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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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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 showed wake promotion characteristics, with no side effects. 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:

Aim:

Primary Objective: to assess whether WakeUp administered to children with ADHD improves alertness attention and function, compared to placebo (based on TOVA tests).
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).

Secondary Endpoints

- To study the safety of the beverage in children with ADHD: subjective complaints and/or hemodynamic changes.

Methods:

This was 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. The study was proved by the Carmel Medical Center institutional review board (IRB, Helsinki committee) and all the participants (their parents) have signed an informed consent prior to participation.

Thirty children with ADHD were recruited via the Pediatric Neurology Unit/ADHD clinic. Initial assessment of inclusion and exclusion criteria took place on the primary visit, and once participants have met the criteria for participation and their mother or father have signed an informed consent, they have entered the study and underwent randomization. Fifteen participants had drank beverage A first and then beverage B, and the other 15 had first B beverage and the A (one was Wakeup and one placebo). It was permitted for participants to have any chronic disease (such as allergy, epilepsy or diabetes) if they were stable and controlled. Participants continued taking their own medications (as long as they were not stimulants or sedating, in which case the subject were excluded). Participants who were on stimulant treatment had ceased their stimulant medications for 2 days prior to each day of study, and immediately continued taking them the following day. Inclusion and exclusion criteria were as follows:

Inclusion and exclusion criteria

Inclusion Criteria:

- Boys 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

Study procedure and schedule

This was a single center, double-blind, placebo controlled trial comprised of a single drink of WakeUp® beverage compared to placebo given to children with ADHD.

The following visits and schedule have comprised the study:

- Screening visit: In this visit study procedures were expained, inclusion/exclusion criteria determined, and informed consent signed.

- ❖ Visit 1: Participants underwent a first set of studies (see below). Immediately thereafter the participant drank the tested beverage (marked A or B, randomized order regarding which beverage was drank at each specific study day, blinded to the participant and the staff). One hour after drinking, a second set of studies took place (exactly equal to the previous set of studies).
- ❖ Visit 2 was exactly like visit 1, just that the beverage was the other one (B or A).
- ❖ Visit 3: An optional telephone call was offered to the participants one week after the study (if they chose to) to make sure there were no side effects and to close participation. Obviously, families were instructed reporting the researchers any new symptom or sign or any potential side effect.

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

Blinding

Blinding was kept by the manufacturer of the beverages (Frutarom USA, Inc). The two beverages (placebo and WakeUp) were marked by a letter (A or B) which was blinded to the participants and the staff of the study. Only after the completion of the study (all 30 participants), and statistical analysis the keys were exposed and unblinded.

Set of testing for each 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 were performed:

Vital signs (blood pressure and pulse rate)

Asking about side effects

A computerized and standardized TOVA test (see below).

TOVA test

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 coloured 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.

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

Results:

Of the 30 children participated, 3 were dropped out due to incompleting the tests. The remaining 27 participants completed all parts of the study.

Their ages were 11.5±3.0 years (range 6-17). No side effects or complaints have been observed following drinking "Wake up" or placebo. Neither subjective complaints nore hemodynamic changes between prior to and following drinking either WakeUp or placebo were noted. As for the TOVA tests, in the Wake Up group 3 children have converted their total TOVA score from pathologic (ADHD range) into normal range (11%) as compared to only 1 (3.7%) in the placebo group. In the WakeUp group 13 children showed improvement in at least 2 dimenssions of the TOVA, and 5 children in at least 3 dimennsions of the TOVA, compared to 11 and 3 children, respectively. In almost all aspects of the TOVA test there was a trend for improvement following drinking Wake Up compared to placebo, although this trend did not reach statistical significance (probably due to the under-powered study – too small sample size, along with relatively high variability of the results.

Table 1 summarizes these results:

	Wake Up	Placebo	P
Change in Variability	0.45±0.75	0.39±0.8	0.4
Change in Reaction time	0.89±0.97	0.96±0.96	0.28
Change in Commission	1.04±0.94	0.82±0.93	0.08
Change in Ommission	0.7±0.91	0.6±0.85	0.24
Improvement in total score	0.56±0.64	0.43±0.51	0.20
Number of children converted to normal	3/27	1/27	NS

Table 1: Summary of changes in scores prior to drinking the beverage and following it, such that improvement was rated as 2, partial improvement as 1, and no improvement as 0. The larger the number is indicative of a better improvement. As can be seen in all aspects apart from reaction time there was a trend for better improvement with WakeUp compared to placebo, albeit due to too small sample size and too large variability these differences did not reach statistical significance. The best improvement was in comission (p=0.08). For the total score, there was a substantial greater improvement with Wake Up compared to placebo (0.56 vs 0.43), yet to P was only 0.2 due to the above mentionedreasons. Yet, this is a substantial finding that with Wake Up 3 children convertertheir TOVA score from ADHD to normal range (11% !). These results are very encouraging indicationg that at least in a portion of these children ADHD can be substantially improved up to a normal range of function by drinking herbal healty beverage. The results of this study are best judged as a small sample sized pilot study, encouraging to generate a larger study to test the effect of Wake Up on children with ADHD.

Conclusions:

This small sample sized pilot study showed a non-significant trend for improvement in most aspects of the Test Of Variables of Attention (TOVA) scores in children with ADHD following drinking WakeUp herbal beverage compared to placebo (omission, comission variability and total score), with 3 of 27 children converting from ADHD range to normal scores. The results showed only a trend and not statistical significance most probably due to underpowered sample size (n=27) with relatively high variability of scores. There were no any side effects, subjective or hemodynamics, following drinking WakeUp. We believe these results are encouraging to performing a larger scale study to test the effect of WakeUp beverage on these scores.

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