IMPAQ INTERNATIONAL LLC

Post-marketing Surveillance of Generic Drug Usage and Substitution Patterns

U01FD004855
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October, 2015 FDA Presentation

Presentation Topics

- Project Overview
- Aims 1 (Literature Review), 2 (Claims Analysis), and 3 (Survey)
  - Background
  - Methods
  - Results
  - Discussion
- Study Conclusion

Study Background

- Generic drug substitution is an effective tool to reduce prescription drugs costs, which may lead to increased accessibility and compliance for patients
- Generic drugs are the same as those brand name drugs in dosage form, strength, route of administration, quality, performance characteristics, and intended use
- Generic drugs must demonstrate bioequivalence
- Increased availability of complex generic products and demand for faster access to safe and effective generic drugs led to development of non-conventional bioequivalence methods

Study Purpose

- To conduct a review of the safety and/or effectiveness of three drug products, because:
  - Recent increase in the number of complex drug molecules/products
  - Growing need for non-traditional bioequivalence methods for ANDA approval
  - Need for proactive monitoring of safety and effectiveness for drugs approved using these non-traditional methods

Study Aims

- Assess whether differences in safety and/or effectiveness exist between brand and generic products through:
  - Systematic literature review
  - Retrospective cohort study using claims data
  - Patient and Physician survey
- Evaluate 3 products:
  - Acarbose tablet
  - Calcitonin salmon nasal spray
  - Venlafaxine extended-release (ER) tablet

Generic Products Studied

- Acarbose (Precose)
  - Minimal systemic absorption after oral dosing – therapeutically desirable
  - 7 AB-rated generic products
- Calcitonin salmon NS (Miacalcin)
  - Poorly absorbed
  - Spray device impacts product performance
  - Product- and process-related factors for immunogenicity
  - 2 AB-rated generic products
- Venlafaxine ER tablet
  - Different ER technology affects absorption
  - *In vivo* fasting studies waived due to safety concerns
  - 1 AB-rated generic product

Aim 1: Literature Review

Search Strategy

- Published prior to March, 2014
- Databases: MEDLINE, EMBASE, IPA, Cochrane CENTRAL, Cochrane systemic reviews, Web of Science, Scopus
- Inclusion Criteria (Hierarchy Order):
  - Articles published in English
  - The data or research population from the U.S.
  - Human studies*
  - Exposure includes drug of interest
  - Clinically relevant outcome measurements
  - Brand and/or generic drug identified in the article

*Exception: Two in vitro studies conducted by generic manufacturers were included for nasal calcitonin.

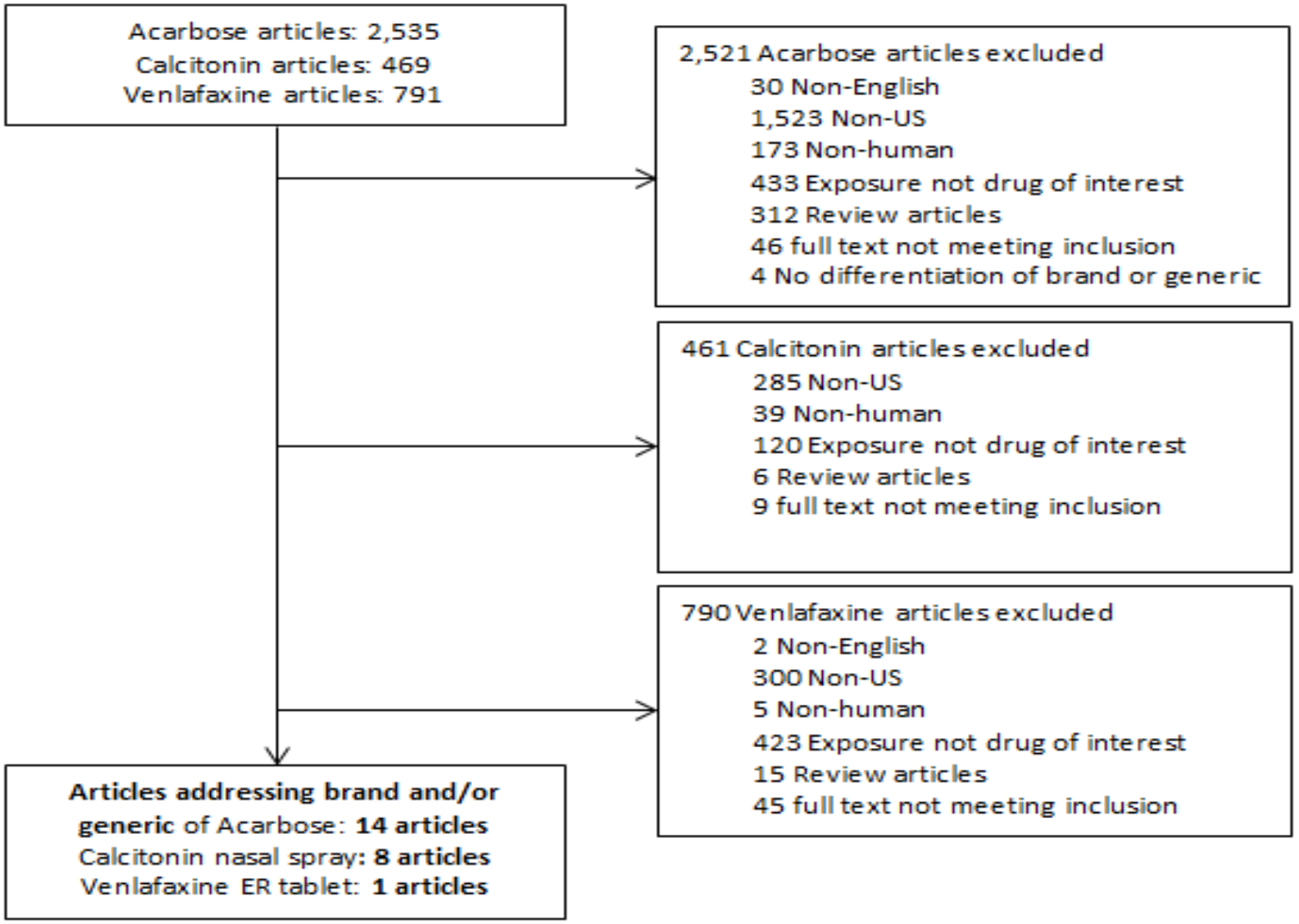
Methods- Search Terms

General Search Terms		
adverse	efficacy	postmarket*
bioavailab*	equivalen*	quality
bioequivalen*	fail*	reaction*
biological availability	formulat*	risk
brand	generic*	safety
drug substitution	inequivalen*	substitut*
drug toxicity	interchang*	surveillance
drugs, generic	orange book	switch
effect*	outcome*	therapeutic equivalency
	performance	therapeutic*
		Treatment

Acarbose tablet	Calcitonin-salmon nasal spray	Venlafaxine ER tablet
absorption	adverse	absorption
adverse	anaphylaxis	alcohol
harm	complication	dissolution
permeability	contamina*	dose dumping
permeable	hypersensitivity	extended release
permeat*	immune response*	fasted
side effect*	immunogen*	fasting
solubility	impur*	fed
soluble	purity	solubility
	side effect*	tablet* AND size*

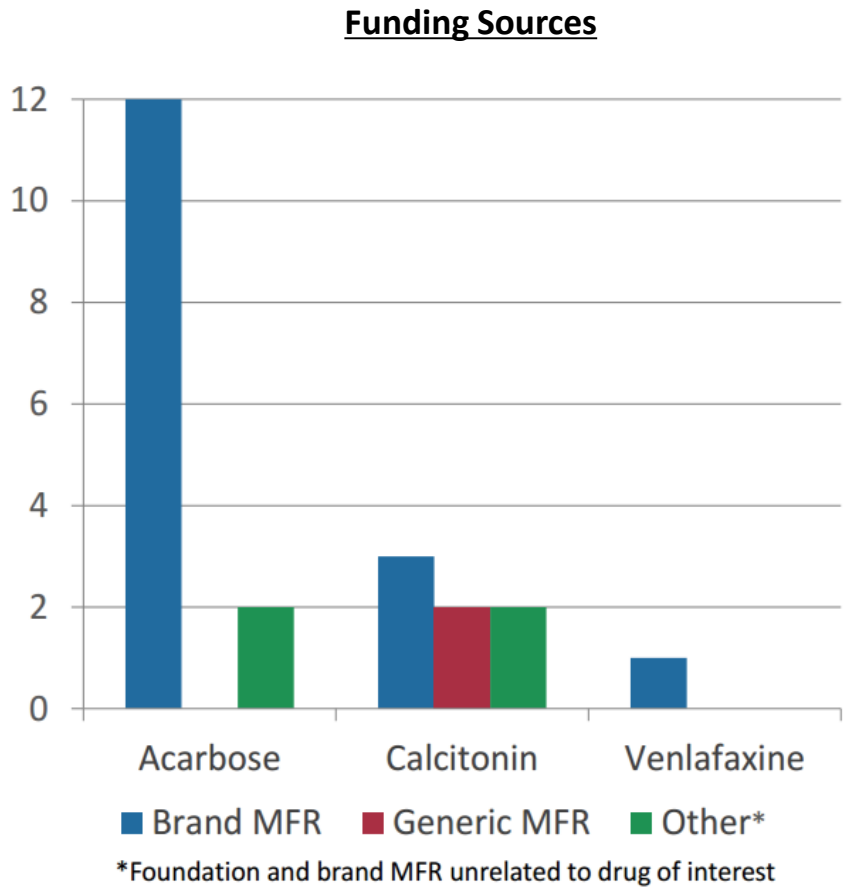
*Finds all terms that have the given root word

Articles Retrieved



Results

- Acarbose tablet
  - Precose® vs. Placebo (n=11)
  - Single-arm Precose® (n=3)
- Calcitonin-salmon nasal spray
  - Miacalcin® vs. Placebo (n=5)
  - Miacalcin® vs. AB-rated generic (n=1)
  - Miacalcin® vs. Fortical® (n=1)
  - Miacalcin® vs. Oral recombinant (n=1)
- Venlafaxine ER tablet
  - Effexor® capsule vs. Venlafaxine ER tablet by Osmotica (n=1)



Discussion

- Lack of published literature that compares efficacy and safety differences between brand and generic products
  - Few published *in vitro* studies, no *in vivo* studies
  - No incentives for generic manufacturers to publish *in vivo* studies
- When approved via non-conventional methods, additional information on substitutability of a generic drug may be useful for clinicians and patients
  - Especially with increased number of complex drug molecules
  - Need to explore additional methods to monitor generic products in a post-marketing setting

Aim 2: Claims Analysis

Claims Analysis Sub-Aim 1

- To describe **monthly utilization** of the drugs of interest between 2006 and 2011

Claims Analysis Sub-Aim 2

- Aim 2a: To evaluate **time to switch** to generic among Medicare beneficiaries who were users of the brand product of interest before the generic was available and comparing to positive and negative controls
- Aim 2b: To evaluate **time to switchback** to brand from generic among Medicare beneficiaries who were users of the generic product of interest from Aim 2a and comparing to positive and negative controls

Switch and switchback definition

First generic acarbose marketed

Patient	Group	Jan 2008	Feb 2008	Mar 2008	Apr 2008	May 2008	Jun 2008	Jul 2008	Aug 2008	Sep 2008	Oct 2008	Nov 2008	Dec 2008
Patient 1	1			B	B	B	B	B	B	B	B	B	B
Patient 2	2								G1	G1	G1	G1	G1
Patient 3	3	B	B	B	B	G1	G1	G1	G1	G1	G1	G1	G1
Patient 4	3	B						G1	G1	G1	G1	G1	G1
Patient 5	4	B	B			B	B	G1	G1	B	B	B	B
Patient 6	4	B	B			G1	G1	G2	G2	B	B	B	B
Patient 7	5	B	B	B	B	G1	G1	B	B	G1	B	G1	G2

B-brand acarbose; G1-generic acarbose 25 mg; G2-generic acarbose 50 mg; blue-switch from brand to generic; red-switchback from generic to brand; green-switch between generics

Claims Analysis Sub-Aim 3

- Aim 3a: To evaluate the impact of **switching** to generic on (1) mortality and (2) the composite outcome of hospitalization or emergency department visits, among those on the brand product
- Aim 3b: To evaluate the impact of **switching back** to brand on (1) mortality and (2) the composite outcome of hospitalization or emergency department visits, among those on the generic product

Methods- Data Source

- Chronic Condition Data Warehouse (CCW)
  - Medicare fee-for-service institutional and non-institutional claims, enrollment and eligibility files
  - 5% random sample
  - 2006-2011
- Medicare Part D prescription drug files

Methods- Control Selection

- Products for which the first generic was approved between 2006 and 2010 to allow for sufficient follow up within our available claims data
- Have an indication for the same condition/disease as the targeted drug
- Commonly prescribed

Methods- Control Definitions

- Negative Controls
  - No safety concern has been associated with switching from the NDA to ANDA versions of the medication
- Positive Controls
  - Has reported safety concerns associated with switching from the NDA to ANDA

Methods – Antidepressants

Medications of Interest-Venlafaxine

Generic Name	Control Type
bupropion extended release tablet – 300 mg	Positive
paroxetine extended-release tablet	Negative
sertraline tablet	Negative

Methods – Antidiabetic Medications

Medications of Interest-Acarbose

Generic Name	Control Type
nateglinide tablet	Negative

Methods – Antiosteoporosis Medications

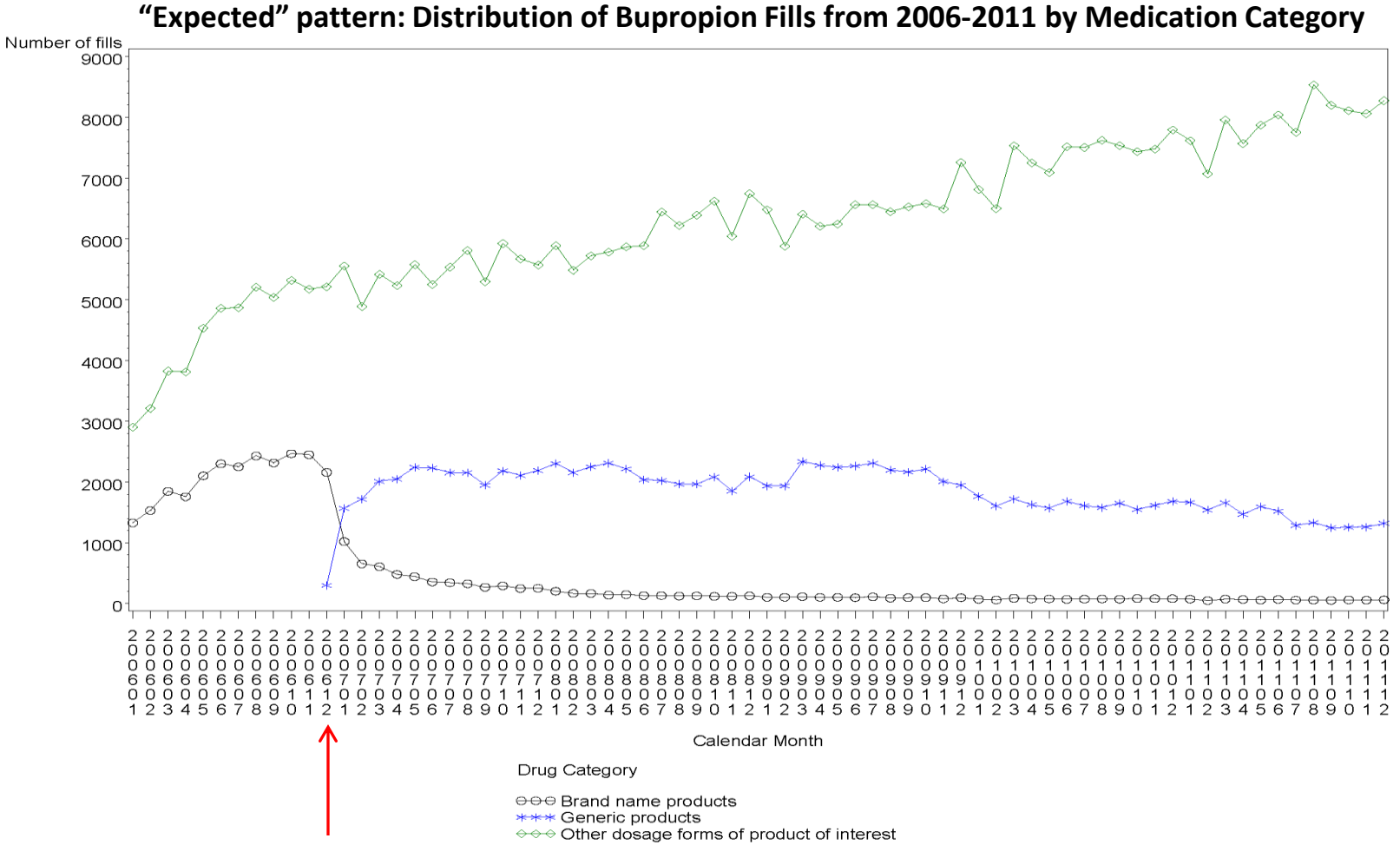
Medications of Interest-Calcitonin

Generic Name	Control Type
alendronate tablet	Positive (?)

Study Cohort

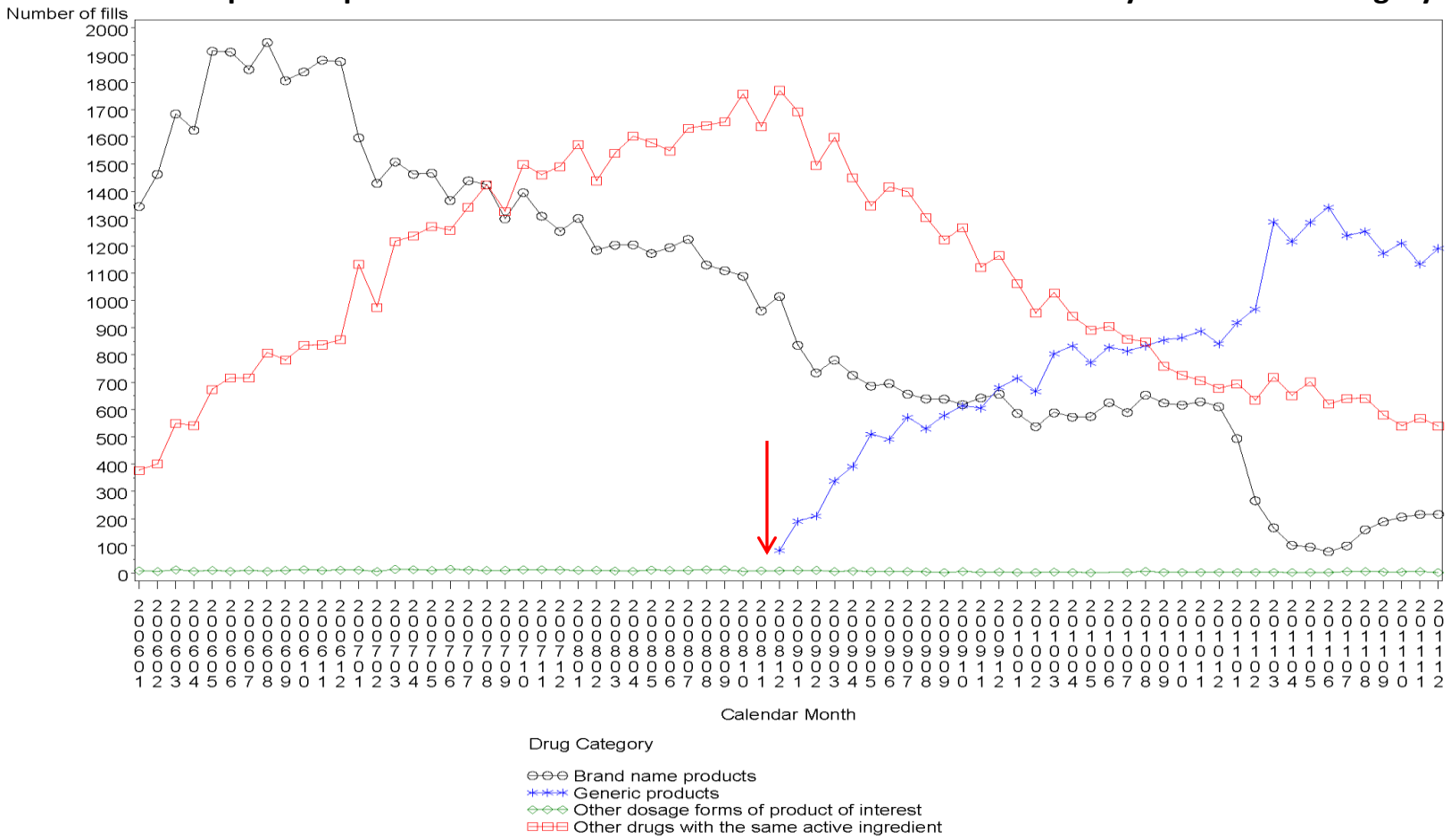
- Utilization
  - All prescription fills for drugs of interest
- Time to switch/switch impact on outcomes
  - Required one brand prescription fill in the 3 months prior to the generic approval per drug
  - Fee-for-service Medicare beneficiary during study period
- Time to switchback/switchback impact on outcomes
  - Met switch cohort criteria
  - Switched from brand to generic

Utilization Results- Example of an "Expected" Pattern



Utilization Results – Example of an "Unexpected" Pattern

"Unexpected" pattern: Distribution of Calcitonin Fills from 2006-2011 by Medication Category



Results- Utilization Summary

- ↑generic prescriptions filled with a corresponding ↓ in the number of the prescriptions filled for the brand, once generic are available
- Exceptions:
  - calcitonin nasal spray
    - ↓ brand prior to generic approval, likely due to other drugs in class with the same active ingredient
  - venlafaxine ER tablets

Results – Demographics for Switching to Generic

Drug class	Drug	Earliest generic approval date	N	Age, years mean (SD)	White %	Female %
Antidepressants	venlafaxine	8/18/2010	843	64 (16)	90	73
	bupropion	12/14/2006	1,919	57 (15)	90	67
	paroxetine	6/29/2007	1,562	67 (16)	88	75
	sertraline	8/11/2006	26,948	71 (16)	88	76
Antidiabetics	acarbose	5/07/2008	554	72 (11)	66	58
	nateglinide	9/09/2009	1,567	75 (11)	74	63
Antiosteoporosis	calcitonin	11/17/2008	1,458	79 (11)	92	94
	alendronate	2/06/2008	34,395	76 (10)	86	93

Results- Likelihood of Switch to Generic

Medication	HR (95% CI)	Positive control compared to study medication	Negative control compared to study medication
Antidepressants			
venlafaxine	1.00		
bupropion	**3.27 (3.02, 3.55)**	More likely	
paroxetine	**3.24 (3.00, 3.49)**		More likely
sertraline	**1.39 (1.29, 1.49)**		More likely
Antidiabetics			
acarbose	1.00		
nateglinide	**0.82 (0.77, 0.88)**		Less likely
Antiosteoporosis Medications			
calcitonin	1.00		
alendronate	**1.75 (1.70, 1.80)**	More likely	

Green=positive control; blue=negative control; **bold=statistically significant using alpha=0.05**

Results – Demographics for Switchback to Brand

Drug class	Drug	N	Age, years mean (SD)	White %	Female %
Antidepressants	venlafaxine	128	66 (16)	91	75
	bupropion	1,439	56 (15)	90	66
	paroxetine	584	69 (15)	90	78
	sertraline	12,875	72 (16)	91	77
Antidiabetics	acarbose	400	73 (11)	66	60
	nateglinide	1,051	75 (11)	75	63
Antiosteoporosis	calcitonin	478	79 (11)	94	95
	alendronate	27,186	77 (10)	87	93

Results- Likelihood of Switchback to Brand

Medication	HR (95% CI)	Positive control compared to study medication	Negative control compared to study medication
Antidepressant Medications			
venlafaxine	1.00		
bupropion	**0.21 (0.19, 0.24)**	Less likely	
paroxetine	**0.28 (0.24, 0.32)**		Less likely
sertraline	**0.58(0.58, 0.73)**		Less likely
Antidiabetic Medications			
acarbose	1.00		
nateglinide	**1.73 (1.57, 1.91)**		More likely
Antiosteoporosis Medications			
calcitonin	1.00		
alendronate	**0.21 (0.20, 0.22)**	Less likely	

Green=positive control; blue=negative control; **bold=statistically significant using alpha=0.05**

Results- Likelihood of Switchback to Brand with Post Hoc Analysis

Main analysis				Post hoc analysis Revised outcome: switchback to brand, other dosage form, other drug in class, or discontinuing generic versus staying on brand		
Medication	**HR (95% CI)**	**Positive control compared to study medication**	**Negative control compared to study medication**	**HR (95% CI)**	**Positive control compared to study medication**	**Negative control compared to study medication**
Antidepressant Medications						
venlafaxine	1.00			1.00		
bupropion	**0.21 (0.19, 0.24)**	Less likely		1.03 (0.96 , 1.11)	As likely	
paroxetine	**0.28 (0.24, 0.32)**		Less likely	**0.65 (0.61 , 0.71)**		Less likely
sertraline	**0.58(0.58, 0.73)**		Less likely	**0.77 (0.72, 0.83)**		Less likely
Antidiabetic Medications						
acarbose	1.00			1.00		
nateglinide	**1.73 (1.57, 1.91)**		More likely	**0.80 (0.77, 0.82)**		Less likely
Antiosteoporosis Medications						
calcitonin	1.00			1.00		
alendronate	**0.21 (0.20, 0.22)**	Less likely		**0.95 (0.93, 0.97)**	Less likely	

Green=positive control; blue=negative control; **bold=statistically significant using alpha=0.05**

Results- Likelihood of Outcome Comparing Brand-to-Generic Switchers:Non-switchers

	Hospitalization or ED visit		Mortality	
Medication	**HR of switch to no switch (95% CI)**	**Impact**	**HR of switch to no switch (95% CI)**	**Impact**
Antidepressant Medications				
venlafaxine	0.99 (0.85, 1.14)		0.91 (0.66, 1.26)	
bupropion	0.99 (0.94, 1.03)		**0.83 (0.73, 0.94)**	Less likely
paroxetine	**0.84 (0.71, 0.99)**	Less likely	1.08 (0.82, 1.41)	
sertraline	1.00 (0.99, 1.01)		**1.06 (1.04, 1.09)**	More likely
Antidiabetic Medications				
acarbose	**1.17 (1.11, 1.23)**	More likely	**0.88 (0.81, 0.95)**	Less likely
nateglinide	1.02 (0.98, 1.06)		1.07 (1.00, 1.14)	
Antiosteoporosis Medications				
calcitonin	**0.93 (0.89, 0.97)**	Less likely	1.00 (0.94, 1.05)	
alendronate	**1.05 (1.04, 1.06)**	More likely	**0.96 (0.95, 0.97)**	Less likely

Green=positive control; blue=negative control; **bold= statistically significant using alpha=0.05**

Results- Likelihood of Outcome Comparing Switchback to Brand:Non-switchback

	Hospitalization or ED visit		Mortality	
Medication	**HR of switchback to no switchback (95% CI)**	**Impact**	**HR of switchback to no switchback (95% CI)**	**Impact**
Antidepressant Medications				
venlafaxine	0.94 (0.64, 1.38)		1.18 (0.46, 3.03)	
bupropion	1.02 (0.87, 1.20)		0.92 (0.62, 1.37)	
paroxetine	1.23 (0.99, 1.53)		**2.77 (2.05, 3.74)**	More likely
sertraline	**0.92 (0.88, 0.96)**	Less likely	**1.43 (1.36, 1.51)**	More likely
Antidiabetic Medications				
acarbose	**0.74 (0.63, 0.87)**	Less likely	**0.21 (0.12, 0.36)**	Less likely
nateglinide	**0.67 (0.59, 0.77)**	Less likely	**1.41 (1.21, 1.64)**	More likely
Antiosteoporosis Medications				
calcitonin	**1.40 (1.23, 1.59)**	More likely	**0.54 (0.44, 0.67)**	Less likely
alendronate	**0.90 (0.87, 0.93)**	Less likely	**1.13 (1.09, 1.18)**	More likely

Green=positive control; blue=negative control; **bold=statistically significant using alpha=0.05**

Limitations

- Difficulty in linking the ANDA and NDA to the NDC because no comprehensive database exists
- Some small sample sizes when using the 5% sample for 2006-2011; however, estimates were still precise

Discussion - Venlafaxine

- **Switch to generic**
  - All controls were more likely to switch to generic than venlafaxine
    - Factors other than safety concerns influence switching from brand to generic (e.g., marketing)
- **Switchback to brand**
  - All controls were less likely to switchback to brand in the main analysis
  - Redefined switchback was better able to distinguish potential concerns using the positive and negative controls
- **Health care utilization and mortality for switch to generic**
  - Overall, switching to generic did not impact the likelihood of the outcome – except for sertraline with mortality
- **Health care utilization and mortality for switchback to brand**
  - Switching back to brand was not associated with increase in health care utilization
  - Switching back to brand was not associated with an increase in mortality for venlafaxine and bupropion, while it was associated with an increase in mortality for paroxetine or sertraline

Discussion - Acarbose

- **Switch to generic**
  - Nateglinide users were less likely to switch to generic than acarbose users
- **Switchback to brand**
  - Nateglinide users were more likely to switchback to brand in the main analysis
  - Using the redefined switchback definition, nateglinide users were less likely to switch from the generic
- **Health care utilization and mortality for switch to generic**
  - For acarbose, switching to generic was associated with an increase in health care utilization, while it was associated with a reductions in the likelihood of mortality
  - Nateglinide switching to generic had no impact on either outcome
- **Health care utilization and mortality for switchback to brand**
  - For acarbose, switchback to brand was associated with a decrease in the likelihood of both health care utilization and mortality
  - For nateglinide, switchback to brand was associated with a decrease in health care utilization and an increase in mortality

Discussion - Calcitonin

- **Switch to generic**
  - Alendronate users were more likely to switchback to generic than calcitonin users
- **Switchback to brand**
  - Alendronate users were less likely to switchback to brand in the main compared to calcitonin in the main and revised analyses
- **Health care utilization and mortality for switch to generic**
  - For calcitonin, switching to generic was associated with better or neutral outcomes.
  - For alendronate, switching to generic was associated with increase in health care utilization and a decrease in mortality
- **Health care utilization and mortality for switchback to brand**
  - Calcitonin switchback to brand has higher likelihood of health care utilization and lower likelihood of mortality
  - Alendronate switchback to brand is associated with a lower likelihood of health care utilization, and a higher likelihood of death

Conclusions

- Observed differences across selected medications and their controls, suggesting the patterns are drug-specific
- The strength of the signal varies with controls selected and switchback definition
- Composite switchback patterns may be used to detect generic concerns, but further research is needed

Aim 3: Survey

Background-Perceptions

- Patient and physician perceptions of brand name and generic drugs may affect generic drug use
- Quality- Physicians and patients may be concerned with the quality of generic drugs
- Costs- Higher costs of brand name drugs are a concern for patients and may influence brand to generic drug substitution

Methods-Physician Surveys

Acarbose Tablet Surveys	Calcitonin Salmon Nasal Spray Surveys	Venlafaxine ER Tablet Surveys
Current/past prescriber of acarbose or Precose® tablet	Current/past prescriber of calcitonin salmon nasal spray or Mialcalcin®	Current/past prescriber of Sun's venlafaxine ER tablet or Osmotica's venlafaxine ER tablet

Methods-Physician Surveys

- Recruitment
  - Inclusion Criteria
    - Current or previous prescriber of the study drugs
  - Posting on LinkedIn
  - Created Facebook page "Depression, Diabetes and Osteoporosis"
    - Postings on disease related groups through our created page
  - Paid advertisements on Facebook

Methods-Patient Surveys

Acarbose tablet surveys	Calcitonin salmon nasal spray surveys	Venlafaxine ER tablet surveys
Current user of acarbose tablet	Current user of calcitonin salmon nasal spray	Current user of Sun's venlafaxine ER tablet
Current user of Precose® tablet	Current user of Mialcalcin®	Current user of Osmotica's venlafaxine ER tablet
Past user of acarbose or Precose® tablet	Past user of calcitonin salmon nasal spray or Miacalcin®	Past user of Sun's venlafaxine ER tablet or Osmotica's venlafaxine ER tablet

Methods-Patient Surveys

- Recruitment
  - Inclusion Criteria
    - ≥ 18 years of age
    - Previously or currently taking one of the study drugs
  - Created Facebook page "Depression, Diabetes and Osteoporosis"
    - Postings on disease related groups through our created page
  - Paid advertisements on Facebook
  - PatientsLikeMe (PLM) Platform (venlafaxine survey only)

Results-Physician Surveys

Facebook Advertising Metrics

Campaign	Reach	Unique clicks	Unique click-through rate*	Cost per click (USD)	Page likes
Acarbose Survey	1994	7	0.35	1.43	0
Calcitonin survey	1946	7	0.36	1.43	0
Venlafaxine Survey	1898	14	0.74	0.71	0

*Unique Click-Through Rate Per 100 Users: number of people who clicked on ad divided by the number of people reached * 100

No physicians completed the surveys

Results-Patient Surveys

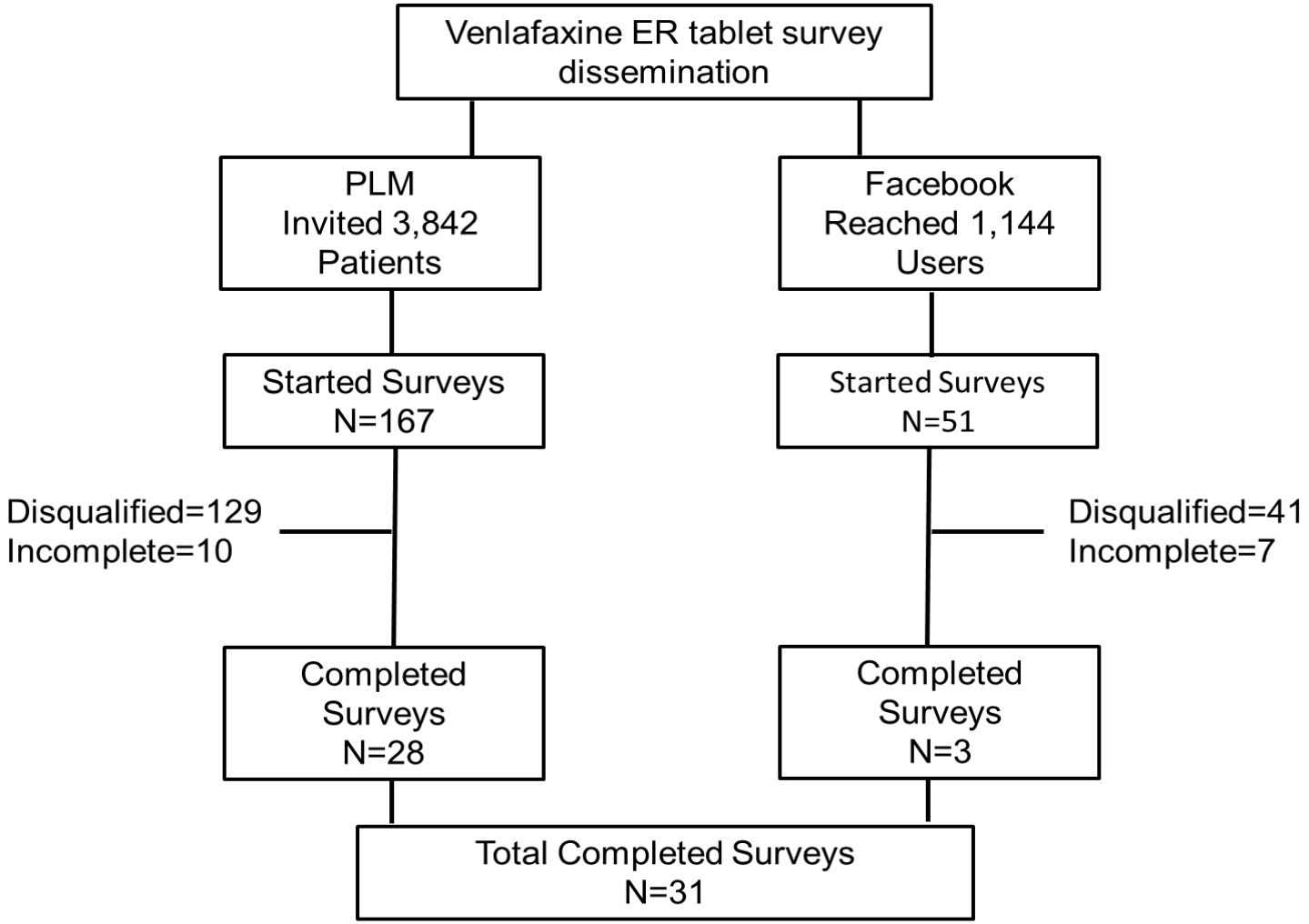
Facebook Advertising Metrics

Campaign	Reach	Unique clicks	Unique click-through rate*	Cost per click (USD)	Page likes
Acarbose Survey	1064	33	3.10	0.29	1
Calcitonin-Salmon Nasal Spray Survey	441	48	10.88	0.18	1
Venlafaxine Survey	1144	34	2.97	0.26	0

*Unique Click-Through Rate Per 100 Users: number of people who clicked on ad divided by the number of people reached * 100

No patients completed the acarbose or calcitonin surveys

Results- Venlafaxine Patient Surveys



Results-Patient Surveys

- 39% of participants did not have a preference when taking brand name or generic drugs
- 68% of participants thought that generic drugs are of the same quality as brand name drugs
- 77% of participants thought that generic drugs are equally effective and cause the same amount of side effects as brand name drugs
- 90% were not aware of the modified method used to approve generic venlafaxine
  - When informed, 65% were comfortable taking generic venlafaxine instead of brand name venlafaxine vs. 74% prior to being informed ($p = 0.03$)

Limitations

- Participation rate was very low
  - Study addressed a complex issue with low visibility
  - No incentive
  - Restricted eligibility
  - Short advertisement period
- Convenience sample
- Self-reported data, possibly resulting in bias

Discussion

- Social media might not be a good avenue to conduct research with physicians
- Findings support previous research regarding patient perceptions of generic and brand name drugs
- No study has previously assessed the change in comfort level with taking generic drugs after being informed of alternative approval methods
  - Most patients were unaware of the non-traditional bioequivalence approach used to approve generic venlafaxine ER tablet
  - After being informed, comfort level with taking generic venlafaxine ER tablet decreased

Study Conclusion and Recommendations

- Aim 1: Lack of published literature that compares efficacy and safety differences between brand and generic products

  Recommend incentives for generic manufacturers to publish bioequivalence *in vitro* and *in vivo* studies as well as brand manufacturers to conduct additional studies

- Aim 2: Administrative claims data are an option for pharmacovigilance and the selection of control medications and definitions of switching influences the findings
- Aim 3: Given the popularity of social media in the general public, further exploring the use of social media and online communities to survey patients might be worthwhile for future research

Thank you!