A Systematic Review of Generic Drug Substitution in Special Populations

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BACKGROUND

Bioequivalence studies that compare a reference drug formulation to an investigational generic drug formulation are typically conducted in healthy adult volunteers and occasionally conducted in patients. These healthy volunteers are known to have different drug pharmacokinetic properties compared to special populations such as children, women, racial and ethnic minorities, older adults, and people with poor kidney or liver function. Therefore, due to their unique physical, biological, and physiological considerations, there is need to monitor generic drug substitution in these special populations for differences in clinical outcomes and adverse events.

The purpose of this study was to collect evidence of the appropriateness of generic substitution and outcomes associated with generic substitution among special populations. This poster summarizes the methods used in the systematic literature review as well as the review results and conclusions.

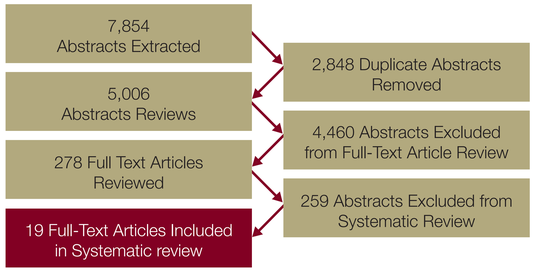
OBJECTIVES

- Describe the current literature related to generic substitution in special populations
- Describe generic drug use and generic drug substitution in terms of practices and patterns, and post-marketing surveillance activities in special populations
- Identify research needs and strategies to monitor generic drug substitution in special populations

METHODS

Using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), we:

- Reviewed four biomedical literature databases to identify studies that examine generic drug use or generic substitution in special population
- Developed search term list representing 3 domains:
  - Drug use or substitution
  - Special population
  - Generic drug or generic substitution
- Established the inclusion/exclusion criteria
- Conducted a Qualitative Review of 5,006 articles and included 19 full-text articles in the systematic review



FINDINGS

Difference in Outcome with Brand versus Generic Drug

Special Population	Brand Drug (generic name)	Outcome
Children	Synthroid (levothyroxine)	Decreased TSH suppression with generic drug
	Prograf (tacrolimus)	Decreased serum trough level with generic drug
Older Adults	General	Cost savings with generic drug
Race/Ethnic Minorities	Antiepileptic drugs	Increased side effects with brand to generic switching was associated with being African American
Race/Ethnic Minorities	Immunosuppressants (tacrolimus, cyclosporine)	African Americans exhibit decreased belief of generic and brand equivalency

No Difference in Outcome with Brand versus Generic Drug

Special Population	Brand Drug (generic name)	Outcome
Women	Keppra (levetiracetam)	42.9% switchback to brand drug not associated with gender
Women and Race/Ethnic Minorities	Prograf (tacrolimus)	No differences in pharmacokinetic parameters

CHILDREN

- Brand to generic switching with tacrolimus, levothyroxine and risperidone resulted in lower serum trough levels, significantly elevated thyroid stimulating hormone (TSH) levels, and adverse side effects, respectively.

WOMEN

- Brand to generic topiramate switch resulted in worsening migraine symptoms in a 25 year old woman
- Brand to generic enoxaparin switch led to unstable anticoagulation status in 63 year old woman.
- In contrast, there was no difference in pharmacokinetic parameters in women or other subpopulations who were taking either brand or generic tacrolimus, however nearly 43% of individuals switched back from generic levetiracetam to brand due to increased seizures and adverse events.

OLDER ADULTS

- Brand to generic clozapine switch for a 79 year old male with schizophrenia experienced adverse events
- Among Medicare beneficiaries' ≥65 years old, generic substitution resulted in significant annual savings ($160 for low income subsidy beneficiaries and $127 for non-low income subsidy beneficiaries.

RACIAL & ETHNIC MINORITIES

- A direct, self-report survey study indicated that being African American is associated with increased adverse events when switching from brand to generic antiepileptic drugs (AEDs),
- Among solid organ transplant recipients, African Americans were said to have a decreased belief of generic and brand equivalency compared to other ethnicities
- In contrast, there was no difference in pharmacokinetic parameters for several subpopulations of kidney recipients, including African Americans, who were taking either brand or generic tacrolimus

INDIVIDUALS WITH IMPAIRED KIDNEY AND LIVER FUNCTION

- Studies suggest brand to generic switching of tacrolimus reported significant reductions in serum trough levels; the generic drug required dosage adjustments
- Increased monitoring during brand to generic switching of tacrolimus is necessary to ensure safety
- Nearly 20% of renal transplant patients who were switched from Neoral (brand cyclosporine) to Gengraf (generic cyclosporine) required dosage adjustments to maintain target serum trough levels
- There are cost savings when switching from brand to generic tacrolimus; costs associated with increased monitoring requirements or adverse events were not included
- Patients currently receiving a generic immunosuppressant or with an annual income of <$30,000 expressed higher belief of brand and generic equivalency

LIMITATIONS AND STRENGTHS

LIMITATIONS

- Search strategy yielded a larger number of publications, but only a small subset of studies fit the inclusion criteria
- Fewer publications with older adults, racial and ethnic minorities and women as the study population when generic drug utilization is examined

STRENGTHS

- Use of PRISMA guidelines for review process
- Each article was assessed by two reviewers, and differences discussed and adjudicated with a third reviewer
- Reviewed several different types of studies including case reports and empirical (observational and experimental) studies

RECOMMENDATIONS

- There is a need for in-depth investigation and research objectives that will contribute to accumulation of additional data regarding differential drug metabolism and physiological differences in special populations.
- Researchers and health institutions should focus their efforts on expanding the information and data available for generic drug substitution in special populations.
- Findings should motivate policymakers to fund and conduct studies that focus on, or minimally include, special populations and should be implemented to drive these research objectives

CONCLUSIONS

Policymakers, pharmaceutical drug manufacturers, researchers, health institutions, doctors and pharmacists have a significant impact on the practice and a substitution patterns on the safety, management and well-being of generic drug substitution among special populations.

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