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Bioequivalence and therapeutic equivalence of generic and brand bupropion in adults with major depression: A randomized clinical trial

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Abstract

Controversy persists about bupropion XL300mg generic equivalence to brand product. A prospective, randomized, double-blinded, crossover in 70 adults with major depression in stable remission taking any bupropion XL300mg tested bioequivalence and therapeutic equivalence of available XL300mg products. After 4-week lead-in on patients' existing bupropion, four 6-week phases evaluated brand and three generics. Patients were uninformed of switching. Drug overencapsulation ensured blinding. There were no differences between any generic and brand, or between generics, in plasma C_{max} and AUC_{0-24} for racemic bupropion or major metabolites. All generics met formal bioequivalence criteria for bupropion and metabolites. There were no differences between generics and brand, or between generics, in depression symptoms or side effects, assessed by every 3-week in-person interviews and daily smartphone-based self-report. There were no differences in patients' perceptions of bupropion products. Results show three bupropion XL300mg generic products both bioequivalent and not therapeutically different from brand drug and each other.

Keywords

depression; antidepressant; bupropion; pharmacokinetics; bioequivalence; generic drugs

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Author Contributions

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Introduction

Generic drugs have manifest public health importance and economic impact.^{1,2} Generics comprised 89% of US prescriptions and nearly \$1.7 trillion in healthcare savings over the last decade.³ There are approximately 10,000 FDA-approved generic versions of brand drugs in the US (www.gphaonline.org). Patients may be switched from brand to generic drugs, or between generics, for cost and other reasons, with or without their knowledge or approval. Generic drugs must be bioequivalent to the innovator (brand) product, and both therapeutic equivalence and interchangeability with brand drugs and with each other is desirable.

Major depressive disorder is one of the most common mental disorders and is currently the leading cause of disability in the world. Antidepressant drugs target initial treatment and relapse prevention. Relapse has major consequences, including suffering and suicide risk, and each successive episode is likely to become more chronic and treatment-resistant.⁴ Mental health was one of four therapeutic areas accounting for the greatest savings afforded from generic drugs in 2016.³ Nevertheless, therapeutic non-equivalence of psychiatric medications can have profound health, ethical, cost, and broad economic implications.^{5,6} Patients stabilized on antidepressants may be at increased risk of symptomatic worsening or relapse if drug exposure diminishes, or increased risk of side effects if exposure increases.^{7,8}

Many psychiatrists express concerns about generic drugs.⁶ The assumption of generic equivalency was highlighted in the case of bupropion XL 300mg.^{9,10} Bupropion is a mainstay in treating major depressive disorder.¹¹ Bupropion was marketed first in immediate release, then sustained release, then extended release (once daily dosing, Wellbutrin XL®) forms, followed by generic sustained release and extended release XL 150mg. The first generic bupropion XL 300mg (Budeprion) was approved after a waiver of bioequivalence testing. Approval was based on established bioequivalence of Budeprion XL 150mg and Wellbutrin XL 150mg in healthy subjects, and that pharmacokinetics of 300mg and 150mg doses was not expected to differ.^{9,12} Shortly thereafter, there were numerous reports of clinical issues when switching from Wellbutrin XL to Budeprion XL, and a major controversy ensued.¹² When single-dose bioequivalence of 300mg Budeprion XL to Wellbutrin XL was eventually tested, in healthy subjects, the generic failed,^{9,10} and was withdrawn from the market. The other bupropion XL 300mg generics had not undergone bioequivalence or therapeutic equivalence testing, when this present protocol was conceived.

Therefore, to address the bioequivalence controversy, we conducted a four-treatment, four-period, four-sequence, randomized, double-blinded crossover study following a lead-in period, in individuals with major depressive disorder already stabilized on bupropion XL 300mg, to compare brand and generic products (and between generics). The primary outcome was steady-state bioequivalence using standard pharmacokinetic parameters for bupropion and metabolites. Secondary outcomes were therapeutic equivalence based on clinic-based measurement of antidepressant effectiveness and side effects, and smartphone-based Ecological Daily Assessment evaluation of antidepressant effectiveness and side effects. Another outcome was patients' perceptions of differences in release patterns, antidepressant effectiveness, and adverse events for brand and generic bupropion.

Results

Patient characteristics

Seventy-four subjects entered the lead-in period, two withdrew for scheduling reasons, and one suffered a depression relapse and was withdrawn (Figure 1). Seventy-one subjects thus entered the randomized phase, one withdrew for scheduling reasons before any pharmacokinetic assessments, and pharmacokinetic data were thus available for 70. That group was (median, IQR) 47 yr (37–57), 76 kg (63–94), and BMI 26 (23–33), with 53 (76%) females and 17 (24%) males, and 64 Caucasians (including 2 Hispanics), 5 African Americans, and 1 Asian. One subject withdrew after completing one pharmacokinetic session, one withdrew after completing two pharmacokinetic sessions, and one subject suffered a relapse of depression after the third pharmacokinetic session and was withdrawn. Thus complete bioequivalence data (brand bupropion and three generics) are available for 67 subjects. Pharmacokinetic data are presented for all patients (n=70) and bioequivalence data are presented for patients completing all 4 crossover sessions (n=67).

Study medication adherence was assessed using a combination of pill counts, medication monitoring (MEMS® cap openings), and daily self-report. Using this method, we calculated that participants took 98.6% of bupropion doses.

Bioequivalence

The primary outcome was bupropion pharmacokinetics and bioequivalence, based on plasma bupropion and major metabolite concentrations (Figure 2, Table 1). For plasma bupropion and metabolites, formal bioequivalence analysis showed that the 90% CI of the generic/brand geometric mean for $C_{\max}$ and AUC_{0-24} for all three generics was well within the 80–125% interval for bioequivalence. The 90% CI of the generic/brand mean for $T_{\max}$, for bupropion and major metabolites was also within 80–125%, except the hydroxybupropion $T_{\max}$ for the Watson generic was lower.

The three bupropion generics were also compared to each other as well as to brand bupropion (Valeant) (Table 2). For plasma bupropion and major metabolites, there were no significant differences ($P>0.05$ for all) in $C_{\max}$, AUC_{0-24} or $T_{\max}$ between brand bupropion and any of the three generics.

Clinical results

The main clinical outcome was relapse of major depression. Only one subject experienced a relapse during the randomized crossover phase. Relapse occurred in the middle of the third crossover session (while taking the Watson generic, after PAR and then Valeant (brand)). The subject's pharmacokinetic profile for the Watson generic showed a bupropion trough concentration about half that of the study population but $C_{\max}$ was similar; hydroxybupropion trough and $C_{\max}$ concentrations were half that of the study population. Nevertheless, the profile of the Watson generic resembled that of PAR generic and Valeant (brand) products (Figure 3), during which the subjects had not relapsed.

A second clinical outcome was depressive symptoms: MADRS depression scores were measured using traditional clinical interviews (Figure 4A). Scores were low, and not significantly different between brand and generics, or between generics. MADRS test-retest reliability was low to moderate (correlation=0.37) for the clinical assessments. Depressive symptoms were also evaluated using smartphone-based EDAs (90% completion). Test-retest reliability of smartphone-based EDA MADRS scores was good (ICC=0.70), measured by correlating weekly average scores within sessions within participants. Weekly average smartphone-based MADRS scores were not significantly different between generics and brand bupropion, and between generics (Figure 4B). There was no time-dependent increase of MADRS scores within any 6-week drug period, evidencing no loss of antidepressant effect subsequent to product switch.

The third clinical outcome was drug side effects. Results are shown for the composite ASEC side effect scores (comprising 6 individual side effect scores) during the four randomized phases, measured during the clinical interview (Figure 4C). Similar to depression scores, total side effect scores were not significantly different between generics and brand bupropion, and between generics. Results were similar for weekly ASEC scores assessed by cellphone-based EDAs (Figure 4D).

The fourth assessment was subjects' retrospective perceptions of differences in release patterns, antidepressant effectiveness, and adverse events for brand and generic bupropion. Subjects were asked whether they had perceived any differences among the four drug products, and if so, what was the specific difference recalled (feeling better or worse). Many subjects (36–53%) recalled, in general, some (any) difference between drug products, how they made them feel, how they affected depression, and side effects, but few (16%) recalled feeling different throughout the day (Table 3). There were no differences between brand and generic products, or between generic products, however, in subjects' perceptions of the specific clinical effects or side effects. Subjects recalled perceiving drug products as being different, despite bioequivalence and clinical data showing no differences.

Discussion

This investigation addressed controversies about generic bupropion, and tested the bioequivalence and rate of recurrent depression of available generic bupropion products to the innovator (brand) product and to each other. The major findings are that three generic bupropion XL 300mg products (PAR, Watson, Mylan) were bioequivalent to brand bupropion XL 300mg and showed similar, essentially zero, rates of recurrence and symptomatic roughening, in patients with major depressive disorder.

The first objective determined steady-state bioequivalence between brand and generic bupropion XL 300mg products, and between generics, in patients with major depressive disorder, based on the standard equivalence definition (90% CI of the generic/brand geometric mean ratio is within 80–125% for both $C_{\max}$ and AUC).^{13,14} The primary bioequivalence result was that for the three generics, the 90% CI for bupropion $C_{\max}$ and AUC_{0–24} was well within 80–125%. In addition, although $T_{\max}$ is not part of formal bioequivalence testing, and there is recognized variability in $T_{\max}$ for extended release drugs

at steady-state,¹⁵ $T_{\max}$ is potentially important.¹⁶ The 90% CI for bupropion $T_{\max}$ was also well within 80–125% for the three generics. Secondary bioequivalence assessment evaluated the major bupropion metabolites, because one or more is considered biologically active and clinically contributory.^{17–19} Specifically, bupropion effects have been attributed to hydroxybupropion with minimal contribution by bupropion,²⁰ and hydroxybupropion was even evaluated for clinical development.²¹ Steady-state exposures for hydroxybupropion, erythrohydrobupropion, and threo hydrobupropion were approximately 25-, 2.5- and 11-fold greater than bupropion. Secondary bioequivalence results were that for the three generics, the 90% CI for hydroxybupropion, erythrohydrobupropion, and threo hydrobupropion $C_{\max}$, AUC_{0-24} , and $T_{\max}$ were well within 80–125%. Lastly, between the three generics, there were no significant differences in bupropion or metabolites $C_{\max}$ and AUC_{0-24} . In addition to testing for sameness (bioequivalence), data were also analyzed for differences, with none found, which strengthens the findings. Therefore, the first major finding was that bupropion XL 300mg generics from PAR, Watson, and Mylan were bioequivalent to Valeant brand, and to each other, in patients with major depressive disorder.

The second objective was to compare recurrence rates of depression with each bupropion product using measures of depression and side effects. There were no differences in recurrence rates between any of the four drug products, measured with both traditional clinic-based and daily smartphone-based evaluations of antidepressant effectiveness. Recurrence rates are highly population-dependent after drug withdrawal,²² and based on past experiences, a drug with no bioavailability would be expected to have an approximately 10% greater rate of relapse than continued effective treatment over a short treatment phase.^{7,22} Only one patient relapsed during the randomized crossover. Patients switched to a bupropion product having lower exposure might show increasing depressive symptoms over time, but not reach formal criteria for relapse, hence temporal analysis and/or sub-relapse symptomatic roughening may be more sensitive than relapse.²³ Nonetheless, such worsening was not observed with any of the four bupropion products. Therefore, the second major finding was that brand and three generic bupropion XL 300mg drug products were not clinically different from each other with respect to treating major depressive disorder in stable remission.

The third objective was to compare patients' self-reported clinical differences (domains of perceived release patterns, antidepressant effectiveness, and adverse events) between bupropion products (brand vs generics, and between generics). Many patients reported feeling one or more general domain differences between products, however there were no significant differences between specific products. In addition, these perceptions were not reflected in the antidepressant effectiveness or side effect data, or bioequivalence between products. Therefore the third major finding is that patients' retrospective perceptions of bupropion may not accurately reflect objective measures of disposition, therapeutic effect, or side effects.

This investigation had several notable features. It was conducted in treated patients under clinically relevant conditions rather than healthy volunteers, evaluated steady-state rather than single dosing, compared all available marketed generics, evaluated bioequivalence of both parent drug and major metabolites, evaluated a larger cohort than many bioequivalence

studies (minimum of 12 and typically 24–36 healthy volunteers), and used a crossover rather than parallel group design, which is robust for treatment effect studies in major depressive disorder.^{7,22} It evaluated not just bioequivalence, but also therapeutic effect, including depression recurrence and side effects. Trial sensitivity is informed by prior studies showing the robustness of this design.^{23,24} It used three assessments of patient compliance, which was remarkably high. Subject retention was also high. Multiple methods of assessing depression and side effects were used, including structured in-person interviews and novel smartphone-based ecological daily assessments. The findings of these methods agreed well with each other. Compared with traditional written diaries, the smartphone-based system has numerous advantages, including subject convenience, real-time assessment rather than relying on memory and recall, and instantaneous data transmission (no risk of losing a survey containing weeks of data). While the Watson generic was voluntarily withdrawn in 2013,²⁵ it was already in the protocol, and was retained for completeness. Although the Watson generic was deemed not therapeutically equivalent to Wellbutrin brand, bioequivalence data are not publically available,²⁵ It is thus not apparent why Watson bupropion was bioequivalent brand in the present, but not previous investigation, but we note that the brand manufacturer has changed from GlaxoSmithKline to Valeant.

There are also potential limitations. Results are likely generalizable to larger patient populations, but not to other generic bupropion products. The study did not include an arm designed to induce a relapse (i.e. placebo or known subtherapeutic bupropion dose) and establish a relapse rate. Such a design could have limitations or be considered questionably ethical because patients could be harmed by relapse,²⁶ as well as potentially unfeasible, not cost-effective, and/or unlikely to recruit sufficiently (i.e. patients willing to voluntarily undergo likely relapse) within the required study duration, and would have necessitated a less powerful parallel group design. Subjects were studied on each bupropion preparation for six weeks. It is possible that longer evaluation might have found clinical differences between bupropion products. Nonetheless, antidepressant effectiveness was measured not only by relapse but also by daily symptoms, using the sensitive method of Ecological Daily Assessment, and there was no evidence of differences between bupropion products.

Generic drug use is widespread and cost-effective.³ Generics accounted for 89% of the 4.3 billion US prescriptions in 2016 but only 26% of total drug costs, and market share rose substantially, from 47% of prescriptions in 1999 to 89% in 2016. Cost savings also increased, from \$60B in 2002 to \$253B in 2016. Although a majority of patients and practitioners favor generic drugs, there is nevertheless lingering skepticism or frank negative perceptions,^{27,28} and ongoing tension between generic and brand-name drugs.²⁹ Aside from obvious cost advantages of brand-generic switching, generic-generic switching also occurs due to availability, stocking from specific manufacturers, pharmacy-negotiated costs, and requirements by third-party payers.³⁰ Switching decisions may be made by prescribers, pharmacists, or patients. Interchangeability of generic drugs influences drug prescribability (whether initial treatment is with brand vs generic drug) and switchability (brand to generic, or generic to generic).³¹ Prescribers and patients may not be aware when switching has occurred.

The key premise underlying generics is therapeutic equivalence to the brand innovator, and by extension, to each other. Bioequivalence is used as a surrogate for therapeutic equivalence.^{13,14,16,32,33} Generics are considered bioequivalent to brand drug if the active compound exhibits the same rate and extent of absorption (more generally, systemic exposure, determined from C_{max} and AUC). Generics must also show pharmaceutical equivalence (same active ingredients, route of administration, dosage, form, strength) to the brand drug. Drugs are considered therapeutic equivalents if they are both pharmaceutical equivalents and bioequivalent, obviating the need for therapeutic equivalence testing. However, therapeutic non-equivalence can occur despite bioequivalence, such as with antibiotics, antiepileptics, and heparin.^{34,35} Moreover, bioequivalence need only be tested in normal healthy subjects, not the intended patient population. In addition, single-dose studies in healthy volunteers may not predict steady-state bioequivalence in patients, particularly for modified release forms.³⁶ Administrative claims data and health records can be used to surveil health services use and drug discontinuation after brand-to-generic switching,³⁷ along with other postmarketing data, as surrogates for equivalence testing. However there are relatively few randomized trials, like the present one, comparing clinical outcomes of generic and brand drugs.³⁸

There has been ongoing controversy about the equivalence of generic bupropion XL 300mg products since their introduction. Approval of the first generic bupropion XL 300mg (Budeprion XL) in 2006 was based on extrapolating a prior comparison of 150mg Budeprion XL and brand Wellbutrin XL in healthy subjects.^{9,12} A bioequivalence waiver was granted and Budeprion XL 300mg was not tested, because pharmacokinetics were not expected to differ between 300mg and 150mg bupropion XL generics. Shortly thereafter, however, FDA received 85 post-marketing reports (January-June 2007) of clinical issues when switching from Wellbutrin XL to Budeprion XL, including 78 with worsening depression and 7 with new or worsening side effects. FDA suggested that the recurrent nature of major depressive disorder, rather than a drug problem, provided a scientifically reasonable explanation for patients' reports of worsening depression following a switch to a generic.¹² Nevertheless, FDA did subsequently sponsor a single-dose bioequivalence study in healthy subjects comparing 300mg Budeprion XL to Wellbutrin XL (completed August, 2012). Budeprion bupropion AUC and C_{max} were only 86% and 75% that of Wellbutrin, respectively, and were <40% in some subjects. Hydroxybupropion C_{max} also failed bioequivalence.^{9,10} Based on failed Budeprion XL 300mg bioequivalence, the manufacturer withdrew it from the market. In 2013, FDA reviewed all four then-marketed bupropion 300 mg XL products: Actavis, Inc. (later merged with Watson), Mylan Inc, Par Pharmaceutical (formerly Anchen Pharmaceuticals), and Watson. FDA determined the Watson generic non-equivalent to Wellbutrin, and Watson voluntarily withdrew the product, furthering the bupropion controversy.²⁵

This is the first bioequivalence and clinical equivalence study to compare generic and brand bupropion using a real-world population of actual patients using the drug for therapeutic purpose. Results demonstrate that generic bupropion XL 300mg products from Par Pharmaceuticals, Mylan Pharmaceuticals, and Watson Labs were bioequivalent and clinically similar to brand bupropion from Valeant Pharmaceuticals. These data provide

clinically actionable information to patients and practitioners, and should help address existing controversies.

Methods

Protocol

This prospective, randomized, double-blinded, 4-period, balanced, single-center crossover comparing bioequivalence and therapeutic equivalence of three bupropion XL 300mg generics to brand Wellbutrin XL 300mg bupropion (NCT02209597), was approved by the Washington University Institutional Review Board and the FDA Research Involving Human Subjects Committee. All subjects provided written, informed consent. Enrollment was June, 2014 to January, 2016, with follow-up completed August, 2016.

Inclusion criteria included males and females 18–75 yr, with major depressive disorder in remission and taking bupropion XL 300mg once daily for 4 months. Major exclusions included hepatic or renal disease; drugs influencing CYP2B6; cognitive impairment; bipolar or psychotic disorder, abuse of alcohol or other substances in the past 6 months; suicidal ideation.

During a 4-week lead-in, subjects continued their bupropion product (now over-encapsulated) and underwent daily smart phone-based self-report assessments. Lead-in was followed without washout by four 6-week periods with the four bupropion XL 300mg test drugs (Valeant Pharmaceuticals brand Wellbutrin, and generics from Par Pharmaceutical, Mylan Pharmaceuticals, and Watson Labs, all over-encapsulated) in a randomized crossover. There were 16 sequences, with subjects randomized into 5 blocks, so that order was balanced. Randomization schedules and drug allocation sequences were generated by the hospital investigational pharmacy. Subjects received each bupropion product for 6 weeks, and then switched to another without washout, by the pharmacists according to randomization. Subjects and research staff were not informed a switch, to minimize bias. Subject visits occurred every 3 weeks for objective assessment of depression and side effects, and pill counts. Adherence was monitored by electronic pill containers, pill counts, and daily (via smartphone). After the 28-week study, subjects resumed their prestudy bupropion product.

Subjects underwent pharmacokinetic evaluation after an overnight fast, 10–20 days after starting each drug product to allow for steady-state. Venous blood samples were obtained 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24 hr after dosing, and all urine was collected for 24 hr. Concentrations of bupropion and the metabolites hydroxybupropion, erythrohydrobupropion, and threo hydrobupropion were determined by liquid chromatography-mass spectrometry using validated assays.^{39,40} Interday variation was <10% at all analyte concentrations. Each subjects' samples from the four study sessions were analyzed in the same batch. Results are reported achirally.⁴¹

Depression was assessed with the Montgomery-Asberg Depression Rating Scale (MADRS, 10 items rated 0–6; total 0–60)⁴² using a structured interview,⁴³ every 3 weeks. Subjects with 2 point increase from average baseline lead-in MADRS score underwent the SCID

depression module. If that revealed major depressive disorder, a relapse was declared. Side effects were assessed with the self-report Antidepressant Side-Effect Checklist (ASEC).⁴⁴ To gather more frequent information, daily depressive symptoms (8 MADRS items) and 5 most common bupropion side effects were also assessed by Ecological Daily Assessments (EDA) implemented via smartphone.

At the conclusion of the investigation, subjects were queried about their retrospective perceptions of differences in release patterns, antidepressant effectiveness, and adverse events regarding the study drugs. A questionnaire asked the following five questions: Among the 4 bottles of study medication (1st bottle, 2nd bottle, 3rd bottle, and 4th bottle) did you notice (Y/N) any difference 1) between them, 2) in how they made you feel, 3) in how they made you feel at different times during the day, 4) in how they affected your depression, and 5) in any drug side effects? A follow-on after each question asked If yes, which bottles, and please describe the differences.

Sample Size Justification

Target enrollment was 60 evaluable (completing) subjects. A 20% drop-out rate was conservatively assumed; enrollment estimated at 75 subjects. However, only 71 were enrolled because completion goals were satisfied (60 subjects completing). Sample size and power calculations were based on confidence intervals for the ratio of pharmacokinetic parameters for generic (Budeprion XL) vs innovator (Wellbutrin XL).⁴⁵ Power analysis for the two one-sided tests (TOST) approach was per FDA guidance on bioequivalence, using SAS 9.3 Proc Power. Using a 90% confidence interval and ratios needing to be 0.80–1.25, power was computed for sample sizes ranging from 60 to 75. If generics were bioequivalent (ratio=1.0) then power would be >0.999 for AUC and 0.98 for $C_{\max}$. If the generic was 10% under (or over), e.g. ratio=0.90, then AUC power would be 0.78–0.83 for a significant difference between products ($\alpha=0.05$) even if the CI for the ratio was still within 0.80–1.25.

Statistical Analysis

Analyses were conducted using intention-to-treat and prespecified statistical plans. All pharmacokinetic data for all subjects was included in the final analysis. No interim analysis was planned or conducted.

Primary (bioequivalence) outcome: Bioequivalence was determined per FDA Guidance,^{13,41} using the standard equivalence definition (90% CI of the generic/brand geometric mean within 80–125%). Primary metrics were maximum plasma concentration ($C_{\max}$) and area under the plasma concentration-time curve over the 24hr dosing interval (AUC_{0-24}), using non-compartmental methods. For each parameter a repeated measures mixed model ANOVA was fit. The two one-sided test procedures determined whether each generic product parameter was significantly more or less than brand bupropion XL. Time to $C_{\max}$ ($T_{\max}$) was also analyzed. Of main interest was bupropion, however bioequivalence was also evaluated for the three main metabolites. In addition to comparing generics to brand, all pairwise comparisons between bupropion products were computed for bupropion and metabolites. Tukey adjustments corrected for multiple comparisons.

Secondary (therapeutic equivalence) outcomes: Therapeutic equivalence was defined as no statistically significant difference in depressive symptoms or side effects. One planned analysis was relapse of major depression, or drug discontinuation due to side effects. Because these are rare, a repeated measures mixed model ANOVA also evaluated symptomatic changes (MADRS scores during each bupropion product) and side effects (ASEC), and each individual side effect was examined using a complementary generalized linear mixed model with a logit link function. Smartphone-based EDAs of depressive symptoms and side effects were analyzed using a weekly average of the sum of the 8 MADRS items, and the sum of the ASEC items, analyzed as a repeated measures mixed model ANOVA. Primary analyses were for values within treatment periods for each generic against brand bupropion XL. To estimate reliability of each method of administering the MADRS, an intraclass correlation coefficient (ICC) was computed for the two clinical assessments within each period and for the 6 weekly mean cell phone administered assessments. For the questionnaire on subjective experiences, the proportion of “felt worse” vs “felt better” responses was compared across the four drugs using a chi square test where the p-value was determined via Monte Carlo using the R function `chisq.test`.

Results are reported as mean $\pm$ standard deviation (SD) for normally distributed data, or the median (25th – 75th percentile, interquartile range, IQR).

A full protocol is available in the Supplement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The widely used antidepressant bupropion XL300mg is available as generic products, saving healthcare resources, and but equivalence to brand drug has been highly controversial for many years

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the bioequivalence and therapeutic equivalence of brand and three generic bupropion XL300mg products in adults with major depression.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

There were no differences between any generic and brand, or between generics, in bioequivalence (parent drug and metabolites plasma C_{max} and AUC_{0-24}) and no therapeutic differences (depression symptoms or side effects) of bupropion XL300mg products. Patients' perceptions of the four products did not differ.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Prescribers and patients can use these generic bupropion products with assurance of equivalence to brand drug. The value of real world clinical studies, in patients, to test both bioequivalence and therapeutic equivalence, is shown.

Bioequivalence and Clinical Effects of Generic and Brand Bupropion

Figure 1.
CONSORT diagram

Figure 2.

Bioequivalence of brand and generic bupropion. Shown are steady-state plasma concentrations of bupropion and major metabolites in subjects with major depressive disorder receiving bupropion XL 300mg brand (marketed by Valeant) and generic (marketed by Par, Watson, and Mylan). Results are shown as the mean $\pm$ standard deviation. Standard deviations are shown for the Valeant data and others are omitted for clarity. The standard deviations for the other drug products were of the same magnitude as those for Valeant.

Figure 3. Steady-state plasma concentrations of bupropion and major metabolites in the patient who suffered a major depression relapse. The subject withdrew in the middle of the third crossover session, while taking the Watson generic (after first PAR and then Valeant (brand) products in the first two sessions). The pharmacokinetic profile of the Watson generic resembles that of the PAR generic and Valeant (brand) products.

Figure 4.

Therapeutic comparison of brand and generic bupropion. Results are MADRS depression scores from (A) clinic visits and (B) cell phone assessments, and ASEC side effect data from (C) clinic visits and (D) cell phone assessments. Box plots represent the median (solid horizontal line), mean (diamond), 25th and 75th percentile (box boundaries), 10th and 90th percentiles (whiskers), and individual outliers.

Table 1

Bupropion Pharmacokinetic Parameters

	Parameter ¹	Valeant (brand)	PAR	Watson	Mylan
Bupropion	C _{max} (ng/ml)	81 (68–106)	79 (68–101)	82 (65–99)	88 (67–102)
	bioequivalence (%)		99 (94, 104)	97 (92, 102)	105 (100, 111)
	T _{max} (hr)	4.9 ± 1.4	5.0 ± 1.6	4.8 ± 1.2	4.9 ± 1.1
	bioequivalence (%)		102 (95, 110)	98 (90, 105)	100 (93–108)
hydroxybupropion	AUC (hr ² ·μg/ml)	0.84 (0.71–1.04)	0.88 (0.72–1.08)	0.83 (0.68–0.99)	0.89 (0.70–1.06)
	bioequivalence (%)		103 (98, 108)	96 (92, 101)	102 (98, 107)
	C _{max} (ng/ml)	1167 (849–1382)	1129 (877–1472)	1184 (881–1370)	1160 (923–1495)
	bioequivalence (%)		101 (96, 106)	97 (92, 102)	102 (97, 108)
erythrohydrobupropion	T _{max} (hr)	7.3 ± 3.3	7.4 ± 3.0	6.2 ± 2.1	6.9 ± 2.4
	bioequivalence (%)		101 (91, 111)	84 (74, 95)	95 (85, 106)
	AUC (hr ² ·μg/ml)	20.9 (15.5–25.5)	20.9 (15.9–28.1)	21.8 (15.9–26.5)	21.6 (15.9–27.7)
	bioequivalence (%)		103 (97, 108)	98 (93, 103)	104 (98, 109)
threohydrobupropion	C _{max} (ng/ml)	102 (81–132)	97 (78–134)	102 (75–123)	107 (87–126)
	bioequivalence (%)		98 (93, 104)	94 (89, 100)	97 (91, 102)
	T _{max} (hr)	7.5 ± 3.6	7.6 ± 2.2	6.9 ± 2.0	7.9 ± 3.3
	bioequivalence (%)		100 (90, 111)	92 (82, 103)	105 (94, 115)
threohydrobupropion	AUC (hr ² ·μg/ml)	2.09 (1.52–2.59)	2.05 (1.47–2.57)	1.98 (1.48–2.34)	2.02 (1.61–2.50)
	bioequivalence (%)		100 (94, 106)	96 (91, 102)	98 (92, 103)
	C _{max} (ng/ml)	516 (398–704)	479 (385–733)	466 (384–584)	506 (394–620)
	bioequivalence (%)		100 (95, 106)	94 (88, 99)	97 (91, 103)
	T _{max} (hr)	7.0 ± 2.4	7.5 ± 2.3	6.3 ± 1.9	7.2 ± 2.1
	bioequivalence (%)		106 (97, 114)	90 (82, 98)	102 (94, 110)
	AUC (hr ² ·μg/ml)	9.38 (7.21–13.27)	9.05 (7.21–13.27)	8.57 (6.83–11.57)	8.78 (7.25–12.49)
	bioequivalence (%)		101 (95, 107)	94 (89, 100)	96 (91, 102)

Abbreviations: AUC, area under the plasma concentration-time curve over the dosing interval (24 hr).

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Pharmacokinetic data are shown for subjects completing at least one evaluation session (Valeant n=68, PAR n=68, Watson n=69, Mylan n=67). Parameters which were non-normally distributed (C_{max} , AUC) are the median (Interquartile Range in parentheses), and those normally distributed (T_{max}) the mean $\pm$ standard deviation.

² Bioequivalence data are shown for subjects completing all four drug product sessions (n=67). Bioequivalence for C_{max} and AUC was calculated as the difference (brand-generic) of log-transformed measure and expressed as the geometric mean (antilog of the means of the logs) and 90% confidence interval (in parentheses). For T_{max} the confidence intervals were computed on an arithmetic scale. As long as the 90% confidence interval is totally in the interval 80%–125% the generic is considered bioequivalent (two one-sided test procedure).

Table 2

Bupropion pharmacokinetic statistical comparisons

Parameter ¹	Comparison	Mean Difference	SE	p ²
AUC	Valeant-Mylan	−0.010	0.012	0.85
	Valeant-PAR	−0.013	0.012	0.71
	Valeant-Watson	0.017	0.012	0.52
	PAR-Mylan	0.003	0.012	0.99
	Watson-Mylan	−0.026	0.012	0.13
	Watson-PAR	−0.029	0.012	0.07
C _{max}	Valeant-Mylan	−0.021	0.014	0.44
	Valeant-PAR	0.005	0.014	0.98
	Valeant-Watson	0.014	0.014	0.74
	PAR-Mylan	−0.026	0.014	0.25
	Watson-Mylan	−0.035	0.014	0.06
	Watson-PAR	−0.009	0.014	0.92
T _{max}	Valeant-Mylan	−0.023	0.220	1.00
	Valeant-PAR	0.105	0.220	0.96
	Valeant-Watson	0.072	0.220	0.99
	PAR-Mylan	0.081	0.220	0.98
	Watson-Mylan	−0.096	0.220	0.97
	Watson-PAR	−0.177	0.220	0.84

¹Units for AUC and C_{max} are log10²P values are adjusted for multiple comparisons with the Tukey method

Table 3

Patient perceptions of clinical differences between bupropion drug products

<i>Among the 4 bottles of study medication did you notice any difference:</i>	Any Difference		Specific Difference		P-value
	No	Yes	Felt Worse	Felt Better	
<i>between them?</i>	38	28			0.168
Valeant (brand)			9	3	
Mylan			13	2	
PAR			4	5	
Watson			14	5	
<i>in how they made you feel?</i>	31	35			0.271
Valeant (brand)			5	2	
Mylan			10	3	
PAR			5	6	
Watson			11	3	
<i>in how they made you feel at different times of the day?</i>	57	9			1.000
Valeant (brand)			4	0	
Mylan			3	1	
PAR			3	0	
Watson			3	0	
<i>in how they affected your depression?</i>	38	28			0.069
Valeant (brand)			6	4	
Mylan			8	3	
PAR			3	8	
Watson			8	2	
<i>in any drug side effects?</i>	42	24			1.000
Valeant (brand)			7	1	
Mylan			7	1	
PAR			5	1	
Watson			10	1	

Based on 66 completed questionnaires