HISTORICAL CONTROL WITHDRAWAL TO MONOTHERAPY

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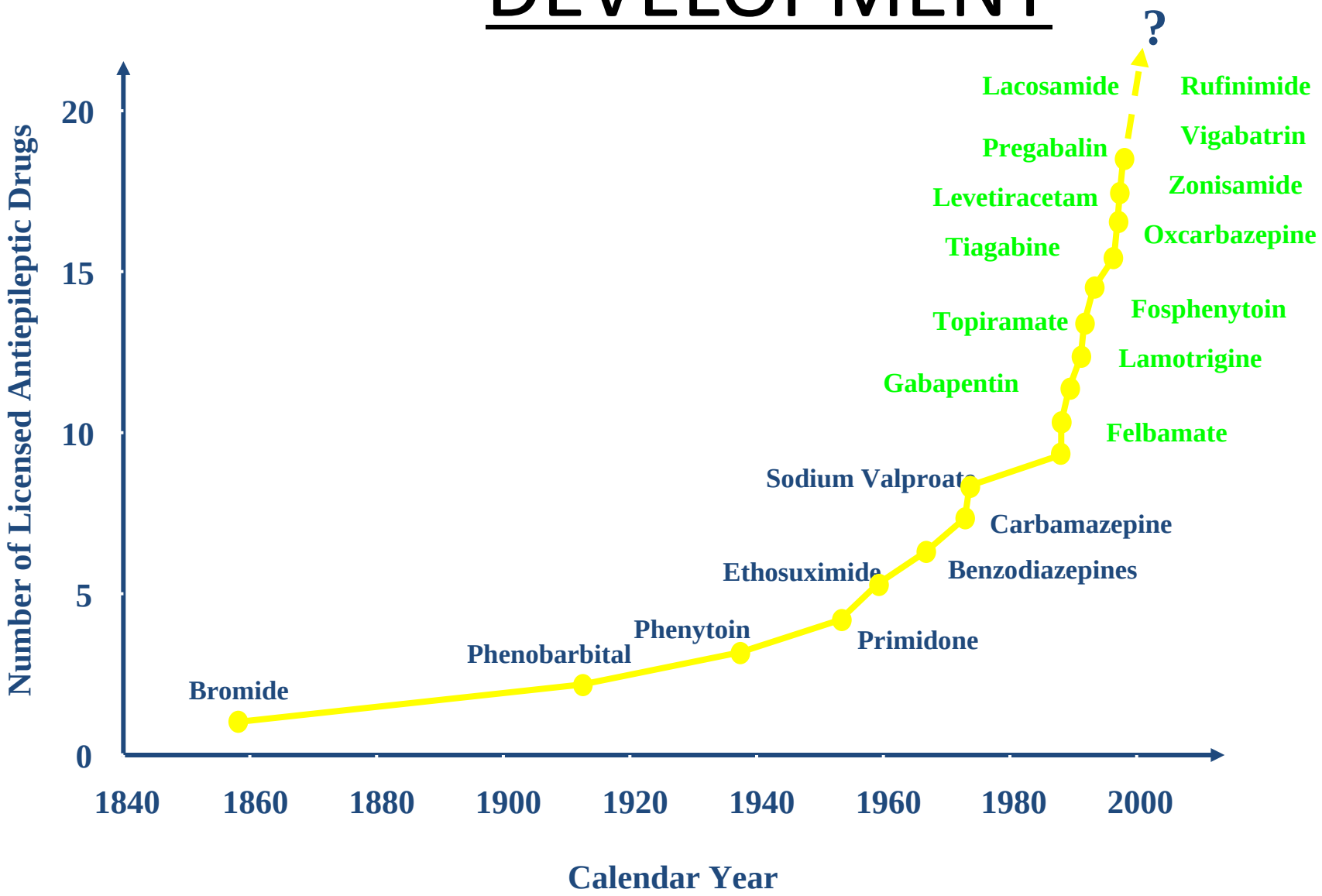
ANTIEPILEPTIC DRUG DEVELOPMENT



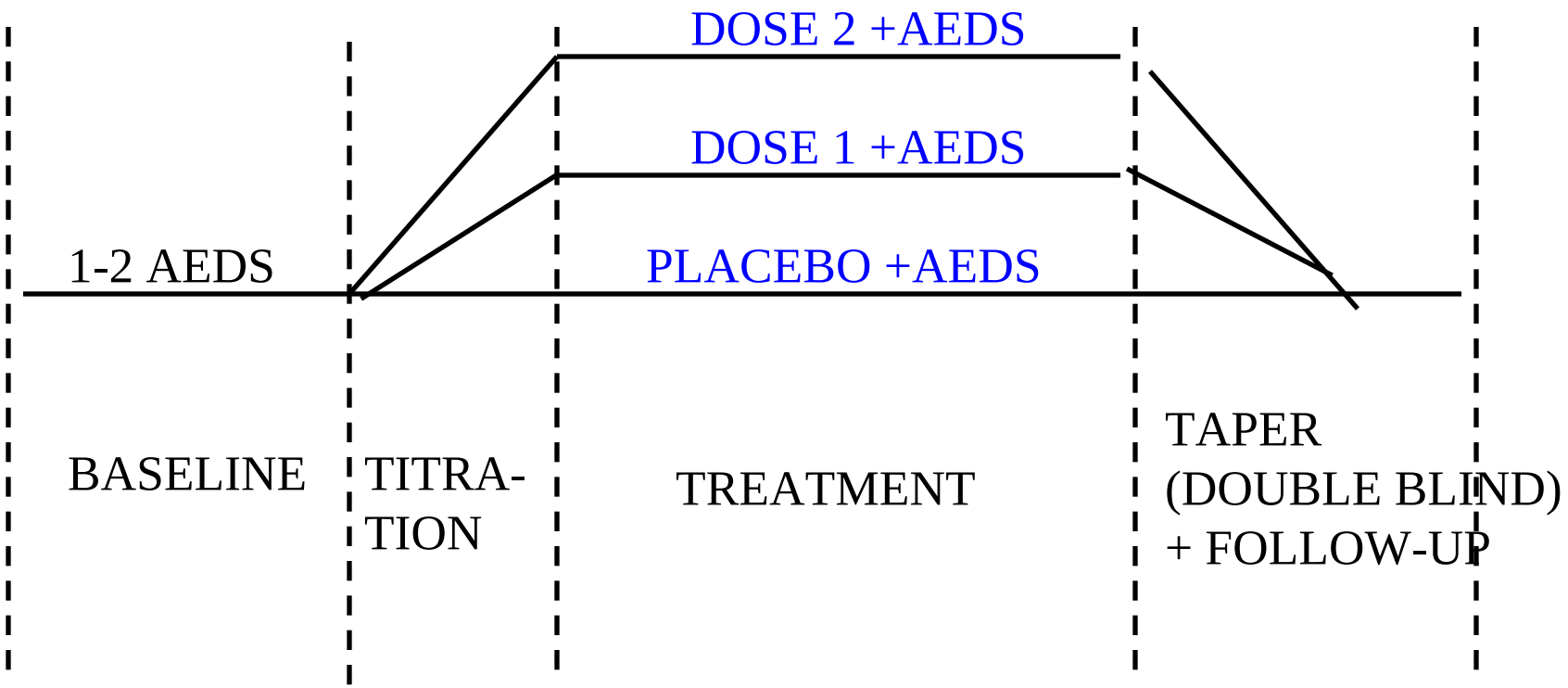
INTRODUCTION

- Approval of new AEDs as monotherapy lagging behind general approval
- Of the 12 new anti-epileptic drugs (AEDs) approved for use in the United States over the last 2 decades, only 4 are approved for any use in monotherapy (oxcarbazepine, felbamate , lamotrigine and topiramate), and only two for initial monotherapy (oxcarbazepine and topiramate).

Introduction

- Older AEDs (phenytoin, carbamazepine, phenobarbital, valproate) were "grandfathered in"
- No new monotherapy approvals have been issued since 2005, despite 4 new AED releases since then

DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL



Why do we want to treat with Monotherapy?

- LESS SIDE EFFECTS(SHORT AND LONG-TERM)
- FEWER INTERACTION
- BETTER COMPLIANCE
- LESS TERATOGENIC

Some scenarios where monotherapy is clearly clinically imperative

- When a patient is having side effects from their current therapy. A new drug is added, and is effective-the toxic therapy should be withdrawn!
- When a woman is contemplating pregnancy and is on a teratogenic drug

DO WE NEED MONOTHERAPY APPROVAL?

- Add on trials lead to adjunctive indications
- We can use drugs off-label, BUT:
  - Insurance may not permit us to use in newly diagnosed patients
  - Potential liability in event of bad outcome
  - Less physicians feel comfortable using off-label, so older AEDs may continue to be considered “first line therapy”, particularly among general neurologists and primary care physicians.

- The difficulty in obtaining US monotherapy approval for AEDs arises from the fact that the FDA, in accordance with the International Conference on Harmonization (ICH), prefers trials that contain an internal, interpretable control group, i.e one where the test drug shows superiority to the control.

THE PROBLEM WITH SUPERIORITY

- Very difficult to demonstrate superiority in epilepsy patients
  - In treatment resistant patients, they are already on drug, so monotherapy would have to be withdrawal to monotherapy. Can't be comparative, because they have already been exposed to (and failed) comparator
  - with newly diagnosed disease, as pts very *sensitive* to Rx, and all comparative trials to date have ended in a "no difference" efficacy outcome. Our new drugs represent improvements in safety, tolerability, PK more than efficacy
  - Therefore, placebo-controlled (or low-dose-controlled) trials have been the only mechanism to establish superiority
- Are placebo-controlled trials an ethical/practical alternative for individuals with diagnosed epilepsy (a potentially life-threatening condition) who have access to already proven therapies?

Add-on Indication

- “This (Add-on) design is common in trials of therapy for cancer, heart failure, and epilepsy, in which omitting standard therapy would generally be unacceptable”

Robert Temple, talking about
Add-on trials
Annals of Internal Medicine, 2000

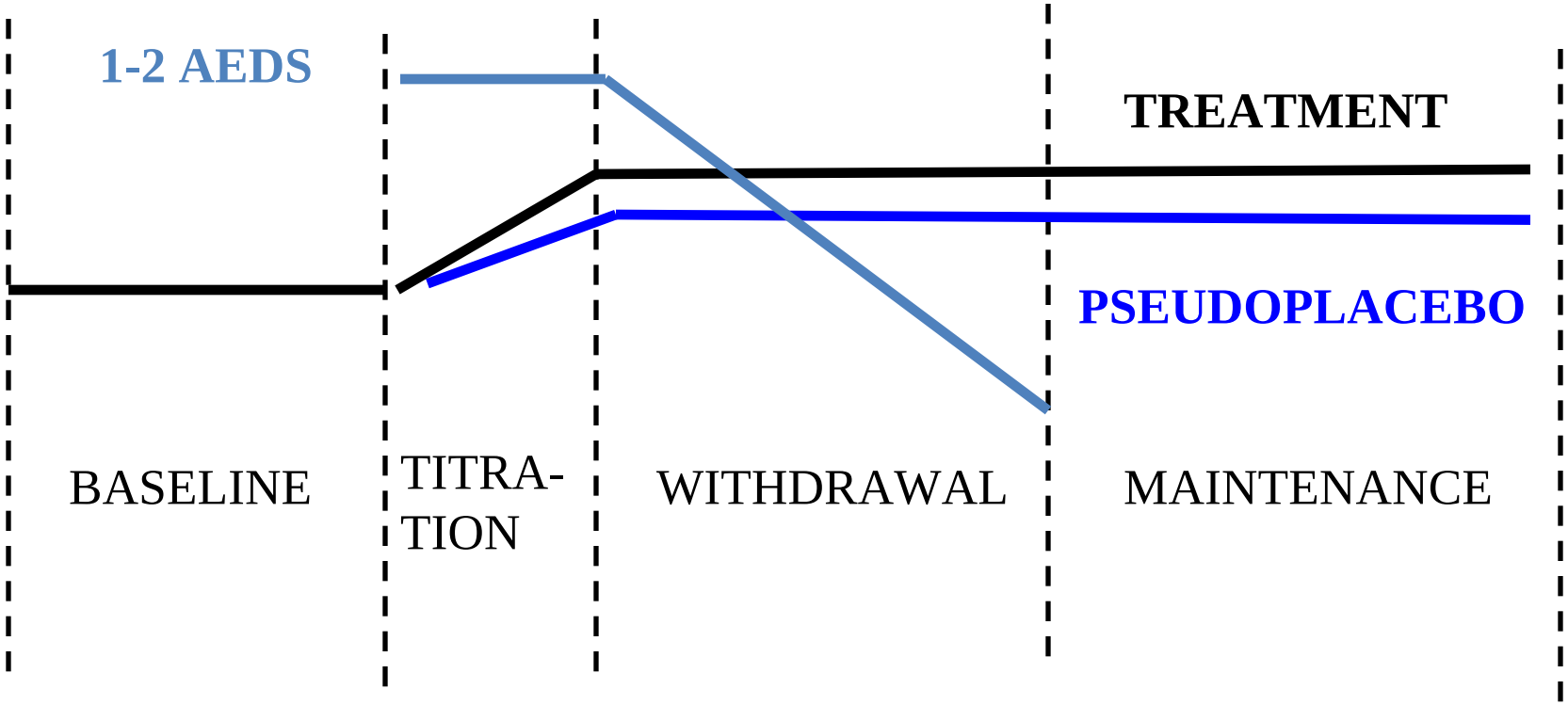
Placebo-Control

- Question of whether placebo-controlled trials are an ethical/practical alternative for individuals with diagnosed epilepsy (a potentially life-threatening condition) who have access to already proven therapies
- Thus, several strategies emerges using so-called "pseudoplacebo"

Pseudoplacebo Trials

- Assign patients to receive study drug vs a suboptimal maintenance dose of a safe and effective approved drug (e.g. valproic acid 1,000 mg/day, or low-dose of the study drug)
- The endpoints for these trials are described as “therapeutic failure” or “escape criteria.” In other words, they are intended to demonstrate clinical worsening of the subject (withdrawal to monotherapy) or less seizure control (initial monotherapy)

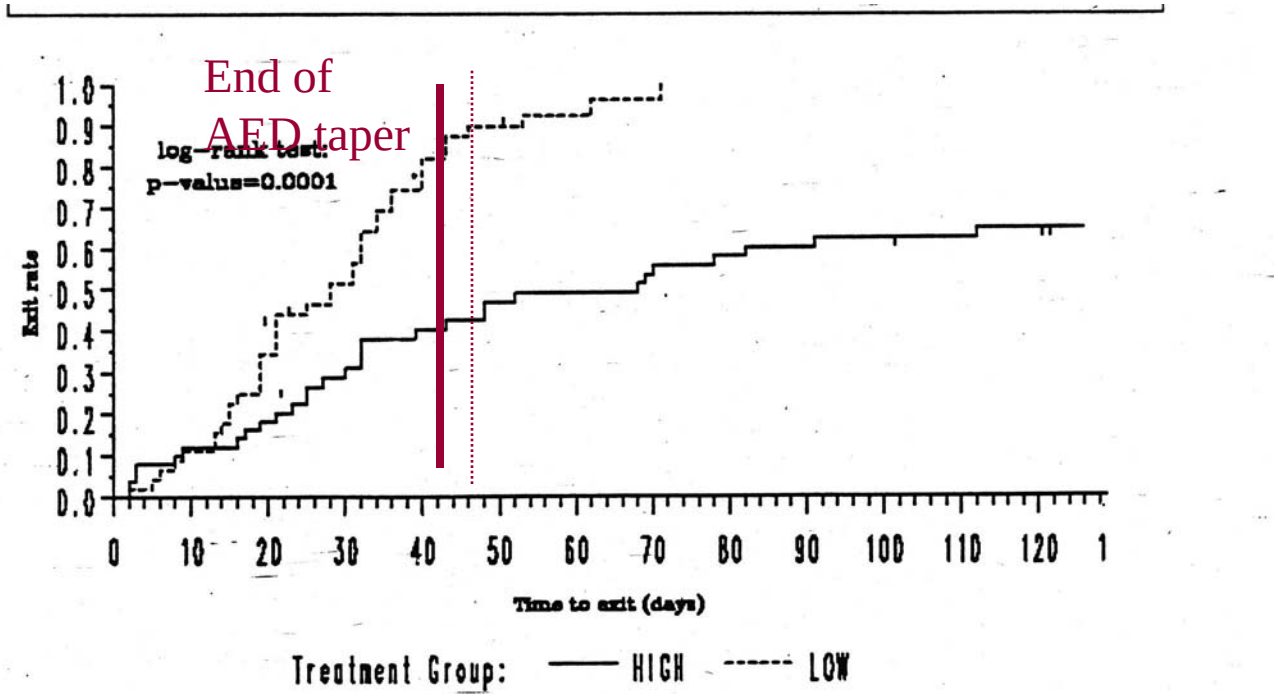
OUTPATIENT WITHDRAWAL TO MONOTHERAPY



ESCAPE CRITERIA

- Doubling of average monthly seizure rate
- Doubling of highest consecutive 2-day seizure rate
- Emergence of new, more severe seizure type
- Clinically significant prolongation of generalized tonic-clonic seizures

OXCARBAZEPINE 300 VS 2400 (AED W/DRAWN PRIOR)



FDA summary basis of approval

- The types of SAEs observed in previously performed lamotrigine withdrawal to monotherapy :
  - There were five SAEs in the active treatment group and five in the pseudo-placebo group; however, the types of SAEs were very different.
  - Patients in the lamotrigine group experienced chest pain, pneumonia, rash, Stevens-Johnson syndrome, and suicidal ideation, which are AE's one might expect to result from active treatment.
  - Patients in the pseudo-placebo group experienced exacerbation of convulsions, increased seizures, paranoid ideation, status epilepticus, and sudden unexplained death.
  - These adverse outcomes are a direct result of trial design, not study treatment and we have to take that into account when evaluating the ethics of these studies.

Monotherapy Meeting (March 2001)

- Epilepsy community was concerned about lack of monotherapy indications
- Brought together physician community, NINDS, FDA to discuss possible trial designs

CONSENSUS CONCLUSIONS

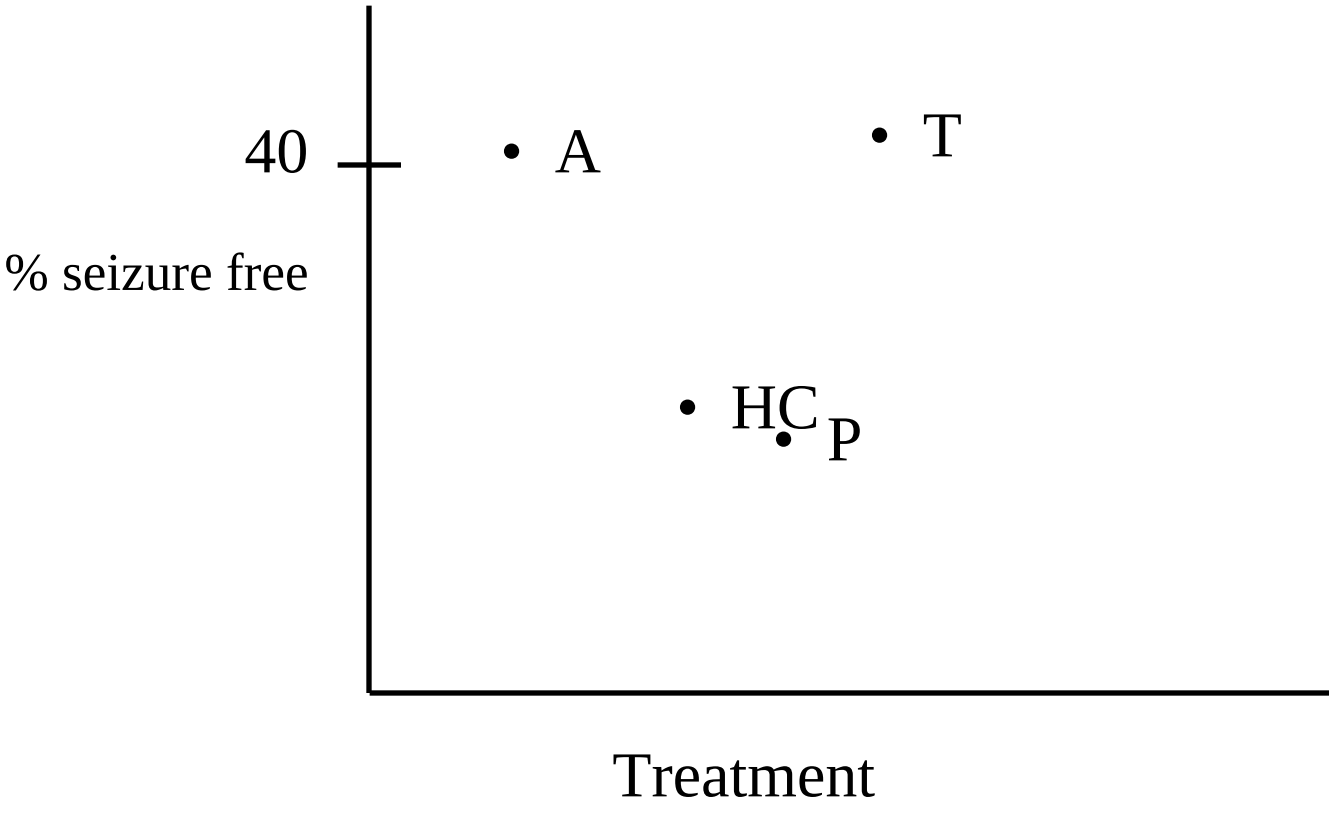
- We understand that the ideal methodology to prove the effect of an antiepileptic drug in monotherapy would be a comparison trial designed to show a difference. This could be in a newly diagnosed or refractory population
- There are convincing reasons why such a design is problematic in the epilepsy population.

THEREFORE

- We will investigate historical control in outpatient refractory monotherapy situation

HISTORICAL CONTROL

- Instead of using placebo as control group, use "expected" behavior of placebo, based on prior trials
- Not the same as "natural history", because it is linked to a specific trial design and population.
- Question we asked: Can we look at existing data from trials to generate a historical control, and eliminate placebo/pseudoplacebo?


40
% seizure free
A
T
HC
P
Treatment

HISTORICAL CONTROL IN REFRACTORY PATIENTS

- Ten studies have been performed in which patients were randomized to either a “pseudoplacebo” or active study drug, and then withdrawn towards monotherapy.
- These studies no longer considered ethical
- Similar methodology was used for all studies.
- *We performed a meta-analysis of all pseudo-placebo arms to determine whether they could serve as a historical control for future monotherapy trials.*

RESULTS

- In order to create a valid historical control, it was essential to obtain all similarly designed trials that have been performed.
- This included a review of the literature, searching for controlled clinical trials, epilepsy, and monotherapy in which antiepileptic drugs were withdrawn leading to monotherapy; query of colleagues to determine other trials that had been performed with this methodology; and direct inquiry to companies with drugs in development to determine if such a trial had been performed but not published.

- Review of the literature revealed 7 randomized controlled trials in which patients with refractory partial seizures were randomized to either active compound or “pseudo-placebo”, before (6 trials) or after (1 trials) being withdrawn towards monotherapy.
- Three additional unpublished trials were discovered by direct inquiry of companies with new AEDs in development.

- Once all trials were identified, each company was asked to provide primary individual patient data from the pseudoplacebo arm only of the study in question.
  - Data submitted to statisticians (Warnock, Temkin)
- Further information was obtained from study protocols where available, information available in the FDA Summary Basis of Approval (SBA), and study publication, when available.

METHODS

- In order to establish a historical control, it is imperative to establish that the studies had similar characteristics across the trials. It is therefore essential to ascertain that those trials had similar designs, exit criteria, and that they randomized patients with similar demographic characteristics .
- All but one study used similar inclusion criteria
  - Refractory partial seizures
  - 1-4 seizures/month minimum
  - Receiving one or two antiepileptic drugs at baseline

Methods

- All the trials were randomized, double-blind, parallel group design with a baseline phase followed by a double-blind phase divided into a conversion phase and a monotherapy phase. In all but one of the trials, patients were randomized prior to withdrawal of the baseline AED. One trial randomized patients after AED withdrawal.
- The conversion phase ranged from 4 to 10 weeks, and the monotherapy phase ranged from 11 to 16 weeks across the trials.

Exit Criteria

1. A two-fold increase in partial seizure frequency in any 28-day period compared to baseline. (All studies, although Study 1 used the highest 4 consecutive weeks in baseline and the others used the average frequency in baseline).
2. A two-fold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase. (All studies, although Study 2 required 3 seizures if the highest daily count in baseline was one seizure, and Study 8 did not use this criterion if the highest daily count was one seizure).

Exit Criteria (Continued)

3. Occurrence of a single generalized seizure if none had occurred in the previous 6 months (Study 6, Ref 14) , within two years of study entry (Study 1, Ref 13), during baseline (Studies 3, 5, 7, 8, Refs 18, 19, 17, 15), and “emergence of a more severe seizure type (which would include generalized seizure) (Study 2, Ref 16).
4. A prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention for all trials (although Studies 2, 5, and 7 require the worsening seizures to be generalized) or episode of serial seizure/status epilepticus for Studies 3,7,8, and episode of status epilepticus for study 1.

Background AEDs

- All trials allowed either one or up to two baseline AEDs.
- In Trial 5, the baseline AED had to be CBZ.
- For the five trials that allowed 2 AEDs at baseline, four required that one of the baseline AEDs be taken at less than 50% of the minimum recommended dose or that the serum concentration be less than 50% the minimum effective serum level.

Outcome Measure

- Outcome measure: Percent of patients exiting the trial.
- Patients exited the trial if they experienced seizure worsening as identified by predetermined exit criteria
- Four nearly identical exit criteria were used in 9/10 trials. The 10th trial used only 3 exit criteria, and only one matched a criterion used in the other studies. Therefore, this trial was excluded from the analysis.

Studies

Study	Test Drug	Comparator (pseudo-placebo)	Reference
1	Gabapentin	600 mg Gabapentin	Beydoun et al, 1997
2	Lamotrigine	1000 mg Valproic Acid	Gilliam et al, 1998
3	Topiramate	100 mg topiramate	Sachdeo et al, 1997
4	Felbamate	10 mic/mL felbamate	Unpublished
5	Oxcarbazepine	300 mg oxcarbazepine	Sachdeo et al 2001
6	Oxcarbazepine	300 mg oxcarbazepine	Beydoun et al 2000
7	Felbamate	15 mg/kg Valproic Acid	Sachdeo et al 1992
8	Felbamate	15 mg/kg Valproic Acid	Faught et al 1993

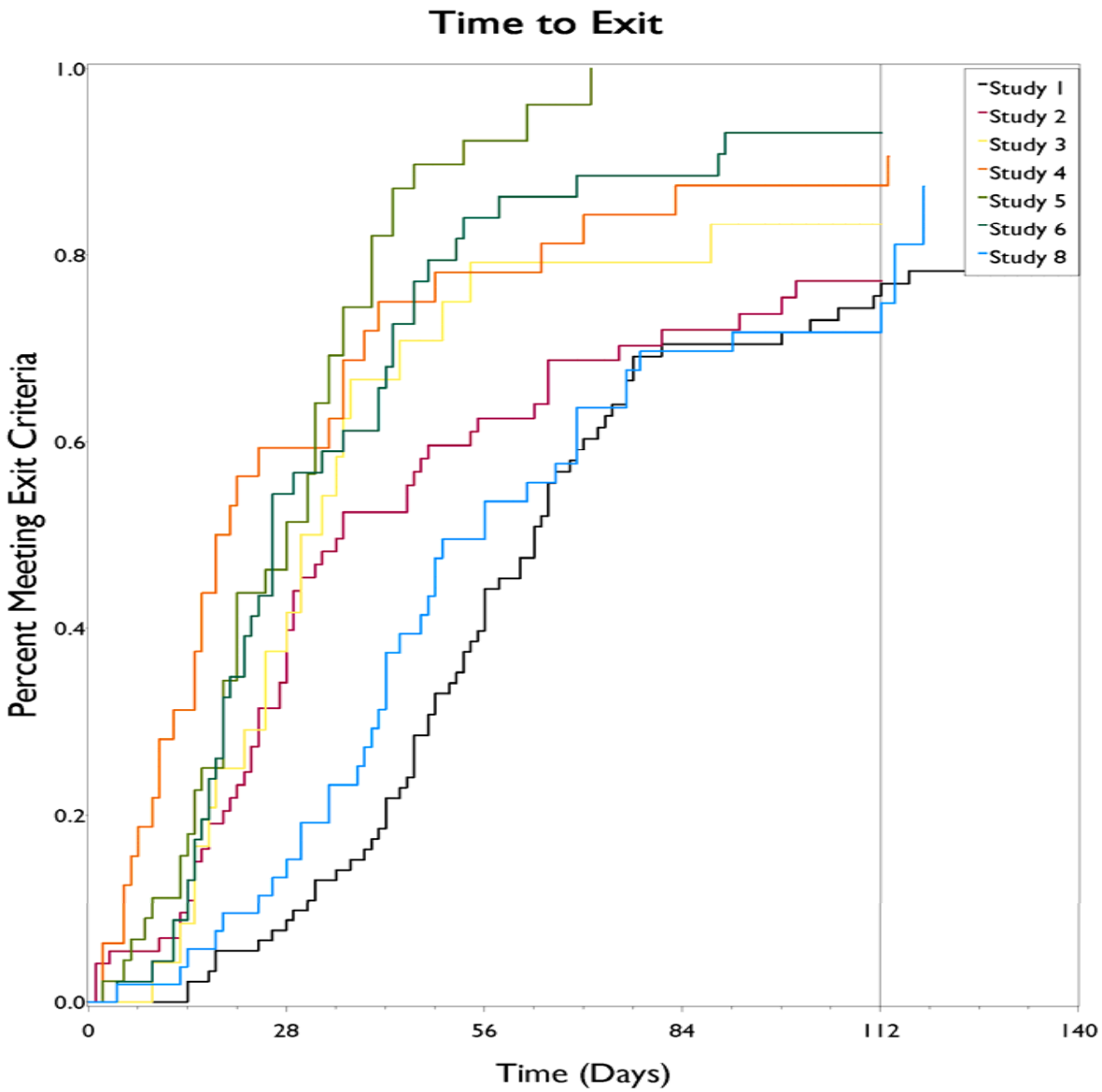
PATIENT CHARACTERISTICS (Published studies)

Study	N[1]	Age (years) Mean (range)	Epilepsy Duration (yrs) Median (range)	Baseline Sz Freq[2] Median/Mean	% Taking CBZ at Baseline	% With CPS
1	94	35 (14-63)	21 (<1-45)	6.5/10.1	64 (average of 3 groups)	95
2	80	36 (14-71)	NA[3]	10.0/NA	58	89
3	24	35 (NA)	21 (mean)	9.5/65.0	63	83
5	45	35 (18-53)	NA	5.5/NA	Not applicable	87
6	46	36 (11-66)	NA	6.5/NA	46	NA
7	22	38[4] (18-62)	NA	NA/15.9	59	NA
8	55	35 (17-67)	NA	NA/21.3	NA	NA

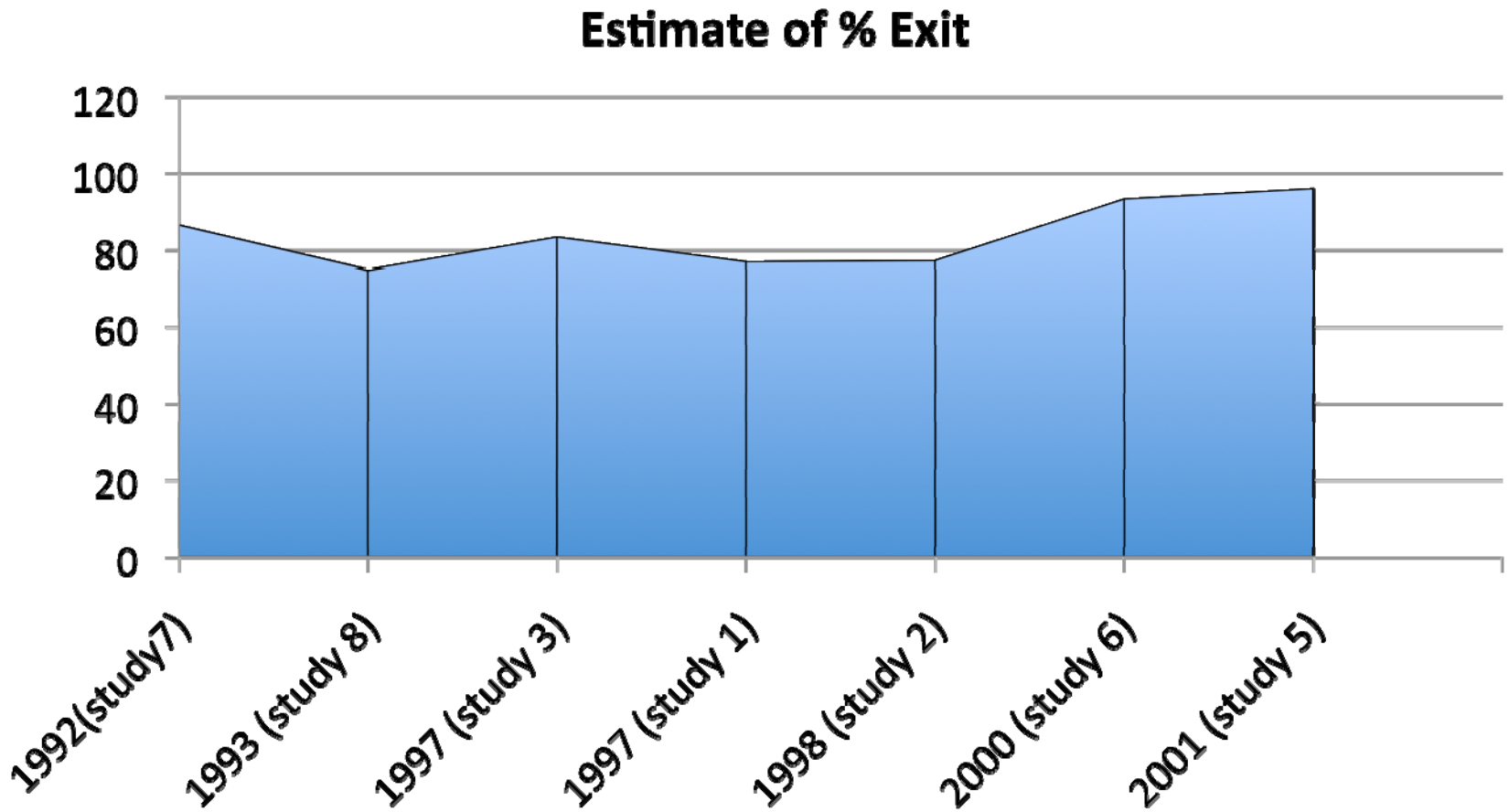
ADVANTAGE OF THIS DATA SET

- Lots of trials with a similar designs and exit criteria
- All trials randomized patients with similar demographic characteristics
- There was **no change** in results over time, as background AEDs changed, despite the fact that the trials spanned a decade when many new AEDs introduced. In fact, most recent trial had *highest* exit rate
  - Rate of withdrawal differed, causing slight differences in shape of curves

KM PLOT


Time to Exit
Percent Meeting Exit Criteria
1.0
0.8
0.6
0.4
0.2
0.0
0
28
56
84
112
140
Time (Days)
Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Study 8

Publication dates of 7 published studies in meta-analysis vs exit rate



“Conservatism” in approach

- Trials use “pseudoplacebo”, so actual placebo withdrawal would lead to more exit!
- All AEDs already have undergone placebo-controlled add-on studies, and are proven effective.

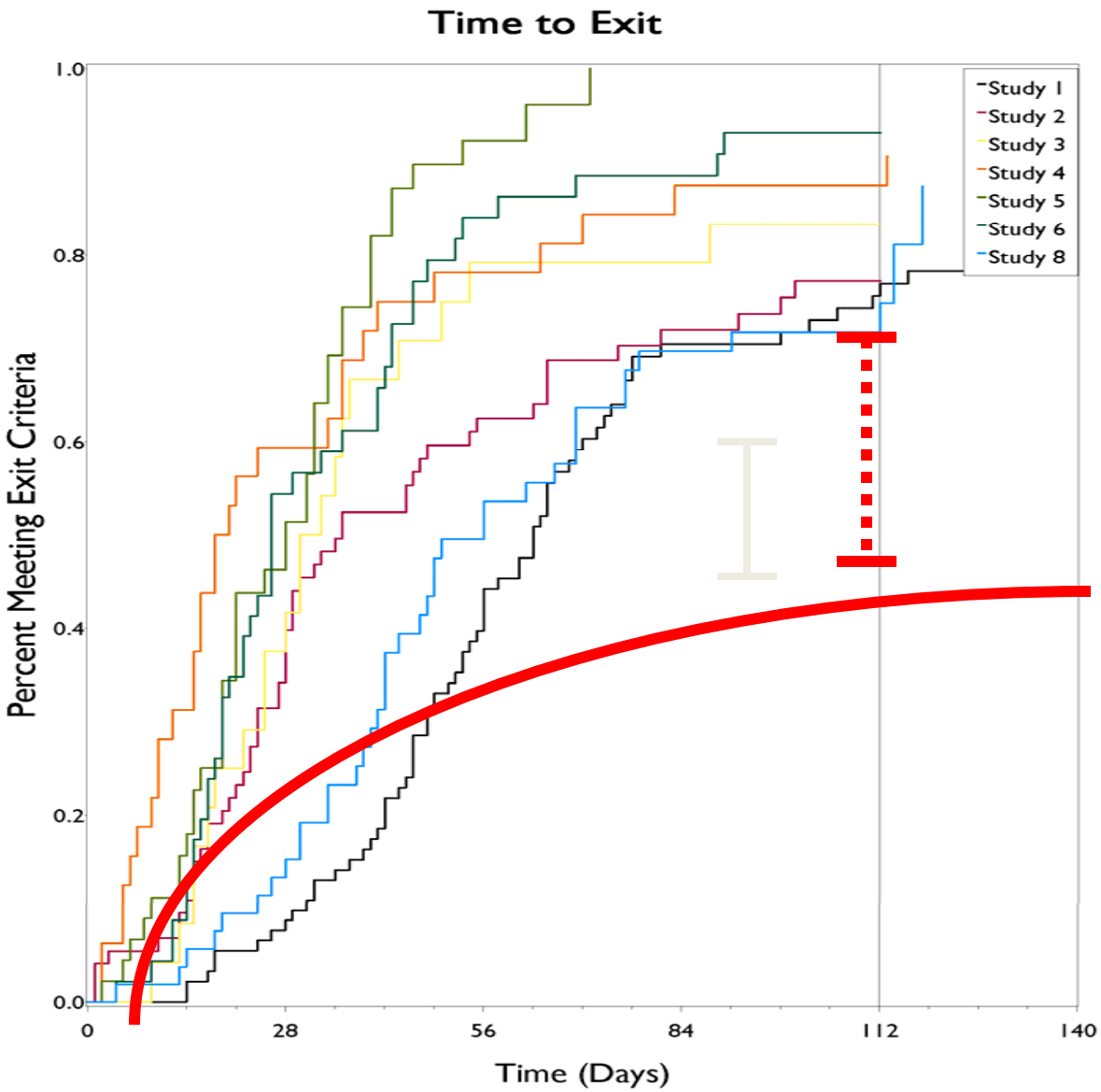
Will Historical Control Remain Stable?

- Often, there is a concern that historical control population will change over time, as therapies become more effective.
- If therapies become more effective, then removing these effective therapies should make people **EVEN WORSE**
- So, *there is little doubt that absence of worsening during withdrawal to study drug is an indication that the study drug is effective*

How do you do a study against historical control?

- Determine an “expected” exit rate for combined studies
- This serves as the “bar” for future studies
- New study must “beat the bar” to prove efficacy
  - “Beating” actually means limboing under
  - Need exit rate to be “lower” than the bar

KM PLOT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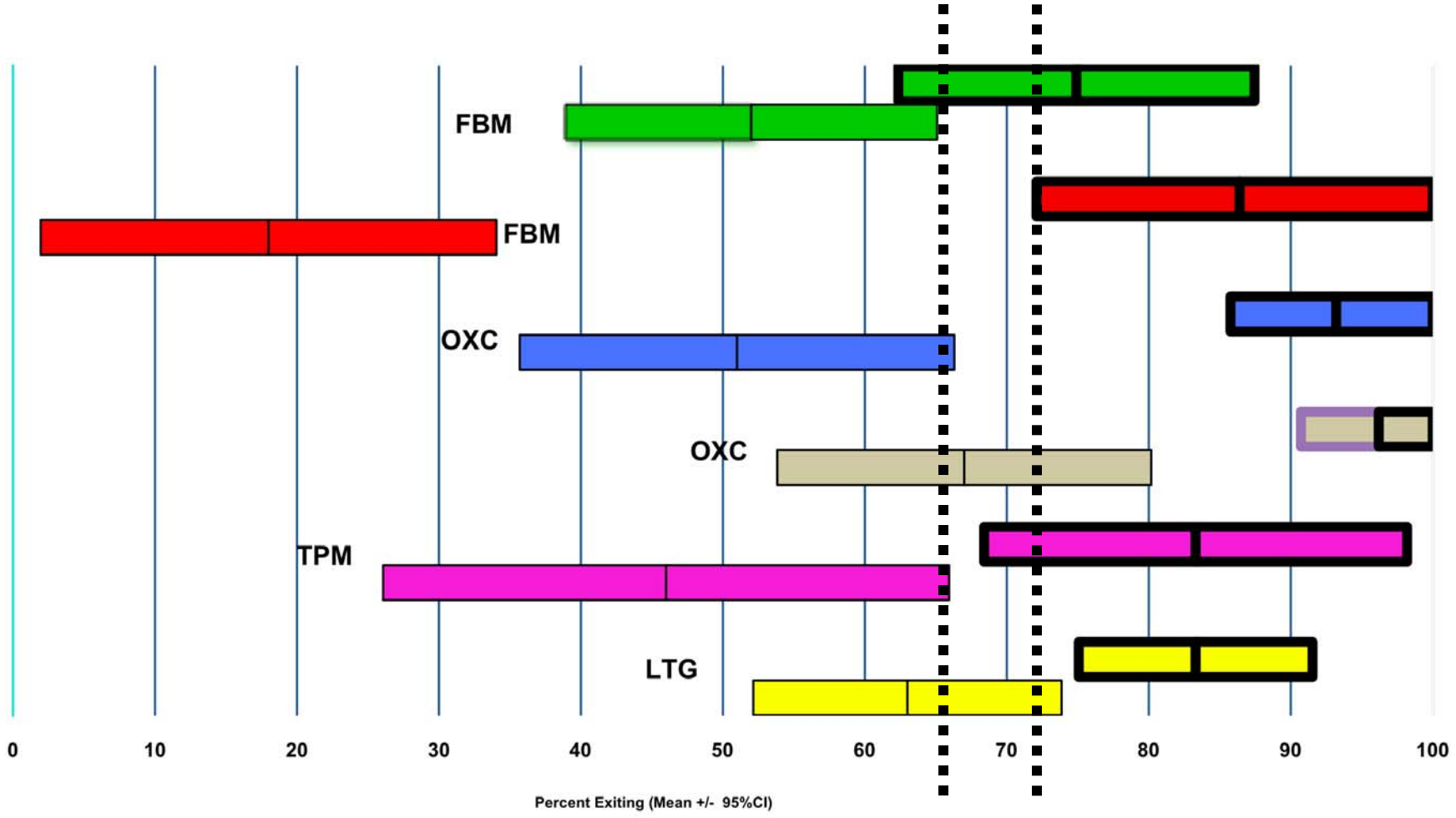
Time (Days)
Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Study 8

Reality check

- Six pseudo-placebo studies had active arms that showed superiority.
- How would they have fared if compared to the different bars considered?

Percent Exiting: Test AED v Pseudoplacebo



Trial issue for Historical Control Study

- Control group needed to match prior study design.
  - Can be an “underpowered” arm
- Need to match prior populations as much as possible
- No opportunity to change trial design

Historical Control for Epilepsy Conversion to Monotherapy: Methodology

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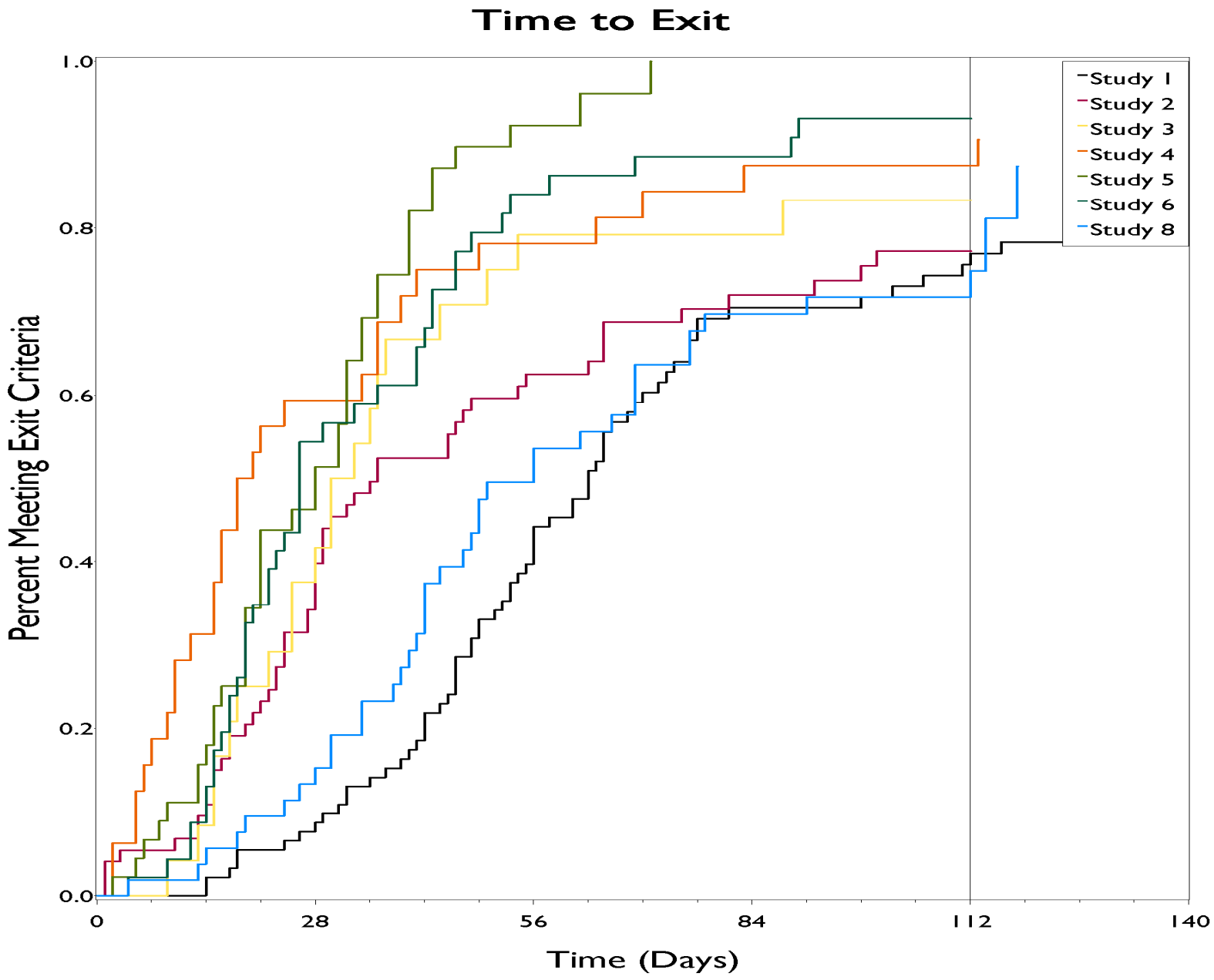
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Time (Days)
Study 1
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Study 3
Study 4
Study 5
Study 6
Study 8

SUMMARY OF PSEUDO-PLACEBO EXIT RATES

- Exit rates range from 74.9% to 100%, with half between 77.2% and 87.5%.
- Median is 84.9%

WHERE TO SET THE BAR

- Best point estimate of (pseudo-)placebo exit rate at 112 days
- Lower bound of confidence interval on exit rate
- Lower bound of prediction interval on exit rate

WHERE TO SET THE BAR

- Best point estimate of (pseudo-) placebo exit rate at 112 days
  - Does not account for variability in rates
  - 50% chance true exit rate is lower than this
  - Very liberal
- Lower bound of confidence interval on exit rate
- Lower bound of prediction interval on exit rate

WHERE TO SET THE BAR

- Best point estimate of (pseudo-) placebo exit rate at 112 days
- Lower bound of confidence interval on exit rate
  - Bounds the true mean exit rate
  - Accounts for variability in point estimate
  - Can set confidence level to make bound more or less conservative
- Lower bound of prediction interval on exit rate

WHERE TO SET THE BAR

- Best point estimate of (pseudo-) placebo exit rate at 112 days
- Lower bound of confidence interval on exit rate
- Lower bound of prediction interval on exit rate
  - Bounds the observed exit rate of a future study
  - Accounts for variability in point estimate of true rate and variability of a single study around this true rate
  - Can set confidence level to make bound more or less conservative

WHERE TO SET THE BAR

- FDA has agreed to the following
- Bar set at
  - One study: Lower bound of a 95% prediction interval
  - Two studies: Lower bound of a 80% prediction interval
- Upper limit of 95% CI on exit rate from new study (or studies) must be under the bar
- Drug must have been approved as add on AED

DETAILS

- Random effects model
  - Includes possible variability of true exit rate among studies included in the historical series
  - Non-iterative method (DerSimonian & Laird, 1986) checked using REML
- For Study 5 with observed 100% exit rate, estimated rate and variability by adding 2 failures and 2 censored observations after the last observed failure time (Agresti & Coull, 1998)
- Hypothetical control group: 50 cases, 80% exit rate

Results

- Mean: 85.1
- Variance components
  - Among historical series 58.6
  - Within historical series 11.0
  - Hypothetical future study 32.0
- Total variance 101.6
- Standard error 10.1
- Lower bound=mean-z*standard error

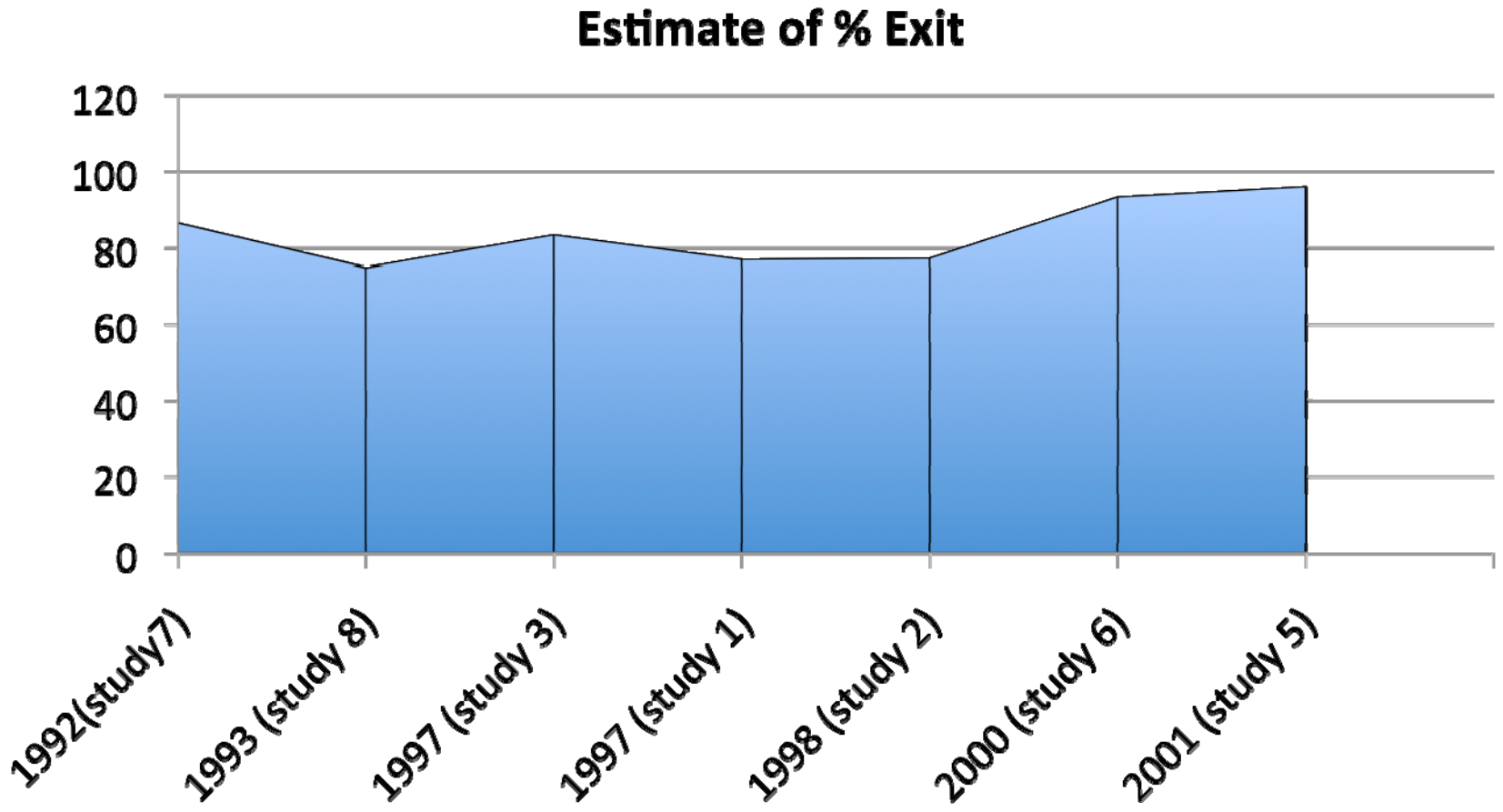
VALUES FOR BAR

- One study: 65.3%
- Two studies: 72.2%

COVARIATES

- Year of publication
- Time for baseline AED withdrawal
- Cox model stratified on study to evaluate other covariates

Publication dates of 7 published studies in meta-analysis vs exit rate



TIME FOR BASELINE AED WITHDRAWAL

Study	Weeks for withdrawal	Exit rate (%)
1	8	76.9
5	6	100
6	6	93.2
3	5	83.3
2	4	77.2
7	4	86.4
8	4	74.9

COX MODEL

Variable	Hazard Ratio	P-value
Age (years)	.991	.12
Gender	.841	.19
Race (white)	1.470	.03
CBZ	1.084	.56

If a non-white person has an 80% chance of exiting by day 112, a white person with the same other characteristics has a 91% chance of exiting

If a person not taking CBZ at baseline has an 80% chance of exiting by day 112, a person with the same other characteristics taking CBZ has an 83% chance of exiting