European Reference Network | Epilepsies (ERN EpiCARE)

European Commission

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Helping patients with rare or low-prevalence complex diseases

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WEBINAR ON PHARMACOLOGICAL TREATMENT OF EPILEPSY MARCH 26TH, 2020

THERAPEUTIC DRUG MONITORING OF ANTIEPILEPTIC DRUGS

Focus on pharmacokinetic variability

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EpiCARE

European Reference Network for rare or low prevalence complex diseases — Network Epilepsies (ERN EpiCARE)

Co-founded by the EU

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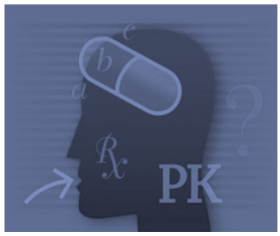
OUTLINE







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THERAPEUTIC DRUG MONITORING

TDM: The measurement and clinical use of serum/plasma drug concentrations to adjust each patient's individual dosage and schedule to each patient's individual therapeutic requirement

- Drug efficacy MAXIMISED
- Adverse effects MINIMISED

Patsalos et al., 2008, 2017, 2018, Johannessen Landmark et al., 2012, 2016, 2020

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TDM AND EPILEPSY

- Epilepsy: 1/3 refractory to various treatment options
- Challenges: Adverse effects, long-term treatment, polypharmacy-interactions, comorbidities
- Adherence: 30-40% variable adherence, 20% intentional poor adherence (WHO: TDM the best way to assess adherence)
- Antiepileptic drugs: Extensive pharmacokinetic variability, unpredictable, serious consequences
- TDM: Traditions for 50 years
- A tool for research & implementation of new knowledge, safe monitoring
- Pitfalls: Few controlled studies to evaluate TDM

WHO, 2003, Patsalos et al., 2008, Johannessen Landmark et al., 2008, 2012, 2016, 2020, Patsalos et al., 2017, 2018, Samsonsen et al., 2014, Mevåg et al., 2017, Henning, CJL et al., 2019a,b,c

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ANTIEPILEPTIC DRUGS

1912 -> 1990 -> 2010 ->

Older	*Newer*	*Newest*
Ethosuximide	Felbamate	*Cannabidiol**
Phenobarbital	Gabapentin	Brivaracetam
Phenytoin	Lamotrigine	Eslicarbazepine
Carbamazepine	Levetiracetam	Lacosamide
Clonazepam	Oxcarbazepine	Perampanel
Clobazam	Pregabalin	Retigabine
Primidone	Tiagabine	*Rufinamide**
Sulthiame	Topiramate	*Stiripentol**
Valproic acid	Vigabatrin	
Other BZ	Zonisamide	*Orphan drugs**

Dosing strategies of AEDs: Learning from history from one dose for all to individualized therapy, taking pharmacokinetic variability into account!

Older vs newer drugs: Efficacy, tolerability, PD, PK, interactions, indications, price, availability

Baftiu, CJL et al., 2015, CJL et al., 2012, 2016, 2020

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PRINCIPLES FOR TDM IN EPILEPSY

- WHY?
- WHAT?
- WHEN?
- HOW?

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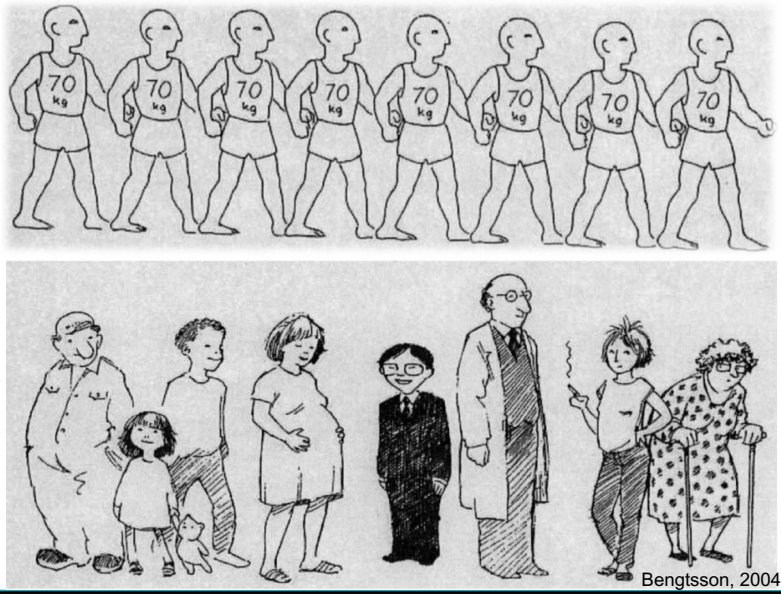
WHY? PHARMACOKINETIC VARIABILITY



Bengtsson, 2004

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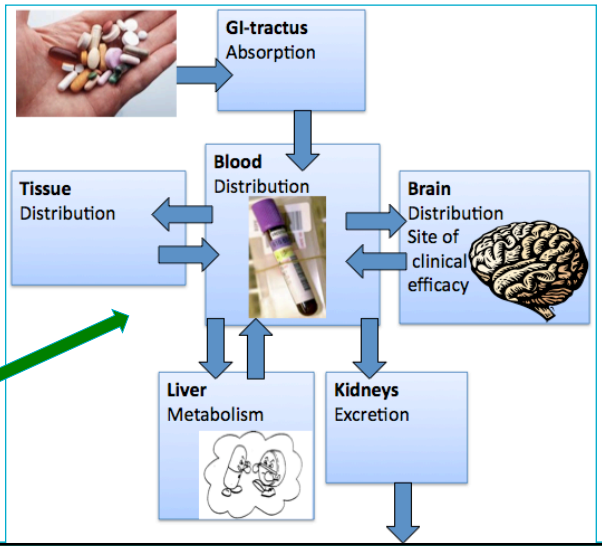
WHY? PHARMACOKINETICS

- EXTENSIVE VARIABILITY WITH AEDS

"Host factors"
- Inter- and intravariability
- Age
- Weight
- Ethnicity
- Genetic differences
- Physiological alterations
- Pathological alterations
- Pharmacokinetic variables
- Polypharmacy
- Interactions
- Pharmacodynamic sensitivity (tolerance...)
- Resistance

Implementation of therapeutic drug monitoring (TDM) contributes to individualized and optimal treatment outcome

Johannessen Landmark et al., 2012, 2016, 2020



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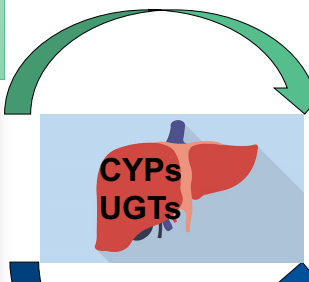
WHY: PK INTERACTIONS WITH AEDS

Enzyme inducers
Increase clearance
Carbamazepine, phenytoin (oxcarbazepine, phenobarbital)

Enzyme inhibitors
Decrease clearance
Valproate, oxcarbazepine, felbamate, stiripentol, ***cannabidiol***



Affected AEDs
Lamotrigine, clobazam, lacosamide, perampanel, ***everolimus, fenfluramine***

Handling
Ask the patient: Efficacy/tolerabilty/toxicity
Increase or decrease the dosage accordingly based on TDM measurements

Adapted from CJL and Brandl, 2020

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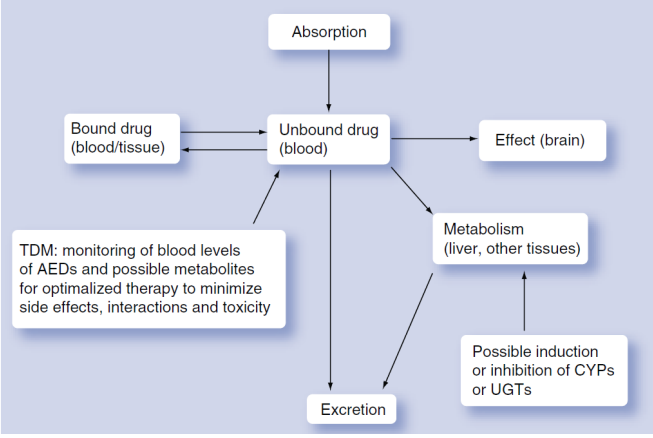
WHAT TO MEASURE?

Plasma/serum

- - Total serum levels
- Only free (non-protein bound) component is pharmacologically active
- Normally, the degree of binding is constant
- Free, unbound serum levels (AEDs > 90% bound) (PHT, VPA, TGB, STP, PER, CLB)
- Altered protein binding in patients with uremia, hypoalbuminemia or chronic liver disease, pregnancy, extreme ages
- Saliva monitoring, may reflect free concentrations
- Dried blood spots



Patsalos et al., 2008, 2017, 2018, Patsalos and Berry, 2013, Johannessen Landmark et al., 2008, 2012, 2016, 2020,

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WHEN TO MEASURE?

- Individual variations in drug utilization occurrs normally and alterations due to disease or physiological state
- Special patient groups (pregnancy)
- Drug interactions
- Adverse effects, toxicity
- Change of formulation
- To reveal non-adherence in patients
- Quality assurance aspects
- Standardized blood sampling time: drug-fasting in the morning at steady-state!

Johannessen Landmark et al., 2012, 2016, 2017, 2018,2019, Svendsen et al., 2016, 2017, 2019, Burns et al., 2016, 2019a,b

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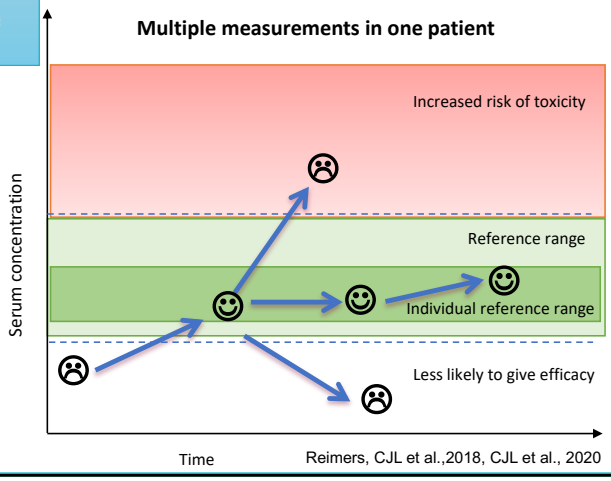
HOW TO DO IT?

- Analytical methods (LC-MS/MS, HPLC, immunological)
- Reference ranges and individual therapeutic concentrations
- Each patient serves as her/his own control over time
- Clinical interpretation of the result, adjustment of dosage
- *"Treat the patient and not the serum level!"*



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IMPLEMENTATION OF TDM IN SPECIAL PATIENT GROUPS

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PHYSIOLOGICAL & PK CHANGES WITH AGE

Neonates, infants, babies (0-1-2 years)–→ children (2-6 years) —→older children (7-12 years) → adolescents - (13-17 years) → adults- → elderly

Absorption: Incomplete absorption, **Cmax, Tmax, AUC**
Distribution: More body water, less fat/muscle, **Protein binding, Vd variable**
Metabolism and excretion: Eliminating organs, **Clearance, half-life**

children vs adults
↑ blood flow
↑ metabolic/renal clearance
Shorter $t_{1/2}$
Often higher dosage per kg body weight than in adults

PK as adults
Adherence
Interactions
Adverse effects

Elderly
PK slow down
↓CL, organ, dose
Polypharmacy
Comorbidities

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Johannessen Landmark et al., 2015, 2016, 2020, Batchelor & Marriott, BJCP 2013, Italiano & Perucca, 2015

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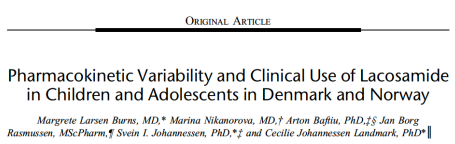
PHARMACOKINETIC VARIABILITY: LACOSAMIDE

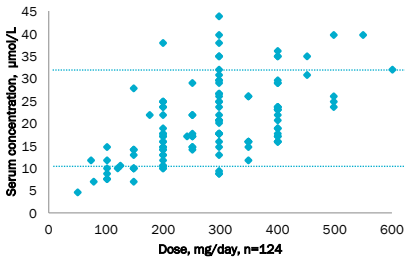
CHILDREN, ADULTS, ID PATIENTS

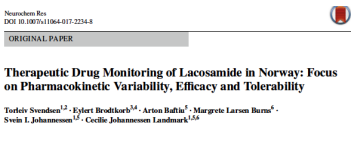


ORIGINAL ARTICLE

Pharmacokinetic Variability and Clinical Use of Lacosamide in Children and Adolescents in Denmark and Norway

Margrete Larsen Burns, MD, Marina Nikanorova, MD,† Arton Baftiu, PhD,‡§ Jan Borg Rasmussen, MScPharm,¶ Svein I. Johannessen, PhD,*‡ and Cecilie Johannessen Landmark, PhD**



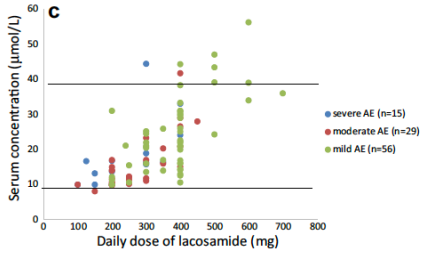


Neurochem Res
DOI 10.1007/s11064-017-2234-8

ORIGINAL PAPER

Therapeutic Drug Monitoring of Lacosamide in Norway: Focus on Pharmacokinetic Variability, Efficacy and Tolerability

Torleiv Svendsen[1,2] · Eylert Brodtkorb[3,4] · Arton Baftiu[5] · Margrete Larsen Burns[6] · Svein I. Johannessen[1,2] · Cecilie Johannessen Landmark[1,3,6]

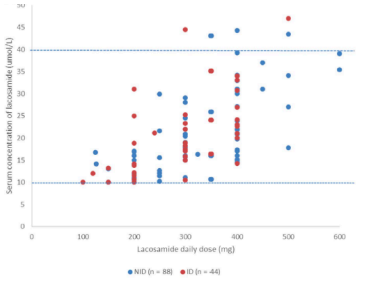


ORIGINAL ARTICLE

Neurologica WILEY

Clinical experience combined with therapeutic drug monitoring of lacosamide

Torleiv Svendsen[1,2] | Eylert Brodtkorb[3,4] | Arton Baftiu[1,5] | Morten I. Lossius[1,6] | Karl O. Nakken[1] | Svein I. Johannessen[1,7] | Cecilie Johannessen Landmark[1,7,8]



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Greenaway et al., 2011, Sattler et al., 2011, Contin et al., 2013, Markuola et al., 2014, Brandt et al., 2018, May et al., 2018, Burns ML, CJL et al., 2019, Svendsen, CJL et al., 2017, 2019

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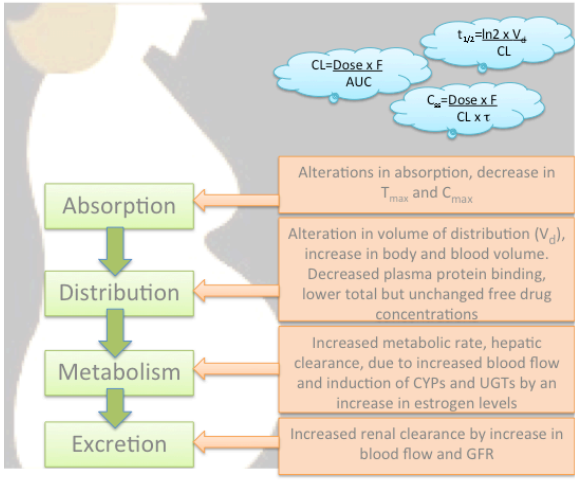
PK VARIABILITY DURING PREGNANCY

- Extensive changes during a short time period

PK variability, CL increase, lower concentrations

- LTG, LEV, OXC, TPM
- Between women
- More seizures?
- Increase the dose
- Keep a stable serum level
- Compare to baseline

- Risk evaluation of mother and fetus
- Dose-dependent risks
- Proper monitoring of AEDs during pregnancy and more knowledge about exposure of drugs may increase safety and reduce the risks for the mother and child



Johannessen Landmark et al., 2012, 2020; Reimers and Brodtkorb 2012; Tomson et al., 2013

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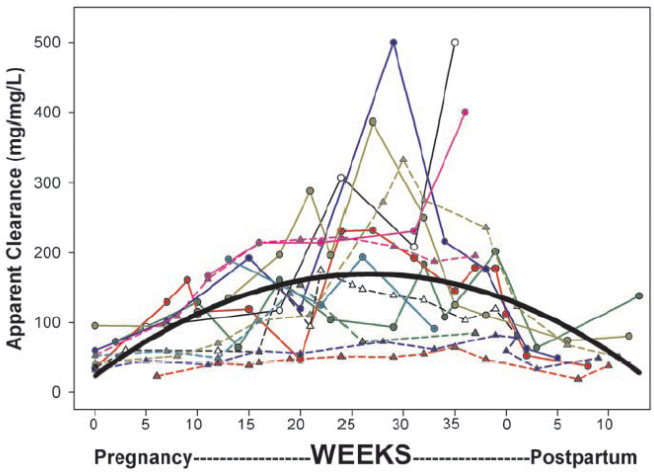
LAMOTRIGINE IN PREGNANCY

- Large variability, unpredictable
- Progessive increase in CL until peak at week 32, >330 % increase from baseline
- Caused by induction of glucuronidation by estrogen, increased 2-N-gluc/LTG ratio
- Increases seizure frequency, most in month 7
- Co-treatment with valproate compensates



Pennell et al, 2004, Petrenaite et al., 2006, Franco et al., 2008, De Haan et al., 2004, Öhman 2006, Tomson, 2006, Pennell et al., 2007

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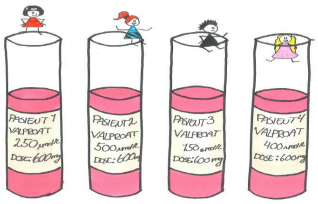
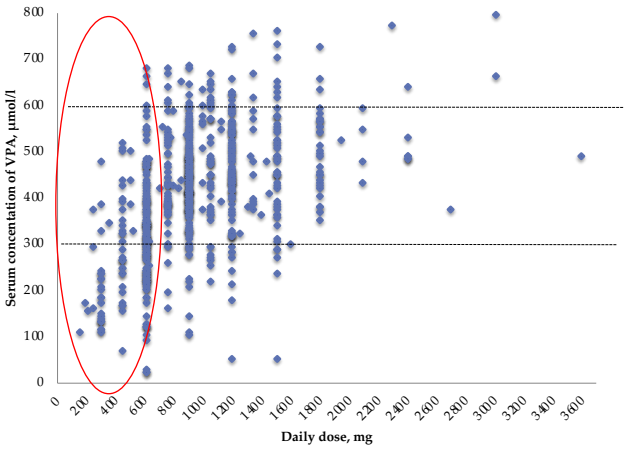
WOMEN X VALPROATE

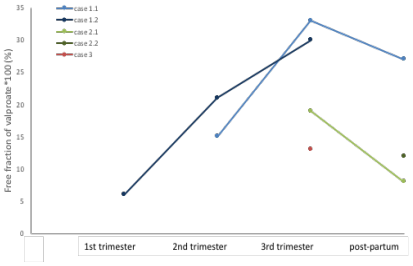




Extensive PK variability of VPA in women of fertile age (n=656). 14-fold variability C/D-ratio. Serum concentrations rather than dose should be used to evaluate VPA exposure.

EMA, 2018, Johannessen Landmark et al., 2017, 2018

What to measure?
Unbound valproate changes during pregnancy



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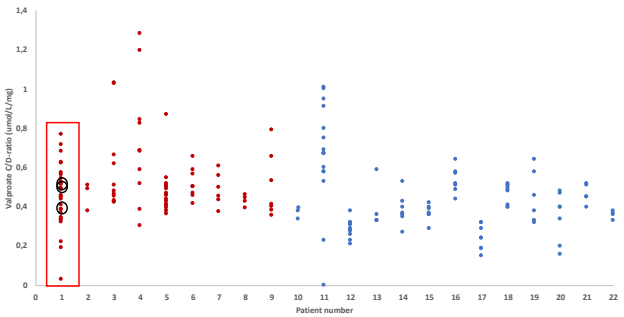
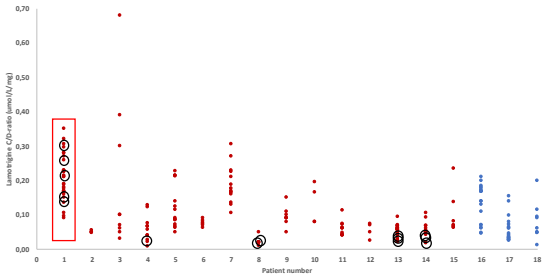
LONG-TERM TDM IN JME





- N=80. Extensive variability within and between patients: 19% (7-47) valproate, 43% (10-83) lamotrigine and 35% (6-111) levetiracetam.
- 15% of serum concentrations below the reference ranges
- 50% had TDM annually, 2/3 appreciated the service

CJL, Syvertsen et al., Epi Res and Epi Behav, 2019a.b

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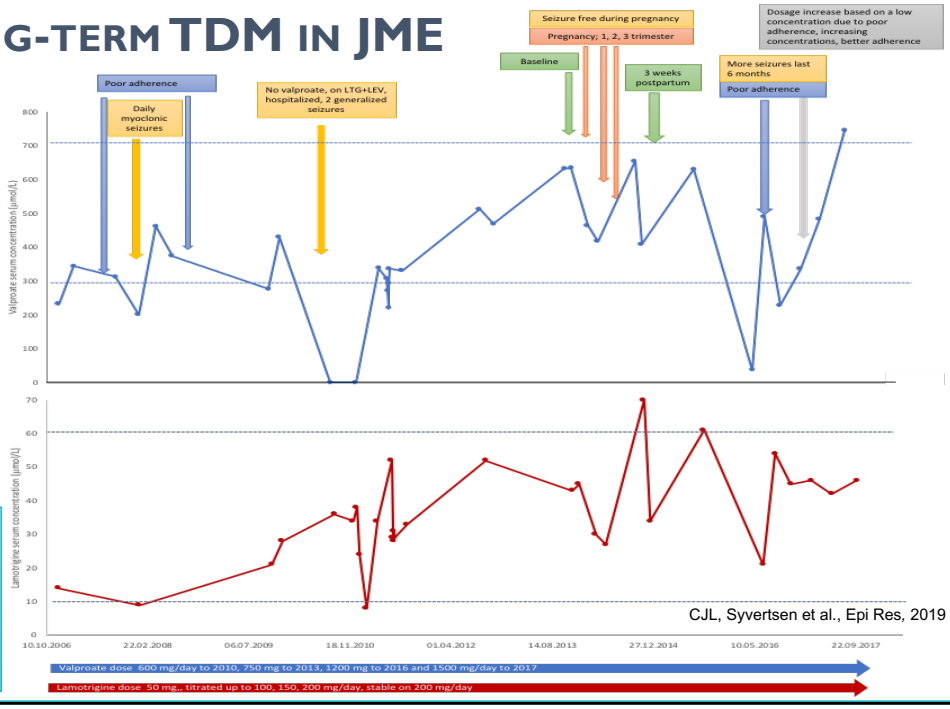
CASE: LONG-TERM TDM IN JME

- Young woman with JME
- Followed for 10 years
- Use of VPA + LTG
- Seizures
- Pregnancy
- Adherence



CJL, Syvertsen et al., Epi Res, 2019

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FUTURE HOLDS FOR TDM IN EPILEPSY

- Individualized and safe treatment
- New drugs-new challenges, also PK
- Increased use of AEDs in non-epilepsy disorders and new patient groups
- PK modeling to assess factors to variability
- Monitoring of biochemical markers of toxicity
- Complementary pharmacogenetic tests, part of precision medicine
- More studies, outcome and cost-effectiveness

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Patsalos et al., 2017, 2018, Reimers, CJL et al., 2018, Johannessen Landmark et al., 2012, 2016, 2020

27 March, 2020 22

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SUMMARY: TDM OF AEDS

TAKING PK VARIABILITY INTO ACCOUNT!

Patient → Prescribed dose → Drug intake → Serum concentration → Efficacy / tolerability

Clinical considerations

- Choice of drug and formulation
- Responder or not?
- Adherence

Patient specific features

- Age
- Gender
- Genetic factors
- Organ function
- Physiological state
- Pregnancy
- Comorbidity
- Polytherapy
- Environmental factors

TDM

- Reporting and evaluation of the measured serum concentration for subsequent management of therapy directed by an inter-professional team
- **Control for pharmacokinetic variability and interactions**
- Identify and adjust for drug interactions
- Control for variable adherence
- Quality assurance of the treatment

CJL, SIJ, PNP, Exp Rev Metab Tox, 2020

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European Reference Networks

THANK YOU

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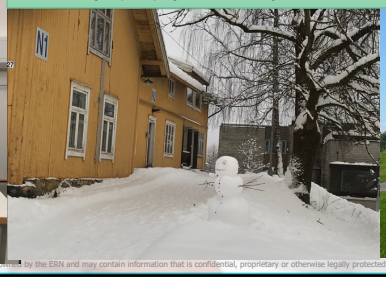
The National Center for Epilepsy in Norway: Comprehensive care for patients with refractory epilepsy for >100 years



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