

# Bioequivalence and Bioinequivalence of Two Original Antidepressant Medications and Their Generics

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# Background:

Generic drugs are lower-cost versions of patent-expired original brand-name medications (1). According to the regulatory agencies of the Canada, US and European Union, a generic drug must be “*identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use*”. Bioequivalence is decreed when the ratio of the generic to the reference compound for the area-under-the-curve and maximum plasma concentration (C<sub>max</sub>) fall within a 0.80–1.25 range. A therapeutic equivalence of generic and brand name medication is, however, not required by regulatory agencies.

Two pharmacokinetic measures are used to determine bioequivalence: the area-under-the-curve (AUC) of the drug concentration-time curve and the maximum plasma concentration (C<sub>max</sub>). Bioequivalence is decreed if the 90% confidence interval (CI) of the ratio of the generic to reference compound for the AUC and C<sub>max</sub> falls within a 80–125% range.

A previous report described a high rate of relapse in patients switched from brand to generic formulation of citalopram (2), and similar cases were observed in Canada since the introduction of generic venlafaxine. It was therefore hypothesized that the generic medication was not bio-equivalent to the original one. The aim of the present study was to compare the pharmacokinetic profile of original and generic formulations of citalopram and venlafaxine.

# Purpose:

Compare the pharmacokinetic profile of original and generic formulations of citalopram and venlafaxine

# Methods:

## Study design:

Open label crossover study.

Washout period corresponding to ten half-life of the drugs studied.

## Drugs:

Celexa®/Gen-citalopram® 40mg and Effexor®/Novo-venlafaxine® XR 75mg were studied. Treatment was randomly assigned.

## Participants:

12 healthy volunteers in each medication group. Male, non-smoking, no history of psychiatric, hepatic, renal, gastrointestinal, and hematological diseases.

## Parameters Analyzed:

➤ The pill / tablet content.

➤ Plasma levels of citalopram and venlafaxine were evaluated at fixed interval after the first medication and at steady state:

- Citalopram: time 60, 90, 120, 150, 180 min and day 8

- Venlafaxine: time 120, 180, 240, 300, 360 min and day 5

➤ Side effects

# Results:

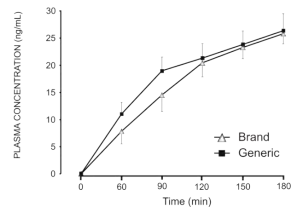
## 1) Pills/Tablets extraction

All tablets (citalopram) and capsule (venlafaxine) went into fine suspension. In each medication group no significant difference were obtained in the amount of drug extract from the generic and the brand medication. However, the extraction of the content of the Effexor® formulation required an additional sonication compared to the generic.

## 2) Plasma level

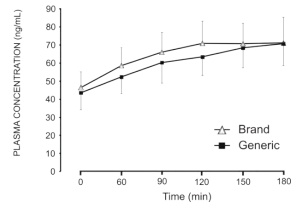
### Citalopram

#### Day 1



The two-way ANOVA for repeated measures (Time x Treatment) only showed an effect of time ( $p < 0.05$ ). The  $C_{max}$  values were  $27 \pm 2$  (Brand) and  $28 \pm 3$  ng/mL (Generic). The ratio (Generic/Brand) of the log-transformed values of  $C_{max}$  was 99%. The corresponding 90% CI was of 97-100%.

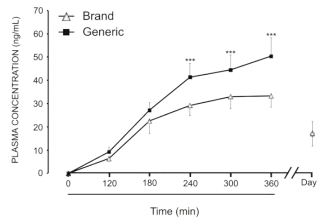
#### Day 8



The two-way ANOVA only showed an effect of time ( $p < 0.001$ ). The concentration of citalopram at steady state was  $47 \pm 9$  ng/mL and  $44 \pm 9$  ng/mL for the Celexa® and Gen-citalopram®, respectively.

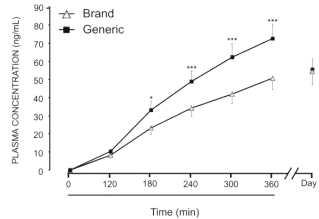
### Venlafaxine

#### Venlafaxine



The two-way ANOVA showed an effect of time, treatment and interaction ( $p < 0.001$ ). The  $C_{max}$  values were  $36 \pm 6$  (Brand) and  $52 \pm 8$  ng/mL (Generic). The ratio (Generic/Brand) of the log-transformed values of  $C_{max}$  was of 150%. The corresponding 90% CI was of 104% - 217%. No difference at steady state.

#### O-Desmethyl-venlafaxine



The two-way ANOVA showed an effect of time, treatment, and interaction. The  $C_{max}$  values were not estimated (peak was not attained) but the level of ODV was higher in the generic group in comparison to the brand-name medication group at time 180-360 minutes (+43 to +48%). No difference at steady state.

## 3) Side Effects

		Brand	Generic
<b>Citalopram</b> ( $P=0.2$ )	Side Effects	12	12
	Participants	(6/12)	(5/12)
<b>Venlafaxine</b> ( $P<0.05$ )	Side Effects	4	14
	Participants	(3/12)	(9/12)

The one-way ANOVA for repeated measures for the number of side effects occurring during the treatment period showed a significant difference between brand-name medication and generic in the venlafaxine-treatment group ( $p < 0.05$ ), but not in the citalopram-treatment group ( $p = 0.2$ ).

# Conclusion:

The results showed that:

- Gen-citalopram® (Genpharm) is bioequivalent to the brand formulation Celexa® (Lundbeck);
- Novo-venlafaxine® (Teva Pharmaceuticals) fail to demonstrate a bioequivalence to the brand medication Effexor® (Wyeth).

The Novo-venlafaxine® formulation was releasing its active ingredient more rapidly than the Effexor® and outside of the prescribed norm; resulting in higher plasma level and more side effects. Further studies are necessary to evaluate the impact of switching from one formulation to the other in depressed patient.