Double blind placebo controlled study to examine the effects of "WakeUp" herbal beverage on attention and function in children with ADHD

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Approvals

Sponsor / יוזם המחקר

Name: Eli Faragi, CEO Signature: _____ Date: _____

Principal Investigator Agreement:
I have carefully read and understood the provisions of this protocol and I am prepared to follow them in every detail in the conduct of this study.

Principal Investigator / החוקר הראשי

Name: Giora Pillar Signature:_____ Date: _____

Protocol Synopsis:

Protocol Number:	**WU ADHD 2020**
Study Title:	Double blind placebo controlled study to examine the effects of "WakeUp" herbal beverage on attention and function in children with ADHD
Study Duration:	Approximately 8 months (from first subject admission to last subject completion of study)
Study Population:	30 boys with ADHD aged 6-18 years
Study Objectives:	Primary Objective • Efficacy - Assess whether WakeUp beverage administered to children with ADHD improves alertness attention and function, compared to placebo Secondary Objective • Safety & Tolerability – approve the safety and tolerability of WakeUp beverage administered to children with ADHD including assessment of blood pressure and pulse rate compared to placebo
Study End Points:	Primary Endpoints ▪ Objective findings from TOVA tests results: Response time variability (consistency); Response time (speed); Commissions (impulsivity), and Omissions (focus and vigilance) Secondary Endpoints ▪ Subjective assessment of attention and vigilance (VAS scale) ▪ Adverse events and beverage-related adverse events including change in blood pressure or pulse rate
Study Design:	This is a single center, double-blind, placebo controlled clinical trial comprised of a single drink of WakeUp beverage compared to placebo given to children with ADHD. Participants will be randomized regarding the order of the beverage (placebo or Wake Up). Thirty boys with ADHD will be included. They will be studied 2 times, in a 1-21 days period, at a similar hour. During each day of the study, the participants will fill a questionnaire including VAS for attention and vigilance, undergo pulse and BP measurements, and undergo TOVA test, prior to and 1 hour following beverage (either Wake Up or placebo).
Assessment Tests	Each set of assessment tests will consist of the following measures: Blood pressure and pulse rate measurements Subjective assessment of vigilance and attention on a visual analog scale TOVA Test (Test of Variables of Attention) Adverse event analysis
TOVA Test (Test of Variables o Attention)	A subject performs the TOVA test on a laptop computer. The following tests will be performed and calculated: **Response time variability (consistency)** **Response time (speed)** **Commissions (impulsivity)** **Omissions (focus and vigilance)** The data will be assessed by an experienced personnel, and the results collected in a data sheet in Microsoft Excel.
Number of Subjects:	30 children with ADHD recruited via ADHD clinics
Inclusion/Exclusion Criteria:	**Inclusion Criteria:** 1. Boy aged 6-18 years, diagnosed with ADHD 2. Agree to be off medications for 2 days prior to each day of study

	3. Volunteers and a parent who are willing and able to sign the informed consent **Exclusion Criteria:** 1. Children aged less than 6 years, or adults over 18 years. 2. Subjects participating in another study 3. Subjects who are unable to comply with the study procedures. 4. Patients in an unstable medical condition. 5. Patients who are treated with sedating or stimulant medications and cannot discontinue them for 2 days prior to each day of study 6. Subjects who have drunk or eaten any caffeine-containing beverage or food after 7:00 in the morning of any test day 7. Any reason that, in the opinion of the investigator, may make the subject unfit for this clinical trial
Statistical Considerations:	The primary and two secondary endpoints will each be analyzed and compared between the study conditions: placebo or WakeUp. One-way ANOVA and student's T-Tests will be utilized to search for statistically significant differences between the study responses to placebo or WakeUp. (Paired T-Tests will be performed for coparing between the results of individuals prior to and following beverage, and between the responses to placebo versus WakeUp). Reports will consist of differences from baseline and between each beverage. All effectiveness analyses will be two-sided at the 5% level of significance.

Introduction

Background

Attention deficit hyperactive disorder (ADHD) is a common disorder, affecting approximately 3-7% of children (1,2). It consists of symptoms such as poor sustained attention, distractibility, hyperactivity, impulsiveness, and irritability. These behavioral deficits arise relatively early in childhood, typically before the age of 7, and may persistent over time (3,4). The etiology of the disorder has not been fully clarified. Abnormalities in the structure and function of the prefrontal cortex and its networks with other brain regions (5,6), as well as catecholamine dysregulation, with dopaminergic dysfunction, in particular, and norepinephrine, indirectly (7), have been suggested.
Several studies have addressed potential sleep problems in ADHD children. Although sleep complaints are commonly reported in these children (8), the nature of their association is not clear (9). Traditionally, ADHD was considered as a problem of over-alertness, nervousness, with the affected child being fidgety and over-stimulated. However, for more than 60 years it is well known that, paradoxically, stimulating medications result in improvement in the majority of children, by reducing their ADHD symptoms (10). Stimulants are the most effective agents for children and adults with ADHD, with ~80% of individuals responding favorably (11).
It has been well documented that sleepy children, unlike adults, may demonstrate hyperactivity and attention deficit behavior rather than excessive daytime somnolence (12,13). Experimental sleep restriction has reported to be associated with ADHD-like behavior and poor cognitive achievements (14,15).

Indeed, we have previously shown that children with ADHD are in fact sleepy during the day rather than hyper-alert (16). Therefore, this can explain the favorable response to stimulants or wake promoting agents. However, these medications may have quiet many side effects and many families decide to avoid them (17). Thus, a herbal-naturally based wake promoting beverage which has so far been studied on over 200 adults and had no side effects, may be a reasonable alternative for these children.

WakeUp beverage and previous results

The relatively newly developed "WakeUp®" beverage (InnoBev Ltd, Tel Aviv, Israel) is a wake-promoting nutritional supplement based on herbal extracts of guarana, ginkgo biloba, elderberry and Fruit-up. It has been previously shown that guarana improves memory performance, mood and increases alertness [18]. Extracts of ginkgo biloba are used in herbal medicine for asthma and cardiovascular disease and have been shown to have favorable effects on memory [19].The main active constituents of ginkgo are considered to belong to two distinct chemical groups: the biflavone glycosides and a sesquiterpene trilactone bilobalide. Most of the pharmacological and clinical work carried out on ginkgo has used an extract containing both of these classes of compounds, and it has been shown that such extracts are antioxidants and vasodilators and can increase cerebral blood flow in animals. Extracts also possess neuroprotective potential, thought to be mediated via inhibition of nitric oxide synthesis [19].The "Fruit-up" (which is a fruit extract containing predominantly fructose) predominantly adds taste to WakeUp, although its glucose content may also improve alertness [20]. In a previous study, we examined whether WakeUp may improve vigilance and function following lunch, compared to caffeine and placebo, and tested the duration of the effect (30 and 120min following drinking it). We found that drinking "WakeUp following lunch improved short-term memory and function similarly to caffeine, but better than placebo, and that the effect was be longer with WakeUp compared to caffeine. While drinking WakeUp after lunch improved vigilance and performance similarly to caffeine and significantly better than placebo 30min following the drink, 120min following the drink, performance and vigilance with WakeUp remained high, significantly superior to both placebo and caffeine[21].
We found that while Caffeine affected blood pressure and pulse rate, WakeUp had no such an adverse effect [21]. WakeUp was not associated with increased pulse and blood pressure in the short term (as opposed to caffeine). Thus, we concluded that WakeUp appears to be an appropriate and effective wake promoting beverage. In a later study (unpublished), we tested a continuous daily dose WakeUp every day after lunch for 30 days in 95 participants, and found that there was no tolerance to one daily dose of this beverage, for at least 30 days. Furthermore, we have also tested in a small group of participants twice daily drink of WakeUp (morning and evening) and found it was still effective in both times as a wake promoting beverage (unpublihed data). Thus, the "Wake-up" beverage is a wake promoting nutritional supplement based on herbal ingredients consisting of standard extracts of Guarana, Ginkgo Biloba, elderbery and fruit-up. It was so far tested on over 200 participants and no side effects were reported. However, it has not yet been studied in children with ADHD. Therefore, the current study is aimed at testing the effect of WakeUp beverage on attention and function of children with ADHD, utilizing a controlled and double blind methodology.

Study Rationale

Since children with ADHD are sleepy during the day, respond favorably to stimulants, but these may have substantial side effects and many families choose not to use them, and since the current remedies are not ideal, introducing this relatively healthy herbal wake promoting beverage may have a substantial effect on children with ADHD and be much more popular with substantial impact on public health. Thus, the rationale is to test this beverage with the following aims:

Primary Objective: to assess whether WakeUp administered to children with ADHD improves alertness attention and function, compared to placebo.

Secondary Objectives: to assess the safety, tolerability and potential adverse effects of WakeUp beverage administered to children with ADHD, including assessment of blood pressure and pulse rate compared to placebo.

Study Endpoints

Primary Endpoints

- Objective findings from TOVA tests results: Omissions (focus and vigilance), Commissions (impulsivity), Response time (speed) and Response time variability (consistency).

  The test of variables of attention (TOVA) is a continuous performance test commonly used as an aid for diagnosis of ADHD and assessment of treatment response. It has been studied and standardized in both children and adults. It is a computerized, continuous performance test comprising a target stimulus and a non-target stimulus. The TOVA stimuli are colored squares with a small black square within, which is adjacent to either the top or the bottom edge. The squares with a small inner square near the top edge are designated targets, and the ones with the small squares near the bottom edge are non-targets. The stimuli appear individually and are presented randomly, based on a determined ratio. The tested subject is instructed to immediately press a button after seeing a target and not respond when a non-target is presented.

Secondary Endpoints

- Alertness (assessed via visual analog scale):

  Very Sleepy FullyAllert

  A 10cm scale in which at any tested time point (prior to and 1 hour following beverage) the participant has to put a hashmark across the line based on his/her feeling at that time point. The length from the left (cm) will be measured off line and this will be the results for that time point. A similar scale will be completed for attention (on the left side: completely unattentive, and on the right one fully attentive):

  completely unattentive fully attentive

- Adverse events and beverage related adverse events including change in blood pressure or pulse rate will be noted. Any change from normal and regular health or mood or spirit of the participants will be collected. The PI will have to assess whether this potential adverse event is related on unrelated to the beverage (prior to knowing which treatment was consumed). In case of serious adverse event, the treatment will be unblinded and the participant treated based on his/her clinical condition.

Methods

This is a randomized, double-blind, controlled study with placebo control, to test the efficacy and safety of WakeUp on alertness attention and function in 30 children ith ADHD.

Participants and recruitment

- Thirty children with ADHD will be recruited via ADHD clinics. Initial assessment of inclusion and exclusion criteria will take place on the primary visit, and once participants have met the criteria for participation and their mother or father sign an informed consent, they will enter the study and undergo randomization. It is permitted for participants to have any chronic disease (such as allergy, epilepsy or diabetes) if they are stable and controlled. Participants will continue taking their own medications (as long as they are not stimulants or sedating, in which case the subject will be excluded). Participants will cease their stimulant medications for 2 days prior to each day of study, and immediately continue taking them the following day.

Inclusion and exclusion criteria

Inclusion Criteria:

- Boy aged 6-18 years, diagnosed with ADHD
- Agree to be off medications for 2 days prior to each day of study
- Volunteers and a parent who are willing and able to sign the informed consent

Exclusion Criteria:

- Children aged less than 6 years, or adults over 18 years.
- Subjects participating in another study
- Subjects who are unable to comply with the study procedures.
- Patients in an unstable medical condition.
- Patients who are treated with sedating or stimulant medications and cannot discontinue them for 2 days prior to each day of study
- Subjects who have drunk or eaten any caffeine-containing beverage or food after 7:00 in the morning of any test day
- Any reason that, in the opinion of the investigator, may make the subject unfit for this clinical trial

Termination of participation

Termination of participation is not expected. The occasions to terminate participation are as follows:

- Serious side effect
- Subjects who do not comply with the study procedures
- Subject who for any reason decide to withdraw from participation
- Subjects who consume caffeine after 7:00 in the morning of any test day.
- Any reason that, in the opinion of the PI, make the subject unfit to continue participation

Study procedure and schedule

This is a single center, double-blind, placebo controlled trial comprised of a single drink of WakeUp® beverage compared to placebo given to children with ADHD. Participants will be randomized regarding the order of the beverage (WakeUp or Placebo).

The following visits and schedule will comprise the study:

1. Screening visit: In this visit study procedures will be expained, inclusion/exclusion criteria determined, informed consent signed.
2. Visit 1: Participants will undergo a first set of studies (see below). Immediately thereafter the

participant drinks the tested beverage (marked A or B, randomized order regarding which beverage is drank at each specific study day, blinded to the participant and the staff). One hour after drinking a second set of studies will take place (exactly equal to the previous set of studies).

3. Visit 2 is exactly like visit 1, just that the beverage is the other one (B or A).
4. Visit 3: An optional telephone call will be offered to the participants one week after the study (if they choose to) to make sure there are no side effects and to close participation. Obviously, in any case of new symptom or sign or any potential side effect will be immediately reported by the families to the researchers.

The time between screening and visit 1 can be any time between 0 (screening and visit 1 on the same day) to 1 month.
The time between visit 1 and 2) can be any time between 1 to 21 days.
Visits 1 and 2 will preferably performed at a similar time of the day to avoid circadian effects on the results.

Randomization

Treatment will be randomized for the order of beverage tested (A or B) in visits 1 and 2 by a computer-generated randomization scheme (randome function written in excel).

Blinding

Blinding will be kept by the manufacturer of the beverages (Frutarom USA, Inc). The two beverages (placebo and WakeUp) will be marked by a letter (A or B) which will be blinded to the participants and the staff of the study. Only after the completion of the study (all 30 participants), and statistical analysis and reporting will the beverages (letters) be unblinded. The only occasion of unblinding prior to study completion will be the unexpected occasion of a serious side effect.

Set of testing for the study

At all testing times (2 times at every visit of visits 1 and 2, prior to and 1 hour after drinking the beverage) the following tests will be performed:
Vital signs (blood pressure and pulse rate)
Asking about side effects
Visual Analog Scale for Alertness and attention (see above).
A computerized and standardized TOVA test (see above).

The indices measured in the TOVA include the following:
Omission errors: this score is evaluated as the failure to respond to the target stimulus. Omission error scores are presented as percentages and are considered to be a measure of inattention.
Commission errors: this score is measured as an inappropriate response to the non-target stimulus. Commission error scores are presented as percentages and are considered to reflect impulsivity or disinhibition.
Response time (in msec): this score is determined as the average of the correct response times. This score denotes response latency in information processing and motor response speed.
Response time variability: this score is evaluated as the standard deviation of the mean of correct response times. It is a measure of the subject's inconsistency in response times. **Response sensitivity**: this score is a response sensitivity score reflecting the ratio of the hit rate to false alarm rate. This score refers to the accuracy of target and non-target discrimination and is interpreted as a measure of perceptual sensitivity.

ADHD score: this score is a composite score generated by the TOVA program. The score is calculated by comparing an individual's performance on the TOVA to those of an ADHD sample collected by the authors of the TOVA. The score describes how similar an individual's performance is to the ADHD profile

Safety and report of adverse events

Information regarding the occurrence of an adverse event (AE) will be captured throughout the study and until follow up is complete (visit 3). Event name, event duration (onset date and time, and resolution date and time), event seriousness, event severity, relationship to study treatments, event outcome, and action taken will be captured in the case report form. In case the AE is defined as a serious adverse event (SAE) this will be immediately reported to InnoBev, and treatment will be unblinded. Action will be taken as needed on a clinical basis. A report to the IRB will take place within 48 hours. AE's will be followed until visit 3.
All concomitant medication (not precluded by the exclusion criteria) and concurrent therapies will be documented throughout the study until visit 3. The following information will be recorded: Generic name, daily dose, units, frequency, route, indication for administration of medication, start and stop dates of administration of medication. All concomitant procedures will be documented throughout the study until visit 3, the reason for the procedure will be considered as AE/SAE, unless it was scheduled prior to study start.

Statistical analysis

All the data of the tests (including BP pulse rate, allertness and attention VAS, TOVA various dimenssions; The primary and two secondary endpoints) will be analyzed and the following comparisons will be made:

- Comparisons between the results between prior to and following the beverage.
- Comparisons between the results and responses (of the previous comparisons) between the placebo and WakeUp.

Paired student's T-Test and one way ANOVA will be utilized to search for statistically significant differences between the various responses (difference from baseline and between treatments).

All effectiveness analyses will be two-sided at the 5% level of significance.

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יש לצרף: מאמר אחד שלם לפחות, CV של החוקר הראשי (כולל חתימה ותאריך בכתב יד).