Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Risk of seizures associated with Ranolazine (Ranexa)

Efe Eworuke, PhD

Division of Epidemiology
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclosures

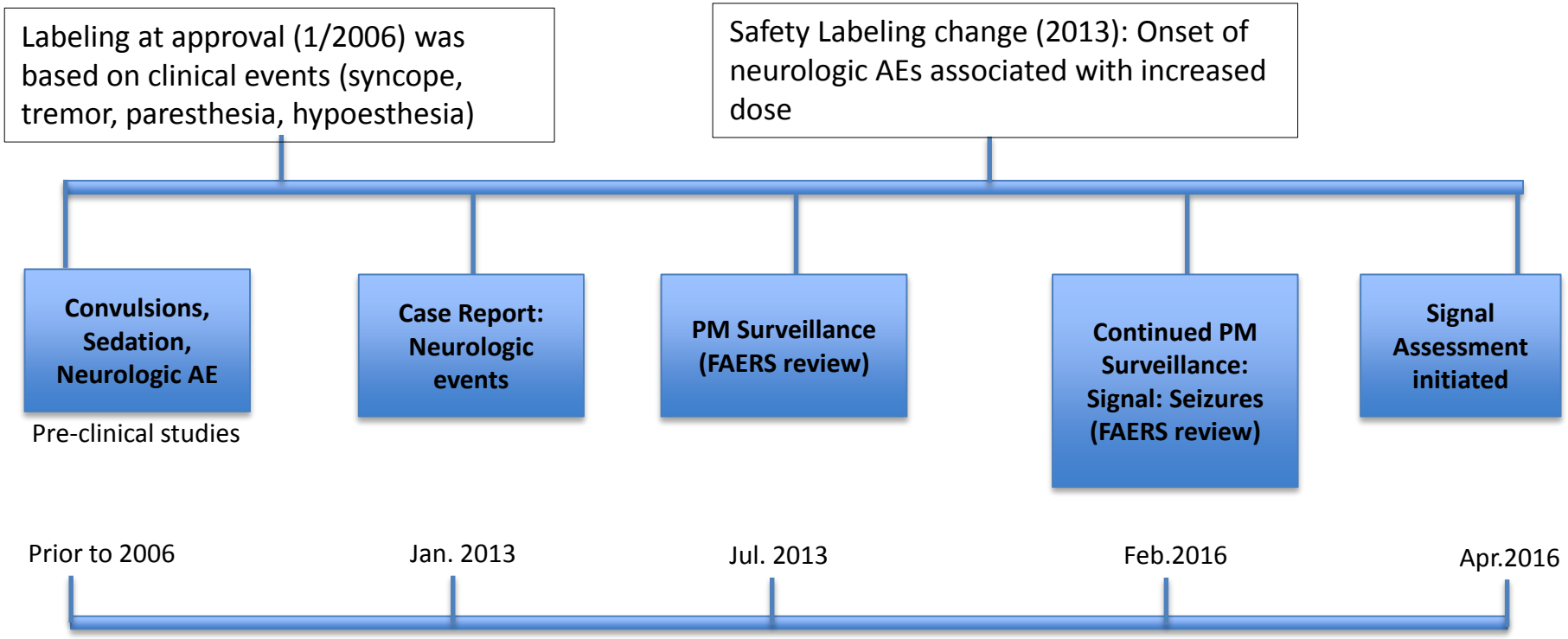
- No relationships to disclose

- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Background

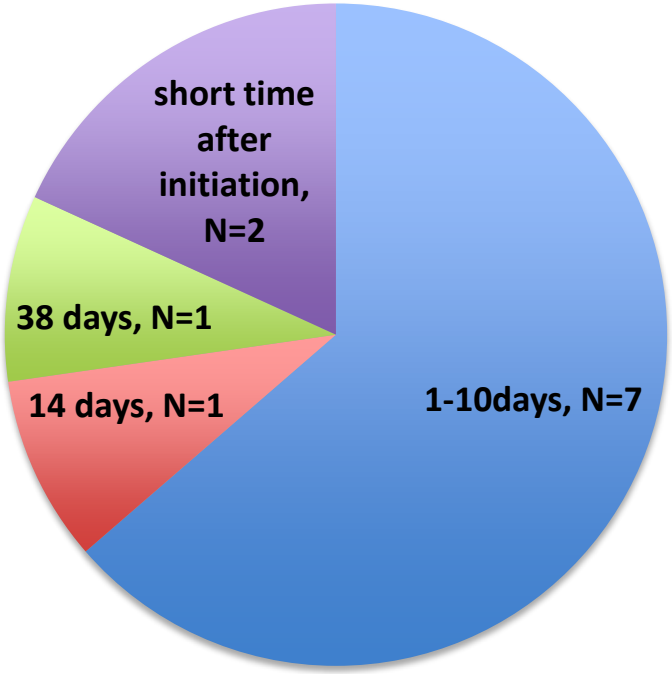
- Ranexa is an oral drug given twice daily for angina
- Angina is chest pain caused by insufficient blood flow to the heart (myocardial ischemia)
  - Possible pharmacological activity:
    - Demonstrated effects on sodium channels which are present in the cardiac, central and peripheral nervous systems

Safety Issue Timeline



Description of FAERS Case Reports

Time to Seizure Onset Following Ranexa Exposure (N=11)



Median Age: 78 years

Outcome: Hospitalization (63.6%);

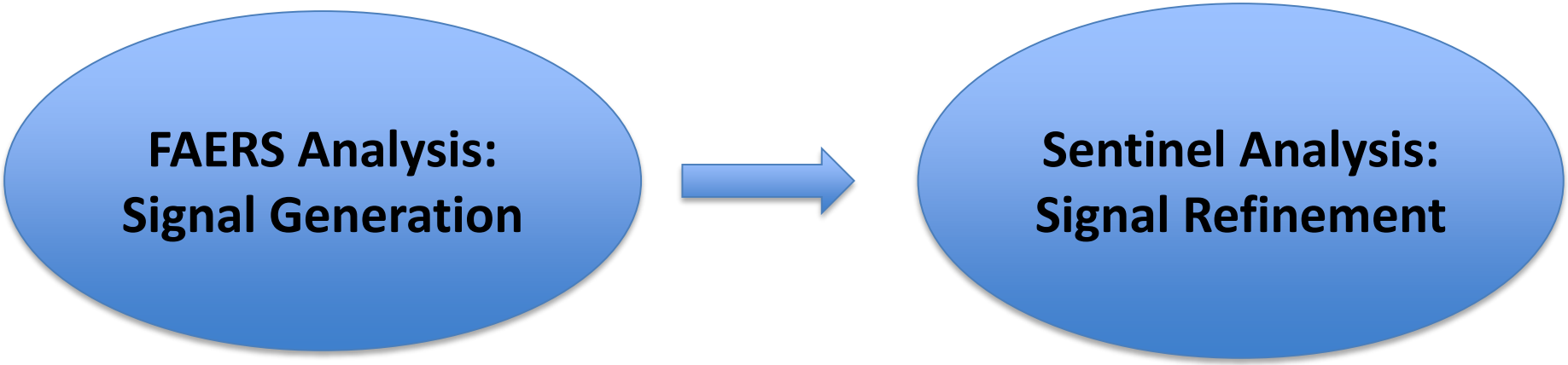
Dechallenge: Positive (72.7%)

Renal status: Chronic renal failure (36.3%); not reported (63.6%)

Temporality/Dechallenge: indicators for possible causality

Study Objective

- To investigate whether Ranexa use is associated with an increased risk of seizures



Isolated Reports

Are seizures temporally associated with initiation of Ranexa?

Study Design Considerations

- Absence of an appropriate comparator
  - AHA* recommends Ranexa in circumstances in which beta blockers, calcium channel blockers, and nitrates are not adequately effective or are not tolerated.

- Self-controlled risk interval design (SCRI)-Level 2 Sentinel modular program
  - FAERS data reveal onset of seizures within a short period after exposure (7 out of 9 cases[ŝ] occurred within 10 days)
  - SCRI design best suited for acute outcome, time-invariant confounders are controlled

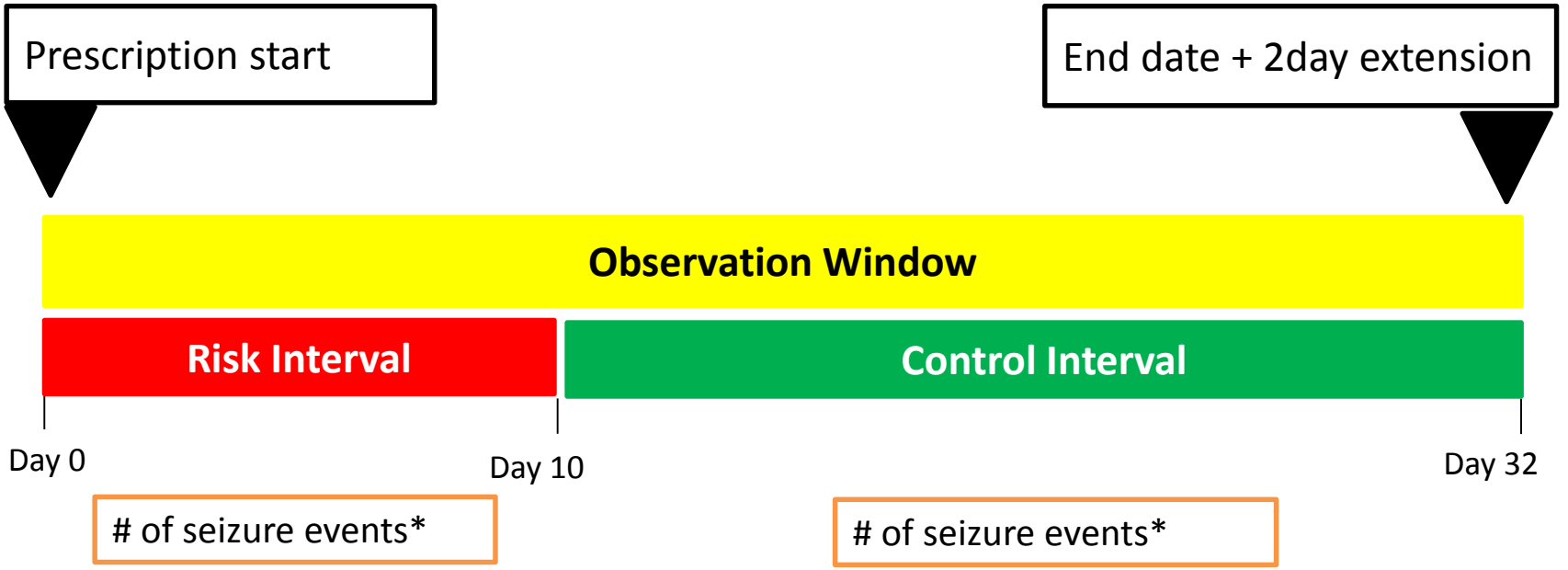
*AHA: American Heart Association

[ŝ] Cases for which onset of seizure was reported

Design Overview

Design	• Self-controlled risk interval design • 12 Sentinel Data Partners, Jan 2006 – Sept 2015
Inclusion	• Patients ≥18 years old with at least 183 days medical and drug coverage
Exclusion	• No epilepsy or seizure diagnosis, no AED • No epilepsy or seizure diagnosis, but had anti-epileptic drug (AED) use at baseline
Exposure	• New use of Ranexa (183 day look back period) • 1st valid 30-day *Rx* + 2-day extension period
Outcome	• Seizures • Inpatient or ED diagnosis

Self-Controlled Risk Interval Design



*Seizure event: ICD-9 codes for Epilepsy (345.X), convulsions (780.3X) or myoclonus (333.2) in Inpatient or Emergency Department discharge record (PPV: 84% - Kee et al. 2012)

Populations of Interest

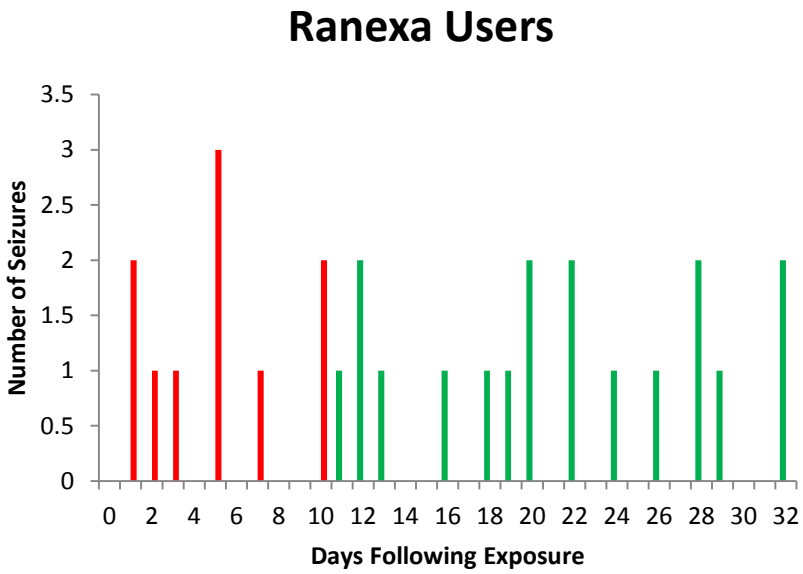
Study Populations	Description
Ranexa Users	Ranexa users with no epilepsy and no use of AED at baseline
Ranexa Users with AED	Ranexa users with no epilepsy at baseline but used AED at baseline
Age categories	55-64 years, 65-74 years, 75+
Pre-existing renal disease	Presence of a diagnosis code for renal conditions including dialysis at baseline
Pre-existing liver disease	Presence of diagnosis code for liver conditions at baseline

Cases Characteristics Summary

Variables	FAERS cases	Sentinel Cases[a]	
		Ranexa users	Ranexa with AED[b]
Number of patients	11	28	11
Age, 55-64	0	5	1
Age, 65-74	2	5	4
Age, 75+	5	16	5
Gender, Female	50%	42.9%	72.7%
Renal Condition	36.3%	64.3%	NR
Liver Condition	NR	17.9%	NR

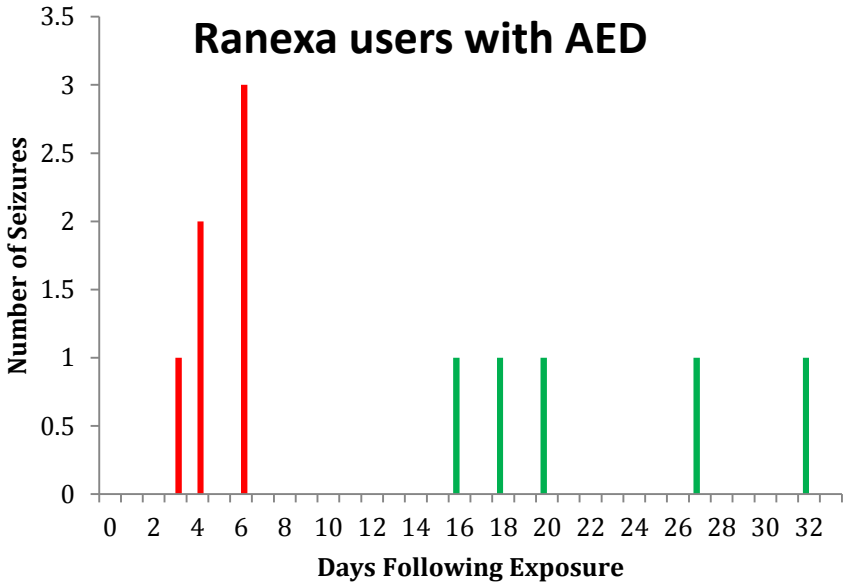
[a]Among 58,285 Ranexa users included in the study
[b]AED: Anti-epileptic Drug
NR: Not Reported

Seizure risk in risk window (RW) vs. control window (CW)



# Events in RW	# Events in CW
10	18

Relative Risk: 1.1 (CI: 0.5-2.6)



# Events in RW	# Events in CW
6	5

Relative Risk: 2.4 (CI: 0.7-7.9)

Seizure risk stratified by population of interest

Population of interest	Number of Events in Risk Window	Number of Events in Control Window	Relative Risk	95% Confidence Interval
Age: 55-64	2	3	1.3	0.2, 8.5
Age: 65-74	3	2	3.0	0.5, 24.1
Age: 75+	5	11	1.0	0.3, 3.0
Pre-existing renal disease	7	11	1.4	0.5, 3.7
Pre-existing liver impairment	1	4	0.5	0.1, 3.8

Results Summary

- Seizures within 10 days of Ranexa initiation are uncommon, and seizure rate in first 10 days does not appear to be higher than in days 11-32
- For Ranexa users with history of AED, there is a non-significant 2.4 fold seizure risk in first 10 vs. next 20 days
  - AED population is a mix of epilepsy patients and those who use AED for other conditions such as pain
    - Role of epilepsy
    - Role of polypharmacy
- Slightly increased (not significant) seizure risk for renal impairment patients as well as older patients (65-74 year olds)

Sentinel's Role in Safety Assessment

- **FAERS data:** Identified a potential seizure signal among Ranexa users
  - Severity of signal, temporality, & dechallenge info. fueled interest in further investigation
- **Sentinel:** Signal refinement
  - Quantify seizure risk among Ranexa users
  - Identified populations for future evaluation– older patients, renal disease condition and use of anti-epilepsy drugs
- Further signal evaluation in Medicare underway

Acknowledgements

FDA

- Margie Goulding
- MaryRoss Southworth

Sentinel

- Emily Welch
- Judy Maro

Many thanks are due to the Data Partners who provided data used in this analysis

Efe.Eworuke@fda.hhs.gov

Back-up 1: Drug List

Beta blockers	CYP3A inhibitor Ca Blockers	Nitrates
acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetolol, levobunolol, metipranolol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, and timolol	Verapamil, Ditiazem, Nicardipine,	amyl nitrite, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin

Back-up 2: Comorbidities

Renal Disease Diagnoses	Liver Disease Diagnoses
Acute and Chronic Renal Disease Patient on Dialysis End Stage Renal Disease	Hepatic encephalopathy Portal hypertension Hepatorenal syndrome Alcohol Hepatitis Liver cirrhosis Liver Damage Chronic Liver disease Liver disorders Unspecified Jaundice Abnormal LTS Liver Transplant

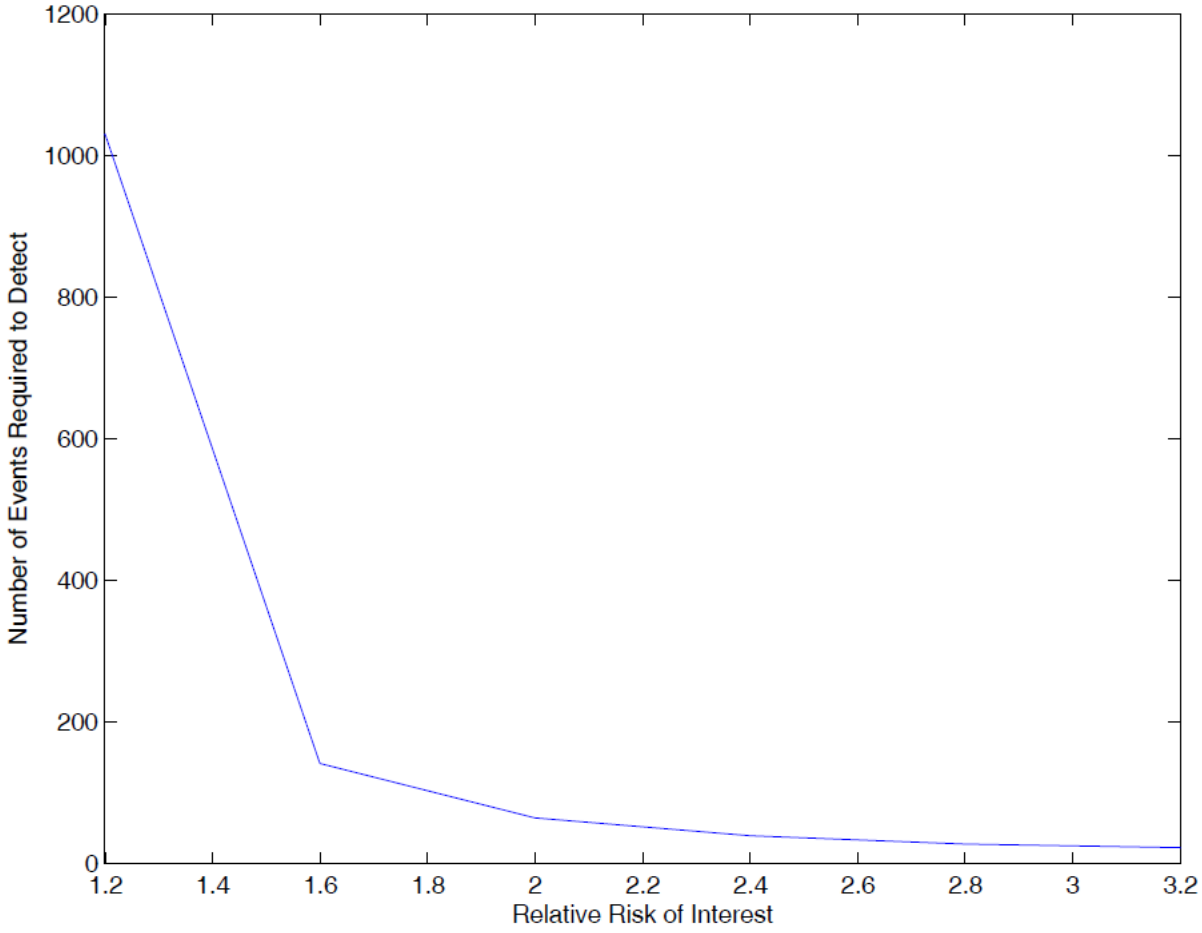
Back-up 3: AET list

Antiepileptic Drugs		
CARBAMAZEPINE (CYP3A4 inducer)	LACOSAMIDE	PREGABALIN
CLOBAZAM	LAMOTRIGINE	PRIMIDONE
CLONAZEPAM	LEVETIRACETAM	RUFINAMIDE
DIVALPROEX SODIUM	LEVETIRACETAM IN SODIUM CHLORIDE, ISO-OSMOTIC	TIAGABINE HCL
ESLICARBAZEPINE ACETATE (moderate CYP2C19 inhibitor)	OXCARBAZEPINE (weak inhibition of CYP3A4/5 (likely not clinical significant; clinical relevant CYP2C19 inhibition)	TOPIRAMATE
ETHOSUXIMIDE	PERAMPANEL (weak inhibitory effect on CYP3A4, CYP2C8 with 30 umol/L; weak inducer of CYP2B6 & CYP3A4?)	VALPROIC ACID (weak inhibitor of some P450 isozymes, not specified in the label)
ETHOTOIN	PHENOBARBITAL (p-gp inducer, CYP inducer, particularly CYP2B6)	VALPROIC ACID (AS SODIUM SALT) (VALPROATE SODIUM)
EZOGABINE	PHENOBARBITAL SODIUM	VIGABATRIN (CYP2C9 inducer)
FELBAMATE	PHENOBARBITAL SODIUM IN 0.9 % SODIUM CHLORIDE	ZONISAMIDE
GABAPENTIN (weak CYP2A6 inhibitor; 14% to 30% inhibition at the highest concentration tested :171 mcg/mL; 1mM)	PHENTERMINE HCL/TOPIRAMATE (topiramate is a mild CYP3A4 inducer and CYP2C19 inhibitor)	FOSPHENYTOIN SODIUM
GABAPENTIN ENACARBIL	PHENYTOIN (label listed a potent inducer of hepatic drug-metabolizing enzymes)	METHSUXIMIDE

Results: Population Characteristics

Variables	All Ranexa	Ranexa-Nitrate users	Ranexa (epileptics)	Ranexa-Nitrate (epileptics)
Number of patients	47, 495	25,762	10, 790	6,241
Age: 18-44 years	3.2%	2.5%	3.5%	2.8%
Age: 45-54 years	13.1%	11.5%	15.9%	14.7%
Age: 55-64 years	27.0%	25.1%	30.9%	29.3%
Age: 65-74 years	27.9%	28.1%	26.8%	27.6%
Age: 75+ years	28.9%	32.8%	23.0%	25.6%
Gender (Female)	37.0%	36.7%	48.7%	47.5%
Gender (Male)	62.9%	63.3%	51.3%	52.5%
Combined comorbidity score	2.5	2.6	2.8	2.9
Angina Pectoris or Prinzmetal Angina	47.7%	53.3%	48.0%	53.6%
Chest Pain	70.2%	74.1%	76.1%	79.6%
Coronary Atherosclerosis	87.9%	92.3%	88.5%	92.5%
Liver Impairment	7.5%	7.7%	9.3%	9.5%
Renal Disease	23.0%	26.6%	30.5%	33.7%
Beta Blockers	77.9%	83.2%	79.2%	83.0%
Calcium Channel Blockers	6.8%	7.0%	8.3%	8.4%
Nitrates	64.8%		68.7%	
Mean number of generic drugs	5	4.9	5.9	5.8
Mean number of unique drug classes	4.6	4.5	5.3	5.2
Mean number of filled prescriptions	17	17.6	22.1	22.5
Mean number of inpatient hospital encounters (IP)	1	1	1.2	1.2
Mean number of non-acute institutional encounters (IS)	0.9	0.9	1.3	1.3
Mean number of emergency room encounters (ED)	1.2	1.2	2.2	2.2
Mean number of ambulatory encounters (AV)	10.4	10.8	13.2	12.5
Mean number of other ambulatory encounters (OA)	5.2	5.5	8.2	8.7

Post-hoc Power Calculation



For 28 events, study had ability to detect 2.8 RR at 80%.
For 22 events, study had ability to detect 3.2 RR at 80%.

And RRs found were from 1.0 – 2.5 so study is UNDER-POWERED.

Methods

- Data: 01/01/2006 – 09/30/2015 from 12 health plans
- Cohort Definition: Patients ≥18 years old with at least 183 days medical and drug coverage
- Eligibility Criteria:
  - New use of Ranexa (no Ranexa during 183 day period (baseline) before use) and No epilepsy or seizure diagnosis and/or no anti-epileptic drug (AED) during baseline period – Ranexa cohort
  - New use of Ranexa (no Ranexa during 183 day period (baseline) before use) and No epilepsy or seizure diagnosis **but use of AED** during baseline period – Ranexa with AED cohort
- First valid 30-day prescription plus a 2-day extension period (observation window)