Selección de Resúmenes de Menopausia

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Juan Enrique Blümel. Departamento Medicina Sur. Universidad de Chile

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A comparison of progestins within three classes: Differential effects on learning and memory in the aging surgically menopausal rat.

Braden BB, Andrews MG, Acosta JI, Mennenga SE, Lavery C, Bimonte-Nelson HA.

INTRODUCTION: For decades, progestins have been included in hormone therapies (HT) prescribed to women to offset the risk of unopposed estrogen-induced endometrial hyperplasia. However, the potential effects on cognition of subcategories of clinically used progestins have been largely unexplored. METHODS: In two studies, the present investigation evaluated the cognitive effects of norethindrone acetate (NETA), levonorgestrel (LEVO), and medroxyprogesterone acetate (MPA) on the water radial-arm maze (WRAM) and Morris water maze (MM) in middle-aged ovariectomized rats. RESULTS: In Study 1, six-weeks of a high-dose NETA treatment impaired learning and delayed retention on the WRAM, and impaired reference memory on the MM. Low-dose NETA treatment impaired delayed retention on the WRAM. In Study 2, high-dose NETA treatment was reduced to four-weeks and compared to MPA and LEVO. As previously shown, MPA impaired working memory performance during the lattermost portion of testing, at the highest working memory load, impaired delayed retention on the WRAM, and impaired reference memory on the MM. NETA also impaired performance on these WRAM and MM measures. Interestingly, LEVO did not impair performance, but instead enhanced learning on the WRAM. CONCLUSIONS: The current study corroborates previous evidence that the most commonly prescribed FDA-approved progestin for HT, MPA, impairs learning and memory in the ovariectomized middle-aged rat. When progestins from two different subcategories were investigated, NETA impaired learning and memory similarly to MPA, but LEVO enhanced learning. Future research is warranted to determine LEVO's potential as an ideal progestin for optimal health in women, including for cognition.

Mol Cell Biol. 2016 Jun 27. pii: MCB.00202-16. [Epub ahead of print]

Follicle Depletion Provides A Permissive Environment for Ovarian Carcinogenesis.

Wang Y, Cai KQ, Smith ER, Yeasky TM, Moore R, Ganjei-Azar P, Klein-Szanto AJ, et al.

We modeled the etiology of postmenopausal biology on ovarian cancer risk using the germ cell-deficient White-Spotting Variant (Wv) mice, incorporating oncogenic mutations. Ovarian cancer incidence is highest in peri- and post-menopausal women, and epidemiological studies have established the impact of reproductive factors on ovarian cancer risk. Menopause as a result of ovarian follicle depletion is thought to contribute to a higher cancer risk. As a consequence of follicle depletion, the female Wv mice develop ovarian tubular adenomas, a benign epithelial tumor corresponding to surface epithelial invaginations and papillomatosis frequently found in post-menopausal human ovaries. Lineage tracing using MISR2-Cre indicated that the tubular adenomas developed in Wv mice were largely derived from MISR2 lineage, which marked only a fraction of ovarian surface and oviduct epithelial cells in wild type tissues. We modeled the etiology of postmenopausal biology on ovarian cancer risk using the germ cell-deficient White-Spotting Variant (Wv) mice, incorporating oncogenic mutations. Deletion of p27, either heterozygous or homozygous, was able to convert the benign tubular adenomas into more proliferative tumors. Restricted deletion of p53 in Wv/Wv mice by either intra-bursal injection of adenoviral Cre or inclusion of MISR2-Cre transgene also resulted in augmented tumor growth. The finding suggests that follicle depletion provides a permissive ovarian environment for oncogenic transformation of epithelial cells, presenting a mechanism for the increased ovarian cancer risk in post-menopausal women.

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Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case-control study.

Abrahamsen B, Eiken P, Prieto-Alhambra D, Eastell R.

OBJECTIVES: To determine the skeletal safety and efficacy of long term (≥10 years) alendronate use in patients with osteoporosis. DESIGN: Open register based cohort study containing two nested case control studies. SETTING: Nationwide study of population of Denmark. PARTICIPANTS: 61 990 men and women aged 50-94 at the start of treatment, who had not previously taken alendronate, 1996-2007. INTERVENTIONS: Treatment with alendronate. MAIN OUTCOME MEASURES: Incident fracture of the subtrochanteric femur or femoral shaft (ST/FS) or the hip. Non-fracture controls from the cohort were matched to fracture cases by sex, year of birth, and year of initiation of alendronate treatment. Conditional logistic regression models were fitted to calculate odds ratios with and without adjustment for comorbidity and comedications. Sensitivity analyses investigated subsequent treatment with other drugs for osteoporosis. RESULTS: 1428 participants sustained a ST/FS (incidence rate 3.4/1000 person years, 95% confidence interval 3.2 to 3.6), and 6784 sustained a hip fracture (16.2/1000 person years, 15.8 to 16.6). The risk of ST/FS was lower with high adherence to treatment with alendronate (medication possession ratio (MPR, a proxy for compliance) >80%) compared with poor adherence (MPR <50%; odds ratio 0.88, 0.77 to 0.99; P=0.05). Multivariable adjustment attenuated this association (adjusted odds ratio 0.88, 0.77 to 1.01; P=0.08). The risk was no higher in long term users (≥10 dose years; 0.70, 0.44 to 1.11; P=0.13) or in current compared with past users (0.91, 0.79 to 1.06; P=0.22). Similarly, MPR >80% was associated with a decreased risk of hip fracture (0.73, 0.68 to 0.78; P<0.001) as was longer term cumulative use for 5-10 dose years (0.74, 0.67 to 0.83; P<0.001) or ≥10 dose years (0.74, 0.56 to 0.97; P=0.03). CONCLUSIONS: These findings support an acceptable balance between benefit and risk with treatment with alendronate in terms of fracture outcomes, even for over 10 years of continuous use.

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Are estrogen-related drugs new alternatives for the management of osteoarthritis?

Xiao YP, Tian FM, Dai MW, Wang WY, Shao LT, Zhang L.

Osteoarthritis (OA) is a chronic degenerative disease involving multiple physiopathological mechanisms. The increased prevalence of OA after menopause and the presence of estrogen receptors in joint tissues suggest that estrogen could help prevent development of OA. This review summarizes OA research with a focus on the effects of estrogen and selective estrogen receptor modulators (SERMs). Preclinical studies and clinical trials of estrogen therapy have reported inconsistent results. However, almost all studies assessing SERM treatment have obtained more consistent and favorable effects in OA with a relatively safety and tolerability profiles. At present, some SERMs including raloxifene and bazedoxifene have been approved for the treatment of osteoporosis. In summary, estrogen-related agents may exert both a direct effect on subchondral bone and direct and/or indirect effects upon the surrounding tissues, including the articular cartilage, synovium, and muscle, to name a few. Estrogen and SERMs may be particularly favorable for postmenopausal patients with early-stage OA or osteoporotic OA, a phenotype defined by reduced bone mineral density related to high remodeling in subchondral bone. At present, no single drug exists that can prevent OA progression. Although estrogen-related drugs provide insight into the continued work in the field of OA drug administration, further research is required before SERMs can become therapeutic alternatives for OA treatment.

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Reproductive Steroid Regulation of Mood and Behavior.

Schiller CE, Johnson SL, Abate AC, Rubinow DR, Schmidt PJ.

In this article, we examine evidence supporting the role of reproductive steroids in the regulation of mood and behavior in women and the nature of that role. In the first half of the article, we review evidence for the following: (i) the reproductive system is designed to regulate behavior; (ii) from the subcellular to cellular to circuit to behavior, reproductive steroids are powerful neuroregulators; (iii) affective disorders are disorders of behavioral state; and (iv) reproductive steroids affect virtually every system implicated in the pathophysiology of depression. In the second half of the article, we discuss the diagnosis of the three reproductive endocrine-related mood disorders (premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression) and present evidence supporting the relevance of reproductive steroids to these conditions. Existing evidence suggests that changes in reproductive steroid levels during specific reproductive states (i.e., the premenstrual phase of the menstrual cycle, pregnancy, parturition, and the menopause transition) trigger affective dysregulation in susceptible women, thus suggesting the etiopathogenic relevance of these hormonal changes in reproductive mood disorders. Understanding the source of

individual susceptibility is critical to both preventing the onset of illness and developing novel, individualized treatments for reproductive-related affective dysregulation.

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Comparison of combined low-dose hormone therapy vs. tibolone in the prevention of bone loss.

Kalder M, Kyvernitakis I, Hars O, Kauka A, Hadji P.

OBJECTIVES: To compare the effects on bone mineral density (BMD) measured by dual-energy X-ray absorptiometry at the lumbar spine, the femoral neck and the total hip following 2 years of treatment with a low-dose combined hormone therapy (HT) comprised of 1 mg estradiol and 0.5 mg norethisterone acetate (E2/NETA) versus 2.5 mg tibolone in postmenopausal women. Additionally, quantitative ultrasonometry (QUS) of the os calcaneus and of the phalanges was performed. METHODS: Changes in BMD, QUS and side-effects were assessed at baseline, 6, 12 and 24 months in 50 postmenopausal women who received either E2/NETA ($n = 26$) or tibolone ($n = 24$) for 2 years.

RESULTS: Compared to women on tibolone, women receiving E2/NETA showed a significant increase in BMD from baseline to 12 and 24 months at the lumbar spine (3.07%, 3.86%; $p < 0.01$ vs. 1.13%, 2.23%; $p < 0.05$), and at the total hip (1.33%, 1.69%; $p < 0.01$ vs. 0.76%, 0.70%) and at the femoral neck from baseline to 24 months (1.10%; $p < 0.05$). QUS indices only showed a significant change with the ultrasound bone profile index with E2/NETA at 6 months (-2.32%; $p < 0.001$). CONCLUSIONS: Low-dose E2/NETA showed a significantly higher increase in BMD compared to tibolone. QUS measurement was not considered to comprise beneficial effects in monitoring drug-induced bone changes.