Pediatric Levetiracetam TDM: **T**herapeutic **D**rug **M**onitoring Must or Just **T**otally **D**on't **M**easure?

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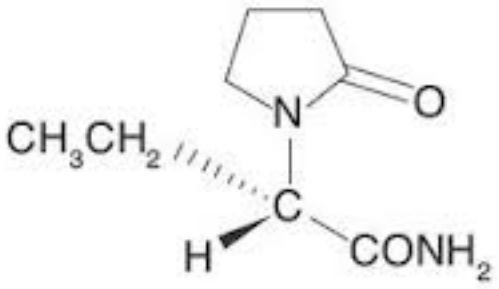
Epilepsy

- Chronic disorder characterized by recurrent unprovoked seizures
- Affects 0.5 – 1% of all children
- Multiple etiologies, electrochemical syndromes and seizure types
- 30% of children with epilepsy develop seizures refractory to medical management

Epilepsy Behav 2011; 20: 691-93
N Engl J Med 2000; 342:314-319

Levetiracetam

Keppra®



- NOC March 2003

- Adjunctive therapy:
  - Epilepsy not controlled by conventional therapy
  - Adult population

- PO dosage form: 250, 500, 750 mg tabs

NOC database. Health Canada 2013
Keppra product monograph. UCB Canada 2011

Levetiracetam
Keppra®

- Dose:
  - Initial: 10 -20 mg/kg/24h div BID
  - Maintenance: 40 – 60 mg/kg/24h div BID

- Mechanism of Action:
  - Binds to synaptic vesicle protein 2A (SV2A)
  - Modulates synaptic vessel exocytosis
    = inhibition of presynaptic neurotransmitter release

Drugs 2011; 71 (4): 489 - 514

Levetiracetam

Keppra®

Pharmacokinetics

- Linear
- Bioavailability 100%
- Distribution similar to TBW
- Protein binding < 10%
- No hepatic metabolism
- T1/2 6 – 8 h (< 12 y = 5 h)
- Excreted in urine

Adverse Effects

- Behavioural symptoms (38%)
- Somnolence (23%)
- N/V/D (15%)
- Headache (14%)
- Rhinitis (13%)
- Weakness (10%)
- Dizziness (7%)

Drugs 2011; 71 (4): 489 – 514
Levetiracetam monograph Pediatric Lexicomp 2012

Levetiracetam

The Ideal AED?

	Characteristic
✔	Rapid absorption after oral ingestion
✔	Complete oral absorption
✔	Rapid penetration of the blood-brain barrier and entrance into the brain
✔	Linear pharmacokinetics
✔	Minimal plasma protein binding
✔	No induction or inhibition of hepatic enzymes
✔	No auto-induction properties
✔	Renal elimination is preferable to hepatic metabolism
✖	Elimination half-life of 12–24h
✔	No drug interactions

Clin Pharmacokinet 2004; 43 (11): 707 - 724

AED TDM

- Rationale:
  - AED treatment is mostly prophylactic
  - Symptoms and adverse effects can be subtle
  - No direct lab parameters for clinical efficacy or the most common side effects

= optimize the seizure suppressing effects of AEDs while minimizing adverse effects

Epilepsia 2008; 49 (7): 1239 - 1276

AED TDM

- Drug Characteristics:
  - Narrow therapeutic range
  - Significant interindividual variability in pharmacokinetics
  - Drug concentration correlates to clinical efficacy and toxicity
  - Pharmacological response not easily measurable
  - *Significant side effect profile*
  - *Drug/disease interactions*
  - *Non linear pharmacokinetics*
  - *Will the results of the drug assay make a significant difference in the clinical decision making process?*

Clin Pharmacokinet 1998 ; 34 (4): 265-279
Ther Drug Monit 2003; 25 (3): 347 - 363

Levetiracetam TDM

- "The relationship between levetiracetam serum concentrations and clinical effect has not been ascertained and consequently, the value of serum concentration measurements has not been established."

- Possible therapeutic range:
  - 35 – 120 umol/L
  - 8 – 26 ug/mL

Clin Pharmacokinet 2006; 45 (11): 1061 - 1075

Texas Children's Hospital®

Clinical Question

P	Children with epilepsy receiving treatment with levetiracetam
I	Therapeutic drug monitoring
C	No therapeutic drug monitoring
O	Mortality Seizure frequency Adverse effects

Search Strategy

Databases	Medline, PubMed, Embase, IPA, Cochrane, Google, Google Scholar, Clinicaltrials.gov
Search Terms	Levetiracetam, Keppra, therapeutic drug monitoring, drug monitoring, drug levels, serum concentrations, pharmacokinetics, seizures, epilepsy, children, pediatrics
Limits	Human, English
Results	1 prospective observational study 2 retrospective observational studies

An initial experience with therapeutic drug monitoring of levetiracetam as reported from a pediatric clinical setting in India

B. S. Mathew, D. H. Fleming, M. Thomas[1], R. Prabha, K. Saravanakumar

Departments of Pharmacology and Clinical Pharmacology, and [1]Neurology, Christian Medical College, Vellore, Tamil Nadu, India

Neurology India | Mar-Apr 2012 | Vol 60 | Issue 2

Mathew et al

Design	SC, prospective, observational
Patients	N = 69 (generalized epilepsy = 40, focal = 26, focal with 2^0 generalization = 3, various etiologies) Inclusion: - Children > 1 y - Seizures - Levetiracetam x 3 m
Objectives	1) To ascertain any difference in serum concentration of levetiracetam between patients who were on enzyme inducers vs. those on enzyme inhibitors **2) To demonstrate any possible correlation between serum levetiracetam concentration and clinical efficacy**

Baseline Characteristics

Table 1: Baseline characteristics of the study population

	Median (range) n=69
Age	6 (1-16)
Weight	18.2 (7-64)
Total daily dose of levetiracetam	800 (100-2000)
Dose in mg/kg	40 (8.3-66.7)
Serum levetiracetam concentration (µg/ml)	14.7 (<1 to 53.8)
Total duration of levetiracetam treatment - months	12 (3-42)
Duration of treatment of levetiracetam with recent dose -months	9 (1-30)

Interpatient Variability

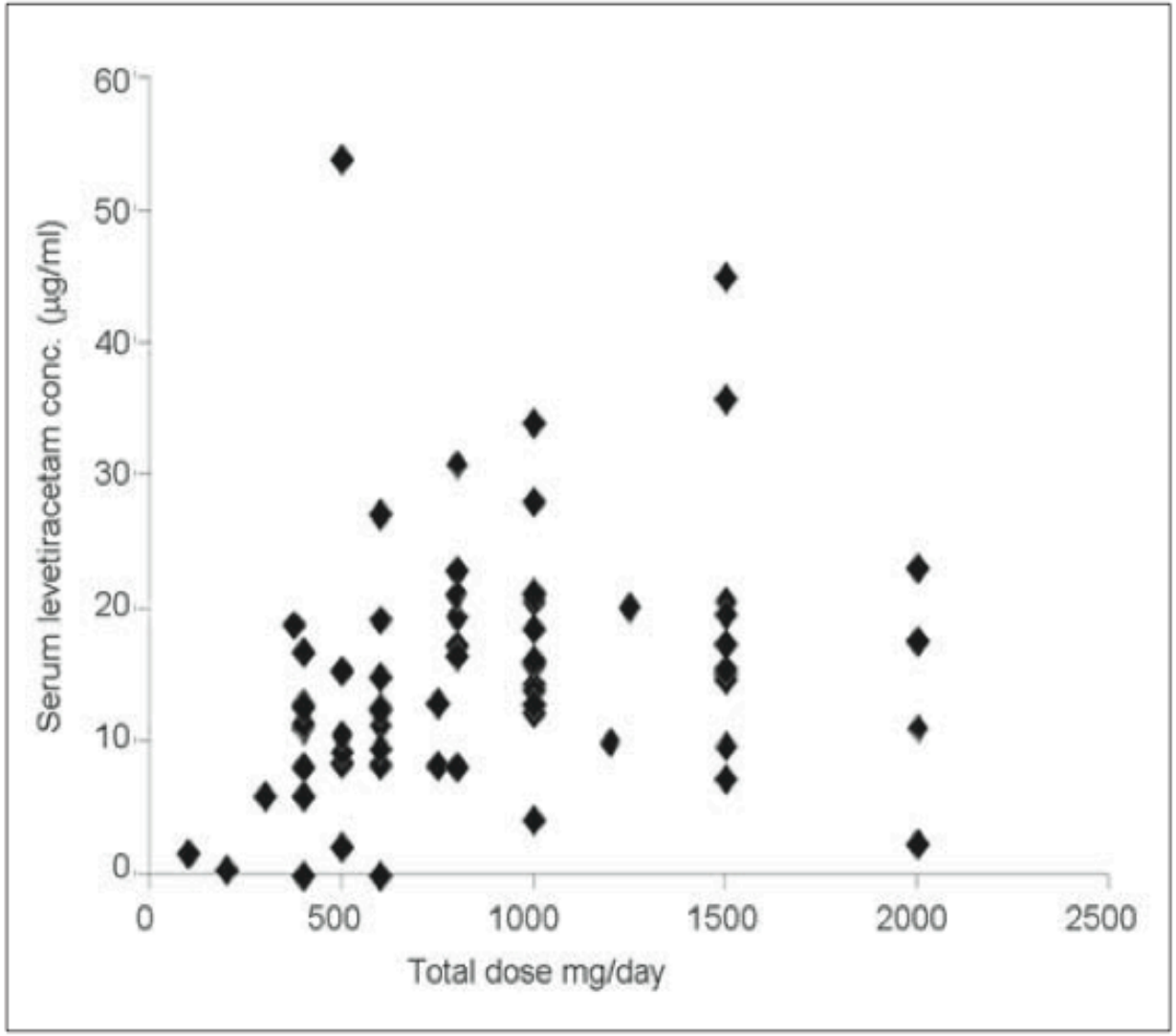


Figure 1: Total levetiracetam dose (mg/d)versus serum levetiracetam (µg/ml) concentration in 69 patients

Concomitant AEDs

Table 2: Serum concentration with and without antiepileptic co-medication

	Serum conc. Median (range;95%CI) µg/ml	Dose normalized serum conc. Median (range;95%CI) µg/ml *
No interfering antiepileptic (n=27)	16.6 (6-44.9; 14.9-20.6)	16.1 (8.1 - 58.7; 13.9-17.3)
Concomitant inducer antiepiletics (n=9)	7.3 (2.2-17.7; 2.2-12.9)	6 (<1 - 19; 2.1-14.8)
Concomitant inhibitor antiepileptics (n=31)	14.4 (<1 -53.8; 12.3-16.8)	14 (<1 -43; 12.3-17.2)
Concomitant inducer+inhibitor antiepileptics (n=2)	7.3	12.3

*- Serum concentration has been normalized to a dose of 40 mg/kg

Response

	N	Median LEV Dose	Median LEV Serum Concentration *
Responders	55	40 mg/kg/day	14.7 ug/mL
Non Responders	8	43 mg/kg/day	12 ug/mL

*P = 0.332
AUROC = 0.630

Authors' Conclusions

- Absence of correlation between serum concentration and seizure control
- Possibility of unexpected alteration of LEV concentration when antiepileptic medications, in particular inducers, are concurrently used; need to increase dosage in non responders who use inducers along with LEV
- Role of individualizing LEV dosing based on maintaining sequential intra-patient measurements with minimum variability yet to be investigated
- Sequential intra-patient data can be useful tool to confirm compliance.
- ***TDM of levetiracetam may not be necessary in routine clinical practice but has role in non-responders, on antiepileptic polypharmacy and with doubtful compliance.***

Analysis

- Observational
- Small sample size
- Large interpatient variability in serum LEV concentration
- Majority of patients on “interfering” AEDs – conflicting information regarding drug interactions
- Parental/patient reporting
- Multiple confounders
- No mention of compliance
- Only one LEV level drawn per patient (nothing mentioned on timing relative to dose)
- Poor description of methods
- Minimal information regarding assay

Therapeutic Drug Monitoring of Levetiracetam by High-Performance Liquid Chromatography With Photodiode Array Ultraviolet Detection: Preliminary Observations on Correlation Between Plasma Concentration and Clinical Response in Patients With Refractory Epilepsy

Frédérique Lancelin, PharmD, Emilie Franchon, PharmS,† Linda Kraoul, PharmD,* Isabelle Garciau, RS,* Sophie Brovedani, PharmD,* Khalid Tabaouti, MD,* Elisabeth Landré, MD,‡ Francine Chassoux, MD,‡ Pascal Paubel, PharmD,† and Marie-Liesse Piketty, PharmD**

Ther Drug Monit • Volume 29, Number 5, October 2007

Lancelin et al

Design	SC, retrospective, observational
Patients	N = 69 (generalized epilepsy = 3, focal = 66), mean age 32 y (13 – 78) Levetiracetam dose: 500 – 3000 mg/day (duration: min 2 m)
Objective	To monitor drug plasma levels in patients treated with LEV for refractory epilepsy and to determine if correlation exists between LEV plasma concentration and therapeutic response or adverse effects.
LEV Levels	81 plasma samples from 69 patients - 12 h after evening dose - On LEV min 1 wk

LEV Plasma Concentrations

Mean LEV concentration (range)	11.7 ug/mL (1.1 – 33.5)
By dose (mg): mean ± SD (ug/mL)	
500	3.1 ± 0.9
1000	6.5 ± 2.4
1500	10.7 ± 5.1
2000	12.4 ± 4.5
3000	16.8 ± 5.9

Baseline Characteristics

TABLE 2. Patient Characteristics and Plasma Levetiracetam (LEV) Concentrations According to Clinical Response Obtained in Patients With Epilepsy Treated With Levetiracetam

	Responders (n = 11)	Nonresponders (n = 31)	Student *t* test
Gender			
Males	37%	58%	
Females	63%	42%	
Age, means (range)	35 years (14–51)	30 years (13–68)	$P > 0.05$
LEV dosage, means (range)	1864 mg/d (750–3000)	1733 mg/d (500–3000)	$P > 0.05$
Diagnosis			
Partial epilepsy	11	30	
Generalized epilepsy	0	0	
Undetermined epilepsy	0	1	
Length of illness, means (range)	23.8 years (3–40)	22 years (5–60)	$P > 0.05$
Age at epilepsy onset, means (range)	11 years (3–25)	10.4 years (0–40)	$P > 0.05$
Concomitant antiepileptic drug, %			
Carbamazepine	36%	29%	
Lamotrigine	45%	29%	
Oxcarbazepine	18%	35%	
Clobazam	9%	19%	
Valproate	18%	0%	
Topiramate	9%	10%	
Phenytoin	0%	13%	
Phenobarbital	18%	6%	
Tiagabine	0%	3%	
Gabapentin	0%	0%	
Clonazepam	0%	3%	
Plasma LEV concentrations (μg/mL)	12.9 ± 4.9	9.5 ± 4.7	$P = 0.06$
Means, (SD), range (minimum–maximum)	4.6–21	1.1–20.9	

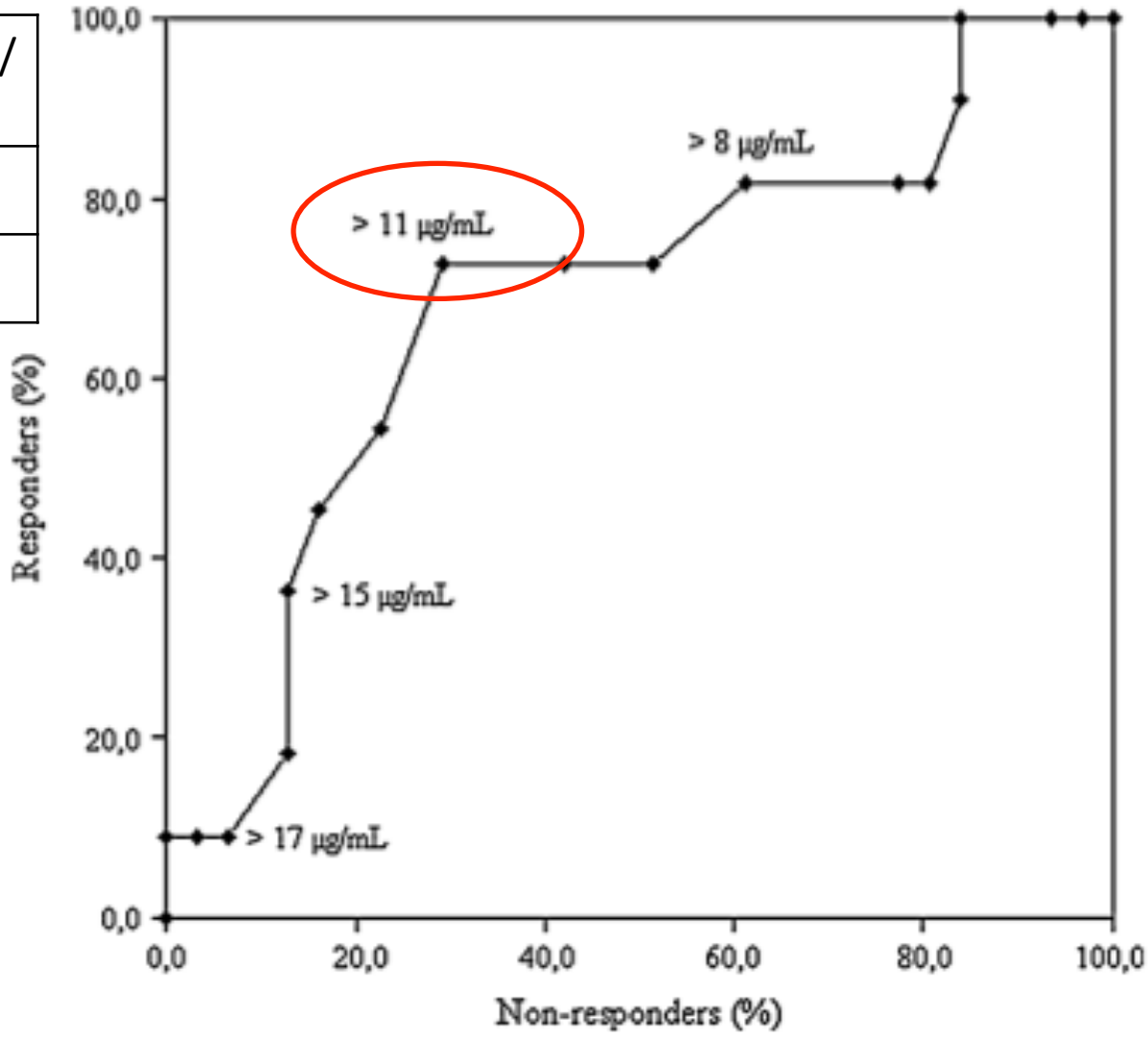
LEV Plasma Concentrations and Clinical Response

	Mean ± SD (ug/mL) LEV Concentration*
Responders (N= 11)	12.9 ± 4.9
Nonresponders (N = 31)	9.5 ± 4.7
* p = 0.06	

LEV Plasma Concentrations and Clinical Response

LEV Serum Concentration 11 ug/ mL	
Sensitivity	73%
Specificity	71%

LR (+)	2.5
LR (-)	0.38



LEV Plasma Concentration and Adverse Effects

	Mean ± SD LEV Concentration *
Adverse Effects	11.2 ± 4.4
No Adverse Effects	10.9 ± 4.9

* $p > 0.05$

Authors' Conclusions

- "The results show a trend toward higher concentrations being associated with a better response in the patients studied, including a majority of patients presenting with refractory epilepsy. However, further clinical studies are needed to recommend a therapeutic range in the clinical management of levetiracetam treated patients with epilepsy."

Analysis

- Retrospective, observational
- Small sample size
- Small number of responders/missing information
- Large interpatient LEV serum concentration variability
- Adult patients included
- Severe refractory seizures
- Multiple confounders
- No mention of compliance

Levetiracetam in children with refractory epilepsy: Lack of correlation between plasma concentration and efficacy

Patricia C. Giroux [a,b], Milagros Salas-Prato [b], Yves Théorêt [c], Lionel Carmant [b,*]

Seizure 18 (2009) 559–563

Giroux et al

Design	SC, retrospective, observational (PK subgroup prospective)
Patients	N = 69 (generalized epilepsy = 21, focal = 48) mean age = 12 y Subgroup: N = 37, mean age 11.4 y Inclusion: - Age $\leq$ 18 y - Dx with epilepsy - Treated with LEV
Objectives	1) Evaluate efficacy and tolerability of LEV in children with epilepsy **2) Determine if there is correlation between LEV plasma concentrations and efficacy/tolerability**

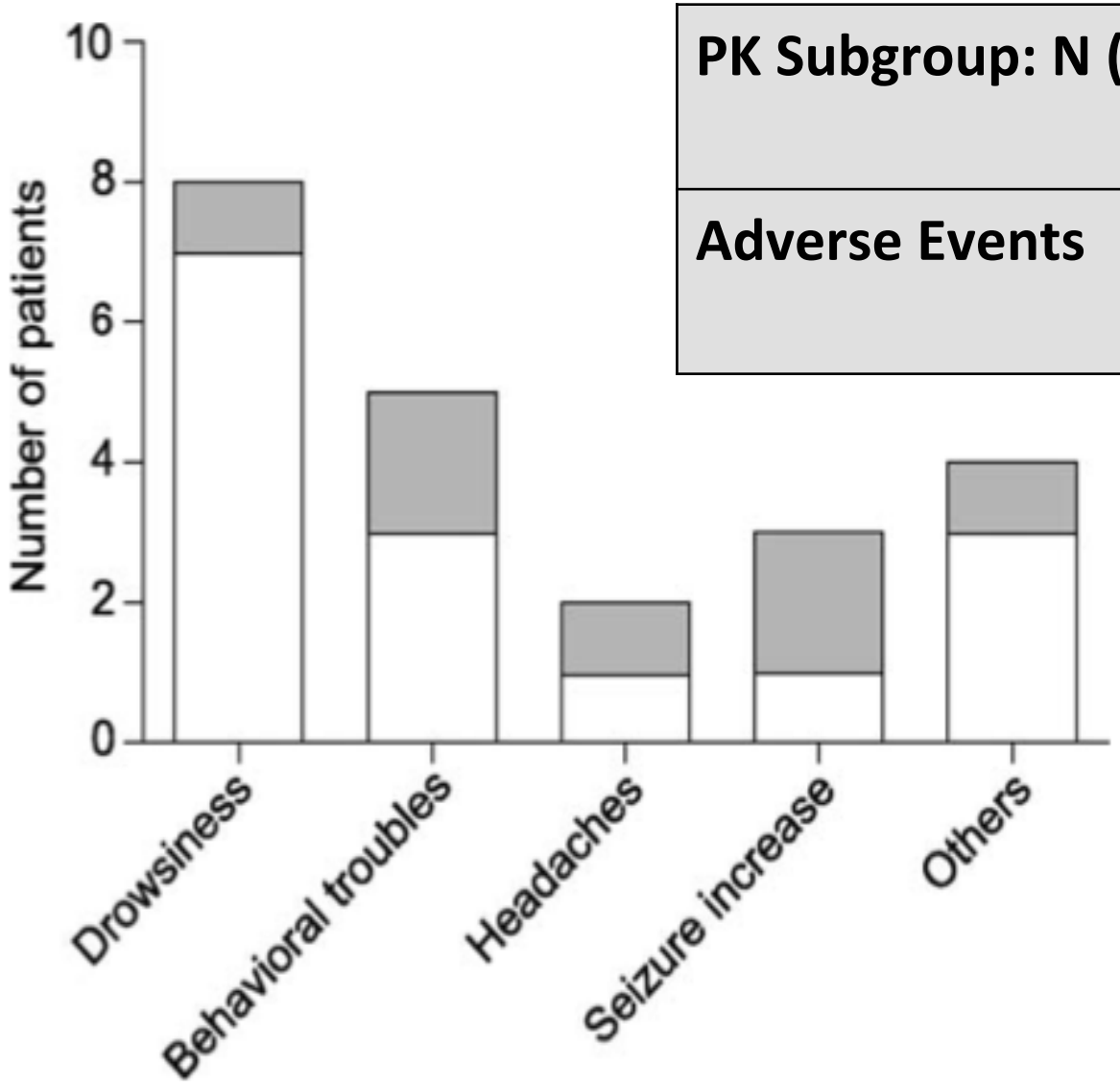
Baseline Characteristics

Population	Total population	Drug levels
Number of patients	69	37
Mean age (year)	12 ± 0.5	11.45 ± 0.8
Age range (year)	2.75–20	2.75–18
Male	39	20
Female	30	17
Mental retardation and/or developmental delay	57	30
Number of patients currently on LEV	57	37
LEV PC range (μg/ml)		1.89–74.44
Mean LEV PC (μg/ml)		27.44 ± 3.0
Mean LEV dose (mg/kg/day)		36.30 ± 3.4
Epilepsy type		
Generalized	21	15
Partial	48	22

Response

PK Subgroup: N (%)	
Responders	30 (81%)
Seizure Free	11 (30%)
Non Responders	7 (19%)

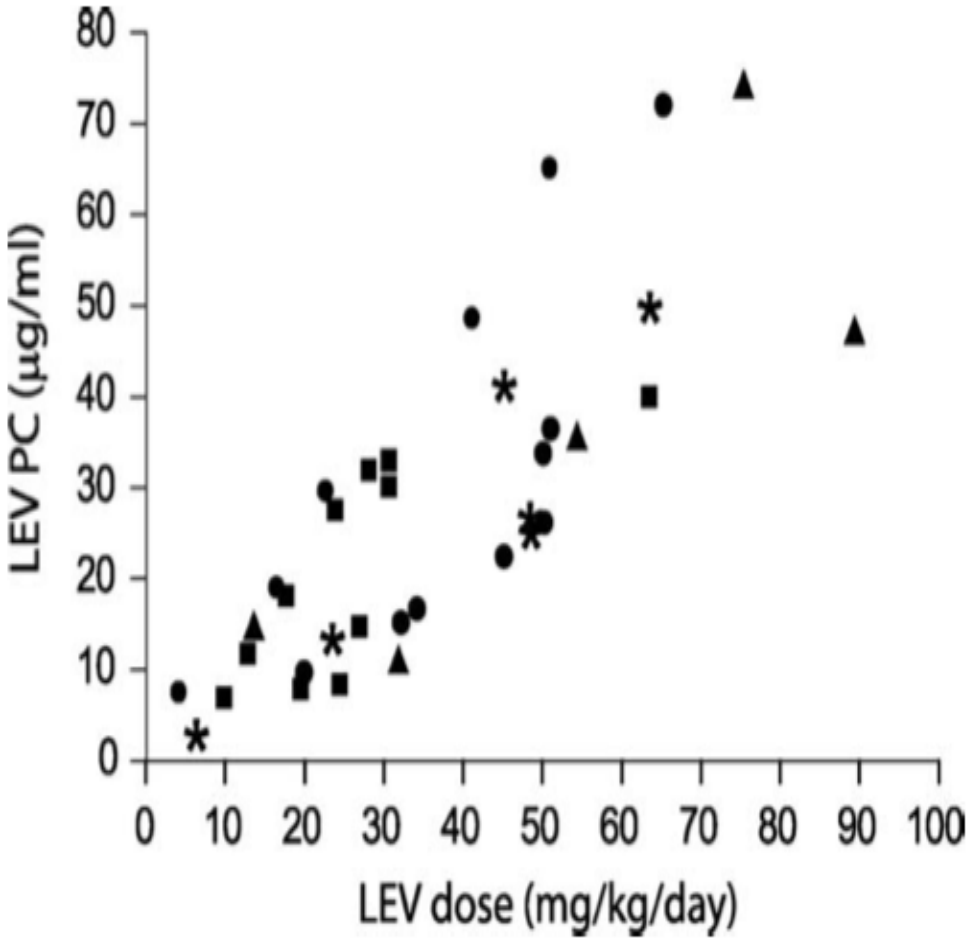
Adverse Effects



PK Subgroup: N (%)	
Adverse Events	18 (26%) (N = 69) 7 (19%) (N = 37)

LEV Concentration and Response

	Dose (Range)	LEV Serum Concentration (Range)
Responders	10 – 50 mg/kg/day	5 – 40 ug/mL
Seizure Free (N = 11)		6.85 – 40 ug/mL
Non Responders (N = 7)		1.89 – 46.66 ug/mL



Authors' Conclusions

- "Our results suggest that LEV is a broad spectrum anticonvulsant in children and can be used with great success also in patients with generalized epileptic syndromes. Its great safety profile, its lack of drug interaction and its efficacy in special populations are novel arguments for its utilization in children with benign as well as refractory epilepsies."

Analysis

- Observational
- Small sample size
- Multiple confounders and missing baseline information
- Single LEV concentration drawn
- No mention of compliance
- Adult patients included
- Poor reporting of statistical methods/results
- No discussion on relationship between adverse events and serum concentration
- No information on timing of blood samples taken relative to LEV dose
- Not all assay characteristics reported
- Author made no conclusions regarding TDM of LEV

Summary

	Mortality	Seizure Reduction	Adverse Events
Mathew et al	✖	✖	✖
Lancelin et al	✖	✖	✖
Giroux et al	✖	✖	✖

	Correlation to Clinical Efficacy	Correlation to Toxicity	Suggested Therapeutic Range
Mathew et al	✖	✖	✖
Lancelin et al	?	✖	> 11 ug/mL
Giroux et al	✖	✖	✖

Conclusion

- No apparent correlation between serum LEV concentration and clinical efficacy or toxicity
- No established therapeutic reference range
- LEV does not possess pharmacological characteristics typically requiring TDM
- Routine monitoring of LEV levels is not recommended

Questions?

Cost

- Texas Children's Hosptial: $ 45 dollars to run one levetiracetam level

Assay Characteristics

- **Sensitivity**: smallest concentration that can be reliably measured by an analytical method
- **Specificity**: ability to measure particular drug with interference (or cross reactivity) by other compounds
- **Precision**: reproducibility; the extent to which a measurement procedure gives the same results when repeated under identical conditions
- **Accuracy**: the closeness of the expected value to the true value of the measured quantity

Sensitivity and Specificity

	Disease Positive	Disease Negative
Test Positive	a	b
Test Negative	c	d

Likelihood Ratios

- $\frac{\text{Odds of given test result in patient with disease}}{\text{Odds of given test result in patient without disease}}$
- LR (+): ability to rule in disease
  - 2 – 5: poor to fair test
  - > 10: good test
- LR (-): ability to rule out disease
  - 0.5 – 0.2: poor to fair test
  - < 0.1: good test

ROC

AUROC:

- Measure of diagnostic accuracy
- Measure of how well a parameter can distinguish between two diagnostic groups