Effect on Body Composition with Albuterol and Caffeine versus Placebo in Adolescents: A Pilot Study

NCT02740660

Protocol Version Date: 05/05/17

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Objectives

1. To assess the change in lean body mass and fat mass with the combination of albuterol and caffeine versus placebo in obese adolescents age 12-17 years.
We hypothesize that the combination of medications will cause an increase in lean body mass and a decrease in fat mass, more than the placebo.

2. To assess the safety of the combination of albuterol and caffeine versus placebo in obese adolescents age 12-17 years.
We hypothesize that adverse events in the caffeine/albuterol group compared to placebo will be similar.

Background

Previous studies done at Pennington Biomedical have demonstrated that the equivalent of oral albuterol 4mg three times a day (tid) with oral caffeine 100mg tid reduces body fat and increases lean tissue in rodents more than the addition of the effect of the two components separately.(Liu, Arceneaux et al. 2015) The combination of albuterol with caffeine changed body composition without changing food intake. An adult male taking albuterol 4 mg orally tid plus caffeine 100mg orally tid increased lean mass by 1.25% and decreased fat mass by 1.2% over a two month period (unpublished). These effects are expected to be even greater in a growing adolescent. This pilot project will take the first step towards trying to understanding the safety and potential efficacy of this drug combination. The prospect of using inexpensive medications already approved in the pediatric population for the treatment of asthma as a novel treatment for adolescent obesity addresses a medical need that is presently unmet.

Food restriction in adolescence is not only difficult to accomplish, but it also raises concerns about growth and development. A medication approved for the treatment of obesity in the adolescent age group that improves body composition by reducing body fat and increasing lean tissue without needing to restrict food intake would be a useful tool for physicians who address the treatment of obesity in adolescents. Albuterol is a medication, approved for ages 6 and older, used for the treatment of asthma and has also been shown to increase muscle strength and lean body mass in children with spinal muscular atrophy (Skura, Fowler et al. 2008) and in healthy young men during an exercise training program.(Caruso, Hamill et al. 2005) A drug approved for the treatment of adolescent obesity that increases lean tissue, decreases fat tissue and can be given in conjunction with lifestyle modifications would be welcomed by both pediatricians who treat these adolescents and by adolescents who are stigmatized by their obesity.

A provisional patent has been submitted by Pennington Biomedical Research Center to protect the combination of caffeine and albuterol in a 1:25 ratio for synergistically

increasing muscle mass and decreasing fat mass as a potential treatment for obesity in adolescents.

Inclusion and Exclusion Criteria
Participants will come to an initial screening visit (SV) after an overnight fast of 10 hours. Consent and assent will be obtained and the inclusion/exclusion criteria below will be assessed. Screening labs (CBC; chem 26 including glucose, BUN, creatinine, sodium, chloride, potassium, carbon dioxide, uric acid, total protein, phosphorus, albumin, calcium, magnesium, total bilirubin, CPK, LDH, AST, ALT, alkaline phosphatase, GGT, amylase, iron, cholesterol, triglycerides, HDL, LDL; fasting insulin; and urinalysis with urine pregnancy test as needed) and an EKG will be done to help determine eligibility.

Inclusion
-Healthy males or females with a BMI ≥ 95th percentile
-Between 12 and 17 years of age inclusive
-Tanner Stage III and above

Exclusion
-Weigh less than 50 kg
-Have a family history of sudden death or hypertrophic cardiomyopathy
-Have a history of unexplained syncope
-Have a marked baseline prolongation of QT/QTc interval (QTc interval >450 ms), a history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome), or use concomitant medications that prolong the QT/QTc interval
-Have history of asthma, hypertension, thyroid disease, or significant neurologic disease such as seizure disorder
-Are pregnant, planning to become pregnant, or nursing. Females who are sexually active must be using adequate contraception.
-Take a medication known to affect weight or body composition like systemic glucocorticoids, atypical anti-psychotics, or weight loss medications
-Take beta-stimulators or beta-blockers on a regular basis
-Take stimulants for attention deficit disorder
-Take monoamine oxidase inhibitors, tricyclic antidepressants, or diuretics
-Take any chronic medication that has not had a stable dose for 1 month or longer
-Have type 1 or type 2 diabetes
-Have any significant cardiac disease (such as heart failure, arrhythmias, or valve disease), uncontrolled pulmonary disease, chronic liver disease, chronic kidney disease, or chronic infectious disease
-Have any significant psychiatric illness that is unstable or untreated such as bipolar disorder, severe depression, or severe anxiety
-Have a history of suicidal ideation
-Have an allergy or hypersensitivity to albuterol
-Are unwilling to discontinue caffeine-containing products while in the study
-Are deemed unfit to participate in the study based on evaluation by the medical investigator

Number of Subjects
We expect to enroll 20 adolescents to complete studies in 12 adolescents.

Recruitment Methods
The Recruitment Core is responsible for recruiting potential participants for clinical trials from a population that includes a wide range of people of various ages, ethnic backgrounds and with varying degrees of health. The PBRC recruitment team creates and implements individualized, trial-specific advertising and awareness campaigns, including mass media, traditional advertising, and novel methods including social media, digital, and email marketing. All advertising and awareness are approved by the PBRC IRB to ensure ethical and disclosure standards are met. The PBRC database may also be utilized to find potential subjects for this study.

Study Timelines
Depending on scheduling, the total duration of this study is approximately 10 weeks (including screening) with 8 weeks of treatment. Following screening evaluations, eligible subjects will be randomized to the study intervention as follows: either 8 weeks of treatment with placebo or 8 weeks with the combination of caffeine/albuterol.
The estimated length of time to complete the entire study (from enrollment of the first subject to completion of the last subject) is 6 months with study analysis to be complete 6 months after the completion of the last subject.

Study Endpoints
The primary endpoint is to assess the effect of the combination of caffeine and albuterol on fat mass and lean body mass via DXA scan in obese adolescents.

The secondary endpoints include assessing the effect of the combination of caffeine and albuterol on hunger and satiety as well as the safety of the combination of caffeine and albuterol compared to placebo.

Procedures Involved
This study will be a double-blinded, randomized, placebo-controlled, pilot study in which subjects will be randomized to receive either placebo or a combination of Albuterol 4 mg and Caffeine 100mg three times per day orally for a total of 8 weeks. Each subject will continue on the study intervention for the entire duration of treatment.

<u>Overview</u>
Prior to study entry the following procedures will be performed:
- obtain written informed consent
- record medical history
- verify conformance with entry criteria

Twelve obese adolescents will be recruited through general advertisement and physician referrals. The study will consist of 6 total study visits. The first study visit will be a screening visit and include a medical history/physical, an electrocardiogram, and screening labs. The Beck Depression Inventory will also be used to screen for depression in these adolescents. A psychologist is available on site to assess anyone whose score indicates further evaluation is necessary, and the adolescent may be referred to outside sources if deemed necessary. Adolescents who qualify will return

for a baseline visit fasting within one month of the screening visit. The adolescent will have a DXA scan for body composition as well as a Visual Analog Scale (VAS) test for hunger and satiety. A parent will complete a Vanderbilt Assessment Scale for ADHD to determine if the adolescent has any signs of attention deficit or hyperactivity at baseline. The adolescent will then be randomized to either the placebo or treatment group (Albuterol 4 mg tid and Caffeine 100 mg tid orally) in a 1:1 ratio. The albuterol and caffeine will be obtained from Spectrum Chemical, Letco Medical, or a similar approved distributor where the pharmacy acquires FDA approved medications. Albuterol is approved for the treatment of asthma in adolescents (12-18) at 4 mg three or four times a day. Starting with the baseline visit and at every 2 week visit, the adolescent and parent will meet with a registered dietitian certified in pediatric weight management. The information provided will include recommendations on healthy eating, increasing physical activity, and family participation as recommended by the Academy of Nutrition and Dietetics. At week 2, 4, 6, and 8, compliance (via pill counts) and adverse events will be assessed. At the week 4 visit, the screening labs will be repeated along with an electrocardiogram as safety measures. In addition to these assessments, at week 4 and 8, the adolescent will come fasting to clinic and having taken their morning dose of study medication. They willhave a repeat VAS scale for hunger and satiety, and a parent will fill out another Vanderbilt Assessment Scale for ADHD as a safety measure. If there are any concerns based on the Vanderbilt Assessment Scale, the intervention will be stopped and the adolescent will be referred to an appropriate health care provider for further evaluation. At the last study visit after 8 weeks of intervention, the adolescent will have an electrocardiogram, a repeat DXA, and repeat labs to compare with the screening labs. Approximately 7 days (± 2 days) later, someone from the study staff will call the participant to assess for any adverse events while off the study intervention.

Study Evaluations

The following study evaluations will be obtained at the screening visit (SV):

- Body weight, height, body mass index (BMI), vital signs
- Complete medical history and physical examination
- Beck Depression Inventory
- Standard 12-lead EKG
- Urinalysis
- Labs including fasting insulin, Chemistry 26 and CBC (~7.5 mL or 1.5 teaspoons of blood)
- Collection of concomitant medications

The following study evaluations will be obtained at the Baseline visit:

- Body weight, height, body mass index (BMI), vital signs
- Family weight management counseling
- Pregnancy test (if applicable)
- DXA scan for body composition
- Randomization to either study intervention
- Dispensing of study medication
- Visual Analog Scale for hunger and satiety
- Vanderbilt Assessment scale for ADHD
- Collection of concomitant medications

The following study evaluations will be obtained at the Week 2 visit

- Body weight, height, body mass index (BMI), vital signs
- Collection of concomitant medications
- Family weight management counseling
- Dispensing and collecting study medication
- Assessment of tolerability and compliance (via pill counts)
- Assessment of adverse events

The following study evaluations will be obtained at the Week 4 visit

- Body weight, height, body mass index (BMI), vital signs
- Collection of concomitant medications
- Family weight management counseling
- Dispensing and collecting study medication
- Assessment of tolerability and compliance (via pill counts)
- Assessment of adverse events
- Visual Analog Scale for hunger and satiety
- Pregnancy test (if applicable)
- Urinalysis
- Labs including fasting insulin, Chemistry 26 and CBC (~7.5 mL or 1.5 teaspoons of blood)
- Standard 12-lead EKG
- Vanderbilt Assessment scale for ADHD

The following study evaluations will be obtained at the Week 6 visit

- Body weight, height, body mass index (BMI), vital signs
- Collection of concomitant medications
- Family weight management counseling
- Dispensing and collecting study medication
- Assessment of tolerability and compliance (via pill counts)
- Assessment of adverse events

The following study evaluations will be obtained at the Week 8 visit

- Body weight, height, body mass index (BMI), vital signs
- Collection of concomitant medications
- Family weight management counseling
- Collecting study medication
- Assessment of tolerability and compliance (via pill counts)
- Assessment of adverse events
- Pregnancy test (if applicable)
- Urinalysis
- Labs including fasting insulin, Chemistry 26 and CBC (~7.5 mL or 1.5 teaspoons of blood)
- DXA scan for body composition
- Standard 12-lead EKG
- Visual Analog Scale for hunger and satiety
- Vanderbilt Assessment scale for ADHD

The following study evaluation will be done at Week 9 over the phone

- Follow up with the participant, or participant's parent(s)/legal guardian if participant is a minor, to assess for any adverse events that may have occurred after stopping the intervention.

Study Procedures

Whole Body DXA scan (Baseline and Week 8)

This scan measures the amount of bone, muscle, and fat in your body. The scan will be performed using a whole-body scanner. You will be required to wear a hospital gown, to remove all metal-containing objects from your body, and to lie down on the table. A scanner emitting low energy X-rays and a detector will pass along your body. The scan takes approximately 5 to 10 minutes. You will be asked to remain completely still while the scan is in progress. This scan is for research purposes only and not for diagnostic treatment.

Study Schedule

Procedures	**SV**	**Baseline**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 9**
Inclusion/Exclusion, Consent and Assent	X						
History and Physical	X						
Beck Depression Inventory	X						
Weight, height, vital signs	X	X	X	X	X	X	
Collection of concomitant medications	X	X	X	X	X	X	
Family weight management counseling		X	X	X	X	X	
DXA scan for body composition		X				X	
Screening labs: blood draw	X			X		X	
Screening labs: urinalysis	X	X		X		X	
Urine pregnancy test (if applicable)		X				X	
EKG	X			X		X	
Dispense and collect medications		X	X	X	X	X	
Tolerability and compliance (pill counts)			X	X	X	X	
Adverse events			X	X	X	X	
Randomization to treatment sequence		X					
Visual Analog Scale for hunger and satiety		X		X		X	
Vanderbilt Assessment scale for ADHD		X		X		X	
Follow up phone call							X

Each visit has a window of ± 2 days

Power analysis
This is a pilot study and no power analysis was calculated. Data from this study may be used to power a larger study.

Data and Specimen Management
The data management will be conducted by the Pennington Biomedical Research Computing Group. There will be limited access to all data including locked cabinets for paper files and password protected computers for electronic data.
Each participant will be issued an ID number that will be utilized throughout the study. A secure master file linking names, addresses and ID numbers will be maintained in a confidential computer file accessible only to the investigators. Access to data files can be made only with permission of the Principal Investigator. Privacy in the context of this study includes confidentiality of data and personal information. During interviews, measurements, and other study-related activities, the study staff will ensure full privacy of participants and will ensure that the data are stored in a secured area. All study staff must be HIPAA certified.

Statistics
Comparisons will be made between the control and intervention groups using chi-squared tests to compare categorical data and t-tests to compare means with 2 time points and analysis of variance for end points with repeated measures with a significant p value of ≤ 0.05.

Provisions to Monitor the Data to Ensure the Safety of Subjects
Participants and their parents will be instructed on symptoms that should prompt them to contact the site or seek medical attention, such as palpitations or lightheadedness. Adverse events will be monitored every 2 weeks at each study visit. The PI and his co-investigator will review lab data on a regular basis throughout the study (screening, Week 4, and Week 8) to ensure the safety of each subject. Any significant health problems coming to our attention during the study will be referred to the participant's usual source of medical care, with his/her parents' permission.
A formal IND application has been filed with the FDA and in addition to the reporting requirements set forth by the IRB, additional responsibilities include:
-Reporting any unexpected fatal or life-threatening suspected adverse reactions to the FDA no later than 7 calendar days after initial receipt of the information
-Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA and to all investigators no later than 15 calendar days
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin)

Withdrawal of Subjects
During the course of the study, participants may be withdrawn from the study for the following reasons:

- Unwillingness to participate in the study or cooperate with study staff

- Presentation of significant medical symptoms or abnormal findings such as a prolonged QTc that would warrant termination of study participation to protect the participant's safety

Data that have already been collected during the course of study participation from a withdrawn participant will be used, unless a specific request is otherwise received. Subjects will be notified of their withdrawal via telephone or mail.

Risks to Subjects

General: More serious risks and adverse effects may occur than those listed below. The combination of caffeine and albuterol has not been well studied and adverse effects may be additive or synergistic with the combination. There may be more risks of ingesting additional caffeine products (such as coffee, tea, Coke® , or Red Bull®) and alcohol while in the study. A list of caffeine-containing products to avoid during the study will be provided as a reference. If a dose is missed, the participant should not double up on the dose because of the possible risk of adverse effects.

Caffeine: This can be found in a variety of foods and beverages. Caffeine is a stimulant and may cause increased heart rate, alertness, tremor, and difficulty sleeping.
Albuterol: This is a prescription medication that is approved for use in treatment of asthma in children as young as 6 years of age. The most common side effects include: nervousness, tremor, headache, tachycardia, and palpitations.

Blood Draws: There is the possibility of infection and/or pain and bruising at the vein on your arm where the needle is inserted. Aseptic (sterile) technique and trained personnel minimize these risks.

Electrocardiogram (EKG or ECG): There are minimal risks associated with this test. There is a small possibility there may be some redness or irritation while cleaning the skin prior to applying the electrodes or if you happen to be allergic to the adhesive on the electrodes.

Whole Body DXA scan: The amount of radiation used for this procedure is very small. The radiation dose for this scan is equivalent to the radiation you are naturally exposed to in the environment in less than one day. Scans will not be performed on any subject who is pregnant, and all females will be provided with a urine pregnancy test prior to the scan.

Visual Analog Scale for hunger and satiety: This is a well-validated scale to assess hunger and satiety and carries little to no risk.

Vanderbilt Assessment scale for ADHD: There is little to no risk in filling out this questionnaire. This is used by pediatricians and parents to identify a child's risk for attention deficit/hyperactivity disorder. This will serve as an additional safety measure and will be obtained at baseline and then every 4 weeks.

Potential Benefits to Subjects

While in the study, participants may demonstrate an improvement in body composition with decrease in fat mass and increase in lean body mass. These changes may not be sustained once the participant stops the intervention.

Vulnerable Populations
Adolescents between the ages of 12 and 17 who are in the midst of puberty will be enrolled in the study. All participants will be provided with an age appropriate assent form in additional to the parental consent form. All questions and concerns will be addressed by the study staff.

Sharing of Results with Subjects
Individual participant results will not be provided; however, results from the study will be submitted for manuscripts in scholarly journals and presentations. All study reports will present only aggregated data to minimize the risks that a participant can be identified form their participation in the study. As required by the FDAAA this study will be registered on ClinicalTrials.gov.

Setting
Potential participants will be recruited utilizing the recruiting services (Recruitment Core) of the PBRC. All research procedures will be performed at the PBRC, namely, in the Outpatient Clinic.

Resources Available
Pennington Biomedical Research Center has had a good track record with recruiting a population of overweight/obese adolescents for a variety of intervention studies. Potential participants come from a variety of sources such as traditional advertising, physician referral, word of mouth, etc.
The clinical research staff are well trained and have to undergo a variety of certifications before performing assessments on study participants.
Medical personnel are available onsite to conduct study visits as well as oversee any adverse events. Psychologists are available on call should the need arise for further evaluation based on screening inventories or other assessments.
Prior to the opening of the study, a start up meeting is held with all of the relevant clinical cores to ensure that proper coordination is in place prior to the first screening visit.

Compensation
Each participant will receive $25 after the completion of the baseline visit, week 2, week 4, and week 6 visits, and $50 after the week 8 visit for a total of $150.

Provisions to Protect the Privacy Interests of Subjects
All attempts will be made to maintain a subject's privacy. Safeguards such as password protected computers and networks have been put in place in order to limit access to subject data. These data will be maintained until the results may be published and will only be accessible by study personnel.
Subjects will be given ample time to read over the consent, ask questions, and agree to participate in the research study. Subjects may decline answering questions they are

not comfortable with. Each procedure will be explained to the subject before it is performed.

Compensation for Research-Related Injury
No compensation will be provided for research-related injury.

Economic Burden to Subjects
All study-related tests and procedures will be at no cost to the subject. The subject will incur transportation costs in getting to PBRC.

Consent Process
The P.I. or one of the designated clinic staff will obtain informed consent from the parent/guardian and separate assent from all of the minor participants in the outpatient clinic during the screening visit. Ample opportunity will be given for the parent/guardian and the minor participant to review the consent/assent and to ask any questions prior to signing any forms.
A parent/guardian is to provide his or her identification along with the child's birth certificate in order to verify the relationship to the minor participant.
As a greater than minimal risk study with the prospect of direct benefit, one parent may provide consent for the minor participant to engage in the study.

Drugs or Devices
Both interventions will be stored in the research pharmacy located in the outpatient clinic. This is locked at all times and only accessible to limited personnel via a key card. The research pharmacist will maintain an inventory of study drugs. Appropriate dispensation of study drug will be confirmed with a second clinic staff member to ensure correct drug is being provided to the correct participant.