Pharmacokinetic Assessment of Two Extended Release Prescription Products

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Support Personnel: The Clinical Research Unit (and possibly other staff at TTUHSC) will provide support. All study personnel will be trained and approved by the IRB prior to participation.

PRN nurses (RNs, trained and approved by the IRB prior to their participation) will be cover the 24-hour periods and possibly the subsequent draws. If a study nurse does not obtain the subsequent draws, a trained phlebotomist or other qualified TTUHSC personnel will perform this task.

Sponsor: Food and Drug Administration

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Sites: For the first 24 hours of the study, subjects will be in an unoccupied NWTHS room on the 4th floor of the Oncology Department (the specific room will vary; study staff will coordinate with NWTHS when scheduling)

After the first 24 hours, subjects will return to TTUHSC for subsequent blood draws.

Hypothesis:

The generic equivalent produces plasma levels in humans that is equivalent to the Wellbutrin trade-name product.

Background:

With the introduction of the Waxman-Hatch Act of 1984, the FDA has evaluated and approved thousands of therapeutic generic products as safe and equivalent to brand products. Their efforts have been widely successful, with some surveys estimating that about 65% of all prescriptions filled today are with generic products. Though successful, there is also a rising tide of skepticism about their safety and the "switchability" between products. Therefore, there is a need for an independent evaluation of some products with respect to their pharmacokinetic parameters. The goal of this project is to perform an independent evaluation of the pharmacokinetics of two extended release bupropion products at an academic clinical setting, so that the FDA can use this pharmacokinetic data to enhance their understanding of patient complaints and/or adverse events and during their drug application reviews.

The objective of this study is to compare two bupropion products in a randomized cross-over fashion to see if the generic equivalent produces plasma levels in humans equivalent to the Wellbutrin trade-name product. We will enroll up to 36 subjects (target: 24 subjects completing the full study) and place IV lines with a slow saline drip (12 to 30cc/hour). Each patient will receive a single oral 300 mg extended release tablet of Wellbutrin or a single generic extended release tablet containing 300 mg bupropion. (Subjects will be randomly assigned by the FDA to receive one or the other first.) We will then take blood samples at 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours following administration of the dose. After at least 15 days for washout, the same subject will undergo the process again using the alternate product (the extended release generic product or Wellbutrin extended release product). This trial will permit the FDA to determine plasma levels of bupropion in the same subject using both the generic and trade-name products.

Identification/Recruitment of Subjects:

Up to 36 subjects (target: 24 subjects completing the full study) will be enrolled in this study. Flyers will be posted at various places in Amarillo/Canyon to recruit subjects. A web advertisement will be posted on Dr. Hale's website and social networking sites. A phone script will be used by study personnel when answering calls from potential subjects.

Inclusion Criteria:

1. Healthy
2. Non-smoking
3. Males and non-pregnant females
4. 18-55 years of age (elimination pharmacokinetics are not affected by age)

Exclusion Criteria:

1. Pregnant women
2. History of:
    a. seizure disorders,
    b. head trauma,
    c. CNS tumors,
    d. severe hepatic cirrhosis
3. Over-the-counter medications including herbal/dietary supplements within 10 days of this study
4. Monoamine oxidase inhibitors (MAOI) Phenelzine (Nardil), Tranylcypromine (Parnate), Isocarboxazid (Marplan), or Selegiline (Emsam) within 30 days of this study
5. Prescription medication, oral contraception, or contraception implants within 30 days of study drug administration
6. Depot injection of a progestogen drug (Depo Provera, etc.) within one year of study drug administration

Study Drugs (Information and Risks):

Wellbutrin (bupropion) 300 mg extended release

Bupropion is a commonly used antidepressant. Its only major complication is dose-related seizures, which usually occur only at higher doses, such as 450 mg, and then only at a rate of 1 in 1000 patients. This number can be reduced by careful elimination of all patients with a reported history of seizure disorders, head trauma, CNS tumors, severe hepatic cirrhosis, or concomitant medications that lower seizure threshold. Other situations that may increase the risk of seizure include: alcohol consumption, addiction to opiates, cocaine, or stimulant use. Other possible complications reported in the package insert include: agitation (2%), anxiety (7%), or insomnia (20%), but these are reported following chronic use and are only a remote possibility with this single-use study.

Study Design:

1. During the screening visit, eligibility requirements will be confirmed, and the informed consent will be reviewed with the subject by a member of the study team. If the subject is eligible and agrees to participate, the subject will sign and date an informed consent document prior to any study procedures. The subject will be asked to complete a health history questionnaire. A physical will be completed by our attending physician. The study staff will then set up a time for the subject's return visit to Northwest Texas Healthcare Systems (NWTHS) where the first phase of the study is being conducted. The form entitled "Information to Subjects" will be given to the subject at this time.
2. For the 48 hours preceding each study visit (until the final blood draw), the subject will be instructed to avoid consuming the following:
    - Alcohol

- Grapefruit juice or whole grapefruits
- Caffeine
- Foods/fluids containing xanthine

3. Subjects will be asked to fast for at least 10 hours prior to each of the two visits in which the study drug is administered. Subjects may drink water up until one hour before the drug administration. Female subjects will be asked to use a form of birth control other than oral contraception, contraception implant, and Depo Provera shots throughout the course of the study.
4. A urine pregnancy test will be performed for each female subject prior to each study drug administration (and also at the end of the study). If the result is positive for pregnancy, the study team will encourage the subject to seek follow-up care with the appropriate health care provider.
5. NWTHS administration has approved the use of an unoccupied room at NWTHS on the 4th floor, Oncology Department. The room will vary; study staff will contact NWTHS personnel for the room number in preparation for each subject's first visit. The subject will remain in the NWTHS room with the study nurse for the first 24 hours of the study.
6. The study nurse will do the following:
    - Take vital signs- (height, weight, temperature, pulse, respirations, and blood pressure)
    - Place an IV line with saline drip
    - Draw an initial sample of blood (6 mL), at pre-dose Hour 0
7. The study nurse will then administer a single Wellbutrin or bupropion extended release tablet and stay with the subject in the NWTHS room for the first 24 hours. If emergency care is necessary, one of the co-investigators (TTUHSC physicians) will be consulted. All co-investigators on this study have privileges at NWTHS. If the co-investigator determines emergency care is required, the subject will be referred/admitted to NWTHS.
8. The subject will drink 240 mL (8 fluid ounces) of water with the study drug.
9. No food will be allowed for at least 4 hours post-dose.
10. Water will be allowed as desired, except for one hour after drug administration.

After the drug administration, the study nurse will collect blood (6 mL for each draw + 5 mL of waste) at hours 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72. With the first blood draw, an IV line will be placed to keep the vein open (KVO), avoiding numerous venipunctures. The study nurse will maintain this IV line with a saline drip throughout the 24-hour stay following the study drug administration; the IV rate will be KVO.

Normal saline will be infused at a rate of 5-10 mL/hr (max of 0.2 mL/min) to keep the vein open. Hemodilution will be minimal due to the low infusion rate. Prior to collecting samples, the IV line will be clamped off to stop the flow of NS. Using one of the ports on a 3-way stopcock, 5 mLs of waste will be drawn followed by the sample. The IV line will be unclamped to keep the vein open for the next sample. The IV line will be removed by the nurse when the 24-hour sample is drawn. Subsequent blood samples on return study visits 36, 48, 60, and 72 hours (post pill), will be taken by a phlebotomist or nurse at TTHUSC.

11. The samples will be collected using Vacutainers® containing potassium-EDTA as the anticoagulant. Samples will be centrifuged at 3000 rpm for > 10 minutes at 4 degrees

Celsius. The collected plasma from each tube will be placed into polypropylene tubes. The samples will be stored on dry ice within 2 hours of collection. At the earliest opportunity, the study nurse will transport the samples from the NWTHS room to TTUHSC's -80 freezer. Periodically, when enough samples have been collected for a shipment, they will be sent (by an individual who has completed IATA training) frozen (on dry ice) to the laboratory coordinator at the FDA. The shipment will be sent overnight by FedEx. All samples will be de-identified prior to being sent to the FDA.

12. Subjects will receive standardized meals at post-dose hours 4.5 and 9.5. NWTHS cafeteria will provide the meal from their in-patient menu. An example meal would be one fried egg, one slice of Canadian bacon, one buttered English muffin, one serving of hash brown potatoes, one slice of American cheese, eight ounces of whole milk, six ounces of orange juice = 790 calories, with 17% of the calories from protein, 34% from carbohydrate, and 49% from fat. Meals/beverages will be free of grapefruit products, xanthine, and caffeine. Intake and output will be recorded on the I&O sheet. Vital signs will be taken and recorded pre-dose Hour 0 and post-dose Hours 1, 5, 8, and 24, and at the discretion of research staff.
13. A washout period of at least 15 days is required between treatments, after which, this same process will be followed for the Wellbutrin or bupropion product.
14. Upon conclusion of this cycle at the end of the full study, the study nurse will obtain a final urine sample from females for the pregnancy test.

Data Management:

Name of form	Description	Completed by	When completed	Where it will be completed/stored
Master Key	to track participants, his/her subject number, appointment dates	approved study support staff	when the informed consent is signed	in the CRU in a locked cabinet
Information to Subjects	for the subject to take home as reference for future appointments and what food and drinks to avoid	study nurse	for the 1st cycle info sheet: after the ICD visit for the 2nd cycle info sheet: after visit 5	given to subjects
Physician Checklist	form the Dr will use to confirm eligibility and record health status of the subject	study physician	completed when the study physician completes the history and physical	completed at TTUHSC and kept in each subject's file, locked in the CRU cabinet
Health History Questionnaire	used to record the health status/history of the subject	study nurse	completed at the same visit as the ICD and/or physical – completed 1 time	completed at TTUHSC and kept in each subject's file, locked in the CRU cabinet

Flowsheet	record vital signs and nurses notes	study nurse	throughout the 24-hour stay at NWTHS	completed at NWTHS and kept in each subject's file, locked in the CRU cabinet
Phone Script	for use when potential subjects call to get information about the study	TTUHSC personnel (all approved study members) answering the phone	throughout the study	TTUHSC
I&O	to record the intake and output of subjects during the 24-hour stay at NWTHS	study nurse	throughout the 24-hour stay at NWTHS	completed at NWTHS, kept in each subject's file, locked in the CRU cabinet
Call Log	to record telephone conversations for tracking purposes (# of people who call with interest in the study, general description of enrolled subjects calling with questions/ problems). The information recorded will not be used for any other purpose beyond this research study.	TTUHSC personnel (all approved study members) answering the phone	throughout the study	TTUHSC
Specimen Log	to record the date, time, and timing of processing/storing the blood	study nurse	during each 24-hour period at NWTHS	At TTUHSC after the 24-hour period at NWTHS
Freezer Log	to record the temperature of the freezer and to log sample storage/shipping	study nurse	throughout the study	CRU
Sample Record	to record the timing and procedure of collecting blood samples	study nurse	throughout the study	At NWTHS and at TTUHSC, depending on where the blood is drawn. Forms will be stored in a CRU locked cabinet.

Subject Incentive Payments:

Each subject will receive a total of $500 for completing the study.

For completing each of the 24-hour periods, the subject will receive $100. For each of the blood draws at hours 36, 48, and 60, the subject will receive $25. For each of the two 72-hour blood draws, the subject will receive $75. Payments will be via check through the TTUHSC direct pay system.

Safety Monitoring:

Twenty-four hour medical supervision is to be provided by personnel qualified to provide emergency medical care during confinement. Use of prescription medication, oral contraception, or contraception implants is not allowed within 30 days of drug administration, and depot injection of a progestogen drug is not allowed within 1 year of drug administration. A urine pregnancy test is to be performed for each female subject prior to drug administration in each period and at the conclusion of the study. Vital signs (blood pressure and pulse) are to be monitored at pre-dose Hour 0 and post-dose Hours 1, 5, 8, and 24, and at the discretion of the research staff. If emergency care is necessary, one of the co-investigators (TTUHSC physicians) will be consulted. All co-investigators on this study have privileges at NWTHS. If the co-investigator determines emergency care is required, the subject will be referred/admitted to NWTHS. If a subject experiences a significant side effect due to the drug, the subject is required to remain in the hospital for a period of up to 3 days or until the symptoms clear. Study personnel and the on-call MD who decided on the subject's care will confer with Drs. Hale and Khan to determine whether or not the event was related to the study. Study personnel will report adverse events to the IRB and the FDA.

The Health History Questionnaire administered during the screening process seeks responses regarding mental health status, depression, and suicidal ideation. If participants answer "yes" to any of those questions, they will be referred to their primary care provider. If they do not have one, they will be referred to Dr. Egerton, Family Medicine.

Reporting:

The following adverse events will be reported to the FDA:

- Headache (including migraine)
- Infection
- Abdominal pain
- Asthenia
- Chest pain
- Pain
- Fever
- Hot flashes
- Dry mouth

- Palpitation
- Flushing
- Hypertension
- Hypotension
- Nausea
- Constipation
- Diarrhea
- Anorexia
- Vomiting
- Dysphagia
- Appetite increase
- Dyspepsia

Statistical Analysis:

Statistical Analysis:

None. Standard pharmacokinetic parameters (AUC, Cmax, and Tmax) of the parent drug and the major two metabolites will be determined and compared. Depending upon the results of this pilot study, a sufficiently powered and full-blown study will be carried out to demonstrate the bioequivalence of the two products. The pk parameters of the test and reference products will be compared by descriptive statistics such as their mean values, coefficient of variations, and the ranges. Further, a 90% Confidence Interval (CI) will be determined for ratio of the test/reference of three PK parameters LnAUCt, LnAUCinf, and LnCmax.

No sample size justification was provided, because it is a pilot study.

Samples will be processed and analyzed by the Food and Drug Administration in the Division of Product Quality Research, Building 64 at White Oaks. A validated ultra performance liquid chromatography mass spectrometry (UPLC-MS) bioanalytical method will used for determination of bupropion and its major metabolite concentrations in human plasma samples. Bupropion, its three metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, and its internal standard (IS) n-methyl buproprion, will be extracted from human plasma on cartridge solid phase extraction (SPE) columns. After extraction, filtered samples will be placed in amber UPLC vials and analyzed following automated injection on a Waters Acquity UPLC. Separation will be achieved on a Waters Acquity BEH C-18, reverse phase, 2.1 × 100 mm, 1.7 micron particle size column equipped with a Waters Acquity BEH C-18, 2.1 X 25 mm security guard cartridge. A temperature-controlled (30°C) gradient elution method will be employed utilizing a mobile phase of 10–25% acetonitrile/5 mM formate buffer, pH = 3.2 at a flow rate of 0.4 ml/min. for 3.5 minutes. The injection volume will be 4 µl UV detection of bupropion and its IS will be achieved at 254 nm. Detection and quantitation will be achieved on a Waters single quadrupole (SQ) mass spectrometer using electro-spray ionization in the negative and positive modes. Sample,

chromatographic, and MS data will be analyzed using Waters Empower2 chromatographic control software.

Protection of Confidential Information:

Consent procedures will take place in the CRU or a private room at TTUHSC. Only research team members will be authorized to consent subjects. All PHI and research data will be maintained in a secure location in an office that requires a key for entrance. Study documents with identifiable data (such as the consent forms) will be stored in locked files. Only the research support staff, the Principal Investigator, and the co-investigators will have access to study records. Study-related data will be maintained on password-protected computers. The study data or test results will be part of a research record separate from the subject's medical record.

Blood samples drawn will be de-identified prior to being sent to the Federal Drug Administration (FDA). They will be marked only with "TTU FDA," the subject's assigned study number (the master key maintained in a locked cabinet at the CRU will be the only means of linking these study numbers to individuals), the date and time the sample was obtained, and the initials of the phlebotomist/nurse drawing the sample.

References

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2. Generic drug equality questioned: ConsumerLab.com finds generic antidepressant behaves differently from original drug. May explain complaints by patients. The People's Pharmacy. October 12, 2007. Avalable at www.peoplespharmacy. Accessed July 7, 2008.
3. Review of therapeutic equivalence generic bupropion XL 300 mg and Wellbutrin XL 300 mg. U.S. Food and Drug Administration. Available at www.fda.gov/cder/drug/infopage/bupropion/TE_review.htm.
4. FDA Consum. 2007 Mar-Apr;41(2):4. Generic version of Wellbutrin XL.