Levetiracetam Characterization: Is it an NTI Drug?

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Disclosures

- Research funding: NIH, FDA, Thermo Fisher, Nova Biomedical, Saladax Biomedical, Instrumentation Laboratories
- Consulting/Advisory Boards: Thermo Fisher, Nova Biomedical, Roche Diagnostics, Instrumentation Laboratories

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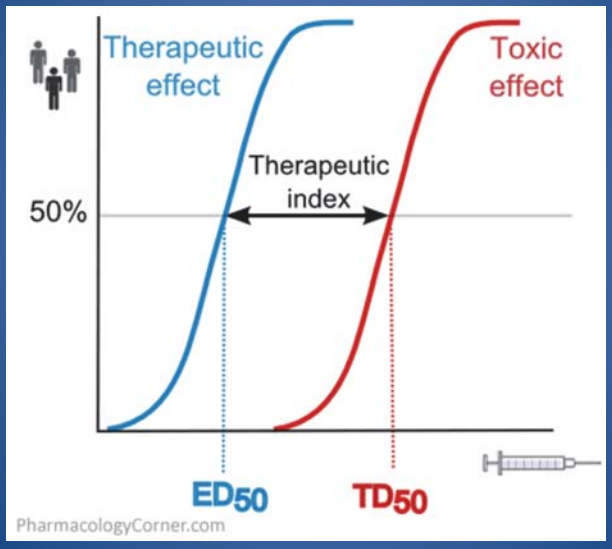
Narrow Therapeutic Index (NTI) Drugs



http://pharmacologycorner.com/therapeutic-index/

Narrow Therapeutic Index (NTI) Drugs

- An NTI drug is one where small differences in dose or blood concentration may lead to therapeutic failure and/or adverse drug reactions (FDA)
  - Also drugs that require PK or PD monitoring
- Drugs that have less than 2-fold difference in the minimum toxic concentration and minimum effective concentration (NC BoP)
  - Wide intra-patient variability that requires blood-level monitoring
- A drug where the ratio of the lowest concentration at which clinical toxicity occurs, to the median concentration providing therapeutic effect ≤ 2 (Health Canada)

Levetiracetam

- Anticonvulsant (Keppra®) introduced in 1999
  - Also used for bipolar disorder, anxiety disorder, and neuropathic pain
  - Introduced as a generic in 2008
- Adverse effects: somnolence, hematologic abnormalities, dermatologic reactions, psychiatric reactions, weakness, respiratory depression
- TDM is utilized for management of this drug
  - HPLC, LC-MS, immunoassay are all available
  - Reported target interval: 12-46 μg/mL

Objectives

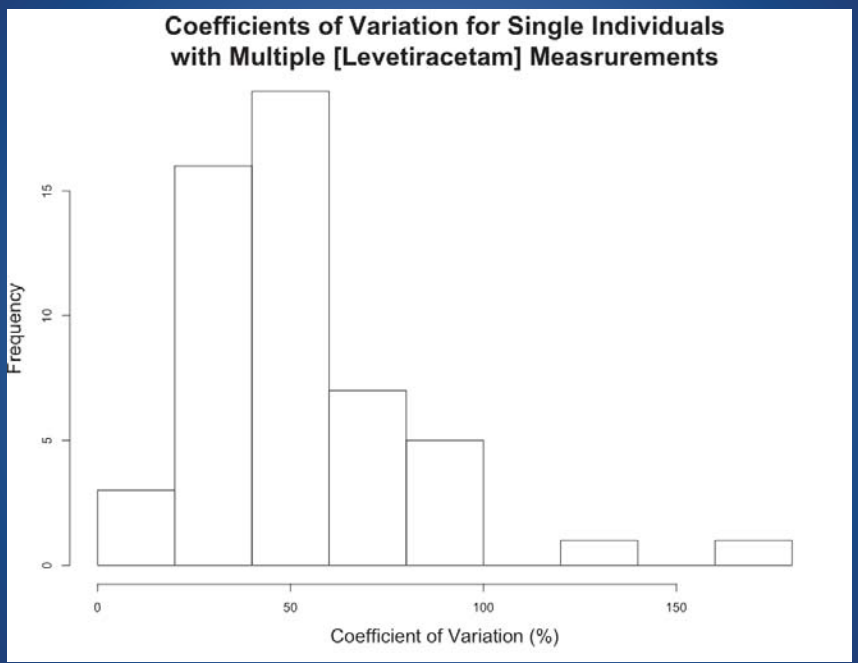
- Retrospective analysis of archived clinical data
  - TDM data, surgical pathology, clinical notes
- Evaluation of variability
  - Intra-individual variability
  - Characterization of variability within a population
- Data-based TI for levetiracetam
  - PK data evaluation (3 sites)
  - PK-PD modeling (2 sites)

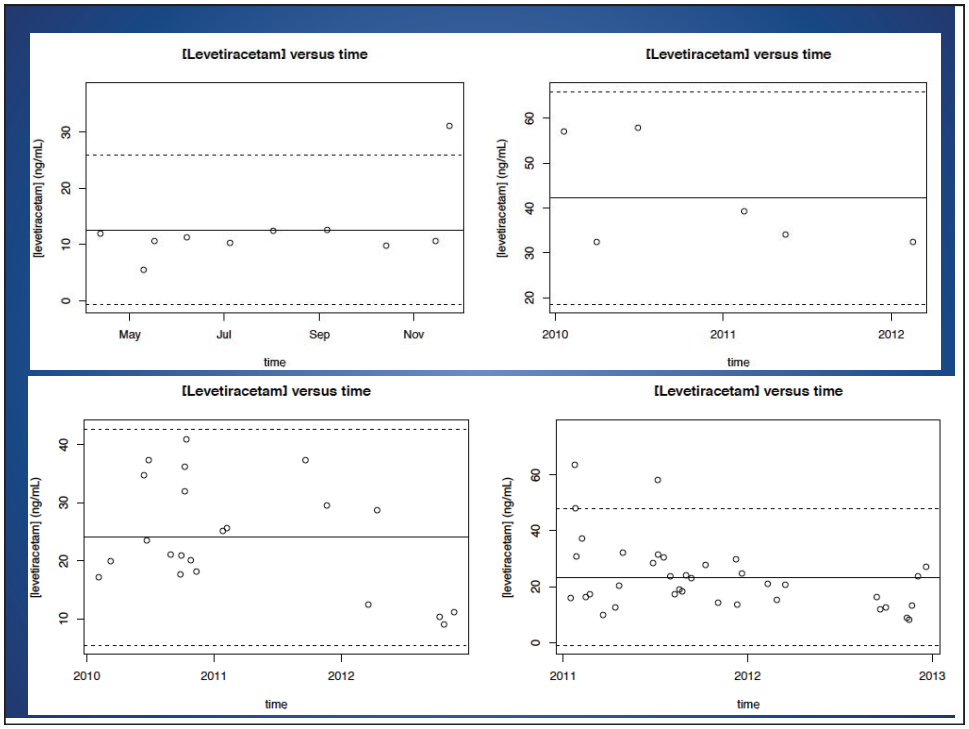
Data Extraction Methods – drug levels

- Raw data were exported from the clinical database – these include every result and record that was electronically stored
- The raw data were filtered with common sense criteria: the record had to contain a results (not re-test records), results had to be from a patient with a valid MRN (not QC/PT runs), the collection time and date had to be recorded for every record
- "Negative" results recorded as below the LOQ had to be encoded as numbers; rather than "<1 ng/mL" these are preliminarily stored as 0.5 ng/mL.

PK Analytics Approach

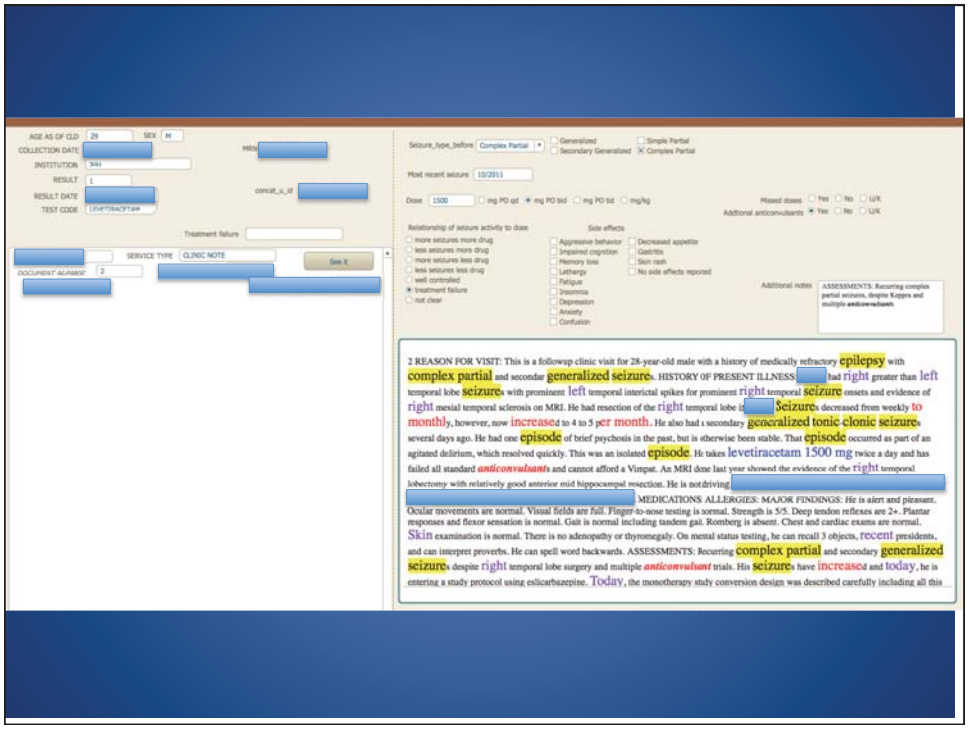
- Levels of each drug represent single or multiple data points from numerous patients.
- Simple histograms are a useful first tool to understand how drug levels are present throughout a population.
- After simple histograms, it is necessary to see how much variance there is within drug-level bins – for example at high drug-levels are the concentrations distributed narrowly or broadly?
- For patients with multiple levels, a plot of drug levels over time provides intra-individual variance





Data Extraction Methods – clinic notes

- After production of a consistent drug level dataset, the medical record numbers were queued to an in-house telnet/Expect/Perl program that emulated human interaction with the electronic medical record repository
- Pertinent clinical records were chosen on the presence of seizure relevant text
- The plain text of pertinent clinical records was screen-scraped from the electronic medical record
- To facilitate recognition of granular data the non-standardized dictated free-text clinical report, html annotation was used to find areas of the clinical notes that were candidate text areas for containing useful information.
- The annotated clinical notes were imported into a Filemaker based graphical user interface for manual review and the population of the granular database

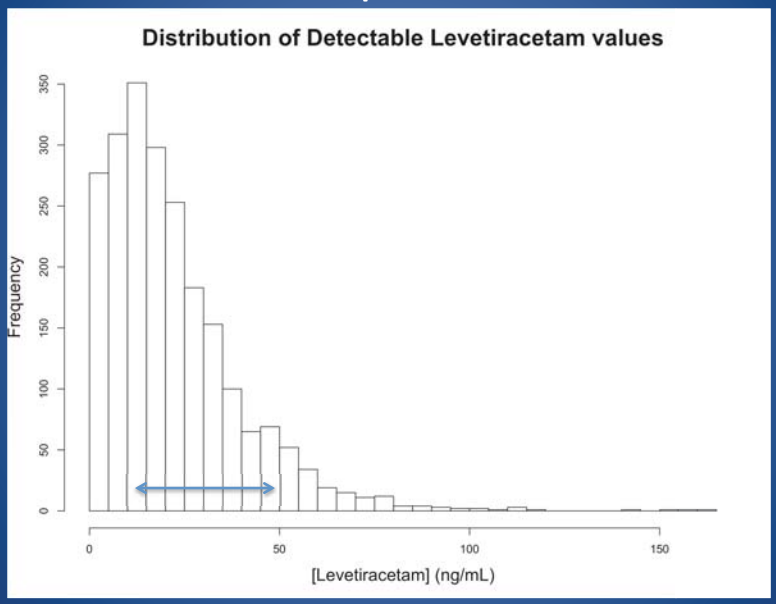


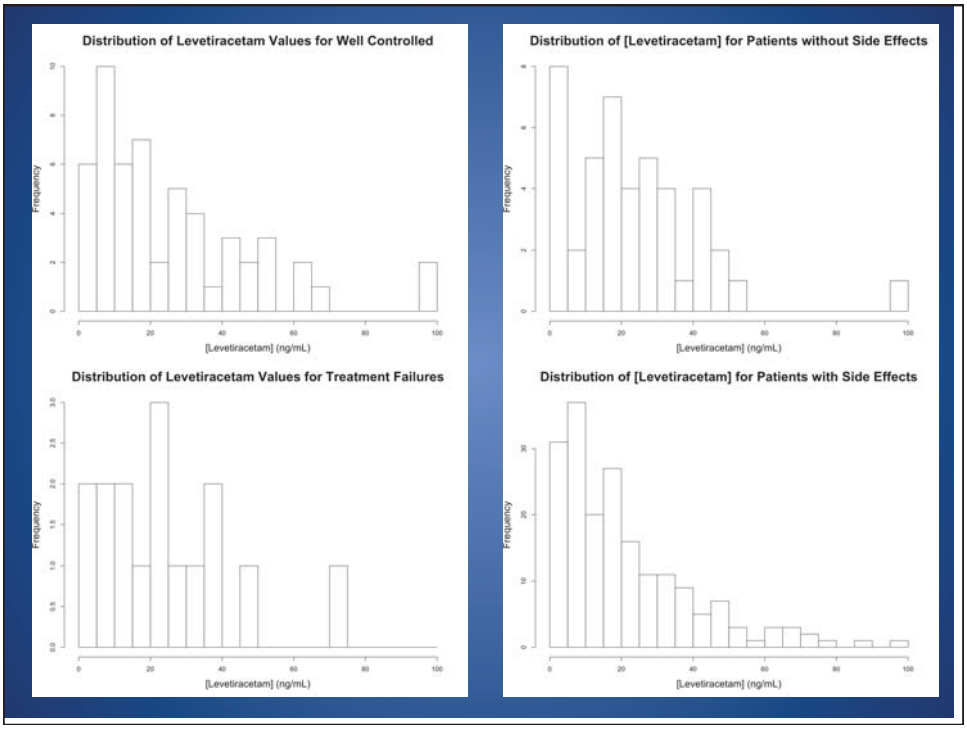
2 REASON FOR VISIT: This is a followup clinic visit for 28-year-old male with a history of medically refractory epilepsy with complex partial and secondar generalized seizures. HISTORY OF PRESENT ILLNESS: [redacted] had right greater than left temporal lobe seizures with prominent left temporal interictal spikes for prominent right temporal seizure onsets and evidence of right mesial temporal sclerosis on MRI. He had resection of the right temporal lobe i[redacted] Seizures decreased from weekly to monthly, however, now increased to 4 to 5 per month. He also had a secondary generalized tonic clonic seizure several days ago. He had one episode of brief psychosis in the past, but is otherwise been stable. That episode occurred as part of an agitated delirium, which resolved quickly. This was an isolated episode. He takes levetiracetam 1500 mg twice a day and has failed all standard *anticonvulsant*s and cannot afford a Vimpat. An MRI done last year showed the evidence of the right temporal lobectomy with relatively good anterior mid hippocampal resection. He is not driving. [redacted] MEDICATIONS ALLERGIES: MAJOR FINDINGS: He is alert and pleasant. Ocular movements are normal. Visual fields are full. Finger-to-nose testing is normal. Strength is 5/5. Deep tendon reflexes are 2+. Plantar responses and flexor sensation is normal. Gait is normal including tandem gait. Romberg is absent. Chest and cardiac exams are normal. Skin examination is normal. There is no adenopathy or thyromegaly. On mental status testing, he can recall 3 objects, recent presidents, and can interpret proverbs. He can spell word backwards. ASSESSMENTS: Recurring complex partial and secondary generalized seizures despite right temporal lobe surgery and multiple *anticonvulsant* trials. His seizures have increased and today, he is entering a study protocol using eslicarbazepine. Today, the monotherapy study conversion design was described carefully including all this

PK-PD Analysis

- After html annotation and manual review, the database contains clinical correlates for drug measurements, so it is possible to plot and model which drug levels actually correlate to the best and worst clinical outcomes.
- For narrow therapeutic index drugs, the drug levels for the “good” and “bad” clinical outcomes may be close together, thus, it is necessary to determine how reliably therapeutic drug monitoring is expected to separate these outcomes.
- By incorporating intra-individual, population, and analytical variance into an overall model of the error on drug levels, the confidence of drug levels can be seen by running a Monte Carlo simulation.

Sample Data


Distribution of Detectable Levetiracetam values
Frequency
0
50
100
150
200
250
300
350
0
50
100
150
[Levetiracetam] (ng/mL)


Distribution of Levetiracetam Values for Well Controlled
Frequency
[Levetiracetam] (ng/mL)
Distribution of [Levetiracetam] for Patients without Side Effects
Frequency
[Levetiracetam] (ng/mL)
Distribution of Levetiracetam Values for Treatment Failures
Frequency
[Levetiracetam] (ng/mL)
Distribution of [Levetiracetam] for Patients with Side Effects
Frequency
[Levetiracetam] (ng/mL)

Future analysis

- Complete levetiracetam analysis including data from Mayo Clinic and ARUP
- Additional PK variability analyses for tacrolimus and sirolimus with data from JHH, Mayo, and ARUP
- PK-PD analyses for tacrolimus and sirolimus with data from JHH and Mayo

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