# Comparing clinical outcomes of brand and generic drugs:
## systematic literature review of acarbose, calcitonin nasal spray and venlafaxine ER tablets


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## Introduction

- State laws and health insurance policies promote generic substitution as an important and effective tool to reduce prescription drug costs
- Generic substitution is based on bioequivalence (BE), but there are situations where the traditional *in vivo* pharmacokinetic BE studies may not be the appropriate method to ensure therapeutic equivalence
- Increasing availability of complex generic products and varied BE methods have led to controversy surrounding the approval process for some generic drugs (e.g. citizen petitions)
- Despite economic incentives, patient and physician concerns about generics may result in avoiding generic substitution or switching back to the brand name drug from the generic drug

## Objectives

- Conduct a systematic literature review of clinical trials and observational studies to summarize evidence comparing brand and generic drugs which were approved using non-traditional bioequivalence methods by the US Food and Drug Administration (FDA)
- Determine if clinical or safety differences exist between the brands and generics

## Methods

- A systematic literature review was conducted using multiple databases (Figure 1)
- The search was limited to studies that were English-language articles, performed in the US, and were conducted in human subjects or were relevant in-vitro studies
- Studies were included if they had exposure to the drug of interest**,** included clinically relevant outcomes, and identified brand and/or generic
- Both RCTs and observational studies were included in the literature review
- Identified studies were stratified into three cohorts: studies related to brand and/or generic of 1) acarbose, 2) calcitonin salmon nasal spray, and 3) venlafaxine ER tablet

## Results: Summary of Evidence

**Figure 1. Study Selection**

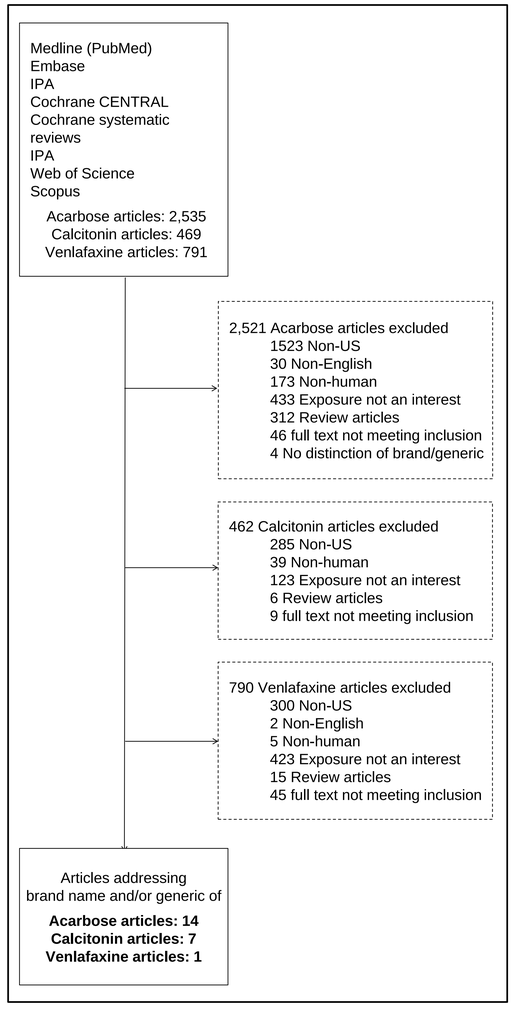



**Table 2. Selected Studies**

| Source | Drugs studied[1] | Efficacy results | Jadad/ NOS[2] |
|---|---|---|---|
| Patel 2013 | Precose vs. PBO | In multivariate analysis: no difference | 2 |
| Shibao 2007 | Precose vs. PBO | Acarbose: ↓ SBP, ↓ DBP, ↑ HR | 2 |
| Krkman 2006 | Precose vs. PBO | No difference in the cumulative rate of frank fasting hyperglycemia | 2 |
| Neuser 2005 | Precose vs. PBO | Mean HbA1cΔ: Precose -0.19% PBO +0.22% | 4 |
| Chang 2004 | Precose vs. PBO | No difference in insulin secretion and acute insulin response to IV glucose | 4 |
| Buse 1998 | Precose and SU[3] | Mean HbA1cΔ: -0.66% | 1 |
| Kelley 1998 | Precose vs. PBO, adjunctive to insulin | Mean HbA1cΔ: Precose -0.58% PBO +0.11% | 3 |
| Rosenstock 1998 | Precose vs. PBO | Mean HbA1cΔ: Precose -0.57% PBO +0.08% | 3 |
| Baron 1997 | Precose and SU | Mean HbA1cΔ: -0.7% | 2[2] |
| Hollander 1996 | Precose vs. PBO, adjunctive to insulin | Mean HbA1cΔ: Precose -0.30% PBO +0.18% | 3 |
| Holt 1996 | Precose vs. PBO | Acarbose increased fecal wet weight; no loss of major macronutrients | 3 |
| Coniff 1995 | Precose vs. PBO | Mean HbA1cΔ: PBO +0.33% 100-300mg -0.45%, -0.40%, -0.77% | 3 |
| Coniff 1995 | Precose vs. precose+ tolbutamide vs. PBO | Mean HbA1cΔ: Precose -0.54% PBO +0.04% | 3 |
| Reaven 1990 | Precose, adjunctive to SU | Mean HbA1cΔ 7.4 ± 0.2% to 6.4 ± 0.2% | 2[2] |
| Binkley 2012 | Oral rSCT[3] vs. Miacalcin vs. PBO | Mean% BMD[4]Δ in lumbar spine: Oral rSCT 1.53% Miacalcin 0.76% PBO 0.47% | 4 |
| Pappa 2011 | Miacalcin | No Δ in spinal BMD z-score at 18 months | 4 |
| Costantino 2009 | Miacalcin vs. generic | Similar protein structure and stability, no impurities, no difference in peptide behavior | N/A |
| Chesnut 2005 | Miacalcin vs. PBO | No BMDΔ at year 2 in both groups | 3 |
| Srivastava 2004 | Miacalcin vs. no treatment | Serum CTx levelΔ at 6 months: Miacalcin -34% no treatment -8% | 2 |
| Podichetty 2004 | Miacalcin vs. PBO | No Δ in pain index, total walking time and distance and SF-36 MCS/PCS[6] | 1 |
| Downs 2000 | Alendronate vs. Miacalcin vs. PBO | Calcitonin: BMDΔ greater at femoral neck, no difference otherwise | 1 |
| Wright 2009 | Venlafaxine ER tablet vs. ER capsule | 90% CIs of Cmax, AUC0–t, AUC0–∞ within range (80-125%) | 2 |

[1]PBO=placebo; [2]NOS=Newcastle-Ottawa Scale; [3]SU=sulfonylurea; [4]rSCT=recombinant salmon calcitonin; [5]BMD=bone mineral density; [6]MCS/PCS=mental component score/physical component score

**Figure 2. Withdrawal rates (brand studies)**

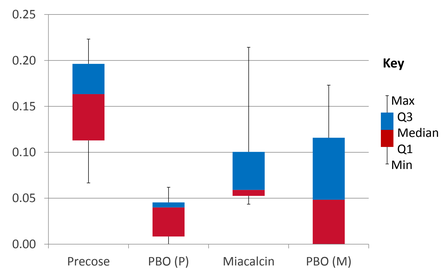



**Figure 3. Funding sources**

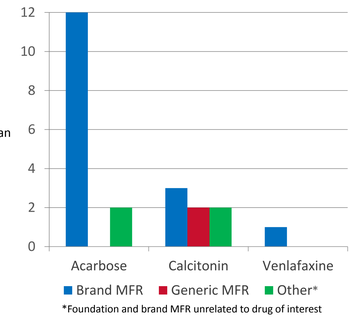
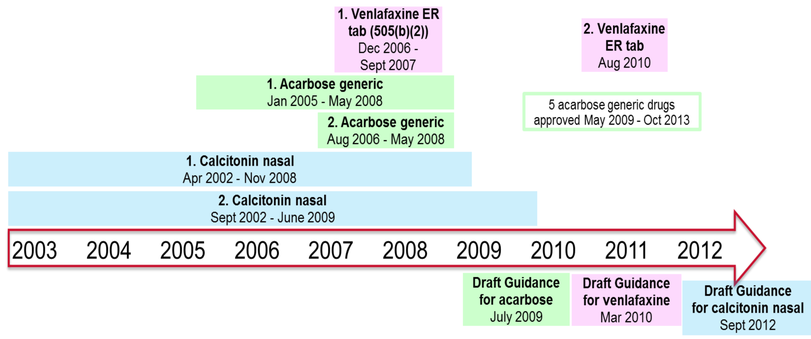



**Figure 4. Generic approval timeline[1]**




| Drug | Company | App Type | BE studies | Comments |
|---|---|---|---|---|
| Acarbose | 1. Watson/ Cobalt | ANDA | *in vitro* and *in vivo* | First generic; FDA amended its regulations for waiver of in vivo testing requirement |
| | 2. Roxane | ANDA | Unknown | Second generic; No data available |
| Calcitonin | 1. APOTEX/ NOVEX | ANDA | *in vitro* only | First generic |
| | 2. PAR Pharma/ Nastech | ANDA | *in vitro* and *in vivo* | Second generic; *in vivo* due to use of different excipient (Chlorbutanol instead of benzalkonium chloride) |
| Venlafaxine | 1. Osmotica Corp. | NDA 505(b)(2) | *in vitro* and *in vivo* | First brand ER tablet; 150 mg waived for testing |
| | 2. Sun Pharma | ANDA | Unknown | First generic; ER tablet 225 mg was not approved[2] |

[1]Information available from summary review documents on Drugs@FDA, [2]Osmotica's citizens petition to FDA in 2012

**Table 1. Study drugs**

| Study Drug | Bioequivalence consideration | TE code* | Brand approval date | 1st Generic approval date |
|---|---|---|---|---|
| Acarbose (Precose®) | Systemic absorption of acarbose after oral dosing is minimal < 2% of the dose is absorbed, therapeutically desirable<br>∴ *in vitro* studies alone if Q1/Q2 the same may be established solely on comparative dissolution | AB (all 7) | Sept 1995 | May 2008 |
| Calcitonin salmon NS (Miacalcin®) | Mean bioavailability of calcitonin spray is approximately 3%<br>spray device impacts product performance<br>product- and process-related factors for immunogenicity<br>∴ *in vitro* studies alone if Q1/Q2 the same active polypeptide ingredient, comparable immunogenicity, spray pattern | AB (2)<br>None (1) | August 1995 | Nov 2008 |
| Venlafaxine ER tablet | Brand tablets are pharmaceutical alternative to Effexor XR® capsules<br>Different ER technology and its effect on absorption<br>Fed state vs. Fasted state (adverse events)<br>∴ *in vivo* fed studies using 150mg product in healthy volunteers<br>*in vitro* dissolution and proportional similarity of formulations needed for wavier requests of *in vivo* testing of other dosages | AB (1) | May 2008 | Aug 2010 |

*TE=therapeutic equivalence; TE codes can be found in FDA's orange book; Q1=qualitatively; Q2: quantitatively

## Conclusions

- The literature that directly compares brand and generic drugs is limited in United States
- Most studies (16 out of 24) were sponsored by brand manufacturer
  - Studies do not specify whether brand or generic drug was used for the study, unless it was sponsored by a brand name manufacturer
- Most studies conducted by generic manufacturers are used for drug approval, but are not published
- Neutral sponsored (e.g., foundations) studies use brand drugs or do not specify
- FDA's regulation for waiver of the *in vivo* testing requirement appears to be appropriate for certain medications, considering their mechanism of action and safety profile
- Summary reviews* reveals FDA's thorough review of molecular structure, pharmacokinetic, pharmacodynamic and clinical studies (*in vivo*)

*Available at Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

## Supplemental work

- Retrospective observational study using administrative claims from 5% random sample of Medicare beneficiaries to examine generic drug use, switch from brand to generic, and switch back from generic to brand
- Surveys of patients' and physicians' experience about brand and generic drug use to determine if controversy around generic drug approval has impacted perceptions of generic drugs

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