Giora Pillar, MD, PhD
Associate Professor, Faculty of Medicine
Technion – Israel Institute of Technology
Head, Sleep Laboratory
Rambam Medical Center,
Haifa 31096, ISRAEL
Tel: 972-4-8542646
Fax: 972-4-8542441

Longitudinal open label prospective study to assess the efficacy and tolerance of daily usage of the wake promoting beverage "WakeUp®" following lunch on vigilance and function of healthy volunteers.

PI: Prof. Giora Pillar

Co-Investigators: Adi Segev, Dr. Noam Meiri

Abstract:

Post lunch dip is a very well established phenomenon which results in substantial deterioration of function and productivity following lunch, between noontime and 16:00. The newly developed WakeUp® drink (Inno-Bev Ltd, Tel Aviv, Israel) is a wake promoting drink based on herbal ingredients consisting of extracts of Ginkgo Biloba, guarna, elderberry and fruit-up. In a double blind placebo and active controled study we have previously shown that a single drink of WakeUp® beverage (100cc) after lunch improved vigilance and performance. While 30 minutes following the drink the improvement was similar to caffeine, at 120 minutes following drink it was superior to caffeine. The purpose of the current study was to assess these effects during 30 days of a daily use of the beverage after lunch. Ninety-five healthy volunteers participated. They drank the beverage for 30 days after lunch and underwent performance and subjective scaling of vigilance and affectiveness in 3 different days: Day 1 (first day of drink), Day 30 (last day of drink), Day 31 (one day after the study, without drink). In every studied day they underwent tests before luch and again 1 hour following luncy (and WakeUp® beverage after lunch in days 1 and 30). WakeUp® beverage resulted in improvement of both ojective performance and subjective assessment of vigilance, focusing and work effectiveness similarly in Day 1 and Day 30 of the study, without adverse effects on hemodynamic measures. We believe the WakeUp® beverage is a safe and effective drink to counteract the fatigue and reduced performance of the post lunch dip.

Background:

Post lunch dip is a very well established phenomenon which results in substantial deterioration of function and productivity following lunch, between noontime and 16:00 hours. Indeed, in several places around the world it is common to take a nap ("siesta") between 13:00-15:00 or 14:00-16:00. The reason for this mid-day post lunch sleep propensity is complex, and consists of hormonal, circadian, and nutritional/gastrointestinal mechanisms. Temperature changes, decreased cortisone levels, and re-distribution of blood following lunch contribute to this sleepiness following lunch. It has been shown that this post-lunch dip during these 2-3 hours following lunch has a substantial impact on work performance. There is a reduced productivity and decreased quality of work during these hours, as well as increase in errors and work accidents. A recent study which sampled 28,902 adults aged 18 to 65 found that fatigue results in lost productive time that can cost the employers 136.4 billion dollars annually, an excess of 101 billion dollars annually compared with workers without fatigue.

A wake promoting drink may reduce this phenomenon and result in significant improvement of vigilance, productivity and work achievements. One potential way to achieve this wake promotion is by drinking coffee. Caffeine containing drinks may improve vigilance and function by blocking adenosine receptors and by inhibiting phospho-di-esterase (PDE) which results in increased cAMP and adrenergic activity. However, caffeine has a short half-life and potential side effects (such as increased pulse rate and blood pressure). In addition, regular coffee drinking results in tolerance and substantial reduction of the effect of caffeine.

The newly developed WakeUp® drink (Inno-Bev Ltd, Tel Aviv, Israel) is a wake promoting drink based on herbal ingredients consisting of extracts of Ginkgo Biloba, Guaraná, and Fruit-Up.

Guaraná (Paullinia cupana) seeds have a long history of usage as a stimulant by Amazonan tribes. The putative stimulant properties were generally assumed to reflect the presence of caffeine, although it comprises only 2.5–5% of the extracts dry weight. However the psychoactive properties of guaraná may also be attributable to relatively high content of other potentially psychoactive components, including both saponins and tannins, which may also account for antioxidant properties of the plant. It has been previously shown that guaraná improves memory performance and mood, and increases alertness, even in relatively low doses. The Ginkgo Biloba is a unique tree which can be found predominantly in China. Extract of Gincko Biloba are believed to have some important healing properties, and are used in herbal medicine for asthma, bronchitis, fatigue, and tinnintus. On top of its vigilance promoting, it has been shown to have favorable effects on memory. It is currently being used predominantly in Asia as a preventive treatment for Alzheimer's disease and other types of dementia. It also has been shown to reduce vertigo. The Fruit-Up adds to the WakeUp® drink predominantly taste, although its glucose content may also improve alertness. It has a relatively low glycemic index which stabilizes the blood glucose levels and may have implications in reducing morbidity. In addition, unrelated to allerness, the WakeUp® drink includes also

elderberry extract, which has been shown to have efficient anti-viral activity, effective especially against influenza. Thus, this drink has the potential to improve vigilance and performance, and alleviate the undesired effects of the post-lunch dip.

Indeed, in a double blind placebo and active controlled study we have previously shown that a single drink of WakeUp® beverage (100cc) after lunch improved vigilance and performance 30 min following the drink, similarly to caffeine and significantly better than placebo. Following 120 minutes taking the beverage, performance and vigilance with WakeUp® remained high, significantly superior to both placebo and caffeine. While caffeine was associated with increasing pulse and blood pressure in the short term, with WakeUp® there were no hemodynamic differences compared with placebo, both 30 minutes and 120 minutes following consumption. Thus, we concluded that WakeUp® is a good and effective drink to counteract the somnolence and reduced performance during the post lunch hours. However, these data were based on a single use. Thus, in the present study we sought to assess the wake promoting and hemodynamic variables associated with a daily use of the beverage. We attempted to collect data regarding potential habituation / tolerance or alternatively cumulative positive effect.

Aim:

To study the effects of daily usage of the wake promoting beverage WakeUp® on vigilance, function and hemodynamic measures.

We hypothesized that drinking WakeUp® following lunch on a daily basis will not induce tolerance, and the effects will be similar in Day 1 and Day 30 of usage.

Methods:

Ninety-fivehealthy volunteers were studied in 3 different days: The first day of usage ("Day 1"), after 30 days of drinking WakeUp® every day ("Day 30"), and in the first day after 30 days of usage, without drinking the beverage ("Day 31"). In Day 1 and Day 30 of the study the volunteers reported to the hospital on 11:45 and had a standard and consistant lunch. Right after lunch they underwent a battery of functional tests and hemodynamic measurements [see below], and then drank one bottle of WakeUp® (100cc). After an hour (at13:00) they underwent a repeated battery of the same tests. On Days 2-29 of the study the participants were instructed to drink every day after lunch one bottle of the beverage in their home. On Day 31 of the study the participants had the same regimen with lunch at 11:45 and tests at 12:00 and 13:00, except that they did not drink WakeUp® after lunch. In each visit participants had battery of tests performed right after lunch and one hour later. These battery of tests consisted of measurement of vital signs, blood pressure, and validated commonly used standard function and vigilance tests such as an immediate word recall test (short term memory), digit symbol substitution test (concentration), and subjective rating (on a visual analogue scale - VAS) of their vigilance, ability to focus, and effectiveness at work. In each visit the results of the tests at 12:00 and 13:00 were compared to each other, and in addition the results of the tests on the 3

days of visit (1, 30, 31) were compared to each other, utilizing either paired t-test or one way analysis of variance, with $p<0.05$ considered statistically significant.

Results:

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

Overall, 95 volunteers (40 males and 55 females) participated. Their average age was 37±11 years (range 19-63 years), and their average BMI was 24.5 ± 1.7 Kg/m^2 (range 19.7-34.7). The results of their functional tests before and following the drink in days 1 and 30, and in day 31 with no drink are presented in Table 1. As can be seen, in the first day WakeUp® resulted in an overall objective imrovement of 8.5% and subjective improvement of about 14%. In day 30 WakeUp® resulted in an overall objective imrovement of 7.3% and subjective improvement of about 11.5%. In day 31, without WakeUp®, the results of the objective tests deteriorated by 7.1%, and the subjective VAS measures deteriorated by about 11.7 percent.

Interestingly, even regardless of the beverage, over the progress of the study there was a baseline improvement in the results of the various tests [Table 1, Fig 1-4]. Word recalled at baseline increased from day 1 to day 30 by 5.5% and further increased in day 31 by additional 4.2 percent. Similarly DSST score increased from a baseline of 79 in day 1 to 87 in day 30 (rise of 10%) and to 93 in day 31 (additional rise of 6.9%). There was a similar trend in the VAS scores for vigilance, focusing and effectiveness (rises of 5-7% from the baseline of day 1 to the baseline of day 30, and a further rise of 6-7.5% to day 31). These data are presented in figures 1-4 (left panel, at 12:00) and in Table 1.

The hemodynamic measures at the various times are presented in table 2. As can be seen, WakeUp® did not result in any significant change in blood pressure or heart rate. The reduction of 0.4-2.5% in pulse rate and blood pressure following WakeUp® drink probably reflects the post lunch dip phenomemnon, as is also seen in Day 31.

Conclusions:

The current study confiims that without WakeUp® beverage there is a post lunch dip phenomenon as can be concluded from the observations in Day 31.

Objective performance tasks deteriorated by 7.1% and subjective allertness, focusing ability and work effectiveness by 11.2-11.9%. Pulse and blood pressure droped by an average of 2.4%. However, with WakeUp® beverage right after lunch these drops not only blocked, but there was actually an improvement in both objective tast performances and in subjective assessment of alertness, focusing ability and work effectiveness. The magnitude of these improvements ranged in day 1 between 8-14.9 percent. Thus, given the expected drop, the net effect of the beverage seems close to 20 percent! Furthermore, this study demonstrates that a daily use of the beverage over 30 days (one bottle of 100cc per day) does not result in tolerance or habituation, since the improvements observed in day 30 are similar to those observed in day 1, and range between

6.6-12.8 percent. Very importantly, these effects throughout the entire study did not adversly affect hemodynamic measures.

Finally, surprisingly, even baseline scores before drinking imroved between Day 1 and Day 30 (by some 8%), and further improved in Day 31 (additional improvement of about 5%). The reason for this observation may be technical (learning curve of the performance tasks) but can also be a cumulative aditive long term effect of the beverage. Subjective VAS cannot be associated with a learning curve yet they demonstrated longitudinal baseline improvement in allertness, focusing ability and work effectiveness from day one to Day 31.

Thus, we believe the WakeUp® beverage is a safe and effective drink to counteract the fatigue and reduced performance of the post lunch dip.

Table 1:

	Day 1			Day 30			Day 31		
	Before WU	1h after WU	Change (%)	Before WU	1h after WU	Change (%)	After Lunch	1h after Lunch	Change (%)
iWRT	9.1±3.7	9.8±3.4	+8.0	9.6±3.9	10.3±3.9	+6.6	10.0±3.8	8.9±3.3	-10.8
DSST	79±14	86±15	+8.9	87±15	93±16	+8.0	93±17	90±19	-3.5
Vigilance	5.9±2.1	6.9±1.9	+14.9	6.3±2.0	7.911.8	+12.8	6.7±1.8	6.0±2.0	-11.2
Focusing	6.0±1.9	6.9±1.8	+14.8	6.3±2.0	7.1±1.9	+11.4	6.8±1.7	6.0±2.0	-11.9
Effectiveness	6.4±1.9	7.3±1.3	+12.5	6.7±2.0	7.4±1.8	+10.4	7.1±1.6	6.3±2.0	-11.9

iWRT = immediate Word Recall Test; DSST = Digit Symbol Substitution Test. WU = WakeUp® Beverage.

Table 2:

	Day 1			Day 30			Day 31		
	Before WU	1h after WU	Change (%)	Before WU	1h after WU	Change (%)	After Lunch	1h after Lunch	Change (%)
Pulse	74±11	73±10	-0.4	77±10	75±11	-2.5	76±11	73±11	-3.5
Systolic BP	122±12	120±13	-1.9	121±13	119±12	-1.5	119±18	118±14	-0.2
Diastolic BP	76±10	74±9	-2.5	74±9	73±9	-1.7	75±9	72±9	-3.5

Fig 1: Effect of WakeUp® beverage after lunch on immediate word recall test.

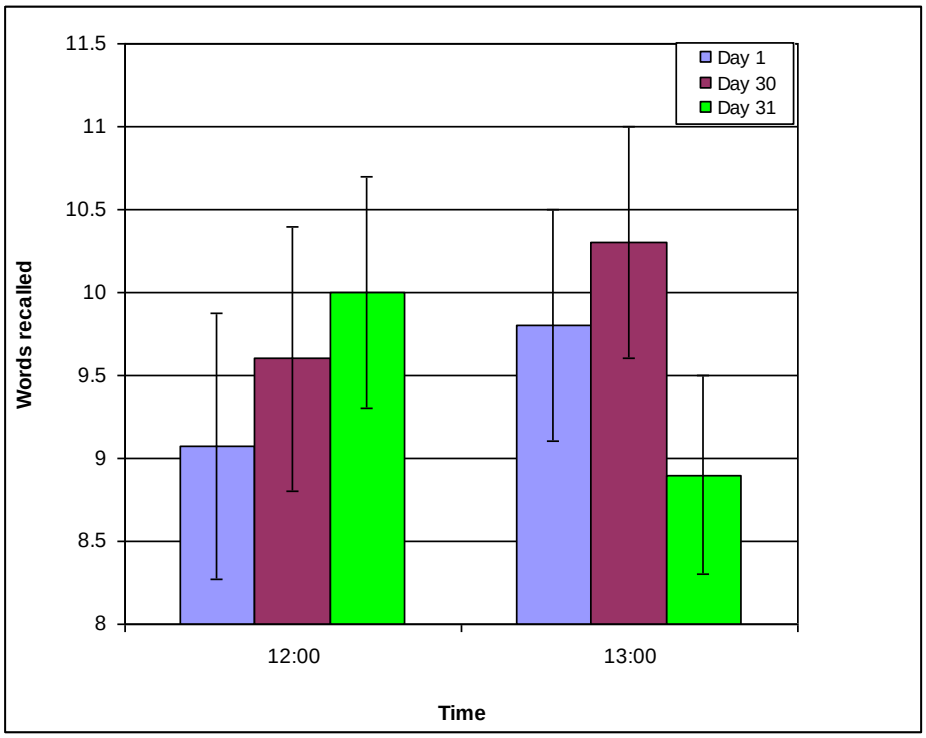

Fig 2: Effect of WakeUp® beverage after lunch on Digit Symbol Substitution Test.

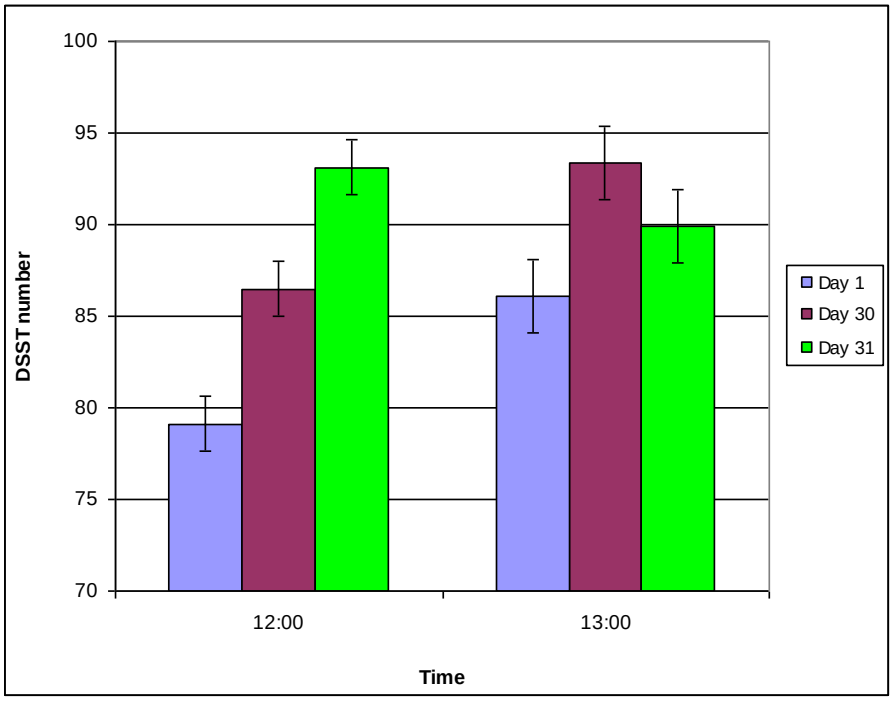

Fig 3: Effect of WakeUp® beverage after lunch on subjective vigilance (visual analog scale).

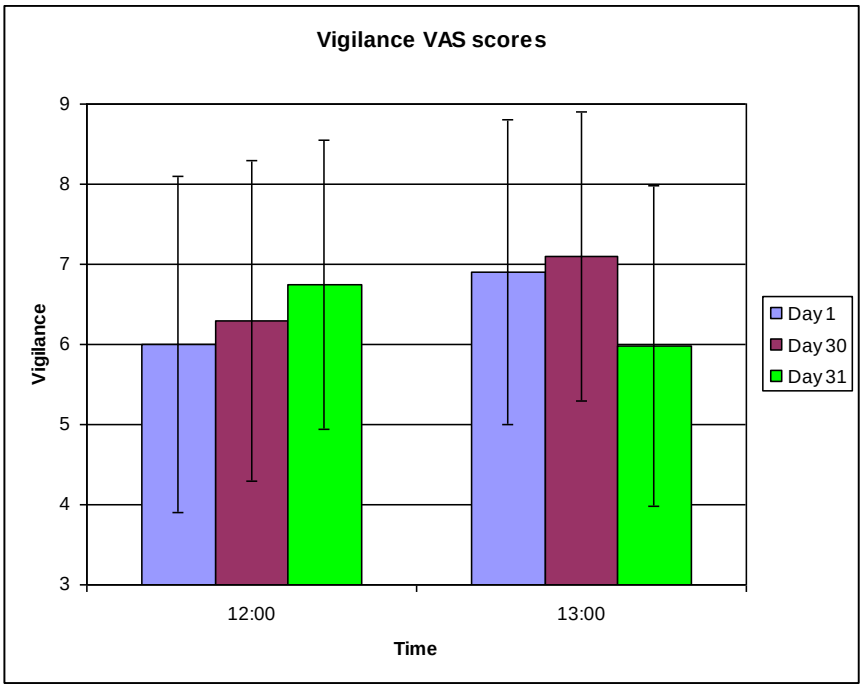

Fig 4: Effect of WakeUp® beverage after lunch on subjective effectiveness (visual analog scale).