SEX STEROIDS TO MAINTAIN COGNITIVE FUNCTION IN WOMEN AFTER THE MENOPAUSE: A META-ANALYSES OF TREATMENT TRIALS.

It is still debated whether estrogen treatment after the menopause could result in improved cognitive function in women. This debate is based on many animal and cell culture data showing that estrogens can positively affect the aging brain. Observational data also show a halved risk of dementia in women who took estrogens around the age of menopause. However, large treatment trials have shown negative effects of long-term treatment with estrogens in older women. The present meta-analyses included 36 randomised treatment trials and tested various hypotheses which have been developed to attempt to explain discrepant data. Results indicated that, contrary to expectations, age of women and duration of time elapsed when treatment was initiated since menopause (‘window of opportunity’ hypothesis) did not significantly affect treatment outcome, nor did it matter whether women were symptomatic or not. It was not clear whether bilateral oophorectomy affected the outcome, as this effect was based on only a few studies from the same group and some observational studies show negative effects on cognition in surgical menopausal women treated with hormones for more than 10 years. Duration of treatment overall significantly affected outcome. More negative effects were seen in longer studies, where positive effects were mainly seen in short term studies (<4 months). Treatment with combined estrogens and progestagens also negatively affected the outcome. Whether women with symptoms should be treated for a couple of months or using other (intermittent) modes of treatment and whether this could have long-term positive consequences remains to be investigated.

Maturitas. 2010 Mar 2

LEPIDIUM MEYENII (MACA) INCREASES LITTER SIZE IN NORMAL ADULT FEMALE MICE.

BACKGROUND: Lepidium meyenii, known as Maca, grows exclusively in the Peruvian Andes over 4,000 m altitude. It has been used traditionally to increase fertility. Previous scientific studies have demonstrated that Maca increases spermatogenesis and epididymal sperm count. The present study was aimed to investigate the effects of Maca on several fertility parameters of female mice at reproductive age. METHODS: Adult female Balb/C mice were divided at random into three main groups: i) Reproductive indexes group, ii) Implantation sites group and iii) Assessment of uterine weight in ovariectomized mice. Animals received an aqueous extract of lyophilized Yellow Maca (1 g/Kg BW) or vehicle orally as treatment. In the fertility indexes study, animals received the treatment before, during and after gestation. The fertility index, gestation index, post-natal viability index, weaning viability index and sex ratio were calculated. Sexual maturation was evaluated in the female pups by the vaginal opening (VO) day. In the implantation study, females were checked for implantation sites at gestation day 7 and the embryos were counted. In ovariectomized mice, the uterine weight was recorded at the end of treatment. RESULTS: Implantation sites were similar in mice treated with Maca and in controls. All reproductive indexes were similar in both groups of treatment. The number of pups per dam at birth and at postnatal day 4 was significantly higher in the group treated with Maca. VO day occurred earlier as litter size was smaller. Maca did not affect VO day. In ovariectomized mice, the treatment with Maca increased significantly the uterine weights in comparison to their respective control group. CONCLUSION: Administration of aqueous extract of Yellow Maca to adult female mice increases the litter size. Moreover, this treatment increases the uterine weight in ovariectomized animals. Our study confirms for the first time some of the traditional uses of Maca to enhance female fertility.

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EFFECT OF THREE DIFFERENT CULTIVARS OF LEPIDIUM MEYENII (MACA) ON LEARNING AND DEPRESSION IN OVARIECTOMIZED MICE.

BACKGROUND: Lepidium meyenii Walp. (Brassicaceae), known as Maca, is a Peruvian hypocotyl growing exclusively between 4,000 and 4,500 m altitude in the central Peruvian Andes, particularly in Junin plateau and is used traditionally to enhance fertility. Maca is a cultivated plant and different cultivars are described according to the color of the hypocotyls. METHODS: The study aimed to elucidate the effect of Yellow, Red, and Black Maca on cognitive function and depression in ovariectomized (OVX) mice. In all experiments OVX mice were treated during 21 days and divided in four groups: control group, Yellow Maca, Red
Maca and Black Maca. Latent learning was assessed using the water finding task and the antidepressant activity of the three varieties of Maca was evaluated using the forced swimming test. Animals were sacrificed at the end of each treatment and the uterus were excised and weighed. RESULTS: Black Maca was the variety that showed the best response in the water finding task, particularly in the trained mice. The three varieties were effective to reduce finding latency in non trained and trained mice (P < 0.05). In the force swimming test, all varieties assessed reduced the time of immobility and increased uterine weight in OVX mice. CONCLUSION: Black Maca appeared to have more beneficial effects on latent learning in OVX mice; meanwhile, all varieties of Maca showed antidepressant activity.


THE INFLUENCE OF MACA (LEPIDIUM MEYENII) ON ANTIOXIDANT STATUS, LIPID AND GLUCOSE METABOLISM IN RAT.

This work focused on the effect of Maca on lipid, anti-oxidative, and glucose parameters in hereditary hypertriglyceridemic (HHTg) rat. Maca (1%) was administered to rats as a part of a high-sucrose diet (HSD) for 2 weeks. Rosiglitazone (0.02%) was used as a positive control. Maca significantly decreased the levels of VLDL (very low density lipoproteins), LDL (low density lipoproteins), and total cholesterol, and also the level of TAG (triaclyglycerols) in the plasma, VLDL, and liver. Maca, as well as rosiglitazone, significantly improved glucose tolerance, as the decrease of AUC (area under the curve) of glucose showed, and lowered levels of glucose in blood. The activity of SOD (superoxide dismutase) in the liver, the GPX (glutathione peroxidase) in the blood, and the level of GSH (glutathione) in liver increased in all cases significantly. Results demonstrate that maca seems to be promising for a positive influence on chronic human diseases (characterized by atherogenous lipoprotein profile, aggravated antioxidative status, and impaired glucose tolerance), and their prevention.


AQUEOUS EXTRACT OF BLACK MACA (LEPIDIUM MEYENII) ON MEMORY IMPAIRMENT INDUCED BY OVARIECTOMY IN MICE.

The present study aims to test two different doses of aqueous extract of black maca on learning and memory in ovariectomized (OVX) mice and their relation with malonalehyde (MDA), acetylcholinesterase (Ache) and monoamine oxidase (MAO) brain levels. Female mice were divided into five groups: (i) naive (control), (ii) sham, (iii) OVX mice and OVX mice treated with (iv) 0.50 g kg(-1) and (v) 2.00 g kg(-1) black maca. Mice were orally treated with distilled water or black maca during 35 days starting 7 days after surgery. Memory and learning were assessed using the water Morris maze (from day 23-27) and the step-down avoidance test (days 34 and 35). At the end of each treatment, mice were sacrificed by decapitation and brains were dissected out for MDA, Ache and MAO determinations. Black maca (0.5 and 2.0 g/kg) increased step-down latency when compared to OVX control mice. Black maca decreased MDA and Ache levels in OVX mice; whereas, no differences were observed in MAO levels. Finally, black maca improved experimental memory impairment induced by ovariectomy, due in part, by its antioxidant and Ache inhibitory activities.

Evid Based Complement Alternat Med. 2008 Oct 9

HEALTHCARE SEEKING AND TREATMENT FOR MENOPAUSAL SYMPTOMS IN THE UNITED STATES.

OBJECTIVES: A population-based study was used to describe healthcare seeking behavior for menopausal symptoms and treatment among women 40-65 years old in the United States. METHODS: Participants were recruited into the Menopause Epidemiology Study from the KnowledgePanel(SM), which is selected by random digit dialing and probability sampling from the US population. From this source, 6,201 women 40-65 years old were contacted and 4,402 women participated. From the 3,135 peri- and postmenopausal women, detailed information was obtained on menopausal symptoms, healthcare seeking, medication usage, and symptom relief from the medication. RESULTS: Many women (60%) reported seeking health care for their menopausal symptoms. More than half of these women sought health care in the past 12 months. Vasomotor symptoms were the most frequently reported menopause symptoms across all races/ethnicities, and the most common symptoms discussed with a health care professional. One-third of the women (34%) used only hormone therapies, 12% used complementary and/or alternative medicines, and 16% used both for treatment of menopausal symptoms. CONCLUSIONS: This study has shown that a large number of women consult healthcare providers for menopausal symptoms, indicating these symptoms are bothersome. Yet, in the United States, there is considerable variation in the symptomatology, healthcare seeking, and use of therapies for menopausal symptoms across cultures. To alleviate these symptoms women have tried alternative treatments as well as hormone therapies, yet many women did not get complete relief of specific symptoms.

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RISKS AND BENEFITS OF ESTROGEN PLUS PROGESTIN IN HEALTHY POSTMENOPAUSAL WOMEN: PRINCIPAL RESULTS FROM THE WOMEN’S HEALTH INITIATIVE RANDOMIZED CONTROLLED TRIAL.
CONTEXT: Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain. OBJECTIVE: To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States. DESIGN: Estrogen plus progestin component of the Women’s Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998. INTERVENTIONS: Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8102). MAIN OUTCOMES MEASURES: The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. RESULTS: On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10,000 person-years. CONCLUSIONS: Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

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EFFECTS OF CONJUGATED EQUINE ESTROGEN IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY: THE WOMEN’S HEALTH INITIATIVE RANDOMIZED CONTROLLED TRIAL.

CONTEXT: Despite decades of use and considerable research, the role of estrogen alone in preventing chronic diseases in postmenopausal women remains uncertain. OBJECTIVE: To assess the effects on major disease incidence rates of the most commonly used postmenopausal hormone therapy in the United States. DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blind, placebo-controlled disease prevention trial (the estrogen-alone component of the Women’s Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. Enrolled were 10,739 postmenopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity. INTERVENTION: Women were randomly assigned to receive either 0.625 mg/d of conjugated equine estrogen (CEE) or placebo. MAIN OUTCOME MEASURES: The primary outcome was coronary heart disease (CHD) incidence (nonfatal myocardial infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects. RESULTS: In February 2004, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided to end the intervention phase of the trial early. Estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major clinical outcomes available through February 29, 2004 (average follow-up 6.8 years), were: CHD, 0.91 (0.75-1.12) with 376 cases; breast cancer, 0.77 (0.59-1.01) with 218 cases; stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; colorectal cancer, 1.08 (0.75-1.55) with 119 cases; and hip fracture, 0.61 (0.41-0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01-1.24); total cancer, 0.93 (0.81-1.07); total fractures, 0.70 (0.63-0.79); total mortality, 1.04 (0.88-1.22), and the global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant 2 events per 10,000 person-years. CONCLUSIONS: The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

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A DOUBLE-BLIND, RANDOMIZED, PILOT DOSE-FINDING STUDY OF MACA ROOT (L. MEYENII) FOR THE MANAGEMENT OF SSRI-INDUCED SEXUAL DYSFUNCTION.
We sought to determine whether maca, a Peruvian plant, is effective for selective-serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction. We conducted a double-blind, randomized, parallel group dose-finding pilot study comparing a low-dose (1.5 g/day) to a high-dose (3.0 g/day) maca regimen in 20 remitted depressed outpatients (mean age 36+/−13 years; 17 women) with SSRI-induced sexual dysfunction. The Arizona Sexual Experience Scale (ASEX) and the Massachusetts General Hospital Sexual Function Questionnaire (MGH-SFQ) were used to measure sexual dysfunction. Ten subjects completed the study, and 16 subjects (9 on 3.0 g/day; 7 on 1.5 g/day) were eligible for intent-to-treat (ITT) analyses on the basis of having had at least one postbaseline visit. ITT subjects on 3.0 g/day maca had a significant improvement in ASEX (from 22.8+/−3.8 to 16.9+/−6.2; z=−2.20, P=0.028) and in MGH-SFQ scores (from 24.1+/−1.9 to 17.0+/−5.7; z=−2.39, P=0.017), but subjects on 1.5 g/day maca did not. Libido improved significantly (P<0.05) for the ITT and completer groups based on ASEX #1, but not by dosing groups. Maca was well tolerated. Maca root may alleviate SSRI-induced sexual dysfunction, and there may be a dose-related effect. Maca may also have a beneficial effect on libido.

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**BENEFICIAL EFFECTS OF LEPIDIUM MEYENII (MACA) ON PSYCHOLOGICAL SYMPTOMS AND MEASURES OF SEXUAL DYSFUNCTION IN POSTMENOPAUSAL WOMEN ARE NOT RELATED TO ESTROGEN OR ANDROGEN CONTENT.**

**OBJECTIVE:** To examine the estrogenic and androgenic activity of Lepidium meyenii (Maca) and its effect on the hormonal profile and symptoms in postmenopausal women. **DESIGN:** Fourteen postmenopausal women completed a randomized, double-blind, placebo-controlled, crossover trial. They received 3.5 g/day of powered Maca for 6 weeks and matching placebo for 6 weeks, in either order, over a total of 12 weeks. At baseline and weeks 6 and 12 blood samples were collected for the measurement of estradiol, follicle-stimulating hormone, luteinizing hormone, and sex hormone-binding globulin, and the women completed the Greene Climacteric Scale to assess the severity of menopausal symptoms. In addition, aqueous and methanolic Maca extracts were tested for androgenic and estrogenic activity using a yeast-based hormone-dependent reporter assay. **RESULTS:** No differences were seen in serum concentrations of estradiol, follicle-stimulating hormone, luteinizing hormone, and sex hormone-binding globulin between baseline, Maca treatment, and placebo (P > 0.05). The Greene Climacteric Scale revealed a significant reduction in scores in the areas of psychological symptoms, including the subscales for anxiety and depression and sexual dysfunction after Maca consumption compared with both baseline and placebo (P < 0.05). These findings did not correlate with androgenic or alpha-estrogenic activity present in the Maca as no physiologically significant activity was observed in yeast-based assays employing up to 4 mg/mL Maca extract (equivalent to 200 mg/mL Maca). **CONCLUSIONS:** Preliminary findings show that Lepidium meyenii (Maca) (3.5 g/d) reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic and androgenic activity.


**SAFETY AND TOLERABILITY OF DONEPEZIL, RIVASTIGMINE AND GALANTAMINE FOR PATIENTS WITH ALZHEIMER’S DISEASE: SYSTEMATIC REVIEW OF THE ‘REAL-WORLD’ EVIDENCE.**

**BACKGROUND/AIMS:** The purpose of this systematic review was to compare the safety and tolerability of the cholinesterase inhibitors (ChEIs) donepezil, rivastigmine and galantamine for treating mild to moderate Alzheimer’s disease (AD) patients in routine clinical practice. **METHODS:** Electronic databases (Cochrane Library, Med-line, EMBASE; accessed October 2008) and manual bibliographic searches were conducted to identify head-to-head non-randomised studies examining ChEIs for the treatment of AD. Data were extracted by 2 independent reviewers. **RESULTS:** Twelve head-to-head studies comparing ChEIs met the pre-specified inclusion criteria; 6 retrospective analyses and 6 prospective cohort studies. Donepezil was the most widely studied treatment and galantamine the least widely prescribed therapy. Fewer donepezil-treated subjects withdrew due to adverse events (AEs) compared with rivastigmine and galantamine-treated subjects. The incidence of gastrointestinal (GI) AEs was lower following treatment with donepezil compared with rivastigmine and galantamine. Non-GI (CNS and cardiovascular) AEs occurred at a low frequency, and had a similar incidence in subjects treated with the different ChEIs. **CONCLUSIONS:** Subjects with mild to moderate AD treated in routine clinical practice with donepezil were more adherent to pharmacotherapy, and had a lower risk of GI AEs compared with rivastigmine or galantamine. This finding accords with results reported in the randomised clinical trial literature.

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