PIVAL: Pharmacokinetic Interactions Between Valproic Acid and Lamotrigine: A Systematic Review of Literature and Retrospective Chart Review to Identify Site-Specific Practices On Mental Health Wards.

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Background

- Lamotrigine (LTG) is an antiepileptic agent that is also used off-label as a mood stabilizer
  - Mean $t_{1/2}$ of 26.4h
  - Primarily metabolized by hepatic glucuronidation via UDP-glucuronosyltransferase (UGT) enzymes
- Therapeutic synergism between VPA and LTG has been demonstrated in refractory epileptics and in treatment-resistant psychiatric disorders, including bipolar and schizophrenia disorders
- In combination with VPA, LTG plasma levels are elevated secondary to ↑ $t_{1/2}$ and ↓ total clearance
- Data on the mechanism of this PK interaction is lacking
  - Current hypothesis: VPA acts as a potent, broad spectrum UGT inhibitor
- **Objectives:**
  - Summarize current state of knowledge regarding VPA/LTG PK interaction
  - Describe clinical significance and impact of this interaction

Endpoints

- **Primary:**
  - *Frequency* of therapy modification aimed at reducing or treating VPA/LTG interaction risk
- **Secondary:**
  - Quantify *types* of therapeutic modifications
  - Describe *clinical outcomes* experienced
  - Characterize *rationale* for therapeutic modifications

Methods

- **Systematic Review**:
  - Literature search using PUBMED, EMBASE, Google Scholar, TRIP database, CINAHL, ISI Web of Science and PsychINFO (until February 2012), with search terms “lamotrigine,” “valproic acid,” “interaction,” “UGT,” and/or “drug glucuronidation”
    - Inclusion Criteria: English, *in vivo* human studies, quantitative PK data analysis
- **Retrospective Chart Review:**
- Eligible adult patients (N=37) admitted Sept 05 – Sept 11 were identified using Centricity pharmacy software

Inclusion	Exclusion
• Mental Health ward (PASU, 2N, 8C, 9A) • Received VPA and LTG concomitantly	• < 18 yoa

- Charts reviewed for study endpoints and analyzed using descriptive statistics

Results of Retrospective Review

Table 1. Baseline Characteristics	N = 37
Sex (female)*	21
Average age (in years)	44.3 (24-79)
Most Responsible Psychiatric Diagnosis	**%**
Bipolar Disorder	95
Major Depressive Disorder	73
Schizophrenia	27
Epilepsy	14
Other	**%**
Polysubstance Abuse **	32
Chronic Alcoholism	27
Hepatitis B carrier	5
Common Concurrent Medications	**%**
Antipsychotic	100
Antidepressant	57
Benzodiazepine	51
Anticonvulsant	16

* 2 transgendered
** marijuana, cocaine, mushrooms, amphetamine use

Figure 1: Frequency of Interventions

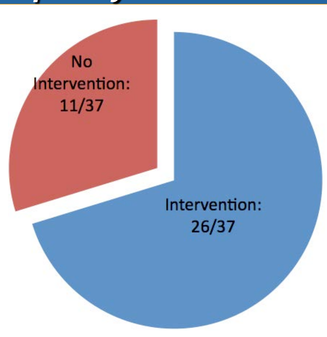


Figure 2: Clinical Outcomes Experienced

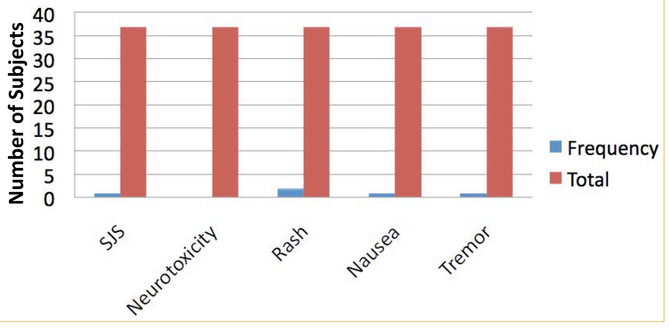
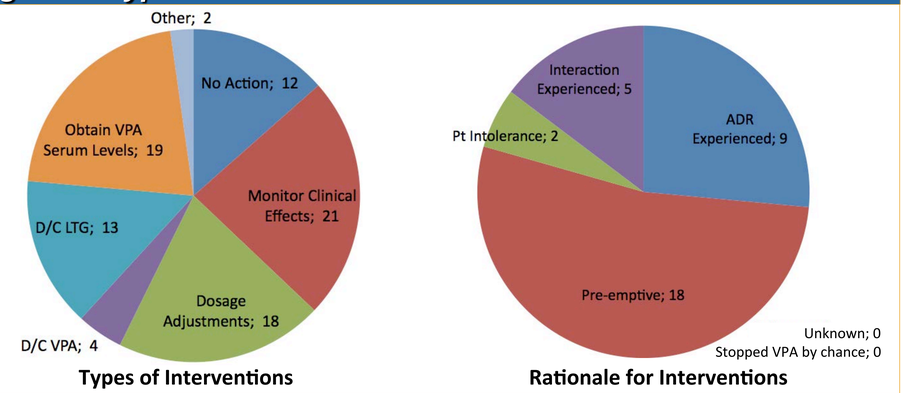


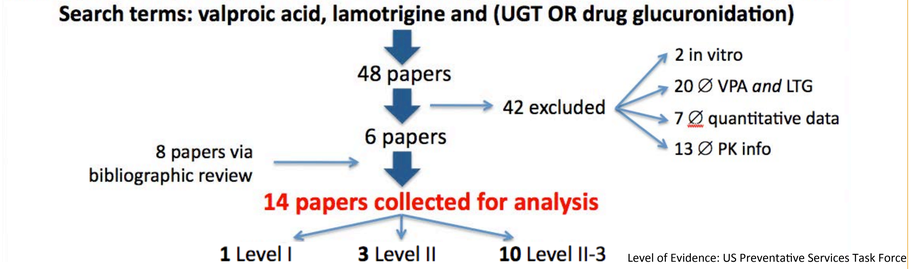
Figure 3: Types of Interventions and Rationale



Results of Systematic Review

Medline, EMBASE, Google Scholar, TRIP database, CINAHL, ISI Web of Science, PsychINFO

Search terms: valproic acid, lamotrigine and (UGT OR drug glucuronidation)



Level of Evidence: US Preventative Services Task Force

LTG PK Parameters	Mean t1/2 (h)	Mean Cl (ml/kg/min)	Mean AUC (µg/ml*h)	Mean LDR (µg/ml/mg/kg)
LTG Monotherapy	21.9-37.4	0.3-0.7	25.4-70.9	1.0-1.9
LTG/VPA	38.7-74.6	0.2-0.4	41.4-91.8	3.4-3.6
Mean % Difference (±SD)	↑ **95%** (± 46%)	↓ **49%** (± 21%)	↑ **93%** (± 58%)	↑ **219%** (± 99%)

Conclusion and Recommendations:

- Synergistic LTG/VPA therapy more effective than monotherapy in treatment resistant epilepsy and/or psychiatric mood disorders
- Significant PK interaction with ↑ inter-patient variability → *may* ↑ ADR risk
- Unknown mechanism behind PK interaction → ∅ *in vivo* data quantifying LTG-glucuronide metabolite generated
  - Yet papers continue to cite VPA inhibition of UGT based on unfounded evidence
- Consider starting with ↓ LTG dose (12.5mg vs. 25mg daily) when adding to VPA
- Small minority (N = 5 /37) → transient, non-life threatening ADR suspected to be result of VPA/LTG interaction
- N = 1 /37 → SJS, but liver dysfunction (hepatitis B carrier) confounding risk factor
- LTG/VPA in treatment resistant cases may be safe and effective in those with ∅ other risk factors for LTG toxicity (i.e. liver dysfunction)
  - Monitoring and patient education are necessary

Limitations:

- **Retrospective Chart Review:**
  - Retrospective, single site, ↓ duration, ↓ sample size
  - Not all interventions documented in patient chart
- **Systematic Review:**
  - Poor level of evidence (10/14 papers → Level II-3, uncontrolled), ↓ sample size, ↓ duration of treatment, merged children and adult data

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