

# Choline kinase alpha genotype is related to hippocampal brain volume and cognition in postmenopausal women

[Abigail J Myers](#)<sup>1</sup>, [Callum Potts](#)<sup>2</sup>, [Jenna A Makarewicz](#)<sup>1</sup>, [Elizabeth McGee](#)<sup>2</sup>, [Julie A Dumas](#)<sup>1</sup>

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## Abstract

This study examined how single nucleotide polymorphisms (SNPs) related to choline synthesis and metabolism, processes largely regulated by estrogen, influenced hippocampal volume and neuropsychological function following menopause. We investigated the effect of choline kinase alpha (CHKA) genotype on brain volume and neuropsychological performance in postmenopausal women. The effect alleles of certain CHKA SNPs (*rs6591331* T, *rs10791957* A) are associated with varied responses to choline deficiency and delegation of choline to physiological pathways. The presence of these alleles was hypothesized to correlate with worse cognitive performance in women after menopause. Results from structural MRI scans revealed larger right hippocampal volumes in subjects with a T/T CHKA *rs6591331* genotype compared to A/A subjects. Delayed memory scores from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were lower in subjects with T/T genotypes compared to those with the A/T genotype and the A/A genotype. Based on these findings, we proposed a CHKA-dependent mechanism present within the brain to compensate for the decreased estrogen and biosynthesized choline associated with menopause.

# Efficacy and Safety of Fezolinetant for the Treatment of Menopause-Associated Vasomotor Symptoms: A Meta-analysis.

Krishna Nikhila Bonga, Archana Mishra, Rituparna Maiti, Biswa Mohan Padhy, Bikash Ranjan Meher, Anand Srinivasan  
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**OBJECTIVE:** To evaluate the efficacy and adverse events of fezolinetant for treating vasomotor symptoms (VMS) of menopause.

**DATA SOURCES:** PubMed/MEDLINE, ClinicalTrials.gov, EMBASE, Cochrane Database, Scopus, and WHO International Clinical Trials Registry Platform were searched through June 2023 for publications and randomized controlled trials on fezolinetant compared with placebo in menopausal women who experienced moderate-to-severe VMS.

**METHODS OF STUDY SELECTION:** Our literature search identified 330 articles, of which five studies with six reports were included in our meta-analysis per our eligibility criteria.

**TABULATION, INTEGRATION, AND RESULTS:** The risk of bias was evaluated using Cochrane's RoB 2 (Risk of Bias version 2) tool, quality of evidence was graded using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, and outcome measures data for effect size were pooled in random-effects model and rated. A total of 2,168 participants from five randomized clinical trials (six reports) were included. Fezolinetant significantly lowered VMS frequency, with pooled mean difference of 2.62 (95% CI, 1.84-3.41). The pooled mean difference for fezolinetant compared with placebo for the MENQOL (Menopause-Specific Quality of Life) measure was -0.60 (95% CI, -0.92 to -0.28), and the mean percentage improvement in VMS frequency was 22.51% (95% CI, 15.35-29.67). Fezolinetant was associated with improvement in sleep quality when compared with placebo.

**CONCLUSION:** Fezolinetant is effective in lowering moderate-to-severe VMS frequency and sleep disturbances in postmenopausal women.

# Impact of lithocholic acid on the osteogenic and adipogenic differentiation balance of bone marrow mesenchymal stem cells

[Article in Chinese]

[Cui Wang](#)<sup>1</sup>, [Jiao Li](#)<sup>2</sup>, [Lingyun Lu](#)<sup>3</sup>, [Lu Liu](#)<sup>1</sup>, [Xijie Yu](#)<sup>1</sup>

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## Abstract

**Objective:** To Investigate the effects of lithocholic acid (LCA) on the balance between osteogenic and adipogenic differentiation of bone marrow mesenchymal stem cells (BMSCs).

**Methods:** Twelve 10-week-old SPF C57BL/6J female mice were randomly divided into an experimental group (undergoing bilateral ovariectomy) and a control group (only removing the same volume of adipose tissue around the ovaries), with 6 mice in each group. The body mass was measured every week after operation. After 4 weeks post-surgery, the weight of mouse uterus was measured, femur specimens of the mice were taken for micro-CT scanning and three-dimensional reconstruction to analyze changes in bone mass. Tibia specimens were taken for HE staining to calculate the number and area of bone marrow adipocytes in the marrow cavity area. ELISA was used to detect the expression of bone turnover markers in the serum. Liver samples were subjected to real-

time fluorescence quantitative PCR (RT-qPCR) to detect the expression of key genes related to bile acid metabolism, including *cyp7a1*, *cyp7b1*, *cyp8b1*, and *cyp27a1*. BMSCs were isolated by centrifugation from 2 C57BL/6J female mice (10-week-old). The third-generation cells were exposed to 0, 1, 10, and 100  $\mu\text{mol/L}$  LCA, following which cell viability was evaluated using the cell counting kit 8 assay. Subsequently, alkaline phosphatase (ALP) staining and oil red O staining were conducted after 7 days of osteogenic and adipogenic induction. RT-qPCR was employed to analyze the expressions of osteogenic-related genes, namely ALP, Runt-related transcription factor 2 (Runx2), and osteocalcin (OCN), as well as adipogenic-related genes including Adiponectin (Adipoq), fatty acid binding protein 4 (FABP4), and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ).

**Results:** Compared with the control group, the body mass of the mice in the experimental group increased, the uterus atrophied, the bone mass decreased, the bone marrow fat expanded, and the bone metabolism showed a high bone turnover state. RT-qPCR showed that the expressions of *cyp7a1*, *cyp8b1*, and *cyp27a1*, which were related to the key enzymes of bile acid metabolism in the liver, decreased significantly ( $P < 0.05$ ), while the expression of *cyp7b1* had no significant difference ( $P > 0.05$ ). Intervention with LCA at concentrations of 1, 10, and 100  $\mu\text{mol/L}$  did not demonstrate any apparent toxic effects on BMSCs. Furthermore, LCA inhibited the expressions of osteogenic-related genes (ALP, Runx2, and OCN) in a dose-dependent manner, resulting in a reduction in ALP staining positive area. Concurrently, LCA promoted the expressions of adipogenic-related genes (Adipoq, FABP4, and PPAR $\gamma$ ), and an increase in oil red O staining positive area.

**Conclusion:** After menopause, the metabolism of bile acids is altered, and secondary bile acid LCA interferes with the balance of osteogenic and adipogenic differentiation of BMSCs, thereby affecting bone remodelling.

# Elinzanetant: a phase III therapy for postmenopausal patients with vasomotor symptoms

[Jenifer Sassarini](#)<sup>1</sup>, [Richard A Anderson](#)<sup>2</sup>

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## Abstract

**Introduction:** Menopausal vasomotor symptoms (VMS) are experienced by most women, and are often debilitating and can last for years. While hormone replacement therapy is effective, it carries risks that have impacted its wider use, and it can be contraindicated. There is a large unmet need for a safe, effective non-hormonal therapy.

**Areas covered:** The importance of the neurokinin (NK) system in the hypothalamic regulation of the vasomotor center has become clear. NK antagonists, previously developed for other indications, have therefore been investigated for the treatment of VMS. Elinzanetant is a potent antagonist at both NK1 (endogenous ligand Substance P) and NK3 (neurokinin B) receptors, whereas other related drugs in development are selective NK3 antagonists. Elinzanetant has been investigated in 2 Phase II trials for menopausal VMS, demonstrating rapid onset and dose-dependant efficacy for the relief of VMS and improvement in quality of life for up to 12 weeks. Phase III trials are underway in women both with physiological menopause and after treatment for breast cancer.

**Expert opinion:** Elinzanetant is a very promising non-hormonal approach to a highly prevalent symptom constellation, with rapid onset and high efficacy. Wider indications are being explored in current Phase III trials.

# Carbon dioxide laser therapy for the management of genitourinary syndrome of menopause: A meta-analysis of randomized controlled trials

[Yihua Ni](#)<sup>1</sup>, [Junyu Lian](#)<sup>1</sup>

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## Abstract

Genitourinary symptoms of menopause (GSM) affect ~50% of women after menopause. Recently, CO<sub>2</sub> laser therapy has been used for managing GSM but without high quality evidence. The present review assessed the effectiveness of CO<sub>2</sub> laser therapy in the management of GSM. PubMed, Embase, Web of Science, CENTRAL and Scopus databases were searched for randomized controlled trials (RCTs), published up to June 30, 2023, comparing CO<sub>2</sub> laser and sham laser treatments for GSM management. The outcomes of interest included Female Sexual Function Index (FSFI), Vaginal Health Index (VHI) and visual analog scale (VAS) for dyspareunia, dryness, burning, itching and dysuria. A total of seven RCTs were included in the review and meta-analysis, with 6/7 studies using three sessions of laser therapy, 4-8 weeks apart. Meta-analysis demonstrated no statistically significant difference in FSFI [mean difference (MD), -1.48; 95% CI, -5.85, 2.89; I<sup>2</sup>=45%] and VHI scores (MD, -0.18; 95% CI, -1.66, 1.31; I<sup>2</sup> =72%) between laser and control groups. Meta-analysis also demonstrated no statistically significant difference in VAS scores for dyspareunia (MD, -1.63; 95% CI; -4.06, 0.80; I<sup>2</sup>=91%), dryness (MD, -1.30; 95% CI, -3.14, 0.53; I<sup>2</sup>=75%), burning (MD, -0.76; 95% CI, -2.03; 0.51 I<sup>2</sup>=56%), itching (MD, -0.28; 95% CI, -0.95, 0.38; I<sup>2</sup>=0%) and dysuria (MD, 0.15; 95% CI, -0.37, 0.67; I<sup>2</sup>=23%) between the groups. The included RCTs had low risk of bias. **In conclusion, meta-analyses of high-quality sham-controlled RCTs indicated that CO<sub>2</sub> may not have any beneficial effect on GSM. Limited data and high heterogeneity in meta-analyses in this area of research are important limitations that need to be addressed by future RCTs.**

