Integrated Data Mining and Systems Pharmacology to Explore the Comparative Safety of Brand-Name and Generic Drugs

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Introduction

- The introduction of generics into the market yields approximately $10 billion consumer savings per year[1]
- Along the time, there have been perceptions about generic drugs bio-inequivalence, which can be reflected by the purported lack of efficacy or the adverse events (AE)
- Antiepileptic drugs (AEDs), which were recently linked with an increased risk of suicidal thoughts or actions[1] and clinicians claim of lack of efficacy, have been at the epicenter of the controversy over generic-brand drug substitution
- An impetus exists to mechanistically explore the controversy over antiepileptic generic-brand drug substitution

Objectives

1. To compare the i) number, ii) final outcome and iii) nature of AE from three brand name and generic AEDs: Phenytoin, Levetiracetam and Gabapentin
2. To unearth hypotheses about the mechanistic origin of potential differences between brand name and generic AEDs

Methods

We have undertaken a multidisciplinary approach that integrates data mining and systems pharmacology to elucidate and explain possible differences between brand name and generic AEDs

Data Mining Approach

1. Implement a SAS code to mine the AE records from the three AEDs in the FDA Adverse Event Reporting System (FAERS[1])
2. Assess the age, weight and gender as potential confounders in the current study
3. Retrieve the frequency of AE and the corresponding final outcome for the brand name and generic AEDs throughout a 10-year time window (2004 to 2014)
4. Identify the 5 most commonly reported AE for the two drug categories

Systems Pharmacology Approach

5. Exploit the Molecular Analysis of Side Effects (MASE[2]) integrated software platform to shed light on molecular drug targets and pathways

Data Mining Approach

Figure 1: Assessing age, weight and gender as potential confounding factors. No clinically important differences were observed between the two groups and, therefore, no confounders were taken into consideration.

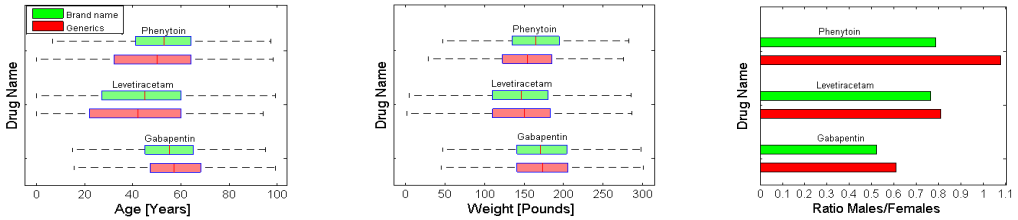

Figure 2: Frequency of AE per Year Quarter over a 10-year period for brand name and generic drugs. The difference in AE between the two drug categories is not compelling, although prescription data are required for an unbiased comparison of AE frequency.

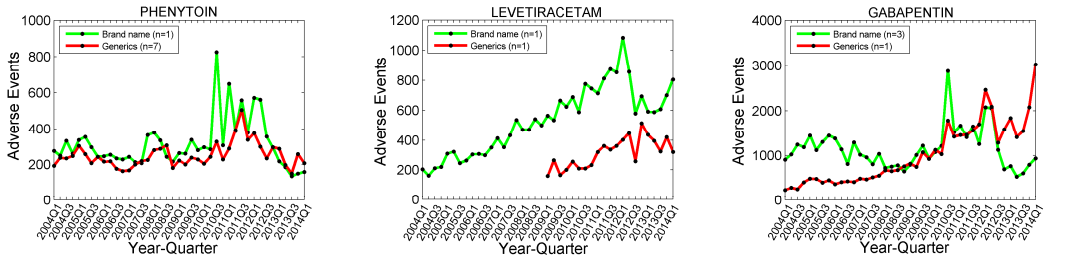

Figure 3: Final patient outcome as a result of the AE shown in Figure 2. The majority of AE led to Other serious outcomes or Hospitalization in both brand name and generic drugs and across all three AEDs.

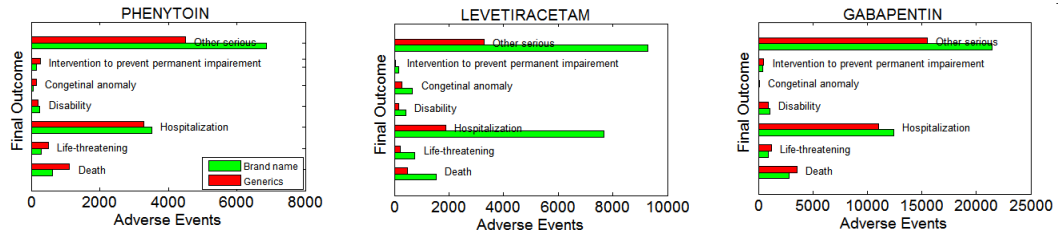

Table 1: Nature of the 5 most common AE reported from 2004 to 2014 for the three AEDs. In some instances, the nature of the prevailing AE differs between brand name and generic drugs. In what follows, thrombocytopenia is used as an example to demonstrate how MASE can be exploited to molecularly dissect differences between brand name and generic AEDs.

	Brand name	Generics
PHENYTOIN	Convulsion	Convulsion
	Stevens-Johnson syndrome	Drug ineffective
	Drug ineffective	Drug interaction
	Anticonvulsant drug level decreased	Stevens-Johnson syndrome
	Anticonvulsant drug level increased	Pyrexia

	Brand name	Generics
LEVETIRACETAM	Convulsion	Convulsion
	Drug exposure during pregnancy	Product substitution issue
	Thrombocytopenia	Drug ineffective
	Condition aggravated	Pregnancy
	Grand mal convulsion	Abortion spontaneous

	Brand name	Generics
GABAPENTIN	Drug ineffective	Drug ineffective
	Pain	Pain
	Suicidal ideation	Vomiting
	Depression	Completed suicide
	Completed suicide	Nausea

Systems Pharmacology Approach

Table 2: Top 20 molecular targets of Levetiracetam ranked by proportional reporting ratio (PRR) and separated into CYP enzymes, transporters and other molecular targets[2]

CYP Enzymes	AE	PRR
Cytochrome p450 2c18	3527	2.67 (2.60-2.74)
Cytochrome p450 2b6	5828	1.90 (1.87-1.93)
Cytochrome p450 2e1	3585	1.59 (1.55-1.63)
Cytochrome p450 3a5	6452	1.56 (1.54-1.59)
Cytochrome p450 2a6	3391	1.52 (1.48-1.57)
Cytochrome p450 2c19	7466	1.51 (1.49-1.53)
Cytochrome p450 3a7	5302	1.50 (1.47-1.53)
Cytochrome p450 2c8	6539	1.29 (1.27-1.31)
Cytochrome p450 1a2	5919	1.25 (1.23-1.28)
Cytochrome p450 2c9	6766	1.19 (1.17-1.21)
Cytochrome p450 3a4	8073	1.14 (1.13-1.15)
Cytochrome p450 2d6	5084	0.96 (0.94-0.98)
Transporters	**AE**	**PRR**
Canalicular multispecific organic anion transporter 1	11404	6.17 (6.15-6.19)
Multidrug resistance protein 1	11404	2.00 (1.99-2.00)
Serum albumin	3908	1.49 (1.46-1.53)
Solute carrier family 22 member 6	3615	1.32 (1.28-1.35)
Other Molecular Targets	**AE**	**PRR**
Voltage-dependent n-type calcium channel subunit alpha 1b	11404	22.32 (22.19-22.46)
Gamma-aminobutyric-acid receptor subunit alpha-1	3347	3.47 (3.37-3.57)
Prostaglandin g/h synthase 1	3229	1.21 (1.17-1.24)
Synaptic vesicle glycoprotein 2a	11404	n/a

- ✓ Prostaglandin g/h synthase 1, also known as COX-1, promotes platelet aggregation[3]
- ✓ Hypothesis: Thrombocytopenia could result from excessive COX-1 inhibition by Levetiracetam

Conclusions

- ✓ No compelling difference was noted between the AE frequency and the final outcome of the brand name and generic products of Phenytoin, Levetiracetam and Gabapentin
- ✓ Prescription data are required for an unbiased comparison of AE frequency
- ✓ Differences in the nature of the prevalent AE were observed between brand name and generic AEDs; MASE was used to generate a hypothesis about the molecular basis of a representative difference
- ✓ Our approach can be applied to any drug class of interest

References
1. http://www.fda.gov/Drugs/
2. https://mase.molecularhealth.com
3. Caughey et al., The Journal of Immunology, 2001