# Randomized, Placebo-Controlled, Double Blinded Clinical Trial of Bupropion (*Wellbutrin) vs. Venlafaxine (*Effexor) for the Treatment of Hot Flashes in Men undergoing Androgen Ablation Therapy for Prostate Cancer

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## A. Study Purpose and Rationale

Hot Flashes pose a significant clinical problem worldwide in men who are undergoing androgen deprivation therapy with gonadotropin releasing hormone analogues, oral anti-androgens, and/or surgical bilateral orchiectomy. Previous research studies and anecdotal information suggested that low-dose, sub-therapeutic antidepressants Venlafaxine (1) and Paxil (2) may assist in minimizing this clinical problem. These studies used anti-depressant medication at subtherapeutic doses, which may or may not have had an antidepressant effect. This study will compare these medicines using lowest possible effective dose to measure whether or not an antidepressive effect is taking place as well as relief of hot flashes. We will also be measuring improvement or decline in sexual function.

## B. Study Design and Statistical Analysis

The study will be a randomized controlled trial, double blinded study without crossover between groups. There will be three arms including Venlafaxine, Bupropion, and Placebo.

### a. Statistical Analysis

Analyses will be performed on an intention to treat basis. Mean hot flash score for each treatment group will be compared using two-sided t-tests. There could also be a scatter plot in the analysis.

### b. Power

Power calculations based upon published data for patients taking low dose venlafaxine indicated that 12 patients were required in each treatment group to detect a reduction a greater than 50% reduction in severe hot flashes per day with 80% power. Recalculating power based upon a more modest reduction of 25% of sever hot flashes indicated that 42 patients were required in each treatment group with 80% power using an unpaired t-test and a 2 sided significance level of 5%.

## C. Study Procedure

There will be no procedures performed in this study.

The study will last 10 weeks total. The first two weeks will have the entire 3 arms, pre-randomization and they will be recording hot flash score, depression score, and sexual function score via three separate tools. After 2 weeks the group will be randomized according to severity of depression, with subjects meeting clinical depression criteria being excluded from the study and referred for medical aide.

Subjects will be recording each hot flash and it's severity (mild, moderate, severe) via an electronic tool being designed for palm pilot use. The tool will generate a daily hot flash score and save daily data.

Depression will be screening via the Zung Self-Rating Depression Scale
http://www.counselingpros.com/zung-scale.pdf (provided in an addendum)

Each subject will take the screening tool and obtain a score at the beginning of the study. Scores greater than 50 are consistent with clinical depression and these subjects will be excluded from the study. Subjects scoring 40-49 will undergo a second tool (NYU online depression screening test -

http://www.med.nyu.edu/psych/screens/depres.html (provided in an addendum). If rated either significant or prominent with this tool, they will be excluded as well. The excluded subjects will be referred for counseling and assistance.

Sexual function will be measured via screening tool called the brief male sexual function inventory. This instrument covers sexual drive (two items), erection (three items), ejaculation (two items), perceptions of problems in each area (three items), and overall satisfaction (one item). Sexual function will be measure at the beginning and end of the study. (Provided in an addendum)

**D. Study Drugs**

1. Bupropion XL will be given by mouth at 150mg daily for the 8 weeks of the study to the first arm. This is an FDA approved treatment for depression and smoking cessation. The most common side effects of Bupropion XL are weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.
2. Venlafxine XR will be given by mouth 75 mg daily for the 8 weeks of the study to the second arm. This is an FDA approved medication for the treatment of depression. The most common side effects are Anxiety, constipation, delayed orgasm, depression, difficulty breathing, dizziness, dry mouth, itching, loss of appetite, loss of strength, nausea, nervousness, problem urinating, sedation, skin rash, sleepiness / sleeplessness, sweating, tingling hands / feet, tremors, vomiting, unusual dreams, weight loss, or weakness.

**E. Medical Device**

There will be use of no medical devices in this study.

**F. Study Questionnaires**

1. The electronic tool for tracking number and severity of hot flashes is still in development

2. The Zung Self-Rating Depression Scale is available at http://www.counselingpros.com/zung-scale.pdf (provided in addendum)

3. The NYU online depression-screening test is available at http://www.med.nyu.edu/psych/screens/depres.html (provided in addendum)

4. The brief male sexual function inventory from Journal of Urology Vol 46 issue 5: please see the section on study procedure for details. (Provided in addendum)

**G. Study Subjects**

**a. Entry Criteria**

- Disease Characteristics**:**
  - Histologically confirmed locally metastatic adenocarcinoma of the prostate and currently undergoing hormonal therapy used in the treatment of prostate cancer which may include the following: Lutenizing hormone-releasing hormone agonists can prevent the testicles from producing testosterone. Examples are leuprolide (Lupron), and goserelin (Zoloadex)
  - Antiandrogens can block the action of androgens (hormones that promote male sex characteristics). Two examples are flutamide (Eulexin), and bicalutamide

(Casodex). Pt's that have undergone surgical bilateral orchiectomy are also eligible.
    - Measurable or evaluable disease
    - No brain or leptomeningeal involvement
- Prior/Concurrent Therapy:
    - Not currently taking medications for depression
- Other:
    - At least 4 weeks since prior investigational drugs
- Patient Characteristics:
    - Age: 18 and over
    - Male
    - Performance status: http://www.ecog.org/general/perf_stat.html
    - ECOG 0-2
- Neurologic:
    - No prior cerebrovascular accident
    - No significant neurologic or psychiatric disorder (psychotic disorder, major depression, dementia, or seizure)
    - Not currently in medical treatment for depression
- Other:
    - No other prior malignancy within past 5 years, except:
    - No other serious illness or medical condition
    - No active infection

**H. Recruitment of Subjects**

Materials for subject recruitment are being formulated. They will consist of mailings, flyers, web-site advertisements, and phone calls.

**I. Confidentiality**

All subjects will be protected under the rules of patient-doctor confidentiality.

**J. Potential Conflict of Interest**

There are no potential conflicts of interest.

**K. Location of Study**

CUMC

**L. Potential Risks**

As described above there are a number of common side effects of both study drugs. Any reported side effects will be addressed immediately, evaluated by the study medical staff and determined whether or not the patient has the ability to continue participation in the study and/or needs some form of medical treatment

**M. Compensation**

There will be no compensation for the subjects and no costs for the subjects.

**N. Potential Benefits**

The potential benefits include a decrease in the severity of hot flashes, a decrease in the amount of depressive symptoms, and an increase in libido and/or sexual function.

You may or may not benefit as a result of participation in this study.

**O. Minors**

Only subjects age greater than 18 can participate.

**P. Radiation**

There will be no exposure to radiation or radioactive substances while participating in this study.