Duke Clinical Research Institute

Clinical Practice Data to Aid Narrow Therapeutic Index Drug Classification

Michael Cohen-Wolkowiez, MD PhD
Associate Professor, Duke University
Director, Pharmacometrics Center
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Background

- For NTIs, small differences in concentrations may lead to serious toxicities or therapeutic failures
- Some drugs lack NTI “status” due to an undefined therapeutic range or dose/concentration-response relationship
- Goal: use clinical practice data with PK/PD modeling to characterize the drug dose/concentration-response relationship and classify drugs with NTI

Classify drugs as NTIs using clinical practice data

- Literature review and data extraction
  - *Safety, efficacy, TDM, PK/PD*
- Electronic medical records
  - *Safety, efficacy, drug levels*
- PK/PD modeling
  - *Characterize concentration-response relationship*
  - *Simulate concentration-response relationship*

Lamotrigine case example

- Indicated for seizures and bipolar disorder
- Therapeutic range poorly defined
- TDM in clinical practice varies substantially
- Adverse events (e.g. rash) possibly related to dosing

Literature review and data extraction

- Literature review
  - Inclusion criteria: All PK, safety, and efficacy (epilepsy) articles for lamotrigine in adults
  - **384** articles in Pubmed
  - **187** articles in Embase
- **132** articles logged in the database
- **78** articles used for data extraction
  - PK/PD, TDM, pivotal efficacy, safety studies
  - **31** PK; **49** safety/efficacy

Lamotrigine literature efficacy data

Study#	Patient population	Number of subjects	Outcome measure	Efficacy results	Dose range
38	Epilepsy	249	Reduction in seizure frequency	Successful monotherapy in 61% of subjects	25–600 mg
44	Epilepsy	226	Percentage of subjects who were seizure- free during 7 weeks	60.4% of subjects were seizure-free at end of 7 weeks	100–200 mg
65	Epilepsy	156	Percentage of subjects on monotherapy	56% patients on monotherapy	100–500 mg
67	Epilepsy	222	Percentage of patients who were seizure- free during 1 year	89% of patients were seizure- free after 1 year of treatment	50–150 mg
74	Epilepsy	131	Percentage of patients who were seizure- free during 40 weeks	26% of patients seizure-free at 40 weeks	100–300 mg

Lamotrigine literature safety data

Study#	Patient population	Number of subjects	Type	Severity	Incidence	Range of drug doses
15, 99, 109	Epilepsy	8 – 334	Rash	Moderate/ serious	1%, 3%, 8%	100–500 mg (serious), 100 mg (moderate)
65, 99	Epilepsy	156 – 334	Stevens-Johnson syndrome	Serious	0.1%, 1%	300–400 mg (study #99), 300 mg/day, and 250 mg bid (study #65)
55	Epilepsy	141	Grand mal seizures	Serious	1%	300–400 mg/day
88	Epilepsy	126	Diplopia	Serious	1%	250 mg
99	Epilepsy	334	Dizziness	Serious	0.6%	100–500 mg
99	Epilepsy	334	Vision blurred	Serious	0.6%	100–500 mg
99	Epilepsy	334	Ataxia	Serious	0.3%	100–500 mg
99	Epilepsy	334	Nausea	Serious	0.3%	100–500 mg

Lamotrigine literature TDM data

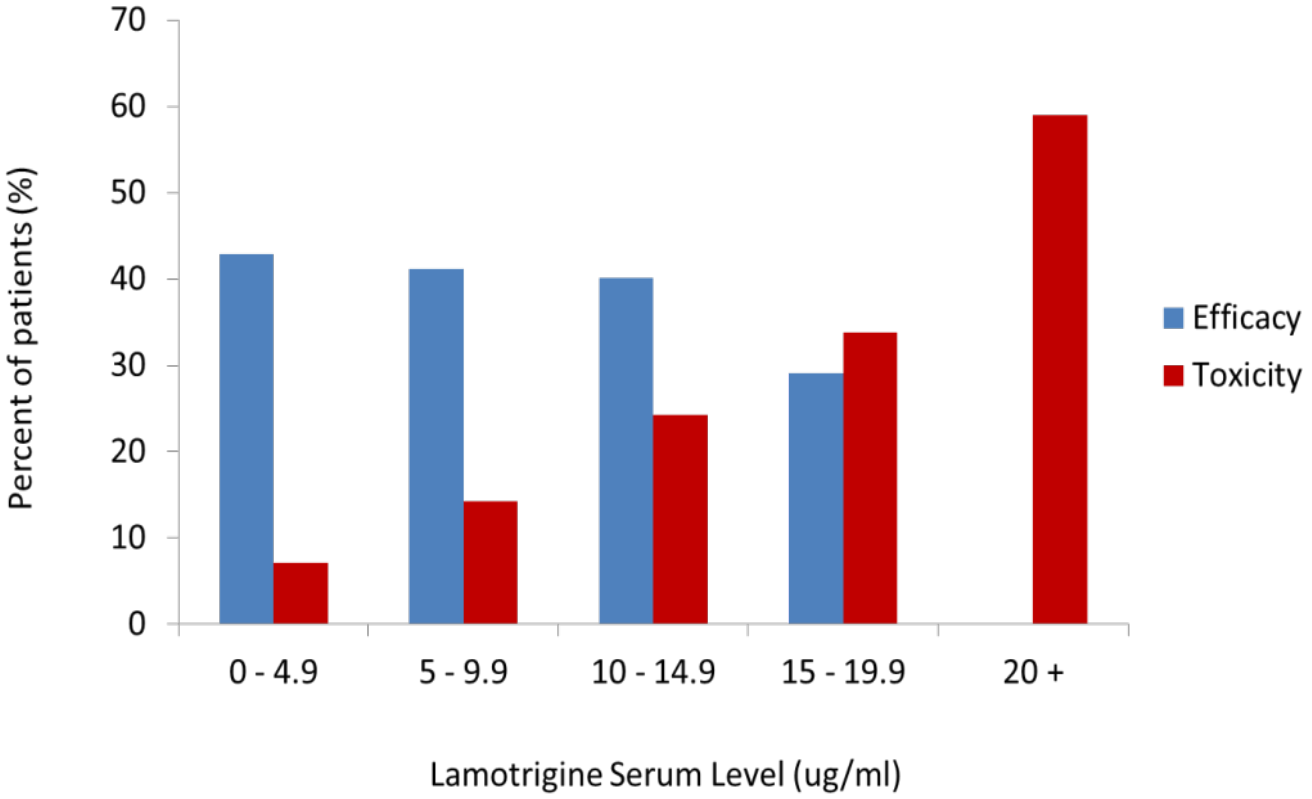
Retrospective study

N=**811**

Lamotrigine monotherapy or combination therapy

Toxicity: side effects significant enough to decrease dose or change to another AED

Therapeutic Index: **1–15** (ED50=1.5-20 mcg/mL; TD50=20 mcg/mL)



Hirsch et al. Neurology 2004; 63 (6): 1022-1026

Lamotrigine electronic medical record data

Number of subjects		46
Age (years)		41.5 (16.16)
Weight (kg)		84.9 (31.07)
Height (cm)		170.9 (11.04)
Male gender		23 (50%)
Race		
	White	30 (65%)
	Black	15 (15%)
	Asian	1 (2%)
Number of lamotrigine doses		244
Doses per subject		5.3 (4.17)
Number of lamotrigine PK samples		55
Number of PK samples per subject		1.2 (0.40)
Concomitant medications		
	Carbamazepine	1/46 (2%)
	Valproic acid	5/46 (11%)
	Phenytoin	6/46 (13%)
	Primidone	0/46 (0%)
	Any AED	12/46 (26%)

*mean (SD) reported; Data extraction period: 01/2012-12/2013; AED: Anti-Epileptic Drug

Lamotrigine Seizure Frequency

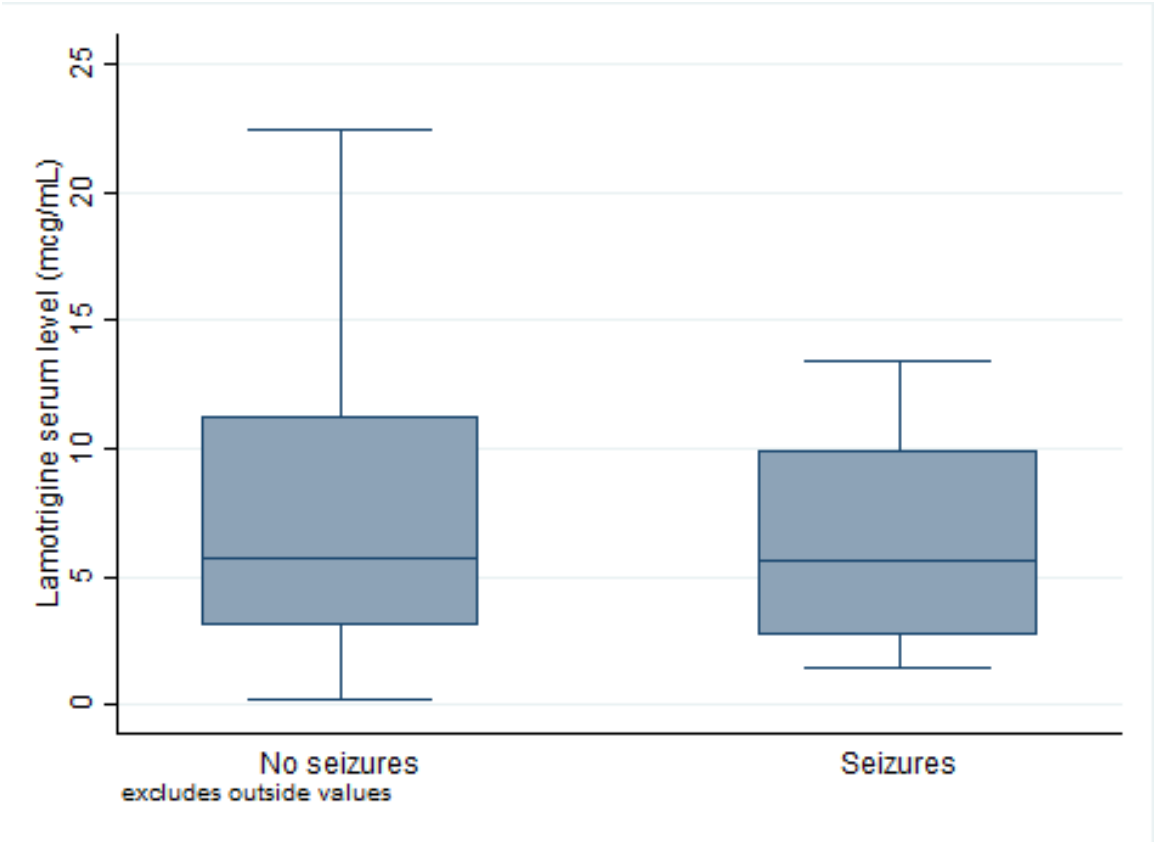
Seizure Frequency

Number of days with ≥ one seizure	22/170 (13%)
Number of subjects with ≥ one seizure	12/46 (26%)
Mean (SD) number of seizures per day	1.5 (10.93)
Method of seizure diagnosis Clinical Electrographic	 17 (77%) 5 (23%)

Lamotrigine Levels (mcg/mL)

	All days	Days with seizure	Days without seizure	p
Mean (SD)	8.9 (10.20)	6.4 (4.20)	9.6 (11.30)	0.35
Median (IQR)	5.7 (3.1, 10.5)	5.7 (2.7, 9.9)	5.7 (3.1, 11.2)	0.74
Min, Max	0.2, 67.1	1.4, 13.4	0.2, 67.1	NA

Lamotrigine levels and efficacy (SZ)

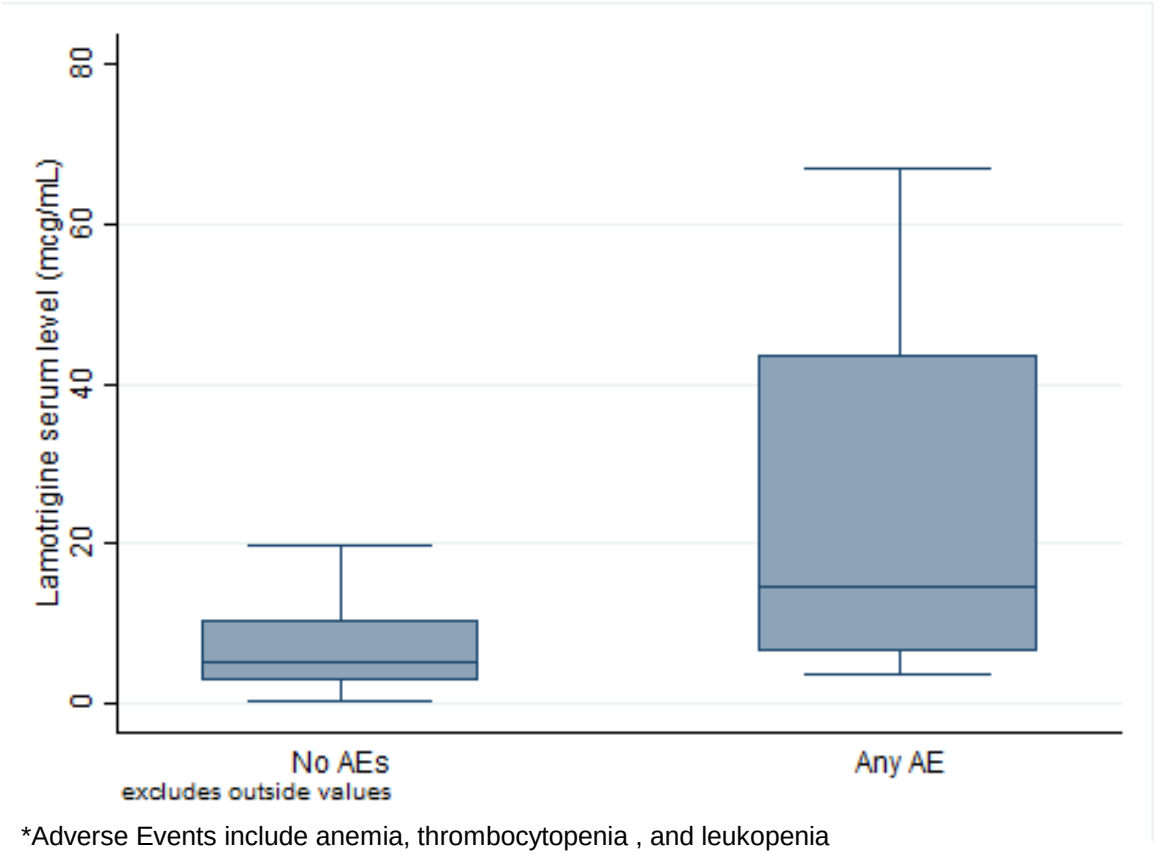


Lamotrigine levels and safety

Anemia	5/46 (11%)
Thrombocytopenia	4/46 (9%)
Leukopenia	1/46 (2%)
Drug decrease due to AE	1/46 (2%)
Any adverse event	8/46 (18%)
Any AE or drug decrease due to AE	8/46 (18%)

N=subjects

Lamotrigine Exposure and Adverse Events



*Adverse Events include anemia, thrombocytopenia , and leukopenia

PK/PD modeling

Conclusions

- Lamotrigine levels 1-20 mcg/mL are associated with efficacy
- Lamotrigine levels >20 mcg/mL are associated with toxicities
- Based on the literature and chart review it seems that the lamotrigine therapeutic range is 1-20

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