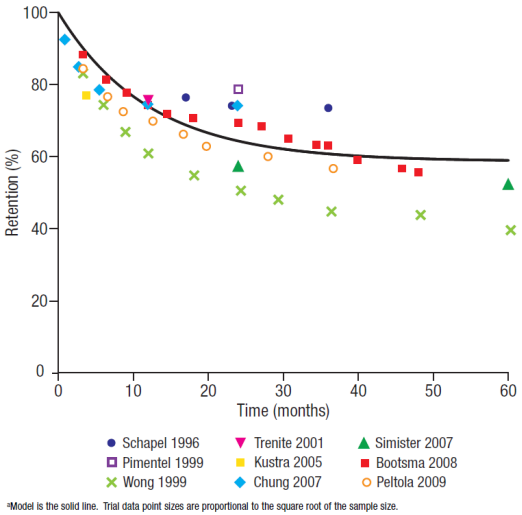
Validation of our proposed approximate method of analysis - results



- 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

Description	Variable	Metric	Raw Data	Digitized Data
Steady-state retention	P_{ss} (%)	Range [10th, 50th, 90th %iles]	[40%, 50%, 57%]	[40%, 50%, 58%]
Steady-state retention	P_{ss} (%)	Coverage 90% CI	67%	71%
Discontinuation hazard	h (mo^{-1})	Range [10th, 50th, 90th %iles]	[0.16, 0.20, 0.27]	[0.16, 0.21, 0.27]
Discontinuation hazard	h (mo^{-1})	Coverage 90% CI	79%	76%

Variability between trials in retention data

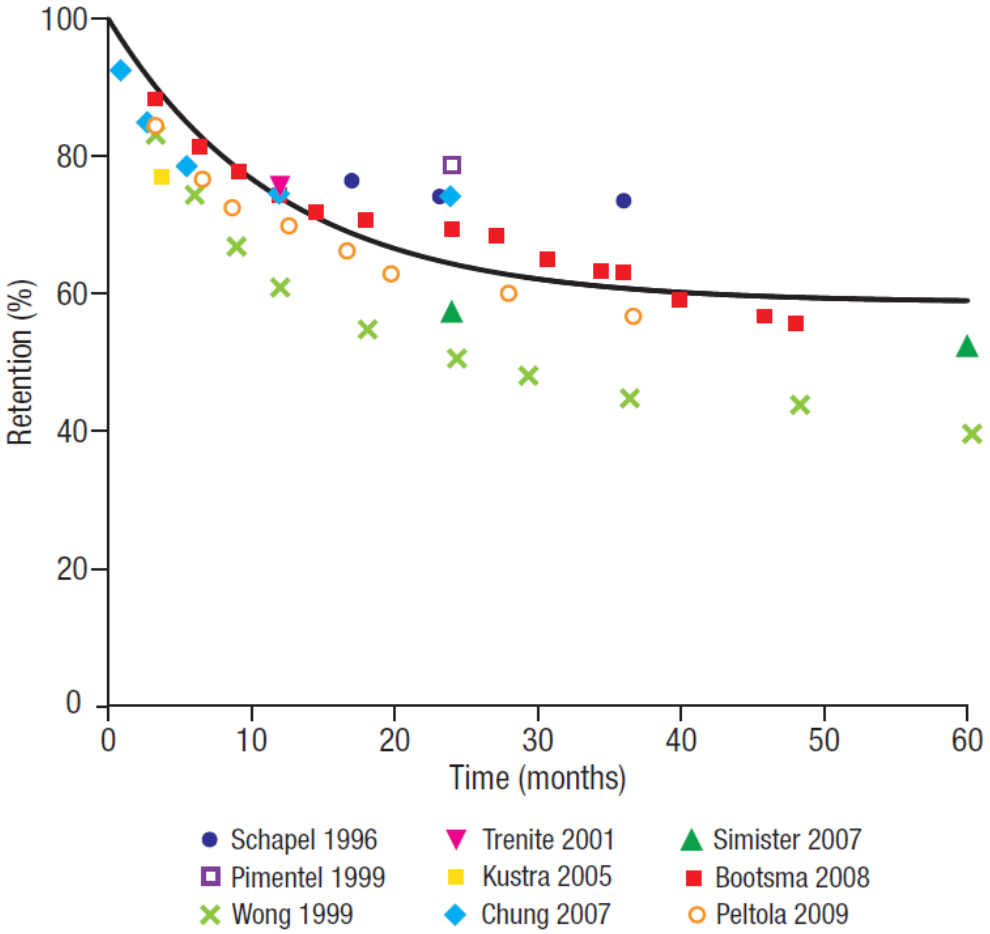


[a]Model is the solid line. Trial data point sizes are proportional to the square root of the sample size.

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

Description	Variable	Metric	Digitized Data
Steady-state retention	P_{ss} (%)	Range [10th, 50th, 90th %iles]	[45%, 49%, 52%]
Steady-state retention	P_{ss} (%)	Coverage 90% CI	83%
Discontinuation hazard	h (mo^{-1})	Range [10th, 50th, 90th %iles]	[0.18, 0.20, 0.22]
Discontinuation hazard	h (mo^{-1})	Coverage 90% CI	83%
Steady-state retention variability	σ_{Pss}	Range [10th, 50th, 90th %iles]	[0.25, 0.37, 0.53]
Discontinuation variability	σ_h	Range [10th, 50th, 90th %iles]	[0.08, 0.21, 0.30]

Model-predicted versus observed retention rates (lamotrigine)

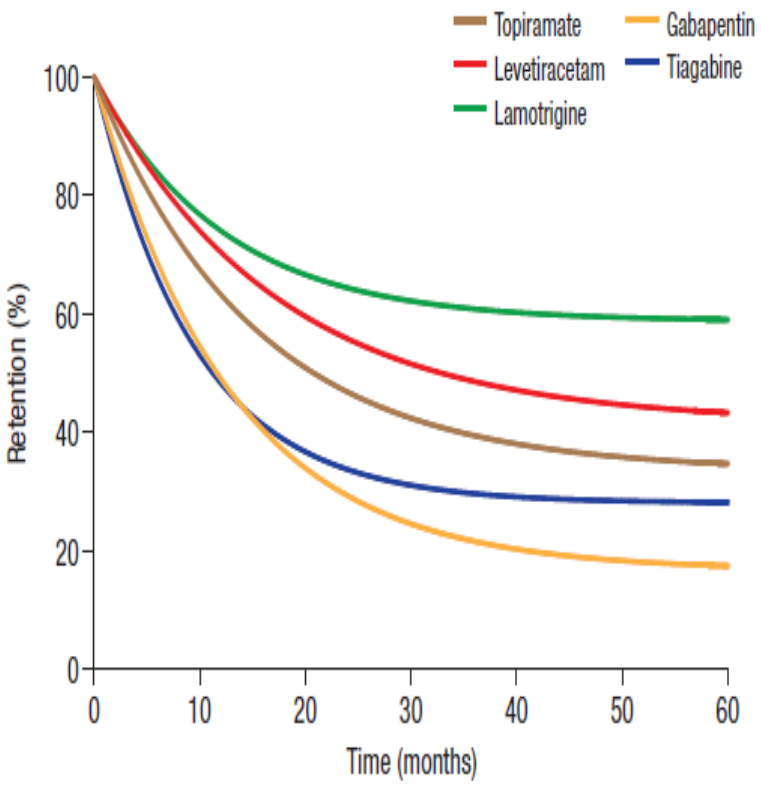


[a]Model is the solid line. Trial data point sizes are proportional to the square root of the sample size.

Modeled-predicted retention rates for five AEDs in the database

AED	Median (Range) Retention, %			
	6 months	1 year	2 years	3 years
Lamotrigine	84 (79-88)	74 (68-80)	64 (58-71)	61 (53-68)
Levetiracetam	83 (78-86)	70 (64-76)	56 (49-62)*	49 (42-55)*
Topiramate	78 (72-83)*†	63 (56-70)*†	47 (40-55)*†	40 (33-47)*†
Gabapentin	69 (60-76)*†‡	49 (39-59)*†‡	29 (21-39)*†‡	22 (15-31)*†‡
Tiagabine	66 (54-78)*†‡	48 (36-64)*†‡	34 (22-55)*†	30 (17-53)*

*P <0.05 vs. lamotrigine.
†P <0.05 vs. levetiracetam.
‡P <0.05 vs. topiramate.



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

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