Via Electronic Mail and First Class Mail

April 19, 2016

Jeffrey Craig Miller, Esq.
Miller Korzenik Sommers Rayman LLP
488 Madison Avenue
New York, NY 10022

RE: Kolé Life Foods

Dear Jeff:

This letter is in response to your email dated April 12, 2016, wherein you passed along a series of some twenty-four questions that Jesse Singal, the Senior Editor for NYMag.com, poses to my client, Kolé Life Foods, regarding its Kolé Tonics product line. Mr. Singal's questions focus primarily on requests for substantiation of the claims made regarding these products. He also asks about the disclosure on the Kolé Life Foods website that makes clear that Dr. Bankole Johson's role with the company has no affiliation with his role as a faculty member at the University of Maryland School of Medicine and that the University of Maryland does not endorse Kolé Tonics.

As an initial matter, in several instances, the formulation of Mr. Singal's questions materially misstates the claims that Kolé Life Foods is making. As Kolé Life Foods has previously stated to Mr. Singal, even prior to receiving any communication from him, the company was (and continues to be) engaged in an effort to further refine its messaging, including on its website and through its product labeling. By way of example, the company expects to post updated product labels on its website within the next several days. These new bottle labels—which will be hitting the market over the next few weeks—will no longer include any reference to Dr. Johnson. The company also has a scientific advisory board and two members of the board of directors who, in addition to Dr. Johnson, are also medical doctors. Dr. Johnson is thus far from the only individual who has had input into the development of the company's products. As our previous correspondence has suggested, based on the nature and tone of the written inquiries that Mr. Singal has made to third parties about Kolé Tonics and Dr. Johnson, Kolé Life Foods believes that it is particularly critical that its claims be accurately represented in Mr. Singal's writing. By way of example, the current website for Kolé Life Foods carefully references the individual ingredients on which functional benefit claims are made. This distinction between finished product claims versus ingredient-specific claims is ignored in the formulation of Mr. Singal's questions but is legally significant for the reasons explained below.

The phrasing of several of Mr. Singal's questions suggests that he (or, perhaps, the medical "experts" that he has consulted) incorrectly believes that dietary supplements such as Kolé Tonics must be proven to be "safe and effective" in order to be made available on the market. In

this respect, Mr. Singal appears to confuse the legal standards applicable to new drug approvals with the standards for dietary supplements under the federal Food, Drug, & Cosmetic Act (FDCA). Under Section 201 of the FDCA, 21 U.S.C. § 321, dietary supplements are regulated as a subset of foods. Section 403(r) of the FDCA expressly allows that a statement for a dietary supplement may be made if –

> "(A) the statement . . . describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient,
> (B) the manufacturer of the dietary supplement has substantiation that such statement is truthful and not misleading, and
> (C) the statement contains, prominently displayed and in boldface type, the following: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

Kolé Tonics meet all of these requirements. The products are formulated with ingredients that are considered Generally Recognized as Safe, or are considered acceptable New Dietary Ingredients, as those terms are defined pursuant to FDA regulations. Kolé Life Foods finds it suspicious that, despite the fact that many other products that can easily be found through a cursory internet search have long been advertised through far more speculative and far less scientifically supportable claims, Mr. Singal appears to be fixated on Kolé Life Foods, a start-up that is attempting to improve the functionality of brain health dietary supplements.

The claims regarding Kolé Tonics refer to supporting healthy structure and functioning of the body. Contrary to what appears to be Mr. Singal's incorrect assumption, dietary supplements like Kolé Tonics do not require finished product substantiation to support such structure function claims. Such not only has long been accepted industry practice, but this standard has been repeatedly upheld in federal court actions, including as recently as the September 24, 2015 ruling in *United States v. Bayer Corporation*, Case No. 2:07-cv-00001, in the United States District Court for the District of New Jersey. In that case, an expert, in making an assumption not dissimilar from what Mr. Singal appears to be doing here, opined that finished product studies were necessary to support claims about probiotic dietary supplements relieving minor digestive issues. In rejecting this conclusion, the court specifically noted that finished product clinical studies have ***never*** been considered the standard for dietary supplement claims substantiation and that the government's expert applied the **wrong legal standard** in forming his expert opinion. Even the government agreed that Bayer had acted in compliance with applicable law in relying on ingredient research (much of which was conducted in diseased populations) in order to support its claims.

The government's expert in the *Bayer* case, while renowned in his medical field, ultimately was found by the court not to have sufficient experience and education about the legal standards applicable to dietary supplements to render a credible opinion. The similarities between the expert in the *Bayer* case and the "angle" that Mr. Singal appears to be pursuing cannot be overstated. Publication of an article containing opinions of so-called medical experts who are not familiar with the legal standards applicable to dietary supplements or the stated positions of Kolé Life Foods may well prove, at the very least, embarrassing to Mr. Singal, the experts upon whom he claims to rely, and his publication, and may well have significant legal repurcussions for all involved. We trust that any experts that Mr. Singal intends to quote as opining about the company or its products will be well versed in the legal framework applicable to dietary supplements like Kolé Tonics and will also have been fully briefed on the company's responses to Mr. Singal's inquiries, including by being provided a copy of this letter.

On April 4, 2016, Kolé Life Foods provided Mr. Singal with references to select study citations that relate directly to the core claims. **These citations are particularly insightful because they reference studies on healthy individuals.** Your client's questions appear to assume that research on healthy populations is required to substantiate dietary supplement claims. This is incorrect. The vast majority of dietary supplement claims on the market today are supported by research conducted in diseased populations. Simply put, very little research is done on healthy people, a fact that underscores the high value of the previously-provided citations. In addition, the ingredient levels in Kolé Tonics are consistent with the levels referenced in the research and with the levels in products currently marketed by leading dietary supplement manufacturers.

It is the practice of Kolé Life Foods to regularly review the available published research and to evaluate ingredients and claims based on the most current science. It will be the work of the company's scientific advisory board to carefully vet and consider these issues. These practices were deemed sufficient by the *Bayer* court and are best practices in the industry.

For your convenience, we have enclosed a copy of the April 4, 2016 communication to Mr. Singal, as well as full abstracts of the studies cited in Kolé Life Foods' April 4, 2016 statement.[1] We have also included abstracts of several select additional studies. To the extent that you are interested in additional literature regarding the ingredients in Kolé Tonics, Kolé Life Foods

[1] Mr. Singal may also review several of the study abstracts at the following website addresses:

Bruce SE et al.: http://www.ncbi.nlm.nih.gov/pubmed/25046515
Murphy SE et al.: http://www.ncbi.nlm.nih.gov/pubmed/16767422
Leyton M et al.: http://www.ncbi.nlm.nih.gov/pubmed/10633491 (previously misspelled as Leveton)
Herxeimer A & Petrie KF: http://www.ncbi.nlm.nih.gov/pubmed/12076414
Waterhouse J et al.: http://www.ncbi.nlm.nih.gov/pubmed/17398311
Attenburrow M et al.: http://www.ncbi.nlm.nih.gov/pubmed/8856838
Stone BM et al.: http://www.ncbi.nlm.nih.gov/pubmed/10947034
Bottari AM et al.: http://www.ncbi.nlm.nih.gov/pubmed/24051943
Meston CM and Worcel M:
http://homepage.psy.utexas.edu/homepage/group/mestonlab/Publications/yohimb.pdf (full article)
Akhondzadeh S et al.: http://www.ncbi.nlm.nih.gov/pubmed/22952481

suggests searching databases such as PubMed.gov. The research that Kolé Life Foods consults is publicly available, but the company's collection of particular studies and the determinations that the company has made regarding them are proprietary. The abstracts enclosed herewith are not the only studies upon which Kolé Life Foods bases its claims.

Finally, there is no reason for Mr. Singal to speculate that the disclosure on the website about Dr. Johnson's role at the University of Maryland Medical School would suggest to anyone that the products have been subjected to controlled effectiveness studies. That this question was even asked is further evidence that Mr. Singal does not understand the distinct legal standards applicable to dietary supplements and drugs. Given all of the above and the damage and distraction already suffered by my client, we strongly suggest that Mr. Singal and NYMag.com reconsider publication of their planned article.

Very truly yours,

Eric N. Heyer

enclosure

Statement By Kolé Life Foods

"Kolé Life Foods has carefully formulated Kolé Tonics with ingredients shown to promote the healthy function of the brain. Great taste combined with scientifically supported ingredients, they are the future of function."

- Dr. Bankole Johnson

Background on Dr. Johnson

Professor Johnson is a senior neuroscientist and psychiatrist. He is credited with 11,225 publication citations and numerous global patents. His scientific impact factor is consistent with that of a pre-eminent scientist. Dr. Johnson's work as a faculty member and researcher is separate from his latest business venture, Kolé Life Foods, maker of Kolé Tonics.

Summary of Select Ingredient Clinical Trials

The Company's formulations are proprietary and a trade secret, and Kolé Life Foods generally does not disclose competitive information. Nevertheless, the Company is willing to provide some examples of relevant clinical findings regarding some of the ingredients used in Kolé Tonics. The list below is not exhaustive. Finished product clinical trials are not required for dietary supplements and all necessary regulatory disclaimers are displayed prominently on the Company's website and bottle.

- INSPIRE™ Tonic contains citicoline and caffeine, which in a randomized placebo-controlled double-blind study of 60 healthy participants, was shown to lead to "significantly faster maze learning times and reaction times on a continuous performance test, fewer errors in a go/no-go task and better accuracy on a measure of information processing speed…and improved P450 EEG amplitude that "indicates a general improvement in the ability to accommodate new and relevant information within working memory and overall enhanced brain activation (Bruce SE et al., Int J Food Sci Nutr. 2014 Dec;65(8):1003-7)".

- HAPPY™ Tonic contains tryptophan, which is well-recognized even in non-scientific circles to have an effect on mood. In a clinical study of 38 healthy women, tryptophan is shown to have "increased the recognition of happy facial expressions and reduced attentional vigilance towards negative words and decreased baseline startle responsivity in the females Murphy SE et al., Psychopharmacology (Berl). 2006 Jul;187(1):121-30", and the depletion of tryptophan and phenylalanine (also in HAPPY) in healthy women "increases vulnerability to lowered mood" (Leveton M, et., Neuropsychopharmacolo gy. 2000 Jan;22(1):52-63).

- DREAMS™ Tonic contains melatonin, which is also widely recognized to have an impact on sleep. In a large meta-analysis, melatonin was determined to be "…remarkably effective in preventing or reducing jet-lag" (Herxeimer A & Petrie KF Cochrane Database Syst Rev. 2002;(2):CD001520, and also substantiated in Waterhouse J et al. Lancet. 2007 Mar 31;369(9567):1117-29). Melatonin has been associated with "increased Actual Sleep Time, Sleep Efficiency, non-REM Sleep and REM Sleep Latency (Attenburrow ME et al. Psychopharmacology (Berl). 1996 Jul;126(2):179-81), and has its best effect, comparable to a benzodiazepine sleep aid, when taken between (18.00 – 24.00 h) but not later when there is increased secretion of endogenous melatonin (Stone BM et al., Sleep. 2000 Aug 1;23(5):663-9).

- IGNITE™ Tonic contains l-arginine, which when combined with other herbals, was demonstrated in a clinical study to "significantly improve sexual function" (Bottari AM et al., Minerva Ginecol. 2013 Aug;65(4):435-44), and when combined with yohimbine (also in IGNITE™) was associated with "substantially increased vaginal pulse amplitude responses to the erotic film at 60 min administration compared with placebo" (Meston CM and Worcel M, Arch Sex Behav 2002 Aug; 31 (4): 323-32), and improvements in erectile function in men with mild dysfunction (Akhondzadeh S et al., Iran J Psychiatry. 2010 Winter;5(1):1-3).

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Int J Food Sci Nutr. 2014 Dec;65(8):1003-7. doi: 10.3109/09637486.201[illegible]

Improvements in concentration, working memory and sustained attention following consumption of a natural citicoline-caffeine beverage.

Bruce SE[1], Werner KB, Preston BF, Baker LM.

Author information

Abstract

This study examined the neurocognitive and electrophysiological effects of a citicoline-caffeine-based beverage in 60 healthy adult participants enrolled in a randomized, double-blind, placebo-controlled trial. Measures of electrical brain activity using electroencephalogram (EEG) and neuropsychological measures examining attention, concentration and reaction time were administered. Compared to placebo, participants receiving the citicoline-caffeine beverage exhibited significantly faster maze learning times and reaction times on a continuous performance test, fewer errors in a go/no-go task and better accuracy on a measure of information processing speed. EEG results examining P450 event-related potentials revealed that participants receiving the citicoline-caffeine beverage exhibited higher P450 amplitudes than controls, suggesting an increase in sustained attention. Overall, these findings suggest that the beverage significantly improved sustained attention, cognitive effort and reaction times in healthy adults. Evidence of improved P450 amplitude indicates a general improvement in the ability to accommodate new and relevant information within working memory and overall enhanced brain activation.

KEYWORDS: Attention; EEG; citicoline; functional beverage; nutrition

PMID: 25046515 [PubMed - indexed for MEDLINE] PMCID: PMC4517431 Free PMC Article

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Journal of Attention Disorders
1–14

DOI: 10.1177/1087054715593633
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The Effect of Citicoline Supplementation on Motor Speed and Attention in Adolescent Males

Erin McGlade[1], Anna Monica Agoston[1], Jennifer DiMuzio[1], Miho Kizaki[2], Eri Nakazaki[2], Toshikazu Kamiya[3], and Deborah Yurgelun-Todd[1]

Abstract

Objective: This study assessed the effects of citicoline, a nutraceutical, on attention, psychomotor function, and impulsivity in healthy adolescent males. **Method:** Seventy-five healthy adolescent males were randomly assigned to either the citicoline group (n = 51 with 250 or 500 mg citicoline) or placebo (n = 24). Participants completed the Ruff 2&7 Selective Attention Test, Finger Tap Test, and the Computerized Performance Test, Second Edition (CPT-II) at baseline and after 28 days of supplementation. **Results:** Individuals receiving citicoline exhibited improved attention (p = 0.02) and increased psychomotor speed (p = 0.03) compared with those receiving placebo. Higher weight-adjusted dose significantly predicted increased accuracy on an attention task (p = 0.01), improved signal detectability on a computerized attention task (p = 0.03), and decreased impulsivity (p = 0.01). **Discussion:** Adolescent males receiving 28 days of Cognizin® citicoline showed improved attention and psychomotor speed and reduced impulsivity compared to adolescent males who received placebo. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

cognition, adolescents, cognitive enhancement, citicoline

Introduction

Citicoline (cytidine-5′-diphosphocoline or CDP-choline) is an organic molecule that is thought to influence cellular metabolism in the brain. It is an essential intermediary component of the synthesis of phosphatidylcholine, a major phospholipid in the brain that aids in neuronal membrane repair (Conant & Schauss, 2004; Secades, 2011), and also contributes to the synthesis of several essential neurotransmitters, including acetylcholine and dopamine (Saver, 2008; Secades, 2011). Citicoline has demonstrated cognitive-enhancing and neuroprotective properties in previous preclinical and clinical studies (Ozay et al., 2007; Parisi, Coppola, Centofanti, et al., 2008; Secades, 2011) and is marketed as a nutritional supplement in the United States. In addition, prior research on citicoline has shown very few side effects, although research thus far has focused primarily on adults (Clark, Wechsler, Sabounjian, & Schwiderski, 2001; Secades, 2011; Zafonte et al., 2009).

Oral supplementation of citicoline is metabolized into choline and uridine within the intestine and is rapidly absorbed, with waste excretion of less than 1% as demonstrated by pharmokinetic studies (Wurtman, Regan, Ulus, & Yu, 2000) . These compounds are distributed throughout the body via general circulation and are utilized in a variety of biosynthetic pathways. In particular, uridine crosses the blood–brain barrier and is synthesized into uridine-5′-triphosphate, which is then metabolized into cytidine triphosphate and CDP-choline (Wurtman, Regan, Ulus, & Yu, 2000). A clinical study measuring in vivo brain chemistry through proton magnetic resonance spectroscopy (MRS) revealed increased plasma choline in young adults (with a mean age of 25) 3 hr after oral supplementation of citicoline (Babb, Appelmans, Renshaw, Wurtman, & Cohen, 1996).

Studies examining exogenous administration of citicoline have found influences in regional brain metabolism and increased dopamine synthesis in certain brain areas (Secades, 2011). A study by Silveri and colleagues used phosphorus MRS to investigate changes in brain metabolism after citicoline supplementation of either 500 or 2,000 mg/day for 6 weeks. The authors noted improved bioenergetics and enhanced phospholipid membrane maintenance in the frontal lobe (Silveri et al., 2008). Frontosubcortical

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Psychopharmacology (Berl). 2006 Jul;187(1):121-30. Epub 2006 May 4.

Tryptophan supplementation induces a positive bias in the processing of emotional material in healthy female volunteers.

Murphy SE[1], Longhitano C, Ayres RE, Cowen PJ, Harmer CJ.

Author information

Abstract

RATIONALE: The serotonin precursor L-tryptophan (TRP) is available as a nutritional supplement and is licensed as an antidepressant in a number of countries. However, evidence of its efficacy as the primary treatment for depression is limited, and the direct action of TRP on the symptoms of depression and anxiety has not been well-characterised.

OBJECTIVES: The present study assessed whether TRP induces cognitive changes opposite to the negative biases found in depression and characteristic of those induced by serotonergic antidepressants in healthy volunteers.

MATERIALS AND METHODS: Thirty eight healthy volunteers were randomised to receive 14 days double-blind intervention with TRP (1 g 3x a day) or placebo. On the final day, emotional processing was assessed using four tasks: facial expression recognition, emotion-potentiated startle, attentional probe and emotional categorisation and memory.

RESULTS: TRP increased the recognition of happy facial expressions and decreased the recognition of disgusted facial expressions in female, but not male, volunteers. TRP also reduced attentional vigilance towards negative words and decreased baseline startle responsivity in the females.

CONCLUSIONS: These findings provide evidence that TRP supplementation in women induces a positive bias in the processing of emotional material that is reminiscent of the actions of serotonergic antidepressants. This highlights a key role for serotonin in emotional processing and lends support to the use of TRP as a nutritional supplement in people with mild depression or for prevention in those at risk. Future studies are needed to clarify the effect of tryptophan on these measures in men.

PMID: 16767422 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support

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Neuropsychopharmacology. 2000 Jan;22(1):52-63.

Effects on mood of acute phenylalanine/tyrosine depletion in healthy women.

Leyton M[1], Young SN, Pihl RO, Etezadi S, Lauze C, Blier P, Baker GB, Benkelfat C.

Author information

Abstract

Catecholamines have been implicated in the etiology and pathophysiology of mood and anxiety disorders. In the present study, we investigated the effects of experimentally reducing catecholamine neurotransmission by means of acute phenylalanine/tyrosine depletion (APTD). Healthy female volunteers ingested: (1) a nutritionally balanced amino acid (AA) mixture (n = 14); (2) a mixture deficient in the serotonin precursor, tryptophan (n = 15); or (3) one deficient in the catecholamine precursors, phenylalanine and tyrosine (n = 12). Mood was measured at three times: at baseline and both immediately before and after an aversive psychological challenge (public speaking and mental arithmetic) conducted 5 hours after AA mixture ingestion. Acute tryptophan depletion (ATD) lowered mood and energy and increased irritability scores. These effects were statistically significant only after the psychological challenge. The effect of APTD on mood was similar to that of ATD. APTD did not attenuate the anxiety caused by the psychological challenge. These findings suggest that, in healthy women, reduced serotonin and/or catecholamine neurotransmission increases vulnerability to lowered mood, especially following exposure to aversive psychological events.

PMID: 10633491 [PubMed - indexed for MEDLINE] Free full text

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Cochrane Database Syst Rev. 2002;(2):CD001520.

Melatonin for the prevention and treatment of jet lag.

Herxheimer A[1], Petrie KJ.

Author information

Abstract

BACKGROUND: : Jet-lag commonly affects air travellers who cross several time zones. It results from the body's internal rhythms being out of step with the day-night cycle at the destination. Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world.

OBJECTIVES: : To assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet-lag after air travel across several time zones.

SEARCH STRATEGY: : We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, PsychLit and Science Citation Index electronically, and the journals 'Aviation, Space and Environmental Medicine' and 'Sleep' by hand. We searched citation lists of relevant studies for other relevant trials. We asked principal authors of relevant studies to tell us about unpublished trials. Reports of adverse events linked to melatonin use outside randomised trials were searched for systematically in 'Side Effects of Drugs' (SED) and SED Annuals, 'Reactions Weekly', MEDLINE, and the adverse drug reactions databases of the WHO Uppsala Monitoring Centre (UMC) and the US Food & Drug Administration.

SELECTION CRITERIA: : Randomised trials in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication. Outcome measures should consist of subjective rating of jet-lag or related components, such as subjective wellbeing, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms.

DATA COLLECTION AND ANALYSIS: : Ten trials met the inclusion criteria. All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment, one had a design fault and could not be used in the assessment. Reports of adverse events outside trials were found through MEDLINE, 'Reactions Weekly', and in the WHO UMC database.

MAIN RESULTS: : Nine of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more

effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. Based on the review, the number needed to treat (NNT) is 2. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time. The incidence of other side effects is low. Case reports suggest that people with epilepsy, and patients taking warfarin may come to harm from melatonin.

REVIEWER'S CONCLUSIONS: : Melatonin is remarkably effective in preventing or reducing jet-lag, and occasional short-term use appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet-lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be. The pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established. The effects of melatonin in people with epilepsy, and a possible interaction with warfarin, need investigation.

Update of

Melatonin for preventing and treating jet lag. [Cochrane Database Syst Rev. 2001]

PMID: 12076414 [PubMed - indexed for MEDLINE]

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THE LANCET FULL-TEXT ARTICLE

Lancet. 2007 Mar 31;369(9567):1117-29.

Jet lag: trends and coping strategies.

Waterhouse J[1], Reilly T, Atkinson G, Edwards B.

Author information

Abstract

The number of travellers undertaking long-distance flights has continued to increase. Such flights are associated with travel fatigue and jet lag, the symptoms of which are considered here, along with their similarities, differences, and causes. Difficulties with jet lag because of sleep loss and decreased performance are emphasised. Since jet lag is caused mainly by inappropriate timing of the body clock in the new time zone, the pertinent properties of the body clock are outlined, with a description of how the body clock can be adjusted. The methods, both pharmacological and behavioural, that have been used to alleviate the negative results of time-zone transitions, are reviewed. The results form the rationale for advice to travellers flying in different directions and crossing several time zones. Finally, there is an account of the main problems that remain unresolved.

PMID: 17398311 [PubMed - indexed for MEDLINE]

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Psychopharmacology (Berl). 1996 Jul;126(2):179-81.

Low dose melatonin improves sleep in healthy middle-aged subjects.

Attenburrow ME[1], Cowen PJ, Sharpley AL.

Author information

Abstract

We studied the effects of single evening doses of melatonin (0.3 mg and 1.0 mg orally) on polysomnographically measured sleep in 15 healthy middle-aged volunteers, using a placebo-controlled, double-blind, cross-over design. Compared to placebo, the 1.0 mg dose of melatonin significantly increased Actual Sleep Time, Sleep Efficiency, non-REM Sleep and REM Sleep Latency. These data are consistent with the hypothesis that low dose melatonin has hypnotic effects in humans. It is possible that administered melatonin may have a role to play in the treatment of sleep disorders.

PMID: 8856838 [PubMed - indexed for MEDLINE]

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Abstract

Sleep. 2000 Aug 1;23(5):663-9.

Hypnotic activity of melatonin.

Stone BM[1], Turner C, Mills SL, Nicholson AN.

Author information

Abstract

OBJECTIVE: To establish the effect of melatonin upon nocturnal and evening sleep.

METHODS: Experiment I: The effect of melatonin (0.1, 0.5, 1.0, 5.0, and 10 mg), ingested at 23:30, was studied on nocturnal sleep (23:30-07:30) and core body temperature in 8 healthy volunteers. Performance was measured 8.5 h post-ingestion. On completion of the experiment dim light melatonin onsets (DLMO) were determined. Experiment II: The effect of melatonin (0.5, 1.0, 5.0, and 10 mg), ingested at 18:00, was studied on evening sleep (18:00-24:00) and core body temperature in 6 healthy volunteers. Performance was measured 6.5 h post-ingestion. Each experiment was placebo-controlled and double-blind with a cross-over design with temazepam (20 mg) as an active control.

RESULTS: Experiment I: Melatonin (5 mg) reduced the duration of stage 3 in the first 100 min of sleep. Melatonin (0.1 mg) reduced body temperature 6.5 to 7 h post-ingestion. Temazepam increased stage 2, reduced wakefulness and stage 1, and increased the latency to REM sleep. Temazepam reduced body temperature 4.5 to 6.5 h post-ingestion. There were no changes in performance compared with placebo. DLMO occurred between 20:40 and 23:15. Experiment II: Melatonin (all doses) increased total sleep time (TST), sleep efficiency index (SEI) and stage 2, and reduced wakefulness. Temazepam increased TST, SEI, stage 2 and slow-wave sleep, and reduced wakefulness. There were no changes in body temperature or performance compared with placebo.

CONCLUSION: Melatonin given at 23:30 has no significant clinical effect on nocturnal sleep in healthy individuals. Hypnotic activity of melatonin when given in the early evening (presumably in the absence of endogenous melatonin) is similar to 20 mg temazepam.

PMID: 10947034 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

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FULL TEXT article at minervamedica.it

Minerva Ginecol. 2013 Aug;65(4):435-44.

Lady Prelox® improves sexual function in generally healthy women of reproductive age.

Bottari A[1], Belcaro G, Ledda A, Luzzi R, Cesarone MR, Dugall M.

Author information

Abstract

AIM: This supplement study evaluates the Female Sexual Function Index (FSFI) of 100 healthy women (37 to 45 years) with moderate sexual dysfunction who underwent a management program of lifestyle, diet, exercise, and stress control. In association with the management program a group of these women also used the supplement Lady Prelox® in tablets (20 mg Pycnogenol® pine bark extract, 200 mg L-arginine, 200 mg L-citrulline and 50 mg Rosvita® rose hip extract) for eight weeks.

METHODS: One group of women was supplemented with Lady Prelox® for 8 weeks. The nine-item FSFI questionnaire was used for evaluation of women's sexual function at inclusion (baseline), after four weeks, and after eight weeks of management and supplementation. Variation in oxidative stress was also evaluated by measuring plasma free radicals.

RESULTS: Following supplementation with Lady Prelox® the mean total FSFI scores increased from 14.96±2.68 to 28.25±2.35 after four weeks and 33.91±2.7 after eight weeks. Treatment values were significantly higher than in controls (who used only the management plan) with baseline values of 17.92±2.32 and scores of 23.45±1.82 after four weeks and to 23.52±2.20 after eight weeks. Women in the Lady Prelox® group had an initial value of plasma free radicals (PFR) of 398±29 Carr units: this value decreased to 344:28 at 4 weeks ($P<0.05$) and 332:31 at 8 weeks ($P<0.05$). Lower changes were observed in controls with an initial value of 389±33, decreasing to 377±32 ($P<0.05$) at 4 weeks and to 365; 33 ($P<0.05$) at 8 weeks (value significantly higher in controls not using Lady Prelox®). The supplementation was well tolerated; no unwanted effects occurred and no women had to stop the supplementation.

CONCLUSION: The study suggests that supplementation with Lady Prelox significantly improves sexual function across all domains evaluated by the FSFI in healthy women of late reproductive age. The improvement in FSFI is also associated with a significant decrease in oxidative stress.

PMID: 24051943 [PubMed - indexed for MEDLINE]

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Archives of Sexual Behavior, Vol. 31, No. 4, August 2002, pp. 323–332 (© 2002)

The Effects of Yohimbine Plus L-arginine Glutamate on Sexual Arousal in Postmenopausal Women with Sexual Arousal Disorder[1]

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Received August 17, 2001; revision received November 30, 2001; accepted December 31, 2001

This study examined the effects of the nitric oxide-precursor L-arginine combined with the α_2-blocker yohimbine on subjective and physiological sexual arousal in postmenopausal women with Female Sexual Arousal Disorder. Twenty-four women participated in three treatment sessions in which self-report and physiological (vaginal photoplethysmograph) sexual responses to erotic stimuli were measured following treatment with either L-arginine glutamate (6 g) plus yohimbine HCl (6 mg), yohimbine alone (6 mg), or placebo, using a randomized, double-blind, three-way cross-over design. Sexual responses were measured at approximately 30, 60, and 90 min postdrug administration. The combined oral administration of L-arginine glutamate and yohimbine substantially increased vaginal pulse amplitude responses to the erotic film at 60 min postdrug administration compared with placebo. Subjective reports of sexual arousal were significantly increased with exposure to the erotic stimuli but did not differ significantly between treatment groups.

KEY WORDS: yohimbine; L-arginine; female sexual arousal; photoplethysmography; nitric oxide; adrenergic.

INTRODUCTION

Physiological sexual arousal in women involves an increase in pelvic vascular blood flow and resultant pelvic vasocongestion, vaginal engorgement, swelling of the external genitalia, and clitoral erection (Levin, 1992). Vaginal wall engorgement occurs with increased blood flow to the local vascular bed, enabling plasma transudation and subsequent lubrication of the epithelial surface of the vaginal wall (Levin, 1991; Schiavi & Segraves, 1995). Female Sexual Arousal Disorder (FSAD) is defined in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 2000) as the "persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement" which causes "marked distress or interpersonal difficulty."

Prevalence estimates of FSAD vary widely between studies, likely due to different operational definitions of the disorder. A recent random survey of over 1,600 female respondents, ages 18–59 years, found that approximately 19% of women reported difficulties with lubrication (Laumann, Gagnon, Michael, & Michaels, 1994). Reported risk factors included health and lifestyle factors (e.g., history of STD, poor health, emotional problems), social status, and sexual experience (e.g., low sexual frequency, history of sexual abuse; Laumann, Paik, & Rosen, 1999). The incidence of FSAD is higher among women of peri or postmenopausal years: One study reported 44% of postmenopausal women experience persistent or recurrent lubrication problems (Rosen, Taylor, Leiblum, & Bachmann, 1993). Studies that have used more stringent diagnostic criteria report lower rates. For example, Lindal and Stefansson (1993) reported a lifetime prevalence of 6% in a large random population sample and Fugl-Meyer and Sjogren Fugl-Meyer (1999) reported a 1-year prevalence of 8% in a large Swedish sample. Both of these studies used the earlier *DSM-III* criteria, which did

[1] A version of this article was presented at the meeting of the International Academy of Sex Research, Paris, France, June 2000.

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Abstract

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Iran J Psychiatry. 2010 Winter;5(1):1-3.

Efficacy and Safety of Oral Combination of Yohimbine and L-arginine (SX) for the Treatment of Erectile Dysfunction: a multicenter, randomized, double blind, placebo-controlled clinical trial.

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Abstract

OBJECTIVE: The objective of this study was to assess the efficacy and safety of SX (combination of yohimbine and L-arginine) in the treatment of erectile dysfunction (ED).

METHODS: This trial was a 4-week, double blind study of parallel groups of patients with mild to moderate ED. Forty married male patients with ED of mild-to-moderate severity were screened for the study entry;among them, those aged 25-50 who reported a minimum of a- 3-month history of ED were eligible to enroll in this study. The severity of ED was based on EF domain scores on the international index of erectile function (IIEF). The scores of 15-25 was considered as mild to moderate ED. Patients were randomized to receive one capsule of SX or placebo on demand in a 1:1 ratio using a computer-generated code.

RESULTS: The difference between the two groups was significant at week 4 (endpoint) (P=0.03). Four adverse events were observed over the study. The difference between the SX and placebo was not significant in the frequency of adverse events.

CONCLUSION: This study indicates that SX is safe and effective for the treatment of mild to moderate ED at least in the short-term.

KEYWORDS: Erectile Dysfunction; L-Arginine; Yohimbine

PMID: 22952481 [PubMed] PMCID: PMC3430403 Free PMC Article

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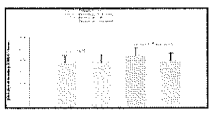

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Oral L-Citrulline Supplementation Improves Erection Hardness in Men With Mild Erectile Dysfunction

Luigi Cormio, Mario De Siati, Fabrizio Lorusso, Oscar Selvaggio, Lucia Mirabella, Francesca Sanguedolce, and Giuseppe Carrieri

OBJECTIVES To test the efficacy and safety of oral L-citrulline supplementation in improving erection hardness in patients with mild erectile dysfunction (ED). L-arginine supplementation improves nitric oxide-mediated vasodilation and endothelial function; however, oral administration has been hampered by extensive presystemic metabolism. In contrast, L-citrulline escapes presystemic metabolism and is converted to L-arginine, thus setting the rationale for oral L-citrulline supplementation as a donor for the L-arginine/nitric oxide pathway of penile erection.

METHODS In the present single-blind study, men with mild ED (erection hardness score of 3) received a placebo for 1 month and L-citrulline, 1.5 g/d, for another month. The erection hardness score, number of intercourses per month, treatment satisfaction, and adverse events were recorded.

RESULTS A total of 24 patients, mean age 56.5 ± 9.8 years, were entered and concluded the study without adverse events. The improvement in the erection hardness score from 3 (mild ED) to 4 (normal erectile function) occurred in 2 (8.3%) of the 24 men when taking placebo and 12 (50%) of the 24 men when taking L-citrulline ($P < .01$). The mean number of intercourses per month increased from 1.37 ± 0.93 at baseline to 1.53 ± 1.00 at the end of the placebo phase ($P = .57$) and 2.3 ± 1.37 at the end of the treatment phase ($P < .01$). All patients reporting an erection hardness score improvement from 3 to 4 reported being very satisfied.

CONCLUSIONS Although less effective than phosphodiesterase type-5 enzyme inhibitors, at least in the short term, L-citrulline supplementation has been proved to be safe and psychologically well accepted by patients. Its role as an alternative treatment for mild to moderate ED, particularly in patients with a psychologically fear of phosphodiesterase type-5 enzyme inhibitors, deserves further research. UROLOGY 77: 119–122, 2011. © 2011 Elsevier Inc.

Nitric oxide (NO) is a physiologic signal essential to penile erection, because it acts both as a neurotransmitter in the penile nonadrenergic noncholinergic nerve fibers and as a vasodilator of smooth muscle cells of the penile arteries, sinusoids, and trabeculae.[1,2] NO activates soluble guanylate cyclase to convert guanosine triphosphate to cyclic guanosine monophosphate (cGMP), which in turn causes penile smooth muscle relaxation. The erection occurs when the sinusoids engorged with blood compress the subtunical veins to closure, thus trapping blood within the penis. The erection eventually subsides when cGMP has been hydrolyzed to inactive GMP by phosphodiesterase type 5 enzymes (PDE-5).

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Submitted: July 13, 2010, accepted (with revisions): August 21, 2010

PDE-5 inhibitors, which increase penile smooth muscle relaxation by preventing cGMP hydrolysis, represent a safe and effective oral treatment of erectile dysfunction (ED); however, their cost, contraindications, and fear, more than the occurrence, of side effects have limited their use. Nutrients acting as NO donors would therefore represent an attractive alternative to the use of PDE-5 inhibitors.

The NO donor L-arginine is a semiessential amino acid present in dietary proteins and produced in the body from L-citrulline, another semiessential amino acid synthesized in the intestinal tract from glutamine.[3] NO synthase isoforms convert L-arginine to NO, which activates the cGMP pathway, and L-citrulline, which can be reconverted by the kidneys into L-arginine to restart a NO-producing cycle.[4] Thus, L-arginine causes in vitro[5] relaxation of isolated corpus cavernosum tissue. In a double-blind placebo-controlled study testing L-arginine versus placebo in men with ED, however, subjective improvement was reported by 31% of men taking L-

0090-4295/11/$36.00
doi:10.1016/j.urology.2010.08.028

NUTRITION RESEARCH XX (2012) XXX–XXX

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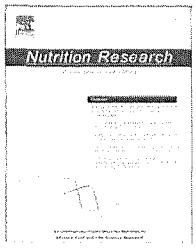

L-glutamine absorption is enhanced after ingestion of L-alanylglutamine compared with the free amino acid or wheat protein

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ARTICLE INFO

Article history:
Received 2 September 2011
Revised 14 February 2012
Accepted 16 February 2012

Keywords:
L-glutamine
L-alanylglutamine
Wheat protein
Absorption
Supplements
Males

ABSTRACT

Differences in plasma L-glutamine (L-Gln) concentrations from ingestion of different formulations of L-Gln were examined in 8 men (26.8 ± 4.2 years old, 181.1 ± 10.9 cm, 85.8 ± 15.4 kg). Subjects reported to the laboratory on 4 separate occasions and randomly consumed 1 of 4drinks containing 60 mg/kg of L-Gln; 89 mg/kg of Sustamine (L-alanylglutamine [AlaGln]; Kyowa Hakko Europe GmbH, Düsseldorf, Germany), which contained an equivalent L-Gln dose as consumed in L-Gln); 200 mg/kg of an enzymatically hydrolyzed wheat protein (HWP) with an L-Gln content of 31 mg/kg; or a control that consisted only of water. It was hypothesized that the AlaGln trial would increase plasma glutamine concentrations greater than the other experimental trials. Ingestion of L-Gln, AlaGln, and HWP resulted in significant increases in the plasma L-Gln concentration, peaking at 0.5, 0.5, and 0.75 hours, respectively. The corresponding mean peak increases were 179 ± 61, 284 ± 84, and 134 ± 36 μmol/L, respectively. Concentrations returned to baseline in all subjects by 2 hours after L-Gln and HWP and by 4 hours after AlaGln. Mean areas under the plasma concentration curve, calculated between 0 and 4 hours, were 127 ± 61, 284 ± 154, and 151 ± 63 $\mu mol \cdot h \cdot L^{-1}$ for L-Gln, AlaGln, and HWP, respectively. When allowance was made for the lower L-Gln dose administered as HWP, the peak plasma concentration and area under the plasma concentration curve were approximately the same as for AlaGln. The results suggest a greater transfer from the gut to plasma of L-Gln when supplied as AlaGln and possibly also as HWP compared with when the same dose was provided as the free amino acid.

1. Introduction

L-glutamine (L-Gln), synthesized from glutamate and ammonia, is a neutral amino acid that is readily transported across plasma membranes [1]. An important intermediate in several metabolic pathways, cellular use of L-Gln can far exceed that of other amino acids particularly within intestinal and immune cells [2,3]. Of the proteogenic amino acids in man, L-Gln provides 50% of the free amino acid pool, with normal concentrations in the range of 0.5 to 0.8 mmol/L in plasma and 20 to 25 mmol/L in muscle intracellular water [4,5]. L-glutamine exhibits several metabolic roles; for example, it is an important form of transport of amino nitrogen and ammonia and a substrate in gluconeogenesis and ammonia-

Abbreviations: AlaGln, L-alanylglutamine; AUC, area under the plasma concentration curve; HWP, hydrolyzed wheat protein; L-Gln, L-glutamine; CTL, control.

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0271-5317/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.nutres.2012.02.003