

Selección de Resúmenes de Menopausia

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Trends in the incidence, prevalence and sales volume of menopausal hormone therapy in Sweden from 2000 to 2021

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Objectives: To describe the trends in the prevalence of use menopausal hormone therapy (MHT) in Sweden over the period 2000-2021 and to analyse the impact of different lengths of run-in on the calculated incident use. **Study design:** Individual-level data on MHT dispensations for 2.5 million women aged 45-69 years for the period 2006-2021 were analysed. Aggregated sales volumes in defined daily dose (DDD) were available for the whole study period (2000-2021). **Main outcome measures:** One-year prevalence and one-year incidence (18-month run-in) per 1000 women and DDD per 1000 women per day of MHT were the main outcome measures. The predictive values for incidence representing first-ever use of MHT were calculated for different run-in periods, which is a defined period without dispensations. **Results:** Both the DDD, from 2000, and the prevalence, from 2006, decreased by over 80 % in women aged 50-54 years, until 2010, when the use of MHT stabilised. The predictive value for incident users to be first-ever users was 88 % in women aged 50-54 years, with a run-in of 18 months, in 2021. The incidence was stable between 2007 and 2016. From 2017 the incidence increased, being most pronounced for women close to menopause. **Conclusions:** MHT use decreased significantly after the turn of the century, but has increased since 2017. A run-in period of 18 months was found suitable and reliable for defining incident users of MHT in the age intervals closest to menopause. Incidence seems to be a more sensitive measure than prevalence or DDD for the early detection of changes in trends in prescriptions of MHT.

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The association of sex steroid hormone concentrations with hearing loss: a cross-sectional study

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Background: Hearing loss is the most prevalent sensory disorder worldwide. Several studies have indicated that sex steroid hormone levels may be vital to hearing. **Objective:** We aimed to explore the associations between speech-frequency hearing loss and sex steroid hormones. **Methods:** We conducted a secondary analysis based on 3558 adult participants' data from the National Health and Nutrition Examination Survey (NHANES) from 2015 to 2016. We defined hearing loss as a pure-tone average (PTA) at 0.5, 1, 2, and 4 kHz ≥ 20 dB in the better ear. Multivariate logistic regression analysis was used to evaluate the association between sex steroid hormones and hearing loss risk. A nomogram model for the risk of hearing loss was constructed. **Results:** There were 560 (15.7%) cases who had hearing loss among the participants enrolled in this study. Participants with hearing loss had a higher total testosterone level and a lower estradiol level. Individuals with estradiol levels in the highest tertile still had lower hearing loss risks than those in the lowest tertile. Nevertheless, the total testosterone level had no influence on the risk of hearing loss. **Conclusion:** Our research indicated that low estradiol concentrations were significantly associated with hearing loss, especially in menopausal women.

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PCOS during the menopausal transition and after menopause: a systematic review and meta-analysis

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Background: Current knowledge about the consequences of PCOS during the late reproductive years and after menopause is limited. **Objective and rationale:** We performed a systematic review and meta-analysis of data on the pathophysiology, clinical manifestations, diagnosis, prognosis, and treatment of women ≥ 45 years of age-peri- or postmenopausal-with PCOS. **Search methods:** Studies published up to 15 April 2023, identified by Entrez-PubMed, EMBASE, and Scopus online facilities, were considered. We included cross-sectional or prospective studies that reported data from peri- or postmenopausal patients with PCOS and control women with a mean age ≥ 45 years. Three independent

researchers performed data extraction. Outcomes: The initial search identified 1400 articles, and another six were included from the reference lists of included articles; 476 duplicates were deleted. We excluded 868 articles for different reasons, leaving 37 valid studies for the qualitative synthesis, of which 28 studies-published in 41 articles-were considered for the quantitative synthesis and meta-analyses. Another nine studies were included only in the qualitative analyses. Compared with controls, peri- and postmenopausal patients with PCOS presented increased circulating total testosterone (standardized mean difference, SMD 0.78 (0.35, 1.22)), free androgen index (SMD 1.29 (0.89, 1.68)), and androstenedione (SMD 0.58 (0.23, 0.94)), whereas their sex hormone-binding globulin was reduced (SMD -0.60 (-0.76, -0.44)). Women with PCOS showed increased BMI (SMD 0.57 (0.32, 0.75)), waist circumference (SMD 0.64 (0.42, 0.86)), and waist-to-hip ratio (SMD 0.38 (0.14, 0.61)) together with increased homeostasis model assessment of insulin resistance (SMD 0.56 (0.27, 0.84)), fasting insulin (SMD 0.61 (0.38, 0.83)), fasting glucose (SMD 0.48 (0.29, 0.68)), and odds ratios (OR, 95% CI) for diabetes (OR 3.01 (1.91, 4.73)) compared to controls. Women with PCOS versus controls showed decreased HDL concentrations (SMD -0.32 (-0.46, -0.19)) and increased triglycerides (SMD 0.31 (0.16, 0.46)), even though total cholesterol and LDL concentrations, as well as the OR for dyslipidaemia, were similar to those of controls. The OR for having hypertension was increased in women with PCOS compared with controls (OR 1.79 (1.36, 2.36)). Albeit myocardial infarction (OR 2.51 (1.08, 5.81)) and stroke (OR 1.75 (1.03, 2.99)) were more prevalent in women with PCOS than controls, the ORs for cardiovascular disease as a whole, coronary artery disease as a whole, breast cancer and age at menopause, were similar in patients and controls. When restricting meta-analysis to studies in which women with PCOS and controls had a similar mean BMI, the only difference that retained statistical significance was a decrease in HDL-cholesterol concentration in the former and, in the two studies in which postmenopausal women with PCOS and controls had similar BMI, patients presented with increased serum androgen concentrations, suggesting that hyperandrogenism persists after menopause, regardless of obesity. Wider implications: Hyperandrogenism appeared to persist during the late-reproductive years and after menopause in women with PCOS. Most cardiometabolic comorbidities were driven by the frequent coexistence of weight excess and PCOS, highlighting the importance of targeting obesity in this population. However, the significant heterogeneity among included studies, and the overall low quality of the evidence gathered here, precludes reaching definite conclusions on the issue. Hence, guidelines derived from adequately powered prospective studies are definitely needed for appropriate management of these women.

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Clinical efficacy of denosumab, teriparatide, and oral bisphosphonates in the prevention of glucocorticoid-induced osteoporosis: a systematic review and meta-analysis

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Background: Continuous use of glucocorticoids (GCs) has become the primary cause of secondary osteoporosis. Bisphosphonate drugs were given priority over denosumab and teriparatide in the 2017 American College of Rheumatology (ACR) guidelines but have a series of shortcomings. This study aims to explore the efficacy and safety of teriparatide and denosumab compared with those of oral bisphosphonate drugs. **Methods:** We systematically searched studies included in the PubMed, Web of Science, Embase, and Cochrane library databases and included randomized controlled trials that compared denosumab or teriparatide with oral bisphosphonates. Risk estimates were pooled using both fixed and random effects models. **Results:** We included 10 studies involving 2923 patients who received GCs for meta-analysis, including two drug base analyses and four sensitivity analyses. Teriparatide and denosumab were superior to bisphosphonates in increasing the bone mineral density (BMD) of the lumbar vertebrae [teriparatide: mean difference [MD] 3.98%, 95% confidence interval [CI] 3.61-4.175%, $P = 0.00001$; denosumab: MD 2.07%, 95% CI 0.97-3.17%, $P = 0.0002$]. Teriparatide was superior to bisphosphonates in preventing vertebral fractures and increasing hip BMD [MD 2.39%, 95% CI 1.47-3.32, $P < 0.00001$]. There was no statistically significant difference between serious adverse events, adverse events, and nonvertebral fracture prevention drugs. **Conclusions:** Teriparatide and denosumab exhibited similar or even superior characteristics to bisphosphonates in our study, and we believe that they have the potential to become first-line GC-induced osteoporosis treatments, especially for patients who have previously received other anti-osteoporotic drugs with poor efficacy.

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Sarcopenia, osteoporosis and frailty

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Muscles and bones are intricately connected tissues displaying marked co-variation during development, growth, aging, and in many diseases. While the diagnosis and treatment of osteoporosis are well established in clinical practice, sarcopenia has only been classified internationally as a disease in 2016. Both conditions are associated with an increased risk of adverse health outcomes such as fractures, dysmobility and mortality. Rather than focusing on one dimension of bone or muscle mass or weakness, the concept of musculoskeletal frailty captures the overall loss of physiological reserves in the locomotor system with age. The term osteosarcopenia in particular refers to the double jeopardy of osteoporosis and sarcopenia. Muscle-bone interactions at the biomechanical, cellular, paracrine, endocrine, neuronal or nutritional level may contribute to the pathophysiology of osteosarcopenia. The paradigm wherein muscle force controls bone strength is increasingly facing competition from a model centering on the exchange of myokines, osteokines and adipokines. The most promising results have been obtained in preclinical models where common drug targets have been identified to treat these conditions simultaneously. In this narrative review, we critically summarize the current understanding of the definitions, epidemiology, pathophysiology, and treatment of osteosarcopenia as part of an integrative approach to musculoskeletal frailty.

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Influence of menopausal status on physical function and performance: A cross-sectional study

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Objective: To compare the physical function and performance in pre-, peri-, and postmenopausal women. Study design: A cross sectional study using convenience sampling method was conducted in 210 women categorized into premenopausal, perimenopausal, and postmenopausal. Main outcome measures: Flexibility, muscle strength, muscle endurance, cardiovascular endurance, static balance, dynamic balance, and gait speed. Results: The mean age of the premenopausal, perimenopausal, and postmenopausal women was 46.55 ± 1.77 , 49.54 ± 3.38 and 54.85 ± 3.77 years respectively. There is significant difference observed between premenopausal, perimenopausal, and postmenopausal women in muscle strength, upper limb endurance, lower limb endurance, static balance, dynamic balance, gait speed, and cardiovascular endurance ($p < .05$) using Kruskal Wallis test. There is no significant difference observed between the groups for flexibility ($p > .05$). Conclusion: It was observed that physical function and performance was impaired in postmenopausal women when compared to pre- and perimenopausal women. Hence, these components should be included during assessment which will provide a holistic and multimodal approach toward the understanding, planning and management of postmenopausal women in community settings.

Drugs Aging. 2023 Jun 21. doi: 10.1007/s40266-023-01043-3. Online ahead of print.

Menopausal Hormone Therapy in Older Women: Examining the Current Balance of Evidence

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Menopause occurs in all women. During the menopause transition, 80% of women experience vasomotor symptoms that can last an average of 7-10 years or longer, sometimes into the seventh and eighth decades of life. Understanding how to manage vasomotor symptoms (VMS) in older menopausal women is important since these symptoms can negatively impact quality of life. This review provides a practical guide on how to approach VMS treatment either with menopausal hormone therapy or non-hormone options. When initiating, as well as continuing hormone therapy, the factors clinicians should consider as they weigh risks and benefits include assessing a woman's risks related to cardiovascular disease, breast cancer, and osteoporosis. Utilizing a shared decision-making approach in regard to menopausal symptom management should aim to support women and help them maintain health and quality of life.

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Age at menopause and all-cause and cause-specific dementia: a prospective analysis of the UK Biobank cohort

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Study design, size, duration: A population-based cohort study involving 160 080 women who participated in the UK Biobank study. Participants/materials, setting, methods: Women with no dementia at baseline, and had no missing data on key exposure variables and covariates were included. Main results and the role of chance: Compared to women with

age at menopause of 46-50 years, women with earlier natural menopause younger than 40 years (1.36, 1.01-1.83) and 41-45 years (1.19, 1.03-1.39) had a higher risk of all-cause dementia, while late natural menopause >55 years was linked to lower risk of dementia (0.83, 0.71-0.98). Compared to natural menopause, surgical menopause was associated with 10% higher risk of dementia (1.10, 0.98-1.24). A U-shape relationship was observed between surgical menopause and risk of dementia. Women with surgical menopause before age 40 years (1.94, 1.38-2.73) and after age 55 years (1.65, 1.21-2.24) were both linked to increased risk of all-cause dementia. Women with early natural menopause without ever taking MHT at baseline had an increased risk of AD. Also, in each categorized age at the menopause level, higher income level or higher number of leisure activities was linked to a lowers risk of dementia. Limitations, reasons for caution: Menopausal age was based on women's self-report, which might cause recall bias. Wider implication of the findings: Women who experienced natural menopause or had surgical menopause at an earlier age need close monitoring and engagement for preventive health measures to delay the development of dementia.

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A phase 1/2, open-label, parallel group study to evaluate the safety and pharmacokinetics of DARE-HRT1 (80 µg estradiol/4 mg progesterone and 160 µg estradiol/8 mg progesterone intravaginal rings) over 12 weeks in healthy postmenopausal women

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Objectives: Primary objectives were to evaluate the safety and systemic pharmacokinetics (PK) of DARE-HRT1, an intravaginal ring (IVR), which releases 17β2-Estradiol (E2) with progesterone (P4) for 28 days in healthy postmenopausal women. **Methods:** This was a randomized, open-label, 2-arm, parallel group study in 21 healthy postmenopausal women with an intact uterus. Women were randomized (1:1) to either DARE-HRT1 IVR1 (E2 80 µg/d with P4 4 mg/d) or DARE-HRT1 IVR2 (E2 160 µg/d with P4 8 mg/d). They used the IVR for three 28-day cycles, inserting a new IVR monthly. Safety was measured by treatment emergent adverse events and changes in systemic laboratories and the endometrial bilayer width. Baseline adjusted plasma PK of E2, P4, and estrone (E1) was described. **Results:** Both DARE-HRT1 IVR were safe. All treatment emergent adverse events were mild or moderate and were distributed similarly among IVR1 versus IVR2 users. Month 3 median maximum plasma (Cmax) P4 concentrations were 2.81 and 3.51 ng/mL and Cmax E2 was 42.95 and 77.27 pg/mL for IVR1 and IVR2 groups, respectively. Month 3 median steady state (Css) plasma P4 concentrations were 1.19 and 1.89 ng/mL, and C_{ss} E2 was 20.73 and 38.16 pg/mL for IVR1 and IVR2 users, respectively. **Conclusions:** Both DARE-HRT1 IVRs were safe and released E2 in systemic concentrations, which were in the low, normal premenopausal range. Systemic P4 concentrations predict endometrial protection. Data from this study support further development of DARE-HRT1 for the treatment of menopausal symptoms.

Medicine (Baltimore). 2023 Jun 9;102(23):e33978. doi: 10.1097/MD.00000000000033978.

Neurokinin 1/3 receptor antagonists for menopausal women: A current systematic review and insights into the investigational non-hormonal therapy

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Background: Over 75% of menopausal women experience vasomotor symptoms (VMS), such as night sweats and hot flashes. Despite the prevalence of these symptoms, there is limited data on non-hormonal therapies to alleviate them. **Methods:** PubMed, Cochrane, Scopus, Ovid, Web of Science, and ClinicalTrials.gov were searched for relevant studies. The search was performed using the following keywords, which were customized to suit the specific databases/registers: menopause, women, neurokinin 3, and/or Fezolinetant. The search was conducted until December 20, 2022. This systematic review was conducted in compliance with the PRISMA Statement 2020 guidelines. **Results:** A total of 326 records were found, with 10 studies (enrolling 1993 women) selected for inclusion. The women received 40-mg doses of NK1/3 receptor antagonists twice daily, with follow-ups at 1 to 3 weeks. Moderately strong evidence was found suggesting that NK1/3 receptor antagonists can help limit the frequency and severity of hot flashes in menopausal women. **Conclusion:** While the results should be interpreted with caution until further clinical trials validate the efficacy and safety of NK1/3 receptor antagonists among menopausal women, these findings suggest that they are promising targets for future pharmacological and clinical studies in addressing vasomotor symptoms.