Levetiracetam Induced Psychosis: The Good the Bad and the Ugly

Greg Egan BSc. Pharm, ACPR
Doctor of Pharmacy Student
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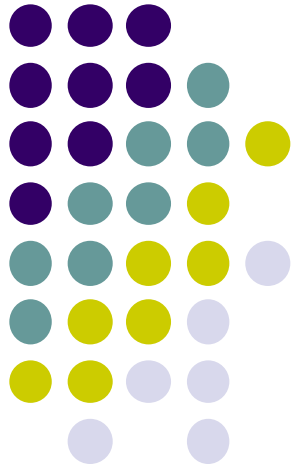


Case

42 y/o Female, 1 week Hx of ↑ Seizure (Sz) frequency

Currently 12 Sz /day (reported by family)

Seen by neurologist 3 months ago ~ 3 Sz/month

Started at levetiracetam (LEV) at that time

Medical Hx	
Alcoholism (90s)	Sober x 6 yrs
Epilepsy (1998) focal secondarily generalized	Multiple AEDs
Non-epileptic Sz (2004)	

Case

Vitals	Tmax 36.4^{0}C, HR 76, BP 130/75, O2 sat 98% on R/A
Mental Status	Alert, orientated to name only Agitated episodes, calling out, flailing arms and legs Can abort episodes by distraction
Physical	No evidence of injury (tongue biting, fecal or urinary incontinence)
Lab	Lytes, CBC, glucose, lactate, CK, & Tox screen within normal limits
Test	CT head nil acute

Impression / Plan

1) Non-epileptic sz / psychosis

2) Obtain video-electroencephalogram (EEG)

Levetiracetam

- Approved US 1999, Canada 2003

- Indications:
  - Status epilepticus (IV)
  - Primary generalized epilepsy
  - Focal +/- secondarily generalized epilepsy
  - Myoclonus

- Mechanism of Action:
  - Modulates synaptic vesicle protein 2A
  - Selectively inhibits N-type Ca^{2+} channels
  - Releases GABA

Levetiracetam

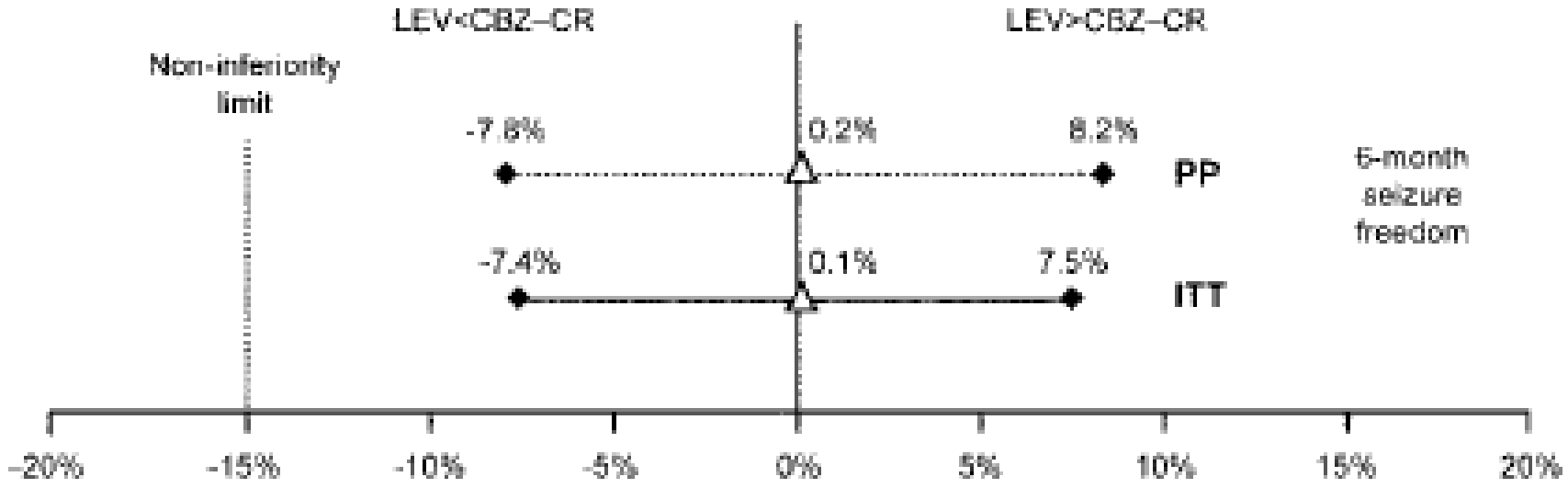
- Approximately 100% oral bioavailability
- Non-saturable Elimination:
  - Hydrolysis in serum (1/3)
  - Renally cleared unchanged (2/3)
  - $t_{1/2}$ 6-8hrs
- Fewer pharmacokinetic drug interactions

Cochrane Review 2012

- Drug-resistant (at least 2 other AEDs) focal epilepsy
  - 50% sz frequency reduction
- 11 RCTs (n=1861)
  - Significant heterogeneity 2º dose and publication year
- Analyzed by LEV daily dose
- 2 RCTs w/ LEV 2000mg/day
  - 38% vs. 7% (LEV vs. PBO) response rate
  - No ↑ response rate with ↑'er doses

Brodie et al. 2007

Patient	> 16 y/o (n= 472) **Newly diagnosed epilepsy** Focal or generalized ≥ 2 sz separated by 48hrs w/in past year
Intervention	LEV 500mg daily up to 2000mg daily
Comparator	CBZ-CR 200mg daily up to 800mg daily
Outcome	**Proportion of patients Sz free at 6 months**
Design	Non-inferiority with NIM 15% RCT, double-blind, allocation concealment Doses titrated to lowest effective dose

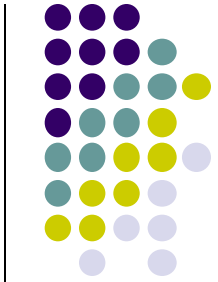


Results	LEV	CBZ
Sz free at 6 mo. (PP)	73%	72%
At least 1 AE	79.6%	80.2%
D/C due to AE	14.5%	17.2%
Psych AE	2.9%	2.1%

AED and Mood Disorder

- Positive effects:
  - gabapentin, tiagabine, lamotrigine
- Negative effects:
  - carbamazepine, levetiracetam, phenytoin
- Levetiracetam RCTs:
  - ↑ aggression in 1 RCT
  - Frequency of psychosis ~1-2% in RCTs
- Limitations:
  - Psychiatric illness excluded from RCT
  - Accurate diagnosis of psychiatric disorder
  - Mixed effects of multiple AED

Psychosis

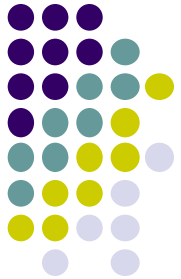


- Refers to a loss of contact with reality

- Clinical Features
  - Changes in thinking (delusions, hallucinations) and mood

- Pathology of Psychosis:
  - Schizophrenia, schizoaffective
  - Bipolar
  - Depression
  - Post-traumatic stress disorder
  - Brief psychotic disorder
  - Drug-induced
  - Secondary to a general medical condition

Non-Epileptic Seizures

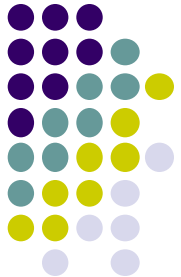


- Somatic manifestation of psychopathology
- Definitive diagnosis is video EEG
- Misdiagnosed as epileptic sz, agitation / aggression
- Mistreated with AED

Clinical Question

P	Adult patients (≥18 y/o) with epilepsy
I	Levetiracetam
C	No therapy, placebo, other AED
O	Incidence of Behavioural Adverse Effects: Depression, anxiety, agitation Psychosis or psychotic symptoms Non-epileptic seizures

Search Strategy



Databases	Medline, Embase, PubMed, Cochrane, Google, Google Scholar, International Pharmaceutical Abstracts
Search Terms	Epilepsy Levetiracetam Behavioural/psychiatric/functional/non-epileptic seizures/pseudo seizures
Limits	Human studies Adult patients English language
Results	147 results: 10 Case reports, 1 Cohort study, 1 Systematic Review
Analysis	**Brief summary of case reports** **Critical review of cohort study and SR**

Case Reports with Levetiracetam

- 8 cases of behavioural symptoms
  - Caused by new LEV use (5 cases) and ↑ dose of LEV (3 cases)
  - All cases had concurrent AED
  - Patient had epilepsy since childhood (6 cases)
  - Patient had psychiatric diagnosis (4 cases)
  - Time to resolution range from 2 days to 2 weeks after D/C of LEV
  - Objective Score (e.g. Naranjo) used in 2 cases only

- 2 cases of non-epileptic sz
  - New prescribing of LEV
  - Both had childhood sz
  - Both cases history of psychiatric diagnoses
  - 1 had previous history of non-epileptic sz
  - Both cases had concurrent AED

Mula et al. 2003

Patient	Rx w/ LEV at a hospital clinic in UK No active psychiatric illness at baseline
Comparison	Clinical details extracted from case records
Outcome	Epileptologists evaluated patients Documented Psychiatric Adverse Event (PAE)
Design	Retrospective cohort Compared patients with and without PAE Univariate analysis Logistic regression analysis

Mula et al. 2003

- Compared LEV users with or without PAE
  - Chi-squared or fisher's exact test for categorical data
  - Non-parametric tests for ordinal and linear data

- Characteristics were considered significant if $p < 0.05$ and these variables were included in the logistic regression model

- Logistic regression analysis with backward selection method
  - Variable was eliminated if removal statistic had probability of $p \geq 0.10$

Mula et al. 2003

- 517 patients, duration of LEV mean 8.3 6.5 months (range)
- Type of Epilepsy
  - Focal 76.6% (cryptogenic 26.5%)
  - Generalized 13% (Idiopathic 8.7%)
  - Other 5% & Undetermined 4.4%
- Patients developed PAE (10.1%):
  - Affective disorder 2.5%
  - Psychotic symptoms 1.2%
  - Aggression 3.5%
  - Emotional lability 2.3%
  - Agitated/hostile behaviour 0.6%
  - Suicidal ideation 0.7%

Mula et al. 2003

Variables	Epilepsy with PAE, n = 53	Epilepsy without PAE, n = 464
Gender, M/F	28/25	222/242
Mean ± SD age, y	34.6 ± 12.5	36.5 ± 11.5
Mean ± SD duration of epilepsy, y	24.9 ± 11.3	25.1 ± 11.6
History of febrile convulsions	22*	92
History of status epilepticus	18†	50
Previous psychiatric history	32†	216
Presence of learning disability	16	122
LEV titration schedule, 1,000 mg every 2 wk/faster/slower	17/5/35	160/31/269
Lamotrigine co-therapy	7	131‡

* $p = 0.001$.
† $p < 0.001$.
‡ $p = 0.02$.

PAE = psychiatric adverse events; LEV = leveteracetam.

Table 2 *Logistic regression analysis of risk variables for PAE during LEV therapy*

Variables	Wald	OR (95% CI)	*p* Value
History of febrile convulsions	9.565	2.90 (1.48–5.84)	0.002
History of status epilepticus	5.78	2.56 (1.17–5.58)	0.018
Previous psychiatric history	10.18	1.19 (1.070–1.328)	0.001
Lamotrigine co-therapy	4.63	0.40 (0.17–0.92)	0.031

PAE = pychiatric adverse events; LEV = levetiracetam; OR = odds ratio.

Mula et al. 2003

- Limitations:
  - No control of unknown factors
  - Exposure to LEV
    - Maintenance dose, Total exposure (mg/day)
  - Ascertainment bias from clinicians
    - Cross-over between definitions of PAE, clinical relevance
  - Retrospective data extraction
  - No description of loss to follow-up from cohort
  - Data obtained from a single center in UK

Cramer et al. 2003

Patient	Industry-run studies for epilepsy, anxiety and cognitive dysfunction
Comparison	LEV 1000-4000 mg/day vs. Control
Outcome	Frequency of treatment-emergent AE: affective, psychotic, suicidal ideation
Design	Systematic review and Meta-analysis from database of LEV clinical study data

Cramer et al. 2003

	Epilepsy	Cognition	Anxiety
Patients	1393	738	1084
Dosing	Mean 2421 mg/day	Mean 906 mg/day	516 mg/day
Follow-up	Mean 77 wks	6-12 weeks	4-12 weeks
Notes	• 4 RCT (n=769) • Studies with different designs (x-over studies, case-series)	• Post-CVA, post-trauma • All controlled trials	Depression X-over studies (pts counted twice)

Outcomes

- Affective – agitation, antisocial, anxiety, apathy, depression, emotional lability, euphoria, hostility, nervousness
- Psychotic symptoms – delusions, hallucinations, mania, paranoia
- Suicidal behaviour – intent to self-harm

Cramer et al. 2003

- Results
  - Affective AE
    - LEV 13% vs. 6% in epilepsy ($p<0.001$)
    - LEV 6.3% vs. 3.1% in cognition (NS)
    - LEV 5.1% vs. 5.5% in anxiety (NS)
  - Psychotic AE
    - LEV 1.4% vs. 0.7% epilepsy trials (NS)
    - < 0.5% in other cohorts for both groups
  - Low incidence of suicidal behaviour
    - < 0.5% across all trials

Cramer et al. 2003

- Limitations:
  - Clinical trial data - exclude patients with psychiatric disorders or complex seizure disorders
  - Inaccurate diagnosis and characterization of psychopathology:
    - Definitions of AE
    - Relied on spontaneous reporting
  - Methodological issues
    - No systematic search
    - Did not report study characteristics / quality assessment
    - No assessment of bias (publication, reporting)
    - No assessment of heterogeneity
    - No sensitivity analyses (LEV dose, epilepsy type)

Summary of Literature Search

- LEV is effective as monotherapy and add-on for drug-resistant epilepsy

- Frequency of psychosis:
  - RCT ~1-2%
  - Cohort 1.2%

- Frequency of behavioural AE:
  - RCT 13%
  - Cohort 10%

Behavioural Effects with LEV

- Susceptible clinical phenotype
  - Febrile seizure
  - Status epilepticus
  - Drug-resistant epilepsy
  - Psychiatric comorbidity
- Forced Normalization
  - Unmasked underlying psychopathology
- Approach
  - Clinical phenotype is not contraindication to LEV
  - Monitor for behavioural AE at initiation and dose titration
  - Index of suspicion for LEV-induced AE is higher with clinical phenotype