Study Protocol and Statistical Analysis Plan
For Research Project:
"Double-blind randomized placebo-controlled trial of the efficacy of the Apollo System for children with ADHD"

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Abstract: The objective of this project is to understand the potential therapeutic benefits of the Apollo System for children with ADHD. Using vibrational therapy, the Apollo System has been previously demonstrated to promote greater balance of the autonomic nervous system. Given the importance of the autonomic nervous system for modulating levels of physiological arousal and in-turn governing aspects of attention and self-regulation; a therapeutic approach to promote better balance of this system may be particularly beneficial for populations such as children with ADHD. Accordingly, using a double-blind randomized placebo-controlled design this investigation will assess the extent to which the Apollo System is effective in reducing symptomatology associated with ADHD.

Aims:

1) To provide a preliminary assessment of the efficacy of the Apollo System for reducing behavioral symptomatology associated with ADHD.

2) To provide a preliminary assessment of the efficacy of the Apollo System for reducing cognitive symptomatology associated with ADHD.

Number of subjects: 100 children with ADHD.

Design: Double blind, placebo controlled Phase 2 clinical trial using serial stratification randomization accounting for biological sex, age, and ADHD symptomatology.

Interventional Study Model: Parallel — Participants are assigned to one of two groups in parallel for the duration of the study.

Study Population: The sample consisted of children ages 8 to 17 (inclusive) years of age with ADHD from the mid-Michigan, USA area.

Eligibility Criteria:

Criteria for inclusion: All individuals that agreed to participate were selected on a first come, first serve basis. No individual was turned down due to sex, race, or ethnicity. The following inclusion criteria exist for all participants:

a. Participants must be 8 years of age or older and under the age of 18.
b. Participants must have diagnosed or suspected ADHD.
c. Participants must have one of the following: 1) on the same treatment plan for over a year with minimal symptom relieve or alleviation, 2) tried two or more treatment approaches but is unable to meet treatment goals, 3) taking medication but still has symptoms, or 4) unwanted or uncontrollable side effects related to the medication.
d. Participants must have normal or corrected-to-normal vision in order to complete the cognitive task.

Exclusion criteria: The following exclusion criteria exist for all participants:

a. Lack of consent.
b. Participants cannot have started a new treatment within the last 30 days.
c. Participants cannot have a history of hydrocephalus, PDD/ASD, schizophrenia, conduct disorder, ODD, active substance abuse, or be on a beta blocker.
d. Participants cannot have previously used the Apollo System.

Recruitment: Participants were recruited from the mid-Michigan community population via social media and list-serve announcements.

Protocol: This investigation was approved by the Michigan State University Human Research Protection Program.

Prior to enrollment participants must complete a screening survey. Participants who pass the screening survey will be contacted to participate in the study.

Pretest: Following consenting for their child to participate — and the child assenting to participate — parents/guardians will be asked to complete a series of questionnaires. Concurrently, participants will complete a series of questionnaires and then a brief cognitive assessment.

Participants who were eligible to continue in the study were then randomly assigned using a serial stratification approach accounting for biological sex, age, and ADHD symptomatology to either the active experimental group or the control experimental group. Participants were told that all participants would receive an Apollo System device, but that half of the devices would use the current pattern of vibrations used in the commercial Apollo System device whereas the other half would use a new ultra-low frequency pattern of vibrations in order to see how different patterns of vibrations vary in their effectiveness.

Experimental arm. The active experimental group received the commercial Apollo System device.

Sham comparator arm. The control experimental group received a placebo device that looked and felt like the commercial Apollo device.

Intervention. Participants were instructed to use the devices at least three times per week for a period of 8 weeks.

Posttest: At the end of the 8 week study period, participants and their parent/guardian completed the same measures as were completed at the start of the study.

Primary Measures:

ADHD-5 Rating Scale: ADHD symptomatology was assessed using the ADHD-V rating scale. The ADHD-V rating scale is a subjective assessment of the frequency of ADHD-related behaviors on a 4-point Likert scale ranging from 0 (never or rarely) to 3 (very often) across 18 items. The behaviors included in the survey are derived from the diagnostic criteria for ADHD established in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Scores are summated into inattentive and hyperactive-impulsive symptom domains and transformed into symptom percentile scores based upon normative data based on age and biological sex. Overall ADHD percentile will be considered as the primary outcome.

Interference subdomain of Inhibitory Control: Interference control was assessed using a version of the Eriksen flanker task. Participants were instructed to attend to and to respond as accurately as possible to a centrally presented stimulus nested amid either congruous or incongruous flanking stimuli. Reaction time was quantified within each congruency as the mean speed of responding following the onset of the stimulus only for correct trials. Response accuracy was quantified within each congruency as the proportion of correct responses relative to the number of trials administered. Given the age group, response accuracy will be considered as the primary outcome.

Response inhibition subdomain of Inhibitory Control: Response inhibition was assessed using a Go/Nogo task. Participants were instructed to attend to and to respond as quickly and as accurately as possible to a target stimulus and to not respond to the no-go stimulus. Reaction time was quantified as the mean speed of responding following the onset of the target stimulus only for correct trials. Response accuracy was quantified as the proportion of correct responses relative to the number of trials administered for target stimulus trails and nogo stimulus trials separately. Response accuracy to the nogo condition will be considered as the primary outcome.

Aims Assessment:

1) *To provide a preliminary assessment of the efficacy of the Apollo System for reducing behavioral symptomatology associated with ADHD.*

   This aim was satisfied by examining device (active vs placebo) by time (pretest vs postest) interactions for the ADHD-5 rating scale composite scores.

2) *To provide a preliminary assessment of the efficacy of the Apollo System for reducing cognitive symptomatology associated with ADHD.*

   This aim was satisfied by:

   a) Examining device (active vs placebo) by time (pretest vs postest) interactions for the Interference subdomain of Inhibitory Control. Given the age group, response accuracy will be considered as the primary outcome.

   b) Examining device (active vs placebo) by time (pretest vs postest) interactions for the Response inhibition subdomain of Inhibitory Control. Response accuracy to the nogo condition will be considered as the primary outcome.

Statistical Analysis Plan:

Data will be analyzed using multi-level modeling as this approach is robust to unbalanced data (i.e., missing observations if any occur) and accounts for a number of sources of variability. Analyses will be conducted with $\alpha = 0.05$ and Benjamini-Hochberg false discovery rate control = 0.05 for post-hoc decompositions. Dependent variables from each primary outcome will be separately assessed using a 2 (Device: active, placebo) × 2 (Time: pre-test, post-test) univariate multi-level model including the random intercept for Participant and Participant by factor interactions.