Comparison of Pharmacokinetic Profiles of Brand-Name and Generic Formulations of Citalopram and Venlafaxine: A Crossover Study

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Background: Generic drugs are lower-cost versions of patent-expired brand-name medications. Bioequivalence is decreed when the 90% confidence intervals for the ratios of the generic to the reference compound for the area under the curve and maximum plasma concentration (C_{max}) fall within a 0.80 to 1.25 range. The aim of the present pilot study was to compare the pharmacokinetic profiles of brand-name and generic formulations of citalopram and extended-release venlafaxine.

Method: Effexor XR/Novo-venlafaxine XR 75 mg and Celexa/Gen-citalopram 40 mg were studied in a randomized crossover design. Healthy male volunteers took either Effexor XR or Novo-venlafaxine XR for 4 days, a 4-day washout was allowed, and then participants took the other venlafaxine formulation for 4 days. This was followed by a washout of at least 7 days. The participants then took Celexa or Gen-citalopram for 8 days, a 14-day washout was allowed, and then participants took the other citalopram formulation for 8 days. In each of the study phases, the sequence of treatment (brand-name × generic) was randomly assigned. Plasma levels of drugs were measured at fixed intervals after participants took the drugs and at steady state. The study was conducted from November 2007 through July 2008.

Results: Twelve participants completed the venlafaxine study. Nine of the participants, plus 3 new participants, were then enrolled in the citalopram study, to maintain a total of 12. The plasma levels of citalopram were similar after ingestion of the brand-name and generic drugs. After ingestion of venlafaxine, the C_{max} values were 36 ± 6 ng/mL and 52 ± 8 ng/mL in the brand-name and generic groups, respectively. The ratio of the log-transformed values of C_{max} was 150% and, therefore, not within the acceptable 80% to 125% range. The concentration of the active metabolite of venlafaxine (*O*-desmethyl-venlafaxine [ODV]) was also significantly increased in the generic group (+43% higher in the generic group at 3 h; +48% higher at 5 h; $p < .05$). No differences were seen at steady state for either ODV or venlafaxine. Participants taking Novo-venlafaxine reported 3 times more side effects than those taking Effexor XR. Pill contents were identical in the 2 groups, but extraction of venlafaxine occurred more readily with the generic formulation than with the brand-name formulation, which required an additional sonication.

Conclusion: Gen-citalopram appeared to be bioequivalent to Celexa, whereas Novo-venlafaxine XR was not bioequivalent to Effexor XR. Consequently, the Novo-venlafaxine formulation released its active ingredient more rapidly and outside the acceptable norm.

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Generic drugs are lower-cost versions of brand-name medications for which the patent has expired. According to the regulatory agencies of the United States, Canada, 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."[1] A therapeutic equivalence of generic and brand-name medication is, however, not required by regulatory agencies. Therapeutic

equivalence implies that the reference and generic drugs provide equal therapeutic effects and depends on the equivalence of selected clinical pharmacodynamic parameters (i.e., efficacy or tolerability). Like bioequivalence, therapeutic equivalence assumes that the reference and generic drug formulations reach the blood in comparable concentrations, but therapeutic equivalence also assumes that the 2 formulations exert equal therapeutic and/or side effects. The proof of therapeutic equivalence will probably be required by the European Medicines Agency in the next few years for the development of biosimilar drugs. This will apply to biopharmaceutical compounds (i.e., high molecular weight compounds, such as interferon, human recombinant insulin, and growth hormone) but not to smaller molecular weight compounds.[2]

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_{max}). Bioequivalence is decreed if the 90% confidence intervals (CI) of the ratios of the generic to reference compound for the AUC and C_{max} fall within an 80% to 125% range. In contrast, manufacturers of innovator medications are held to more stringent rules; their products must not show a greater than 5% variation.[1]

Switching from a generic containing 80% of the active compound to another one containing 125% would then lead to a greater than 50% increase of drug concentration in the blood. In the case of medications with a small therapeutic range, this could lead to toxicity. For example, a patient having a blood level of lithium on the upper therapeutic window (i.e., 1.2 mEq/L) with an 80% generic would then reach a toxic concentration when switching to a 125% generic (1.8 mEq/L). Such toxicity could potentially induce thyroid and/or renal malfunction. One of the worst complications would be in the area of organ transplantation. If patients were treated with a suboptimal antirejection medication, the consequences could be catastrophic. In fact, a lower kidney graft survival was reported in 397 patients treated with generic cyclosporine in comparison to 16,801 patients treated with the brand-name medication (–11% over 1 year).[3] That could be explained by the need of a dose readjustment in 20% of the patients switched from the brand Neoral to a generic cyclosporine[4] as well as by a modification of the bioavailability of a drug often used with cyclosporine, sirolimus.[5] On the other hand, switching from a 125% to an 80% generic would be equivalent to decreasing the dose by about one third.

There are numerous clinical studies showing differences in therapeutic activity between brand-name and generic medications. For example, switching a patient from brand-name clozapine to one of its generics induced a relapse in 20% of cases, whereas no relapse was observed in the control group receiving the brand-name drug.[6] Rosenthal et al.[7] also published a case series report of patients relapsing when switching from a brand-name medication to a generic, but also when switching from one generic to another using citalopram or paroxetine. A recent report described the re-emergence of symptoms and the development of adverse events in patients with anxiety disorders when they were unknowingly switched by their pharmacist from brand-name citalopram (Celexa) to one of its generics.[8] Many studies report bioinequivalence of generics such as mefloquine, diltiazem, diazepam, hydrochlorothiazide, carbamazepine, and estrogens.[9] Furthermore, Vial et al.[10] have evaluated the content of the anticancer agent docetaxel and have demonstrated that, in 31 generic drugs tested (injectable solution), 90% contained insufficient levels of active drug and/or high levels of impurities.

In all fairness, there also are reports showing no significant differences between generics and their respective brand-name medications: for example, levothyroxine[11] and omeprazole.[12] A recent meta-analysis on drugs used in cardiovascular diseases concluded that most but not all (warfarin, furosemide, propranolol) of the generics are equivalent to the brand-name drugs.[13]

Since the introduction of generic venlafaxine in Canada, we observed that some remitted patients treated with the brand-name formulation of venlafaxine extended release (Effexor XR) relapsed when they were switched to a generic formulation (Novo-venlafaxine XR). It was therefore hypothesized that the generic medication was not bioequivalent to the brand-name one. The aim of this exploratory study was to compare the pharmacokinetic profiles of brand-name and generic formulations of venlafaxine and citalopram in healthy volunteers. The parameters studied include both the C_{max} and the concentration of the drugs at steady state that we estimated being the more relevant parameters for the clinical efficacy of the drug.

Limitation of the Study

This study was a pilot study designed to understand the relapses we observed in some patients that have been switched from the brand-name (Effexor XR) to the generic (Novo-venlafaxine XR) formulation of venlafaxine extended release, as well as the relapses observed by Van Ameringen et al.[8] in patients treated with different formulations of citalopram. Therefore, it is important to note that this was not a formal bioequivalence study, which would have evaluated both the C_{max} and AUC parameters. Nonetheless, considering that bioequivalence is established when the ratio of the generic to reference compound for the AUC and C_{max} falls within an 80% to 125% range, a C_{max} ratio of the generic to reference compound greater than 125% was sufficient to demonstrate that the generic compound was not bioequivalent to the brand-name medication.

METHOD

The study protocol was approved by the ethics committee of the Institute of Mental Health Research of Ottawa, Canada. The trial has been performed in accordance with

the Good Clinical Practice guidelines and the Declaration of Helsinki.

Volunteers

Written informed consent was obtained from each volunteer participating in this study. Twelve nonsmoking healthy male volunteers were enrolled in the venlafaxine study. One participant dropped out (due to nausea on day 1) and was replaced by a new enrollee, so that a total number of 12 participants completed the venlafaxine study. After the venlafaxine study was complete, a washout period of at least 7 days followed. Nine of the participants from the venlafaxine study were then enrolled in the citalopram study, plus 3 new participants, for a total of 12 participants. Two of those participants dropped out during the citalopram study (due to nausea on day 1) and were replaced by new enrollees, so that a total number of 12 participants completed the citalopram study.

Volunteers with history of hepatic, renal, gastrointestinal, and hematologic diseases were excluded. The Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Nonpatient Edition (SCID-I/NP)[14] was used to rule out the presence of a psychiatric disorder. Health was ascertained with a complete physical and neurologic examination and with determination of clinically normal laboratory profiles (blood and urine, including urine drug screen). To avoid any drug-drug interaction, participants were asked not to take any medication or grapefruit juice before or during the drug administration period.

Medication

The reference (brand-name) medications were Effexor XR 75 mg (venlafaxine: batch number L434196; expiration date, December 2009) and Celexa 40 mg (citalopram: batch number 2127281; expiration date, June 2012), manufactured by Wyeth Pharmaceuticals and Lundbeck Inc., respectively. The test (generic) drugs were Novo-venlafaxine XR 75 mg (venlafaxine: batch number W06096; expiration date, February 2010; and batch number W06008; expiration date January 2009) and Gen-citalopram 40 mg (citalopram: batch number 6338R; expiration date, July 2008; and batch number 19223R; expiration date, December 2008), manufactured by Novopharm (Teva) and Genpharm, respectively. All of the experiments were performed before the expiration date of the drugs.

Study Design

This was an open-label crossover study. The sequence of treatment (brand-name × generic) was randomly assigned. Participants fasted for 12 hours prior to medication ingestion and for at least 2 hours thereafter. A venous catheter was inserted in a forearm vein for repeated blood drawing. A baseline (time 0) blood sample was obtained before participants took the first capsule/tablet of each medication. The duration of the blood collection was 3 and 6 hours for citalopram and venlafaxine, respectively. To ensure observance of the treatment, medications were given in a pillbox equipped with a chip that recorded the time of opening of the container (MEMS6, AARDEX, Union City, Calif.). The study was conducted from November 2007 through July 2008.

Celexa/Gen-Citalopram

Citalopram (brand-name or generic) was taken by participants once a day (40 mg) in the morning for 8 consecutive days. Blood samples were collected 60, 90, 120, 150, and 180 minutes after participants took the first tablet. An additional blood sample was taken on day 8 (i.e., 24 hours after the seventh tablet), then participants took an eighth tablet and a new time course was performed (blood sample every 30 minutes from 60 to 180 minutes). A 14-day washout period between drug administrations was allowed. The duration of the washout period was based on the half-life of citalopram (33 hours) to ascertain achievement of steady-state level and complete elimination (10 half-lives).

Effexor XR/Novo-Venlafaxine XR

Venlafaxine (brand-name or generic) was taken by participants once a day (75 mg) for 4 consecutive days. Blood samples were collected 2, 3, 4, 5, and 6 hours after participants took the first capsule. An additional blood sample was taken on day 5 (i.e., 24 hours after the last medication). A 4-day washout period between drug administrations was allowed. The duration of the washout period was based on the half-life of venlafaxine (6 hours) and its active metabolite, *O*-desmethyl-venlafaxine (ODV [11 hours]), to ascertain achievement of steady-state level and complete elimination (10 half-lives).

Plasma Levels of Drugs

For each medication group, the blood samples were collected in a serum separator EDTA tube and then centrifuged for 15 minutes at 4000 rpm. The plasma was then transferred into 1.6 mL Eppendorf tubes (Fischer Scientific; Ottawa, Ontario, Canada) (aliquots of 190 µL), frozen at –20°C, and transferred to a –80°C freezer. The person in charge of the dosage was blind to the source of the sample (i.e., the generic or the brand-name drug for each medication).

Extraction of Tablet/Capsule Content

The contents of 1 capsule each (including the capsule material itself [venlafaxine]) or of 1 tablet each (citalopram) were suspended in 15 mL methanol, put in a crimping vial, tightly sealed with a Teflon-coated cap, and sonicated at capacity in a small water bath using a broad-tipped Branson Sonifier 250 (www.sonifier.com). The experimenter was blind as to which capsule or tablet was the brand-name versus the generic formulation. All tablets and capsules went into fine suspension after sonication. Suspensions were centrifuged and supernatants further diluted in blank plasma in order to conform better to the quantification procedures

Table 1. Extraction of Tablet/Capsule Content in Brand-Name and Generic Formulations of Venlafaxine and Citalopram[a]

	Brand		Generic			
			Batch 1		Batch 2	
Drug	Batch No.	Extracted (mg)	Batch No.	Extracted (mg)	Batch No.	Extracted (mg)
Venlafaxine	L434196	49 ± 0.3	W06008	45 ± 0.2	W06096	44 ± 0.3
Citalopram	2127281	22 ± 6.2	6223	29 ± 3.4	19223	23 ± 7.9

[a]Values represent the mean ± SEM of the assays of 2 tablets in each group carried out in triplicate.
Abbreviation: SEM = standard error of the mean.

Table 2. Intervals in Hours:Minutes (mean ± SEM) Between Pills of Citalopram

Drug	Pills 1–2	Pills 2–3	Pills 3–4	Pills 4–5	Pills 5–6	Pills 6–7	Pills 7–8	Pill 7–Blood Draw
Celexa	23:59 ± 0:05	24:13 ± 0:17	24:11 ± 0:17	24:11 ± 0:33	23:24 ± 0:27	23:59 ± 0:07	23:58 ± 0:04	23:54 ± 0:04
Gen-citalopram	24:06 ± 0:12	24:04 ± 0:09	23:50 ± 0:12	24:42 ± 0:24	24:21 ± 0:35	23:32 ± 0:20	24:10 ± 0:04	24:07 ± 0:03

Abbreviation: SEM = standard error of the mean.

routinely used to determine medication levels in our laboratory (i.e., both standard curve samples and participant samples in plasma).

Analysis of Participant Plasma and Extracted Capsule/Tablet

Samples (190 µL) were spiked with 10 µL d3-methadone internal standard (2 µg/mL in methanol; mass transition 313 > 268 m/z) and extracted with 500 µL of –20°C cold acetonitrile. One hundred microliters of supernatant were directly injected into the high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) instrumentation.[15] Chromatographic separation of the analytes was performed on a reverse-phase C18 column (Waters Acquity BEH C18, 1.7 µm, 2.1 × 50 mm; www.waters.com), with a mobile phase gradient starting at 50% acetonitrile and 50% 5 mM formic acid in water and proceeding to 100% acetonitrile over 3 minutes at a flow rate of 0.25 mL/min. Chromatographic peaks were quantified using the mass transitions 325 > 109 m/z for citalopram, 278 > 58 for venlafaxine, and 264 > 58 m/z for *O*-desmethylvenlafaxine.[14]

The standard curve (internal standard, 100 ng/mL d3-methadone) was essentially linear up to the highest concentration tested, i.e., 250 ng/mL (quadratic equation fit, weighting 1/x, r > 0.99). The level of detection was 0.1 ng/mL (at a signal/noise ratio of 3/1), and the level of quantification was 0.5 ng/mL.

Statistical Analyses

The plasma levels of drugs (citalopram or venlafaxine) were analyzed using a 2-way analysis of variance (ANOVA) for repeated measures (time × treatment as main factors), followed by a Holm-Sidak test when appropriate. Statistical significance was set at $p < .05$.

The 90% confidence interval of the mean test value to mean reference value was calculated using the log-transformed C_{max} according to Health Canada guidelines.[16]

RESULTS

Extraction of Tablet/Capsule Content

All tablets (Gen-citalopram batches 19223/6223 and Celexa batch 2127281) and capsule (Novo-venlafaxine XR batches W06008 and W06096) went into fine suspension during the first sonication bout, whereas capsule batch L434196 of Effexor XR had to be sonicated for a second, prolonged time before all granules went into fine suspension.

Of the 75 mg of venlafaxine contained in each of the 2 tablets analyzed from each batch, 45 mg (0.28% coefficient of variation [CV]) could be extracted from batch W06008, 44 mg (0.5% CV) from batch W06096, and 49 mg (0.55% CV) from batch L434196. Of the 40 mg of citalopram contained in each tablet, 23 mg (25% CV) could be extracted from batch 19223, 29 mg (8.3% CV) from batch 6223, and 22 mg (20% CV) from batch 2127281 (Table 1).

Celexa and Gen-Citalopram

Treatment observance. The observance of the treatment was evaluated by using pillboxes with an electronic device recording the time of opening of the cap (Table 2). For 1 of the participants, 1 time of opening was not recorded due to an inadequate closing of the pillbox (day 4, Gen-citalopram treatment). The 2-way ANOVA for repeated measure (treatment and intervals as main factor) did not show any statistically significant difference in the interval between each pill and between the seventh pill and the blood collection on day 8 (treatment, $F = 0.43$, $df = 1,165$; $p = .9$—intervals, $F = 0.99$, $df = 6,165$; $p = .3$—treatment × intervals, $F = 1.53$, $df = 6,165$; $p = .2$).

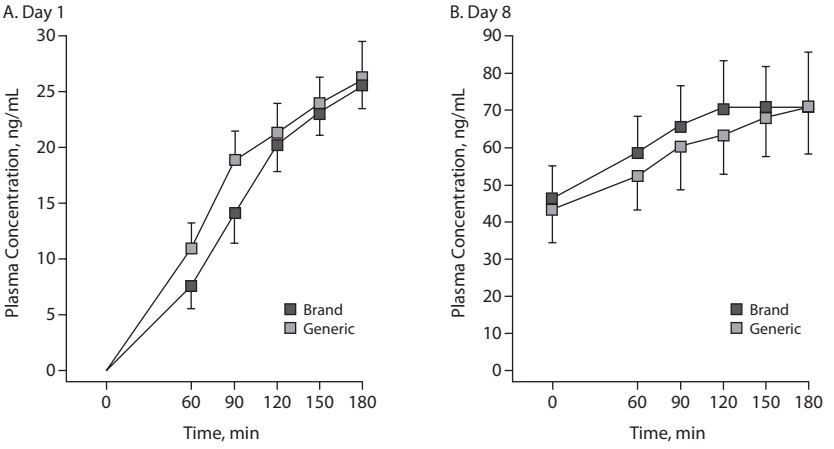
Time of blood collection. On day 1 and day 8, blood draws were collected 60, 90, 120, 150, and 180 minutes after ingesting the tablet. Time of collection of blood was monitored to ensure that, if a difference in blood level of drug was obtained between Celexa and Gen-citalopram, it was not due to a difference in time of collection (higher absorption

Table 3. Actual Time of Blood Collection in Minutes (mean ± SEM) After Participants Took Citalopram on Day 1 and Day 8

	Target Time of Blood Collection (min)				
Drug	60	90	120	150	180
Day 1					
Celexa	60.3 ± 0.5	92.5 ± 1.2	121.2 ± 0.8	151.0 ± 0.7	181.2 ± 0.6
Gen-citalopram	59.8 ± 0.7	90.2 ± 0.2	120.4 ± 0.4	151.3 ± 0.9	180.8 ± 0.4
Day 8					
Celexa	60.1 ± 0.1	90.5 ± 0.3	120.1 ± 0.5	150.5 ± 0.7	180.2 ± 0.1
Gen-citalopram	60.7 ± 0.4	90.3 ± 0.2	120.9 ± 0.6	151.5 ± 0.9	180.3 ± 0.3

Abbreviation: SEM = standard error of the mean.

Figure 1. Mean ± SEM Plasma Concentration–Time Curve of Citalopram After the Ingestion of Brand-Name (Celexa) and Generic (Gen-citalopram) Formulations of Citalopram 40 mg Over 3 Hours in 12 Healthy Male Volunteers on Day 1 (A) and at Steady State on Day 8 (B)



Abbreviation: SEM = standard error of the mean.

or higher metabolization). For each time point, the 1-way analysis for repeated measures did not reveal any significant difference between brand-name and generic medications ($p > .05$ for each group, Table 3).

Plasma levels of citalopram. For the plasma levels on day one, 1 datum was missing (time 90) due to a technical problem. The 2-way ANOVA for repeated measures (time × treatment) for the plasma levels of citalopram (Figure 1A) showed a significant effect of time ($F = 18.8$, $df = 5,143$; $p < .05$) but not of treatment ($F = 1.8$, $df = 1,143$; $p = .2$) and no interaction between these 2 factors ($F = 1.0$, $df = 5,143$; $p = .45$), which therefore indicates no difference between Celexa and Gen-citalopram. However, in both the brand-name and the generic medications, the drug concentrations were still on a rising phase, indicating that the C_{max} was not achieved after 180 minutes. However, since no significant differences were obtained in the plasma levels of drugs between times 150 and 180 minutes, it is presumed that the peak of the plasma concentration was almost achieved.

Estimated mean ± SEM arithmetic C_{max} values were 27 ± 2 ng/mL (brand-name formulation) and 28 ± 3 ng/mL (generic formulation). The ratio (generic/brand-name) of the log-transformed values of C_{max} was 99%. The corresponding 90% CI was 97% to 100% and therefore within the acceptable 80% to 125% range.

The 2-way ANOVA on day 8 (Figure 1B) showed a significant effect of time ($F = 57.6$, $df = 5,143$; $p < .001$) but not of treatment (Celexa/Gen-citalopram). The maximum level of drug was obtained within the 180-minute time course (no significant difference between times 90, 120, 150, and 180 minutes). The mean ± SEM concentration of citalopram at steady state was 47 ± 9 ng/mL and 44 ± 9 ng/mL for the Celexa and Gen-citalopram groups, respectively.

Effexor XR and Novo-Venlafaxine XR

There was 1 dropout in this medication group due to side effects. The volunteer was taking the generic medication. As he did not take the brand-name medication, we cannot conclude whether the side effects were related to the formulation of the drug. Data for this participant were not included in the results.

Treatment observance. Similar to what was done with citalopram, the observance of the treatment was evaluated by using electronic pillboxes (Table 4). No significant differences were observed between groups ($p > .05$).

Table 4. Intervals in Hours:Minutes (mean ± SEM) Between Pills of Venlafaxine

Drug	Pills 1–2	Pills 2–3	Pills 3–4	Pill 4–Blood Draw
Effexor XR	24:02 ± 0:05	24:03 ± 0:10	23:52 ± 0:09	24:00 ± 0:01
Novo-venlafaxine XR	23:51 ± 0:16	24:17 ± 0:12	23:44 ± 0:13	24:01 ± 0:02

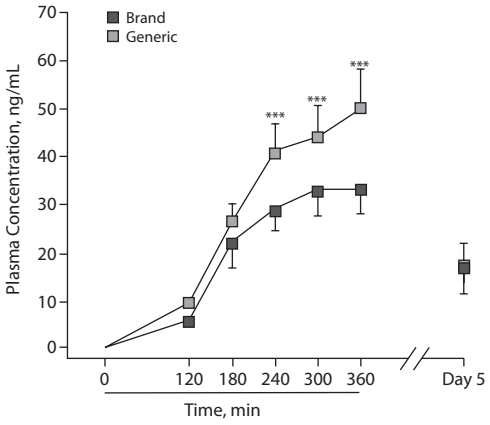
Abbreviation: SEM = standard error of the mean.

Table 5. Actual Time of Blood Collection in Minutes (mean ± SEM) After Participants Took Venlafaxine on the First Day

	Target Time of Blood Collection (min)				
Drug	120	180	240	300	360
Effexor XR	120.0 ± 0.9	181.3 ± 0.7	240.0 ± 0.0	300.3 ± 0.5	360.2 ± 0.2
Novo-venlafaxine XR	120.5 ± 1.1	179.8 ± 0.4	241.7 ± 1.7	299.9 ± 0.6	360.2 ± 0.2

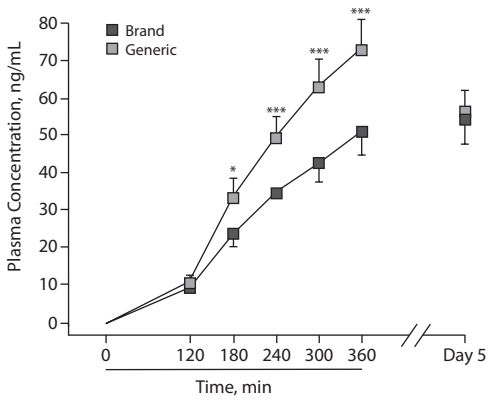
Abbreviation: SEM = standard error of the mean.

Figure 2. Mean ± SEM Plasma Concentration–Time Curve of Venlafaxine After the Ingestion of Brand-Name (Effexor XR) and Generic (Novo-venlafaxine XR) Formulations of Extended-Release Venlafaxine 75 mg Over 6 Hours in 12 Healthy Male Volunteers on Day 1 and at Steady State on Day 5



***p < .001.
Abbreviation: SEM = standard error of the mean.

Figure 3. Mean ± SEM Plasma Concentration–Time Curve of *O*-Desmethyl-Venlafaxine (active metabolite of venlafaxine) After the Ingestion of the Brand-Name (Effexor XR) and the Generic (Novo-venlafaxine XR) Formulations of Extended-Release Venlafaxine 75 mg Over 6 Hours in 12 Healthy Male Volunteers on Day 1 and at Steady State on Day 5*p < .05.



***p < .001.
Abbreviation: SEM = standard error of the mean.

Time of blood collection. On the first day, blood was collected 120, 180, 240, 300, and 360 minutes after ingesting the pills. Time of collection of blood was monitored to avoid any difference between brand-name and generic medications. For each time point, the 1-way analysis for repeated measures did not reveal any significant difference between brand-name and generic medications ($p > .05$ for each group, Table 5).

Plasma levels of venlafaxine. For all volunteers, the washout period was sufficient to have a complete elimination of venlafaxine. The 2-way ANOVA for repeated measures (time × treatment) for the plasma levels of venlafaxine (Figure 2) showed a significant effect of time ($F = 37.1$, $df = 5,143$; $p < .001$) and of treatment ($F = 21.8$, $df = 1,143$; $p < .001$) and a significant interaction between these 2 factors ($F = 5.5$, $df = 5,143$; $p < .001$). The mean level of venlafaxine was significantly higher in the generic group in comparison to the brand-name medication group at times 240 ($p < .001$; +42%), 300 ($p < .001$; +35%) and 360 minutes ($p < .001$; +51%). In the Effexor XR group, the plasma level of venlafaxine was similar at times 4, 5, and 6 hours, suggesting that the peak plasma was achieved. Similarly, no significant differences were obtained 4, 5, and 6 hours after ingestion of Novo-venlafaxine XR.

Estimated mean ± SEM C_{max} values were 36 ± 6 ng/mL (brand-name formulation) and 52 ± 8 ng/mL (generic formulation). The ratio (generic/brand-name) of the log-transformed values of C_{max} was 150%. The corresponding 90% CI was 104% to 217% and, therefore, not within the acceptable 80% to 125% range.

The 2-way ANOVA for repeated measures (time × treatment) for the plasma levels of ODV (Figure 3) showed a significant effect of time ($F = 71.7$, $df = 5,143$; $p < .001$) and treatment ($F = 13.9$, $df = 1,143$; $p < .01$) and a significant interaction between these 2 factors ($F = 11.6$, $df = 5,143$; $p < .001$). The level of ODV was significantly higher in the

Table 6. Reported Side Effects

	Venlafaxine		Citalopram	
Side Effect	Brand	Generic	Brand	Generic
Nausea	1	4	2	2
Sleep disturbance	1	3		3
Asthenia	1	1	3	1
Rash		1	1	1
Nervousness		1	1	
Extra energy		2		
Milky plasma		2		
Headaches	1			
Sexual dysfunction			3	2
Feeling neutral			1	1
No deep thought			1	1
Gastrointestinal				1
No. of side effects	4	14	12	12
Participants, n/N	3/12	9/12	6/12	5/12

generic group in comparison to the brand-name medication group at times 180 ($p < .05$; +43%), 240 ($p < .001$; +43%), 300 ($p < .001$; +48%), and 360 minutes ($p < .001$; +43%). The C_{max} values were not estimated in either group because the peak was not attained 6 hours after the pill ingestion.

At steady state, the 1-way ANOVA for repeated measures did not show any difference between the 2 medications in the mean ± SEM level of venlafaxine (Effexor XR, 17 ± 5; Novo-venlafaxine XR, 16 ± 6 [$F = 0.1$, $df = 1,23$; $p = .7$]) and ODV (Effexor XR, 60 ± 6; Novo-venlafaxine XR, 60 ± 5 [$F_{1,23} = 0.1$, $df = 1,23$; $p = .8$]).

Side Effects

The side effects were reported (or observed) on day 1 as well as at steady state (i.e., side effects occurring between day 1 and steady state). A total of 18 side effects have been reported/observed by participants taking venlafaxine (brand, 4; generic, 14) and 24 after taking the citalopram (12 in each medication group) (Table 6). The 1-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 ($F = 7.9$, $df = 1,23$; $p < .05$) but not in the citalopram treatment group ($F = 1.6$, $df = 1,23$; $p = .2$). The side effects that led to dropout (3 dropouts on day 1: Novo-venlafaxine XR, nausea; Gen-citalopram and Celexa, nausea and vomiting) are not mentioned in the table.

DISCUSSION

The present study was designed to evaluate the pharmacokinetic profiles of 2 generic formulations and their respective brand-name medication in healthy volunteers. The results showed that, within the parameters studied, Gen-citalopram did not significantly differ from the brand-name formulation Celexa, whereas the C_{max} obtained after the administration of the 2 lots of Novo-venlafaxine XR was significantly different from the one obtained after ingestion of the brand-name medication Effexor XR.

The plasma levels of citalopram were similar in both generic and brand-name medication groups and, therefore, could not explain the relapse obtained 4 years ago in the study by Van Ameringen et al.[8] Indeed, the ratio of the maximal concentration obtained in the 180 minutes of the monitoring was of 99% (90% CI = 97% to 100%). This is in line with the product monograph under fasting conditions (C_{max} ratio, 100%; 90% CI = 96% to 104%). Nonetheless, the C_{max} values upon acute administration of the 2 preparations of citalopram were not achieved in the chosen time window. However, C_{max} values were achieved at steady state. These 2 observations would make it highly unlikely that a thorough study could establish bioinequivalence, but this cannot be totally excluded.

The plasma levels of venlafaxine and its active metabolite, ODV, were significantly higher in participants who ingested the generic medication than in those who ingested the brand-name medication. The ratio (generic/brand-name) of the log-transformed values of C_{max} was 150%. The corresponding 90% CI was 104% to 217% and, therefore, was not within the acceptable 80% to 125% range requested to establish bioequivalence of a generic with a brand-name medication. Both the plasma level at steady state and the pills' content were, however, similar in the 2 formulation groups. The extraction of venlafaxine contained in the brand-name medication required an additional sonication in comparison to the extraction of the active compound contained in the generic. Indeed, the processes to extract the whole content of the generic led to the extraction of about only 70% of the content of the brand-name medication. The amount of venlafaxine extracted after a second sonication of the brand-name medication was, however, similar to the amount of venlafaxine extracted from the generic medication (after the first sonication). These differences suggest a variation in the galenic formulation of the 2 drugs. After opening the capsules, it was observed that the brand-name medication (Effexor XR 75 mg) contained spheres of different sizes most likely leading to slow, medium, and fast release of the active compound and, therefore, giving the gradual release properties of the drug (prolonged duration of absorption). In contrast, the generic formulation (Novo-venlafaxine XR 75 mg) contained only 1 size of spheres and, therefore, most likely led to a unimodal release.

This difference in the galenic formulation of the 2 drugs (easier and faster release of the Novo-venlafaxine XR) was most likely responsible for the higher plasmatic level of venlafaxine obtained with the generic formulation. In addition, this could explain the greater number of side effects in the generic group. Indeed, the generic formulation tested appeared to be an intermediate-release formulation between the immediate release (IR) and the true-brand XR formulation. In the product monograph[17] of Effexor XR, there are indications of lower rate of side effects in patients treated with the XR formulation than in those treated with the IR formulation. These include seizures (IR, 8/3082 patients;

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XR, 1/3364 patients) and increased in cholesterol (IR, +9.1 mg/dL; XR, +1.5 mg/dL). This is in line with our observations showing that, after taking the brand-name medication, 25% of the participants reported side effects, whereas 75% did so in the generic group ($p < .05$). One of the participants had headaches with the brand-name medication but not the generic, whereas 7 of them had side effects with the generic but not the brand-name medication.

This higher prevalence of side effects in the generic group could possibly lead to poorer compliance in routine clinical care, thus hypothetically accounting for some relapses observed since the introduction of the generic in Canada. In the product monograph[17] of Effexor, it is stated that the discontinuation rates during phases 2 and 3 were 19% and 12% for the IR and the XR, respectively. It is also possible that this side effect factor could be amplified with doses greater than 75 mg. Previous studies have demonstrated that the potential benefits of the venlafaxine XR formulation over the IR formulation include increased patient compliance and a better risk-to-benefit ratio.[18,19] It has also been demonstrated that venlafaxine XR (75 to 150 mg/day) was significantly more effective than venlafaxine IR (75 to 150 mg/day) during a 12-week flexible-dose study, with a difference in the response rates of 20%.[19,20] It appears counterintuitive that a higher C_{max} is associated with a lower efficacy of the drug. It could be hypothesized that the greater peak-to-trough variation in the generic group could affect the effectiveness of the treatment. Indeed, the C_{max} value in the generic group was 3 times greater than the corresponding steady-state concentration, whereas, in the brand-name medication group, the concentration at steady state represents only 50% of the C_{max}. It is also of interest to notice that, in the comparative bioavailability data included in the product monograph of Novo-venlafaxine[21] (150 mg, under fasting conditions), the percentage ratio of C_{max} (geometric means) is 124.5%, which is therefore within the guidelines of Health Canada. However, the corresponding 90% CI, in that monograph, is described to be 115.6% to 134.1%. Nevertheless, this drug was approved by Health Canada because this agency does not require that the 90% CI of the C_{max} parameter be within 80% to 125%. In contrast, this drug would not have been approved in Europe, since the European Medicines Agency requires that this parameter should be within the interval of 80% to 125%.

Taken together, these results suggest that, in comparison to Effexor XR 75, Novo-venlafaxine XR 75 could induce more side effects and might be less effective in some patients. These features appear crucial because generic drugs are usually prescribed, or delivered, to reduce health care costs. Since they may not always be bioequivalent, they can lead to relapses, prescription of additional drugs to counteract side effects, a switch to another antidepressant medication, or the use of augmentation strategies. All such scenarios require additional consultations. Therefore, using bioinequivalent generics could be associated with an increase of overall medical costs, as it has already been demonstrated, for example, with lamotrigine: the use of generics was associated with an increase in overall costs of approximately $1500 (Canadian dollars) per patient per year despite the lower cost of the generic.[22] Finally, the personal and familial suffering resulting from a potential relapse, and/or treatment discontinuation, should come into consideration when switching from a brand-name to a generic formulation.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), citalopram (Celexa and others), cyclosporine (Gengraf, Neoral, and others), diazepam (Valium and others), diltiazem (Dilt-CD, Diltzac, and others), docetaxel (Taxotere), furosemide (Lasix and others), hydrochlorothiazide (Microzide, Oretic, and others), levothyroxine (Synthroid, Levo-T, and others), lithium (Eskalith, Lithobid, and others), omeprazole (Prilosec and others), paroxetine (Paxil, Pexeva, and others), propranolol (Innopran, Inderal, and others), sirolimus (Rapamune, Torisel), warfarin (Coumadin, Jantoven, and others), venlafaxine (Effexor and others).

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