An Audiology-Centered Trial Protocol to Postpone or Reduce Age-Related Hearing Loss, Alzheimer's, Cancer and Other Age-Related Illnesses

September 25, 2018

Prepared for the Academy of Rehabilitative Audiology for their 2018 bi-annual meeting by Rolf Martin
Howard Raphaelson on behalf of the rest of the
2002-2018 Wild Blueberry Health Study research team.

posted online at

HearingCheck123.com

Howard Raphaelson and I will be co-presenters. today.

Patent acknowledgments:

Four patents have been filed, two approved, one majority owned by Cornell University.

Rolf J. Martin, Barrie S. Sachs and Howard A. Raphaelson on behalf of the entire 2002-2018 Blueberry Health Study team:

Rolf J. Martin[1], J. Wesson Ashford[2], Ines E. Augie[3], Diana J. Burns[4], Richard J. Coppings[5], David L. Doiron[4], Phil Fichandler[4], Marilyn Gerling[4], Kurt E. Gerstmann[6], Kathy Hull[7], James A. Joseph[8], Amy Casdorph Kokesh[6], Rozlyn A. Krajcik[1], Bruce S Kristal[10], Aaron Lukton[11], Michael Luzi[12], Stephen Massardo[3], Dana Mathew[13], Jessica Norton[14], Norman Orentreich[3], Martin Perez[15], Alec Pruchnicki[16], Howard A. Raphaelson[4], Sheri A. Raphaelson[17], Barrie S. Sachs[18], Edwin Sanchez[15], Roseanne Schnoll[19], Paul Satkowski[14], Daniel Smith[14], Joseph H. Vogelman[3] and Anthony Wetherell[20].

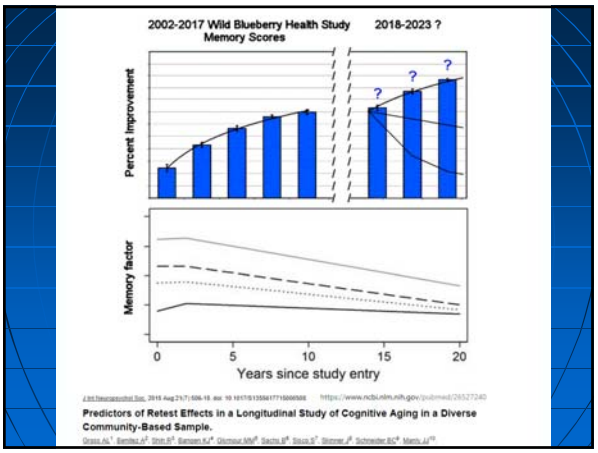
1) Blueberry Health Study / MMT Corp, Sherman, CT, Burke/Cornell Medical Research Institute and Burke Rehabilitation Hospital, White Plains, NY (now retired), 2) Stanford / VA Aging Clinical Research Center, Palo Alto, CA, 3) Orentreich Foundation for the Advancement of Science, Inc., Cold Spring-on-Hudson, NY, 4) Mansfield Senior Center, Mansfield, CT, 5) Lane College, Jackson, TN, 6) New York, NY and Sherman, CT, 7) New Fairfield Senior Center, New Fairfield, CT, 8) Human Nutrition Research Center on Aging at Tufts University, Boston, MA, 9) Raleigh, NC, 10) Weymouth, MA, 11) City University of New York Biochemistry Ph.D. Program, New York, NY (retired), 12) Sherman IGA Supermarket, Sherman, CT, 13) New Fairfield, CT, 14) Foodtown Supermarket, Cold Spring-on-Hudson, NY, 15) C-Town Supermarket, Danbury, CT, 16) Mount Sinai West and Mount Sinai St. Luke's/Mount Sinai Hospital, New York, NY, 17) Midwife Services, Espanola, NM, 18) HR Herbs, Teas and Gifts, Sherman, CT, 19) Health & Nutrition Sciences Dept, Brooklyn College of the City University of New York, Brooklyn, NY, 20) Defence Sci & Tech Lab, United Kingdom (retired).

The secret to conducting a 16-year intervention study is to work with a rock-solid person like

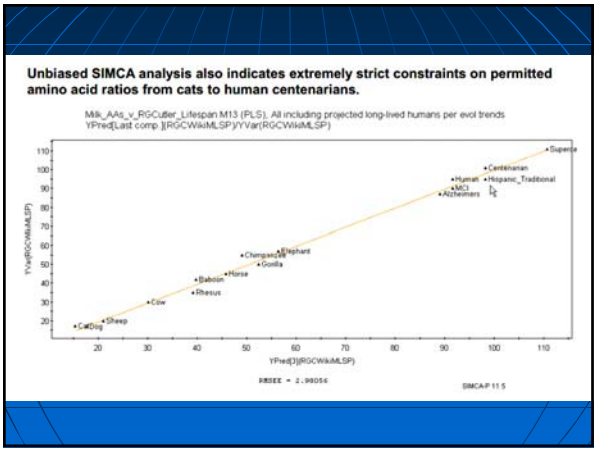
Howard Raphaelson.

The salient Wild Blueberry Health Study result since 2002 has been documentation of a ten-year period of steady, relatively linear word-memory improvement.

This ten year improvement compares favorably with other published results that show two years of improvement (due to practice with tests) followed by a ten- to twenty-year period of linear decline.



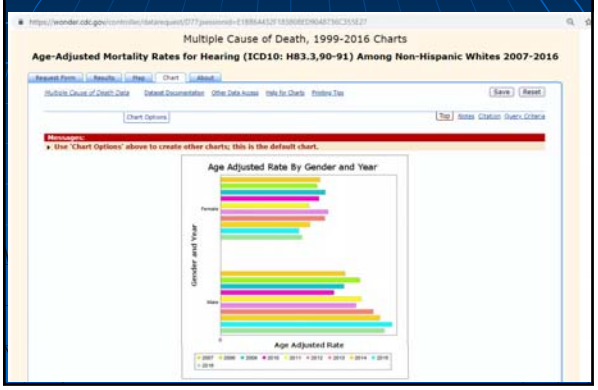
A second important result is development of equations to accurately predict mammalian lifespans based on milk amino acid concentrations, with serine and methionine both having very important roles for humans and elephants.

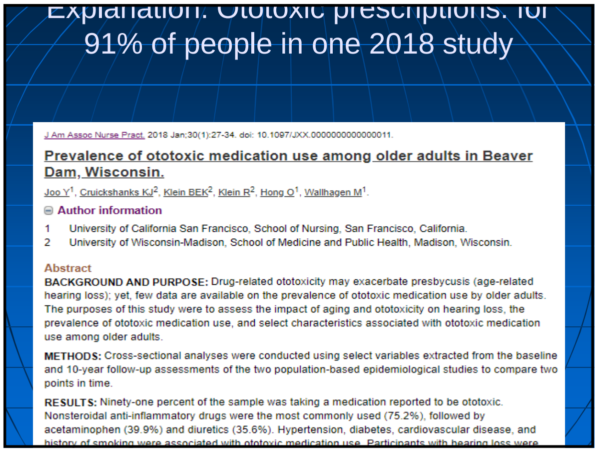


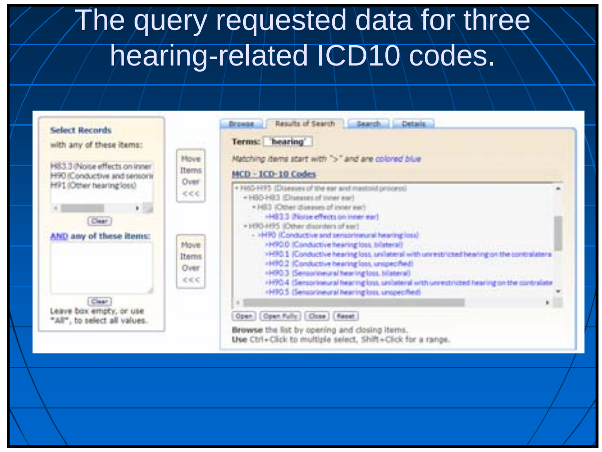
FIRST MAIN POINT TODAY:

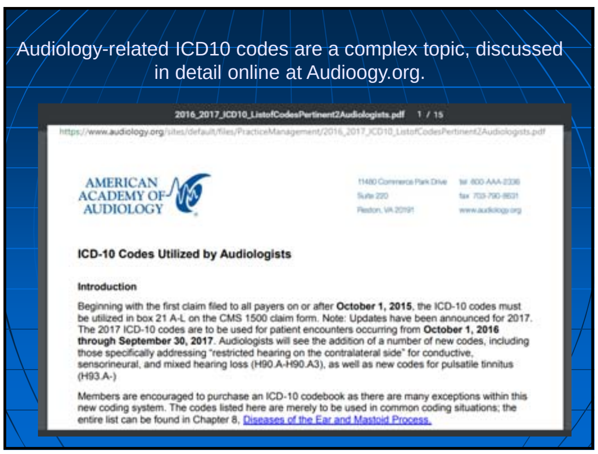
Hearing is more often listed on death certificates for men than women, and the frequency of hearing-associated mortality is rising in the United States.

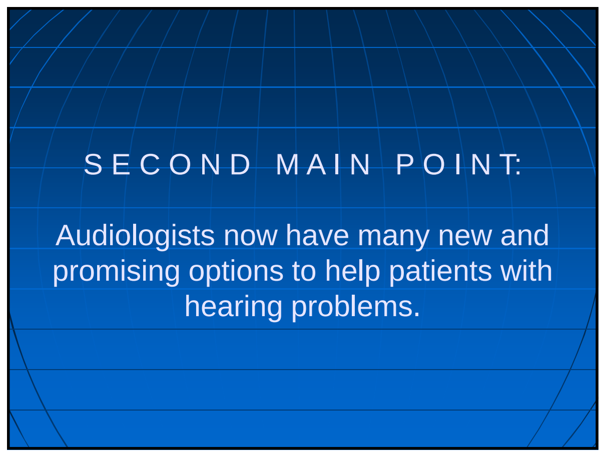
FIRST MAIN POINT:
Hearing-related mortality may be increasing.

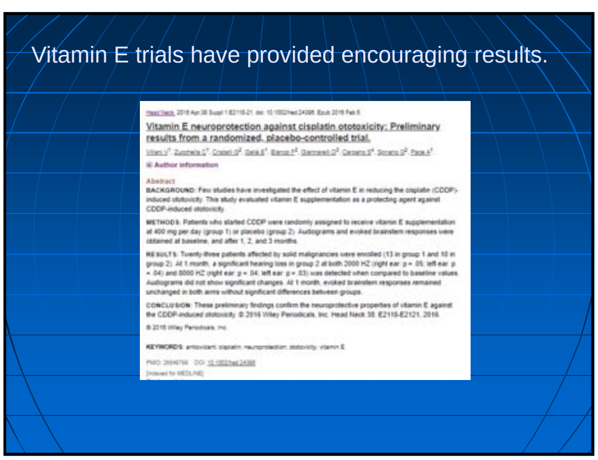


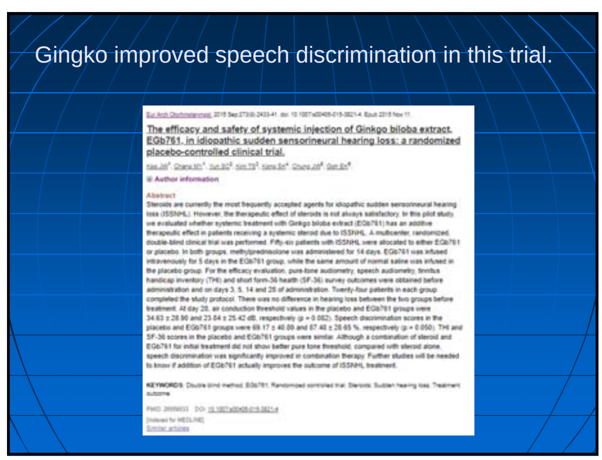

Explanation: Ototoxic prescriptions: for 91% of people in one 2018 study
J Am Assoc Nurse Pract. 2018 Jan;30(1):27-34. doi: 10.1097/JXX.0000000000000011.
Prevalence of ototoxic medication use among older adults in Beaver Dam, Wisconsin.
Joo Y[1], Cruickshanks KJ[2], Klein BEK[2], Klein R[2], Hong O[1], Wallhagen M[1].
Author information
1 University of California San Francisco, School of Nursing, San Francisco, California.
2 University of Wisconsin-Madison, School of Medicine and Public Health, Madison, Wisconsin.
Abstract
BACKGROUND AND PURPOSE: Drug-related ototoxicity may exacerbate presbycusis (age-related hearing loss); yet, few data are available on the prevalence of ototoxic medication use by older adults. The purposes of this study were to assess the impact of aging and ototoxicity on hearing loss, the prevalence of ototoxic medication use, and select characteristics associated with ototoxic medication use among older adults.
METHODS: Cross-sectional analyses were conducted using select variables extracted from the baseline and 10-year follow-up assessments of the two population-based epidemiological studies to compare two points in time.
RESULTS: Ninety-one percent of the sample was taking a medication reported to be ototoxic. Nonsteroidal anti-inflammatory drugs were the most commonly used (75.2%), followed by acetaminophen (39.9%) and diuretics (35.6%). Hypertension, diabetes, cardiovascular disease, and history of smoking were associated with ototoxic medication use. Participants with hearing loss were


The query requested data for three hearing-related ICD10 codes.
Select Records
with any of these items:
AND any of these items:
Terms: hearing
MCD - ICD-10 Codes


Audiology-related ICD10 codes are a complex topic, discussed in detail online at Audioogy.org.
2016_2017_ICD10_ListofCodesPertinent2Audiologists.pdf 1 / 15
AMERICAN ACADEMY OF AUDIOLOGY
11480 Commerce Park Drive
Suite 220
Reston, VA 20191
tel 800-AAA-2336
fax 703-790-8631
www.audiology.org
ICD-10 Codes Utilized by Audiologists
Introduction
Beginning with the first claim filed to all payers on or after October 1, 2015, the ICD-10 codes must be utilized in box 21 A-L on the CMS 1500 claim form. Note: Updates have been announced for 2017. The 2017 ICD-10 codes are to be used for patient encounters occurring from October 1, 2016 through September 30, 2017. Audiologists will see the addition of a number of new codes, including those specifically addressing "restricted hearing on the contralateral side" for conductive, sensorineural, and mixed hearing loss (H90.A-H90.A3), as well as new codes for pulsatile tinnitus (H93.A-)
Members are encouraged to purchase an ICD-10 codebook as there are many exceptions within this new coding system. The codes listed here are merely to be used in common coding situations; the entire list can be found in Chapter 8, Diseases of the Ear and Mastoid Process.


SECOND MAIN POINT:
Audiologists now have many new and promising options to help patients with hearing problems.


Vitamin E trials have provided encouraging results.
Vitamin E neuroprotection against cisplatin ototoxicity: Preliminary results from a randomized, placebo-controlled trial.


Gingko improved speech discrimination in this trial.
The efficacy and safety of systemic injection of Ginkgo biloba extract, EGb761, in idiopathic sudden sensorineural hearing loss: a randomized placebo-controlled clinical trial.

The natural antioxidant N-acetyl cysteine and also ginseng protected hearing in this trial.

Comparison of the effects of N-acetyl-cysteine and ginseng in prevention of noise induced hearing loss in male textile workers.

Author information

Abstract

Previous studies revealed the role of antioxidant agents in prevention of noise induced hearing loss (NIHL). The aim of this study was to compare the protective effect of N-acetyl-cysteine (NAC) and ginseng on protection of NIHL in textile workers exposed to continuous noise in daily working. In this study, 48 participants were randomly allocated to three groups: Group I received NAC 1200 mg/day; Group II received ginseng 200 mg/day; and Group III (control group) received no supplement. Pure tone audiometry and high frequency audiometry were performed pre-shift before and after 14 days (on day 15). Linear regression analysis results showed reduced noise-induced temporary threshold shift (TTS) for NAC and ginseng groups at 4, 6 and 16 kHz ($P < 0.001$) in both ears. Furthermore, the protective effects were more prominent in NAC than ginseng. Our results show that NAC and ginseng can reduce noise induced TTS in workers exposed to occupational noise. Further studies are needed to prove antioxidants benefits in hearing conservation programs.

Vitamins A, C and E and selenium protected hearing during methylprednisolone treatment in this trial.

Vitamins A, C, and E and selenium in the treatment of idiopathic sudden sensorineural hearing loss.

Author information

Abstract

This study evaluated the effectiveness of vitamins A, C, and E, with selenium, in the treatment of idiopathic sudden sensorineural hearing loss (ISSNHL). This was a prospective, controlled study performed at a tertiary teaching and research hospital. Over a 32-month period, patients were treated with either our standard ISSNHL treatment regimen plus vitamins A, C, and E and selenium (ACE+ group) or with only our standard ISSNHL treatment regimen (ACE- group). The demographics, additional symptoms, mean initial and final hearing levels, mean hearing gain, and recovery data were compared between the two groups. The ACE+ group, consisting of 79 (55.5 %) patients, received vitamin A (natural beta-carotene, 26,000 IU), vitamin C (ascorbic acid, 200 mg), vitamin E (dl-alpha-tocopherol, 200 IU), and selenium (50 μg) twice daily for 30 days in addition to our ISSNHL treatment regimen: methylprednisolone at an initial dose of 1 mg/kg body weight per day, tapered over 14 days; Rheomacrodex® (L) 10 g of dextran and 0.9 g of NaCl/100 ml) 500 ml daily for 5 days; Vastarel® (B) 20-mg tablet (20 mg of trimetazidine dihydrochloride) three times daily for 30 days; and ten 60-min hyperbaric oxygen (HBO) sessions (2.5 absolute atmospheres of 100 % O2), once daily, starting the day of hospitalization. The ACE- group comprised 56 (44.4 %) patients, who received only our ISSNHL treatment regimen. The mean hearing gains were 36.2 ± 20.3 dB in the ACE+ group and 27.1 ± 20.6 dB in the ACE- group. The mean hearing gain rates were significantly higher in the ACE+ group than in the ACE- group ($p = 0.014$). Treatment with vitamins A, C, and E and selenium was effective in ISSNHL patients undergoing treatment with methylprednisolone, dexbran, trimetazidine dihydrochloride, and HBO, and might be more effective when the initial hearing level is below 46 dB.

High dose vitamins C may have improved hearing recovery in this trial.

Effect of high dose intravenous vitamin C on idiopathic sudden sensorineural hearing loss: a prospective single-blind randomized controlled trial.

Author information

Abstract

The aim of this prospective single-blind randomized controlled study was to evaluate the therapeutic efficacy of high dose intravenous vitamin C (HDVC) added to systemic steroid in patients with idiopathic sudden sensorineural hearing loss (ISSNHL). Between August 2010 and August 2011, 72 ISSNHL patients who participated in this study were randomly allocated to two groups: 36 to a control group, members of which were given systemic steroid treatment for 15 days, and 36 to a HDVC group, members of which were given HDVC (200 mg/kg/day) for 10 days in addition to steroid therapy followed by oral vitamin C (2,000 mg) for 30 days after discharge. Finally, we analyzed each group: 35 as a control group and 32 as a HDVC group. Auditory evaluations were performed by pure tone audiometry (PTA) before and ~1 month after treatment using Siegel's criteria. HDVC group showed significantly greater complete and partial recovery improvement ($p = 0.035$). In addition, the complete recovery rate in the HDVC group was more than twice that of the control group ($p = 0.031$). In the HDVC group, PTA improved from 67.6 ± 19.8 dB HL before treatment to 37.1 ± 28.8 dB HL at 1 month after treatment, whereas in the control group, PTA improved from 70.3 ± 12.4 to 47.8 ± 25.2 dB HL, which represented a significant intergroup difference ($p = 0.030$). In conclusion, HDVC may enhance hearing recovery in ISSNHL patients, which suggests that HDVC reduces levels of reactive oxygen metabolites produced by inner ear ischemia or inflammation, and that HDVC could be considered for the treatment of ISSNHL.

Failed trials also have occurred, so very careful planning is critically important.

Antioxidant therapy in the elderly with tinnitus.

Author information

Abstract

INTRODUCTION: Several approaches have been tried for the treatment of tinnitus, from cognitive-behavioral therapies and sound enrichment to medication. In this context, antioxidants, widely used in numerous areas of medicine, appear to represent a promising approach for the control of this symptom, which often is poorly controlled.

OBJECTIVE: To evaluate the effects of antioxidant therapy for tinnitus in a group of elderly patients.

METHODS: Prospective, randomized, double-blinded, placebo-controlled clinical trial. The sample consisted of 58 subjects aged 60 years or older, with a complaint of tinnitus associated with sensorineural hearing loss. These individuals completed the Tinnitus Handicap Inventory (THI) questionnaire before and after six months of therapy. The treatment regimens were: Ginkgo biloba dry extract (120mg/day), α-lipoic acid (90mg/day)+vitamin C (500mg/day), papaverine hydrochloride (100mg/day)+vitamin E (400mg/day), and placebo.

RESULTS: There was no statistically significant difference between THI by degree ($p=0.441$) and by score ($p=0.640$) before and after treatment.

CONCLUSION: There was no benefit from the use of antioxidant agents for tinnitus in this sample.

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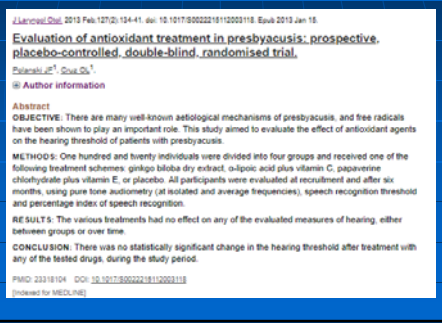
KEYWORDS: Aged; Antioxidants; Antioxidants; Idoso; Tinnitus; Zumbido

Failure may inevitably occur for physiologically older individuals, after aging prevents protective and reparative gene expression.



J Laryngol Otol. 2013 Feb;127(2):134-41. doi: 10.1017/S0022215112003118. Epub 2013 Jan 16.

Evaluation of antioxidant treatment in presbyacusis: prospective, placebo-controlled, double-blind, randomised trial.

Author information

Abstract

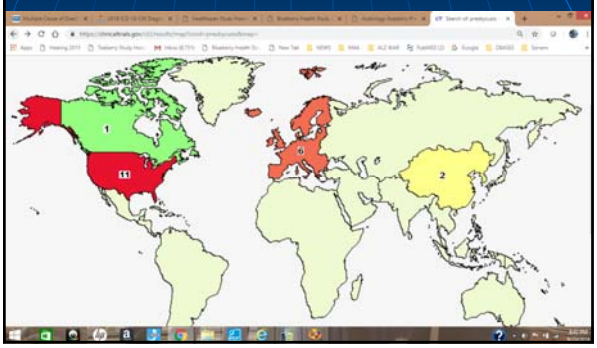
OBJECTIVE: There are many well-known aetiological mechanisms of presbyacusis, and free radicals have been shown to play an important role. This study aimed to evaluate the effect of antioxidant agents on the hearing threshold of patients with presbyacusis.

METHODS: One hundred and twenty individuals were divided into four groups and received one of the following treatment schemes: ginkgo biloba dry extract, α-lipoic acid plus vitamin C, papaverine chlorhydrate plus vitamin E, or placebo. All participants were evaluated at recruitment and after six months, using pure tone audiometry (at isolated and average frequencies), speech recognition threshold and percentage index of speech recognition.

RESULTS: The various treatments had no effect on any of the evaluated measures of hearing, either between groups or over time.

CONCLUSION: There was no statistically significant change in the hearing threshold after treatment with any of the tested drugs, during the study period.

Clinical trials to improve or protect hearing, listed at ClinicalTrials.gov, are few in number. Additional clinical trials are urgently needed.

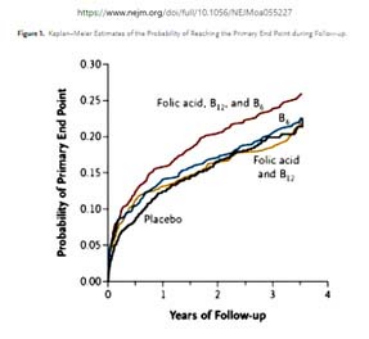


THIRD MAIN POINT:

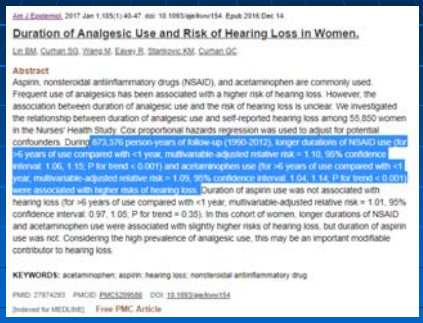
Treatments can be dangerous and even lethal.

Personalized treatment and interventions are therefore needed, with frequent safety checks.

B Vitamins may raise cardiovascular risks as well as cancer risks.



NSAID use increases ARHL risk by 9 to 10%.

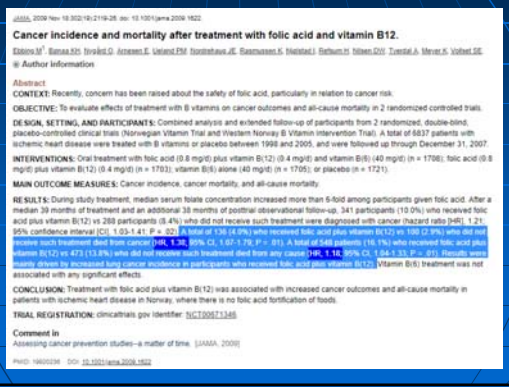

Duration of Analgesic Use and Risk of Hearing Loss in Women.

Abstract

Aspirin, nonsteroidal antiinflammatory drugs (NSAID), and acetaminophen are commonly used. Frequent use of analgesics has been associated with a higher risk of hearing loss. However, the association between duration of analgesic use and the risk of hearing loss is unclear. We investigated the relationship between duration of analgesic use and self-reported hearing loss among 55,850 women in the Nurses' Health Study. Cox proportional hazards regression was used to adjust for potential confounders. During 673,376 person-years of follow-up (1990-2012), longer durations of NSAID use (for >6 years of use compared with <1 year, multivariable-adjusted relative risk = 1.10, 95% confidence interval: 1.06, 1.15; P for trend < 0.001) and acetaminophen use (for >6 years of use compared with <1 year, multivariable-adjusted relative risk = 1.09, 95% confidence interval: 1.04, 1.14; P for trend < 0.001) were associated with higher risks of hearing loss. Duration of aspirin use was not associated with hearing loss (for >6 years of use compared with <1 year, multivariable-adjusted relative risk = 1.01, 95% confidence interval: 0.97, 1.05; P for trend = 0.35). In this cohort of women, longer durations of NSAID and acetaminophen use were associated with slightly higher risks of hearing loss, but duration of aspirin use was not. Considering the high prevalence of analgesic use, this may be an important modifiable contributor to hearing loss.

KEYWORDS: acetaminophen; aspirin; hearing loss; nonsteroidal antiinflammatory drug

B Vitamins may raise cancer risk and all-cause mortality by 38% and 18%.


Cancer incidence and mortality after treatment with folic acid and vitamin B12.

Abstract

CONTEXT: Recently, concern has been raised about the safety of folic acid, particularly in relation to cancer risk.

OBJECTIVE: To evaluate effects of treatment with B vitamins on cancer outcomes and all-cause mortality in 2 randomized controlled trials.

DESIGN, SETTING, AND PARTICIPANTS: Combined analysis and extended follow-up of participants from 2 randomized, double-blind, placebo-controlled clinical trials (Norwegian Vitamin Trial and Western Norway B Vitamin Intervention Trial). A total of 6837 patients with ischemic heart disease were treated with B vitamins or placebo between 1998 and 2005, and were followed up through December 31, 2007.

INTERVENTIONS: Oral treatment with folic acid (0.8 mg/d) plus vitamin B(12) (0.4 mg/d) and vitamin B(6) (40 mg/d) (n = 1706); folic acid (0.8 mg/d) plus vitamin B(12) (0.4 mg/d) (n = 1703); vitamin B(6) alone (40 mg/d) (n = 1705); or placebo (n = 1721).

MAIN OUTCOME MEASURES: Cancer incidence, cancer mortality, and all-cause mortality.

RESULTS: During study treatment, median serum folate concentration increased more than 6-fold among participants given folic acid. After a median 39 months of treatment and an additional 38 months of posttrial observational follow-up, 341 participants (10.0%) who received folic acid plus vitamin B(12) vs 288 participants (8.4%) who did not receive such treatment were diagnosed with cancer (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.03-1.41; P = .02). A total of 136 (4.0%) who received folic acid plus vitamin B(12) vs 100 (2.9%) who did not receive such treatment died from cancer (HR, 1.38; 95% CI, 1.07-1.79; P = .01). A total of 548 patients (16.1%) who received folic acid plus vitamin B(12) vs 473 (13.8%) who did not receive such treatment died from any cause (HR, 1.18; 95% CI, 1.04-1.33; P = .01). Results were mainly driven by increased lung cancer incidence in participants who received folic acid plus vitamin B(12). Vitamin B(6) treatment was not associated with any significant effects.

CONCLUSION: Treatment with folic acid plus vitamin B(12) was associated with increased cancer outcomes and all-cause mortality in patients with ischemic heart disease in Norway, where there is no folic acid fortification of foods.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00671346

Comment in

Assessing cancer prevention studies--a matter of time. [JAMA. 2009]

Injury and even mortality may result for physiologically unique individuals, even after otherwise harmless supplements or medications are prescribed.

Daily blueberries may worsen memory scores for one of every five study participants.

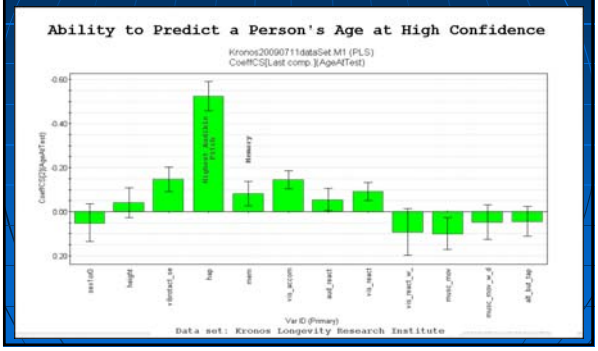
Such sensitive participants were quickly advised to withdraw from our study, so neither negative symptoms nor injuries were seen.

Online audiology studies can employ frequent weekly or biweekly measurements to detect health downturns before serious injuries occur.

FOURTH MAIN POINT:

Audiologists have exceptionally high statistical power at their fingertips because of the precision of hearing measurements.

SIMCA multivariate analysis () of highest audible pitch and chronological age. (Data source: Kronos Science Laboratories, Phoenix, Arizona)



Highest audible pitch (HAP) dominates multivariate regression analysis compared to other metrics.

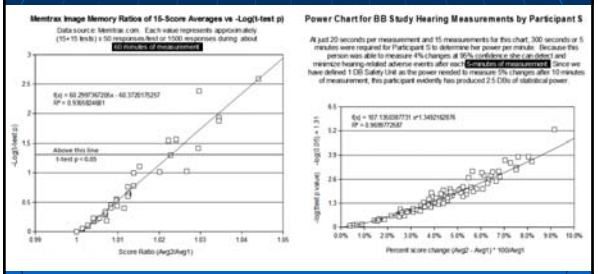
Multiple Linear Regression – Ordinary Least Squares

Variable	Parameter	S.E.	T-STAT H0: parameter = 0	2-tail p-value	1-tail p-value
sex1or0[t]	-1.196296	0.715172	-1.672738	0.094786	0.047393
height[t]	-2.179779	1.059299	-2.057756	0.039951	0.019975
vibrotact_sens[t]	-0.233609	0.051197	-4.562986	6.0E-6	3.0E-6
hap[t]	-0.179123	0.008541	-20.971606	0	0
mem[t]	-0.159643	0.079688	-2.003351	0.045491	0.022745
vis_accom[t]	-0.067197	0.014949	-4.495057	8.0E-6	4.0E-6
aud_react[t]	-0.017892	0.013404	-1.334808	0.182335	0.091167
vis_react[t]	-0.028623	0.012308	-2.325638	0.020297	0.010149
vis_react_w_dec[t]	0.031946	0.008167	3.911375	0.0001	5.0E-5
musc_mov[t]	0.030066	0.007916	3.798041	0.000157	7.9E-5
musc_mov_w_dec[t]	0.018799	0.010196	1.84379	0.065599	0.032799
alt_but_tap[t]	0.007057	0.01036	0.681191	0.495956	0.247978
Constant	88.034714	7.274052	12.102568	0	0

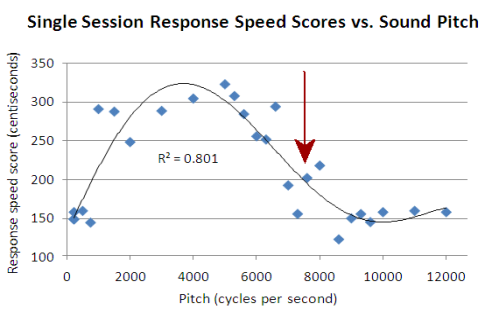
Highest audible pitch (HAP) is assigned over three times more of the partial correlation than any other metric.

Variable	Partial Correlation
sex1or0[t]	-0.06025
height[t]	-0.074049
vibrotact_sens[t]	-0.162465
hap[t]	-0.603438
mem[t]	-0.072102
vis_accom[t]	-0.160109
aud_react[t]	-0.04811
vis_react[t]	-0.083625
vis_react_w_dec[t]	0.139754
musc_mov[t]	0.135781
musc_mov_w_dec[t]	0.066385
alt_but_tap[t]	0.024573
Constant	0.400214

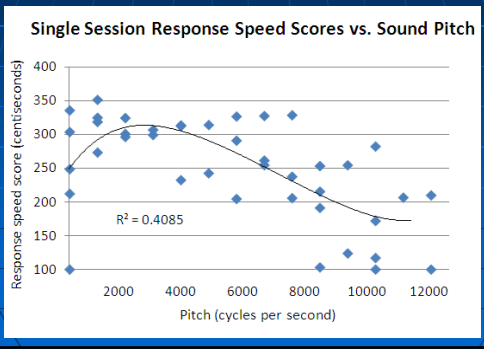
In this comparison, 5 minutes of audiometry produced as much power as 60 minutes of memory measurement.



Online measurements can provide valid hearing acuity vs. frequency data, allowing focused training at selected pitch ranges.



Online measurements are not always so precise for single measurement sessions. However averaging many sessions can give surprisingly significant results.



Significant correlations between blueberries and yogurt, face-memory and hearing can be seen at 95% confidence.

One year of data from Participant F	2-Week Average Hearing	Health Rating	Wild Blueberries	Wild Blueberries and Yogurt	Wild Blueberries plus all supplements	Face % Correct	Face Response Time	Faces Final 10 Response Times	Hearing 2K-1000 msec delay	Hearing 4K-2000 msec delay
2-Week Average Hearing		0.13	0.17	0.26	0.24	0.02	0.13	-0.02	0.64	0.49
Health Rating	0.13		0.11	0.12	0.13	0.16	-0.13	-0.19	0.19	0.15
Wild Blueberries	0.17	0.11		0.58	0.58	0.00	0.00	-0.08	0.02	0.05
Wild Blueberries and Yogurt	0.26	0.12	0.58		0.73	0.17	-0.03	-0.13	0.25	0.44
Wild Blueberries plus all supplements	0.24	0.13	0.58	0.73		0.07	0.00	-0.16	0.12	0.35
Face % Correct	0.02	0.16	0.00	0.17	0.07		-0.34	-0.35	0.19	0.21
Face Response Time	0.13	-0.13	0.00	-0.03	0.00	-0.34		0.37	-0.03	0.00
Faces Final 10 Response Times	-0.02	-0.19	-0.08	-0.13	-0.16	-0.35	0.37		-0.06	-0.12
Hearing 2K-1000 msec delay	0.64	0.19	0.02	0.25	0.12	0.19	-0.03	-0.06		0.35
Hearing 4K-2000 msec delay	0.49	0.15	0.05	0.44	0.35	0.21	0.00	-0.12	0.35	

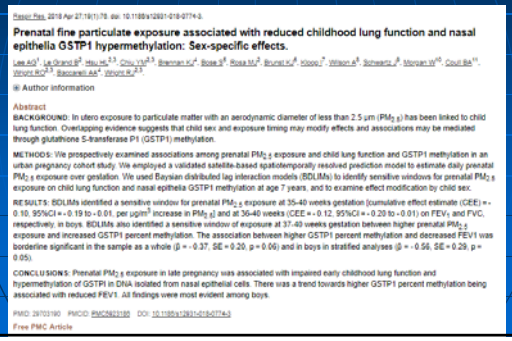
FIFTH MAIN POINT:

The METHYLATION REVOLUTION has reached geroscience, cancer research and audiology.

Genes are frequently shut down by methylation – the addition of CH3 groups that block gene readout.

Methylation occurs steadily during aging, shutting off genes needed to prevent cancer from forming and also turning off genes needed for cell survival and for hearing.

This breakthrough paper from the Mount Sinai Medical Center (NYC), Columbia and Harvard Universities… documented DNA methylation and shutdown of a core Alzheimer's-protective-Nrf2 target gene (GSTP1) to be associated with toxic air pollution even in unborn children.



Respir Res. 2018 Apr 27;19(1):76. doi: 10.1186/s12931-018-0774-3.

Prenatal fine particulate exposure associated with reduced childhood lung function and nasal epithelia GSTP1 hypermethylation: Sex-specific effects.

Lee AG[1], Le Grand B[2], Hsu HL[2,3], Chiu YH[2,3], Brennan KJ[4], Bose S[4], Rosa MJ[2], Brunst K[4], Kloog I[5], Wilson A[4], Schwartz J[6], Morgan W[7], Coull BA[1], Wright RO[2,3], Baccarelli AA[4], Wright RJ[2,3]

Author information

Abstract

BACKGROUND: In utero exposure to particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) has been linked to child lung function. Overlapping evidence suggests that child sex and exposure timing may modify effects and associations may be mediated through glutathione S-transferase P1 (GSTP1) methylation.

METHODS: We prospectively examined associations among prenatal $PM_{2.5}$ exposure and child lung function and GSTP1 methylation in an urban pregnancy cohort study. We employed a validated satellite-based spatiotemporally resolved prediction model to estimate daily prenatal $PM_{2.5}$ exposure over gestation. We used Bayesian distributed lag interaction models (BDLIMs) to identify sensitive windows for prenatal $PM_{2.5}$ exposure on child lung function and nasal epithelia GSTP1 methylation at age 7 years, and to examine effect modification by child sex.

RESULTS: BDLIMs identified a sensitive window for prenatal $PM_{2.5}$ exposure at 35-40 weeks gestation [cumulative effect estimate (CEE) = -0.10, 95%CI = -0.19 to -0.01, per μg/m^3 increase in $PM_{2.5}$] and at 36-40 weeks (CEE = -0.12, 95%CI = -0.20 to -0.01) on FEV_1 and FVC, respectively, in boys. BDLIMs also identified a sensitive window of exposure at 37-40 weeks gestation between higher prenatal $PM_{2.5}$ exposure and increased GSTP1 percent methylation. The association between higher GSTP1 percent methylation and decreased FEV_1 was borderline significant in the sample as a whole (β = -0.37, SE = 0.20, p = 0.06) and in boys in stratified analyses (β = -0.56, SE = 0.29, p = 0.05).

CONCLUSIONS: Prenatal $PM_{2.5}$ exposure in late pregnancy was associated with impaired early childhood lung function and hypermethylation of GSTP1 in DNA isolated from nasal epithelial cells. There was a trend towards higher GSTP1 percent methylation being associated with reduced FEV_1. All findings were most evident among boys.

PMID: 29703190 PMCID: PMC5923180 DOI: 10.1186/s12931-018-0774-3

Free PMC Article

The hope and excitement about methylation (and other epigenetic changes) is that such changes can be controlled by altering key nutrients.

Harvard scientists published a research report this past March documenting partial reversal of key aspects of blood vessel aging in mice.

Reversal of blood vessel aging may be a key to long, healthy lives.

Cell. 2018 Mar 22;173(1):74-89.e20. doi: 10.1016/j.cell.2018.02.008.

Impairment of an Endothelial NAD$^+$-H_2S Signaling Network Is a Reversible Cause of Vascular Aging.

Das A[1], Huang GX[2], Bonkowski MS[3], Longchamp A[4], Li C[5], Schultz MB[3], Kim LJ[5], Osborne B[6], Joshi S[6], Lu Y[3], Treviño-Villarreal JH[4], Kang MJ[5], Hung TT[7], Lee B[7], Williams EO[8], Igarashi M[9], Mitchell JR[4], Wu LE[5], Turner N[6], Arany Z[2], Guarente L[10], Sinclair DA[11].

Author information

Abstract

A decline in capillary density and blood flow with age is a major cause of mortality and morbidity. Understanding why this occurs is key to future gains in human health. NAD precursors reverse aspects of aging, in part, by activating sirtuin deacylases (SIRT1-SIRT7) that mediate the benefits of exercise and dietary restriction (DR). We show that SIRT1 in endothelial cells is a key mediator of pro-angiogenic signals secreted from myocytes. Treatment of mice with the NAD$^+$ booster nicotinamide mononucleotide (NMN) improves blood flow and increases endurance in elderly mice by promoting SIRT1-dependent increases in capillary density, an effect augmented by exercise or increasing the levels of hydrogen sulfide (H_2S), a DR mimetic and regulator of endothelial NAD$^+$ levels. These findings have implications for improving blood flow to organs and tissues, increasing human performance, and reestablishing a virtuous cycle of mobility in the elderly.

KEYWORDS: NAD(+); aging; angiogenesis; endurance; exercise; hydrogen sulfide; ischemia; nicotinamide mononucleotide; sirtuins; skeletal muscle capillaries

PMID: 29570999 PMCID: PMC5884172 [Available on 2019-03-22] DOI: 10.1016/j.cell.2018.02.008

A relatively simple approach to controlling methylation is to remove CH3 (methyl group) precursors from our diet and/or remove them with enzymes from our blood stream.

Links to hundreds of papers on this approach are posted at:

http://www.blueberrystudy.com/Cancer-prevention-and-defense/

57 research reports discussing methylation and hearing are available at:

https://www.ncbi.nlm.nih.gov/pubmed/?term=methylation+AND+(hearing+OR+presbycusis)

SIXTH MAIN POINT:

We now have an IRB-approved, inexpensive study protocol to control methylation and by hypothesis postpone aging, Alzheimer's, and presbycusis while reducing our cancer risks.

To review this protocol, visit

BlueberryStudy.com or

HearingCheck123.com
(under construction)

In a nutshell, this protocol is to consume daily high-polyphenol wild blueberries and (with your physician's and nutritionist's approval) also consume daily **serine**, which reacts with methylation precursors and removes relatively toxic precursor metabolites.

The audiology study protocol under development is one of three complementary study options.

1) Participants shoud consider enrolling in the ALL of US study of the U.S. Natl. Inst. of Hlth. to obtain detailed gene analyses.

https://www.google.com/search?q=ALL+OF+US+study

2) They may also join the Wild Blueberry Health study for weekly cognitive safety and health checks.

http://BlueberryStudy.com

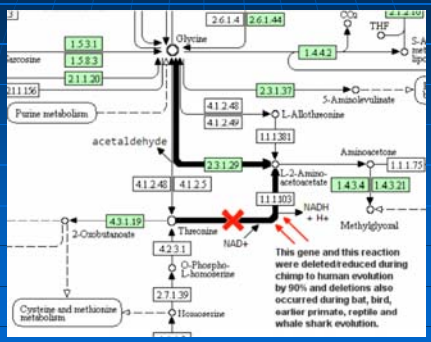
3) And they may also join a hearing study to determine if their hearing improves or declines more slowly year after year (protocol details to be determined).

http://HearingCheck123.com

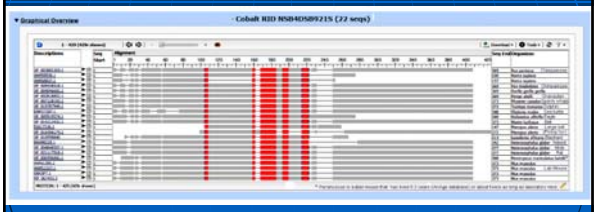
SEVENTH MAIN POINT:

The serine-longevity story is surprising indeed.

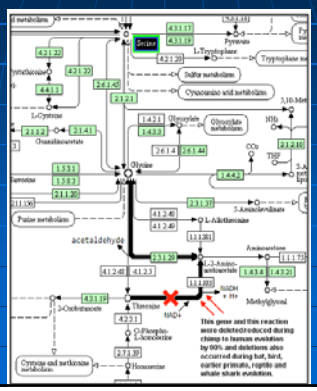
Loss of this gene blocks carbon from from threonine needed for DNA repair and stability.



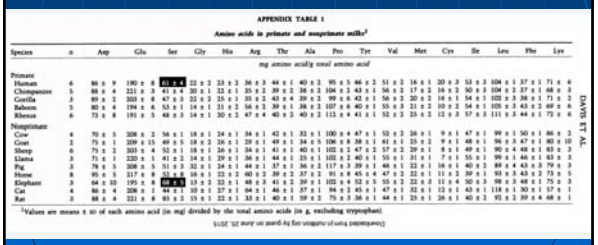
Humans and other unusually long-lived animals have lost large chunks of a key mitochondrial gene related to DNA repair.



Carbon for DNA repair must be obtained from additional SERINE.



To provide their babies with additional serine-carbons to maintain healthy genes during early rapid growth, both human and elephant milk has unusually high amounts of serine.


APPENDIX TABLE 1

Amino acids in primate and nonprimate milks[1]

Species	n	Asp	Glu	Ser	Gly	His	Arg	Thr	Ala	Pro	Tyr	Val	Met	Cys	Ile	Leu	Phe	Lys
		mg amino acid/g total amino acid																
Primate																		
Human	6	86 ± 9	190 ± 8	61 ± 4	22 ± 2	23 ± 3	36 ± 3	44 ± 1	40 ± 2	95 ± 5	46 ± 2	51 ± 2	16 ± 1	20 ± 3	53 ± 3	104 ± 1	37 ± 1	71 ± 6
Chimpanzee	5	88 ± 4	221 ± 8	41 ± 4	20 ± 1	22 ± 1	35 ± 2	39 ± 2	36 ± 2	104 ± 3	43 ± 1	56 ± 2	17 ± 1	16 ± 2	50 ± 3	106 ± 2	37 ± 1	68 ± 3
Gorilla	3	89 ± 3	203 ± 9	47 ± 3	22 ± 2	25 ± 1	35 ± 2	43 ± 4	39 ± 3	99 ± 6	42 ± 1	56 ± 2	20 ± 2	16 ± 1	54 ± 1	103 ± 3	38 ± 1	71 ± 2
Baboon	5	80 ± 4	194 ± 6	53 ± 1	14 ± 1	31 ± 2	56 ± 1	39 ± 1	38 ± 2	107 ± 6	40 ± 1	55 ± 3	21 ± 2	20 ± 3	54 ± 1	105 ± 3	45 ± 3	69 ± 6
Rhesus	6	73 ± 8	191 ± 5	48 ± 3	14 ± 1	30 ± 3	47 ± 4	40 ± 2	40 ± 2	112 ± 4	41 ± 1	52 ± 2	25 ± 2	13 ± 3	57 ± 3	111 ± 3	44 ± 1	72 ± 6
Nonprimate																		
Cow	4	70 ± 5	208 ± 2	56 ± 1	18 ± 1	34 ± 1	34 ± 1	42 ± 1	32 ± 1	100 ± 4	47 ± 1	53 ± 2	26 ± 1	9 ± 1	47 ± 1	99 ± 1	50 ± 1	86 ± 2
Goat	2	75 ± 1	209 ± 15	49 ± 5	18 ± 2	26 ± 1	29 ± 1	49 ± 1	34 ± 5	106 ± 8	38 ± 1	61 ± 1	25 ± 2	9 ± 1	48 ± 1	96 ± 3	47 ± 1	80 ± 10
Sheep	6	75 ± 2	203 ± 4	52 ± 1	18 ± 1	36 ± 1	34 ± 1	43 ± 1	40 ± 1	102 ± 2	47 ± 2	57 ± 2	29 ± 1	8 ± 1	49 ± 1	90 ± 4	48 ± 1	83 ± 3
Llama	3	71 ± 1	220 ± 1	41 ± 3	14 ± 1	29 ± 1	36 ± 1	44 ± 1	35 ± 1	102 ± 2	40 ± 1	55 ± 1	31 ± 1	7 ± 1	55 ± 1	99 ± 1	46 ± 1	83 ± 3
Pig	3	78 ± 5	208 ± 5	51 ± 3	32 ± 1	24 ± 1	44 ± 1	37 ± 1	36 ± 2	117 ± 3	39 ± 1	46 ± 1	22 ± 1	16 ± 1	40 ± 2	89 ± 4	43 ± 3	79 ± 3
Horse	8	95 ± 5	217 ± 8	53 ± 4	22 ± 2	40 ± 2	39 ± 2	37 ± 2	35 ± 2	91 ± 8	45 ± 4	47 ± 2	22 ± 1	11 ± 2	39 ± 1	93 ± 5	43 ± 2	75 ± 5
Elephant	3	64 ± 10	195 ± 8	68 ± 5	13 ± 3	22 ± 1	48 ± 3	41 ± 2	39 ± 1	102 ± 4	52 ± 5	55 ± 2	22 ± 2	11 ± 4	50 ± 3	98 ± 3	48 ± 1	75 ± 3
Cat	4	86 ± 4	208 ± 1	55 ± 2	10 ± 1	37 ± 1	64 ± 1	44 ± 1	37 ± 1	94 ± 3	45 ± 1	47 ± 1	32 ± 1	13 ± 1	63 ± 1	118 ± 1	60 ± 1	57 ± 1
Rat	3	88 ± 4	221 ± 8	85 ± 2	15 ± 1	22 ± 1	33 ± 1	40 ± 1	59 ± 2	75 ± 3	36 ± 1	44 ± 1	23 ± 1	26 ± 1	40 ± 2	92 ± 1	39 ± 4	68 ± 1

[1]Values are means ± SD of each amino acid [in mg] divided by the total amino acids [in g, excluding tryptophan].

DAVIS ET AL.

On average, species that lack functioning mTDH genes or have prominent deletions have evolved to live four times longer than closely-related species.

Additional mutations to make up for the missing thronine-carbons likely are also important.

At least some health professionals are already prescribing serine supplements to help seniors regain some of their lost energy and health.

Serine as phosphatidyl serine has been employed in eight successful clinical trials to improve cognitive performance.


Positive effects of soy lecithin-derived phosphatidylserine plus phosphatidic acid on memory, cognition, daily functioning, and mood in elderly patients with Alzheimer's disease and dementia.

Author information

Abstract

INTRODUCTION: We report previously unpublished, early pilot studies performed with a brain-health food supplement containing a proprietary blend of 100 mg phosphatidylserine (PS) and 80 mg phosphatidic acid (PA) produced from soy lecithin.

METHODS: Serum analysis after single PS-PA ingestion was performed in healthy volunteers. A 3-month double-blind, placebo-controlled study assessed the influence of three PS-PA capsules/day (300 mg PS + 240 mg PA/day) or placebo on memory and mood in functioning, non-depressive elderly people with memory problems, using the Wechsler Memory Scale and the List of Depressive Symptoms. Furthermore, a 2-month randomized, double-blind, placebo-controlled trial assessed the effect of three PS-PA capsules/day (300 mg PS + 240 mg PA/day) or placebo on daily functioning, mental health, emotional state, and self-reported general condition in patients with Alzheimer's disease (AD).

RESULTS: Serum PS peaked 90 min after ingestion, returning to baseline after 180 min. In the elderly, PS-PA (per protocol (PP): n = 31), unlike placebo (PP: n = 26), significantly improved memory and prevented "winter blues" in a pre-post comparison. In the patients with AD, daily functioning (i.e., 7 activities of daily living) under PS-PA (PP: n = 53) remained unchanged, but declined from 5.62 to 4.90 under placebo (PP: n = 39; P = 0.035), with significant group difference (P = 0.021). The PS-PA group had 3.8% deterioration and 90.6% stability in daily functioning, compared to 17.9% and 79.5% under placebo, respectively (P = 0.066). Forty-nine percent of the PS-PA patients reported an improved general condition, compared to 26.3% under placebo (P = 0.084). Approximately, 43% of the PS-PA patients, but none under placebo, continued post-trial supplementation (while double-blinded). No negative side effects were observed.

CONCLUSION: PS is efficiently absorbed after oral consumption. A positive influence of PS-PA on memory, mood, and cognition was demonstrated among elderly test subjects. Short-term supplementation with PS-PA in patients with AD showed a stabilizing effect on daily functioning, emotional state and self-reported general condition. The data encourage long-term studies with PS-PA in AD patients and other elderly with memory or cognition problems.

Phosphatidyl serine (also phosphatidylserine) has been employed in many successful clinical trials to improve cognitive performance – in this case with only short-term benefits.

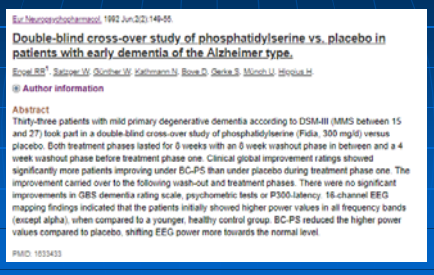

Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation.

Author information

Abstract

70 patients with probable Alzheimer's disease were randomly allocated to four groups: 17 patients received only social support, 18 cognitive training twice a week, in 17 cognitive training was combined with pyritinol 2 x 600 mg/day and in 18 cognitive training was combined with phosphatidylserine 2 x 200 mg/day. Treatment duration was 6 months. Before and after treatment, the patients underwent neuropsychological testing as well as measurement of the regional cerebral metabolic rate for glucose using positron emission tomography and 18F-2-fluoro-2-deoxy-D-glucose. Before treatment the groups were comparable in respect to resting and activated glucose pattern achieved by a visual recognition task. Electrophysiological changes were assessed as EEG power, globally and in 4 frequency bands. This 6-month study in four groups of patients with Alzheimer's disease indicated that phosphatidylserine treatment has an effect on different measures of brain function. Since neuropsychological improvements were best documented after 8 and 16 weeks and faded towards the end of the treatment period, it must be concluded that this symptomatic therapy is mainly of short-term benefit and was overcome by the progressive pathological changes at the end of the treatment period.

Phosphatidylserine showed EEG benefits when consumed during an 8-week intervention period.


Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type.

Author information

Abstract

Thirty-three patients with mild primary degenerative dementia according to DSM-III (MMS between 15 and 27) took part in a double-blind cross-over study of phosphatidylserine (Fidia, 300 mg/d) versus placebo. Both treatment phases lasted for 6 weeks with an 8 week washout phase in between and a 4 week washout phase before treatment phase one. Clinical global improvement ratings showed significantly more patients improving under BC-PS than under placebo during treatment phase one. The improvement carried over to the following wash-out and treatment phases. There were no significant improvements in OBS dementia rating scale, psychometric tests or P300-latency. 16-channel EEG mapping findings indicated that the patients initially showed higher power values in all frequency bands (except alpha), when compared to a younger, healthy control group. BC-PS reduced the higher power values compared to placebo, shifting EEG power more towards the normal level.

Phosphatidylserine showed Alzherimer's benefits when consumed during an 12-week intervention period.

Psychopharmacol Bull. 1992;28(1):61-6.

Effects of phosphatidylserine in Alzheimer's disease.

Crook T[1], Petrie W, Wells C, Massari DC.

Author information

Abstract

We studied 51 patients meeting clinical criteria for probable Alzheimer's disease (AD). Patients were treated for 12 weeks with a formulation of bovine cortex phosphatidylserine (BC-PS; 100 mg t.i.d.) or placebo, and those treated with the drug improved on several cognitive measures relative to those administered placebo. Differences between treatment groups were most apparent among patients with less severe cognitive impairment. Results suggest that phosphatidylserine may be a promising candidate for study in the early stages of AD.

PMID: 1609044

[Indexed for MEDLINE]

Similar articles

Phosphatidylserine showed Alzherimer's benefits when consumed during an 12-week intervention period.

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PMID: 1609044

[Indexed for MEDLINE]

Similar articles

Phosphatidylserine was employed as a postive control at only 200 mg/day and showed little benefit. Serine is prescribed at 10 times this daily dose today.

Selegiline in the treatment of mild to moderate Alzheimer-type dementia.

Author information

Abstract

Selegiline, an inhibitor of monoamine oxidase B, was tested on patients with mild to moderate dementia of the Alzheimer type. Its efficacy and tolerability were compared with that of phosphatidylserine in a randomized, single-blind, parallel fashion. Forty patients (24 men and 16 women) entered the trial. Selegiline was administered in 10-mg tablets once daily and phosphatidylserine in 100-mg capsules twice daily, both treatments lasting three months. Drug efficacy was assessed at baseline and then each month by means of an extensive battery of neuropsychological tests. The assessment of drug safety was based on monitoring for adverse drug reactions and on routine laboratory tests performed before and after treatment. At the end of the study the selegiline group showed improvements statistically significantly superior to those obtained in the phosphatidylserine group on most of the cognitive areas examined. Furthermore, of particular interest was the discovery, found only in the selegiline group, of an increased degree of autonomy in day-to-day activities. Tolerability was good, the only side effect reported in both groups being slight or moderate nausea, which was severe enough to warrant withdrawal from treatment only in one case, a patient in the selegiline group with a history of gastroduodenitis.

[Indexed for MEDLINE]

Similar articles

Phosphatidylserine suggested in 1989 to retard cerebral aging, as a working hypothesis. If cerebral aging can be slowed, then presbycusis may be reduced, delayed and possibly in some cases prevented.

Double-blind study with phosphatidylserine (PS) in parkinsonian patients with senile dementia of Alzheimer's type (SDAT).

Author information

Abstract

Experimental and clinical studies showed that Phosphatidylserine--special preparation from cow's brain by FIDIA, Abano Terme, Italy--is able to influence cerebral changes contributed to the symptoms of senile dementia of Alzheimer's type. The application of the computerized EEG method DYNAMIC BRAIN MAPPING (HZI Research Center, Tarrytown, New York) is able to proof the therapeutic effect of Phosphatidylserine: the acceleration of a slowed EEG in Parkinsonian patients with SDAT. These reactions were seen previous to the favourable clinical influence documented by the Sandoz Clinical Assessment Geriatric Scale (SCAG), which showed a significant amelioration in anxiety, motivation and affectivity by the verum drug. Acute and long-term CEEG results--till 18 months--showed that the so-called Theta anteriorisation can be reduced or even abolished; this is replaced by Alpha waves. Even in preclinical cerebral changes this method open the possibility to show incipient alterations of the brain metabolism. Preliminary therapeutic results leads to this and not prooven hypothesis that prevention or retardation of cerebral ageing might be possible.

[Indexed for MEDLINE]

Similar articles

Phosphatidylserine was safe and slightly lowered diastolic blood pressure in this relatively large (N = 157), low dose, 30-week safety study.

Safety of phosphatidylserine containing omega-3 fatty acids in non-demented elderly: a double-blind placebo-controlled trial followed by an open-label extension.

Author information

Abstract

BACKGROUND: Phosphatidylserine (PS) is a naturally occurring phospholipid present in the inner leaflet of mammalian plasma membranes. Administration of PS extracted from bovine cortex (BC-PS), which contains high levels of omega-3 long chain polyunsaturated fatty acid (LC-PUFA) attached to its backbone, resulted in positive effects on brain functions such as learning and memory. Recently, a novel marine-sourced PS with omega-3 LC-PUFA attached to its backbone was developed (PS-DHA). In the present study, we evaluated the safety profile of the novel PS preparation in non-demented elderly with memory complaints. The efficacy study of this novel formulation indicated that PS-DHA may ameliorate cognitive deficits in non-demented elderly population.

METHODS: 157 non-demented elderly participants with memory complaints were randomized to receive either PS-DHA (300 mg PS/day) or placebo for 15 weeks. Standard biochemical and hematological safety parameters, blood pressure and heart rate were evaluated at baseline and endpoint. 122 participants continued into an open-label extension for additional 15 weeks, in which they all consumed PS-DHA (100 mg PS/day) and were evaluated for their blood pressure, heart rate and weight at endpoint. Adverse events were monitored throughout the double-blind and open-label phases.

RESULTS: 131 participants completed the double-blind phase. No significant differences were found in any of the tested safety parameters between the study groups, or within each group. 121 participants completed the open-label phase. At the end of this phase, there was a reduction in resting diastolic blood pressure and a slight weight gain among participants who consumed PS-DHA for 30 weeks.

CONCLUSIONS: The results of this study indicate that consumption of PS-DHA at a dosage of 300 mg PS/day for 15 weeks, or 100 mg PS/day for 30 weeks, is safe, well tolerated, and does not produce any negative effects in the tested parameters.

TRIAL REGISTRATION: clinicaltrials. gov: identifier: NCT00437983

[Indexed for MEDLINE] Free PMC Article

Phosphatidylserine may also help reduce ADHD symptoms in children.

The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension.

Author information

Abstract

OBJECTIVE: To study the efficacy and safety of phosphatidylserine (PS) containing Omega3 long-chain polyunsaturated fatty acids attached to its backbone (PS-Omega3) in reducing attention-deficit/ hyperactivity disorder (ADHD) symptoms in children.

METHOD: A 15-week, double-blind, placebo-controlled phase followed by an open-label extension of additional 15 weeks. Two hundred ADHD children were randomized to receive either PS-Omega3 or placebo, out of them, 150 children continued into the extension. Efficacy was assessed using Conners' parent and teacher rating scales (CRS-P,T), Strengths and Difficulties Questionnaire (SDQ), and Child Health Questionnaire (CHQ). Safety evaluation included adverse events monitoring.

RESULTS: The key finding of the double-blind phase was the significant reduction in the Global Restless/impulsive subscale of CRS-P and the significant improvement in Parent impact-emotional (PE) subscale of the CHQ, both in the PS-Omega3 group. Exploratory subgroup analysis of children with a more pronounced hyperactive/impulsive behavior, as well as mood and behavior-dysregulation, revealed a significant reduction in the ADHD-index and hyperactive components. Data from the open-label extension indicated sustained efficacy for children who continued to receive PS-Omega3. Children that switched to PS-Omega3 treatment from placebo showed a significant reduction in subscales scores of both CRS-P and the CRS-T, as compare to baseline scores. The treatment was well tolerated.

CONCLUSIONS: The results of this 30-week study suggest that PS-Omega3 may reduce ADHD symptoms in children. Preliminary analysis suggests that this treatment may be especially effective in a subgroup of hyperactive-impulsive, emotionally and behaviorally-dysregulated ADHD children.

TRIAL REGISTRATION: ClinicalTrials.gov NCT00418184

[Indexed for MEDLINE]

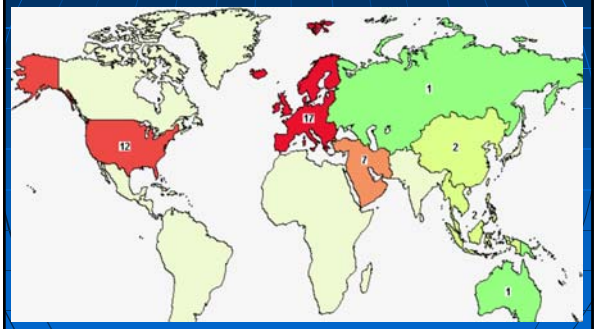
Phosphatidylserine aided dementia patients at 300 mg.day in the earliest (1986) trial listed in the PubMed.gov database.

Double-blind randomized controlled study of phosphatidylserine in senile demented patients.

Abstract

A double-blind randomized controlled study was conducted in 42 hospitalized demented patients to evaluate the therapeutical effect of phosphatidylserine (BS-PS). Half of the patients received 3 X 100 mg of this product, and the other half a placebo of the same appearance. After a wash-out period, prescription lasted for six weeks. To evaluate the patients, two distinct rating scales were used: the Crichton Scale and an original one (Peri Scale) designed in our geriatric unit (see Appendix). A circle crossing test was added. Out of the 35 patients who completed the trial, 18 had received placebo and 17 BC-PS. The results indicated a trend toward improvement in the BC-PS treated patients and an analysis of covariance showed a significant (p less than 0.05) treatment effect on the Peri Scale. The results at the end of the treatment period were compared with those obtained three weeks later. Here again there was a statistically significant difference in the Peri Scale results, indicating that modifications are drug-related. The behavioral improvement shown in this study is in agreement with experimental studies on aged animals.

Map of phosphatidylserine studies showing more are conducted in Europe than the U.S.



Howard Raphaelson will now discuss the work that remains and financial aspects of research in the near future.

Thank you in advance for your questions and recommendations.

Email messages are welcome at BlueberryStudy@gmail.com