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ISOLATION AND CHARACTERIZATION OF A NOVEL BONE FORMING AGENT (CDROSTEOID-II) FROM NATURAL SOURCE

K. Sharan[1], J. Siddiqui[1], G. Swarnkar[1], P. Rawat[2], R. Maurya[2], S. Sanyal[3], N. Chattopadhyay[1]. *[1]Central Drug Research Institute, Endocrinology, Lucknow, India; [2]Central Drug Research Institute, Medicinal and Process Chemistry, Lucknow, India; [3]Central Drug Research Institute, Drug Target Discovery and Development, Lucknow, India*

Objectives: To evaluate osteogenic property of a molecule (CDROsteoid-II) isolated from an Indian terrestrial plant and its mode of action.
Methods: Rat calvarial osteoblasts and Cos-7 cells were used for all *in vitro* experiments. *In vivo* effect of CDROsteoid-II on bone were studied in female *Sprague Dawley* (weaning) rats and adult ovariectomized (OVx) rats.
Results: CDROsteoid-II at 10^{-7}M stimulated osteoblast proliferation, survival, differentiation and mineralization. CDROsteoid-II had no effect on osteoclast differentiation. CDROsteoid-II signals via aryl hydrocarbon receptor (AHR) in osteoblasts. When CDROsteoid-II was given to weaning female *Sprague Dawley* rats (5.0 mg^{-1} kg^{-1} day^{-1}) orally for 30 consecutive days, mineral apposition rate, bone formation rate and mineralization surface, assessed by tetracycline - calcein labeling, were significantly higher than the vehicle treated group. Next, CDROsteoid-II was given to adult OVx *Sprague Dawley* rats (5.0 mg^{-1} kg^{-1} day^{-1}) for 3 months and compared with vehicle treated OVx- or sham surgery rats. OVx + vehicle group had reduced BMD and bone biomechanical strength along with microarchitectural deterioration compared with sham + vehicle group; all these parameters in OVx + CDROsteoid-II group were comparable with sham + vehicle group. Serum osteocalcin and urinary CTx levels were higher in OVx + vehicle than sham + vehicle group and these levels in OVx + CDROsteoid-II group were comparable to sham + vehicle group. CDROsteoid-II had no uterine estrogenicity.
Conclusions: CDROsteoid-II is a novel AHR modulator exerting osteogenic action, thus having therapeutic potential in menopausal osteoporosis.
Keywords: Aryl hydrocarbon receptor, osteogenic, phytochemical, menopausal osteoporosis, bone anabolic, peak bone mass.

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POSTMENOPAUSAL EVALUATION AND RISK-REDUCTION WITH LASOFOXIFENE (THE PEARL TRIAL): GYNAECOLOGICAL OUTCOMES AT FIVE-YEARS

S. Goldstein[1], U. Sriram[2], P. Neven[3], T. Colgan[4], C. Runowicz[5], D. Krpan[6], Z. Giljevic[7], S. Cumming[8], J. Proulx[9], M. Johnson[9], D. Thompson[9], J. Thompson[10]. *[1]New York University School of Medicine, Obstetrics and Gynaecology, New York, United States; [2]Associates in Clinical Endocrinology, Education and Research, Chennai, India; [3]UZ Leuven, Gyn Oncol, Leuven, Belgium; [4]Mount Sinai Hospital, Toronto, Canada; [5]University of Connecticut Cancer Center, Farmington, United States; [6]Poliklinika Lozo, Zadar, Croatia; [7]Klinicki Bolnicki Centar, Zagreb, Croatia; [8]University of California, San Francisco, United States; [9]Pfizer Global Research and Development, New London, CT, United States; [10]Pfizer Global Research and Development, New London, United States*

Objectives: To establish the gynecological safety profile of 5-years treatment with lasofoxifene versus placebo in postmenopausal women at risk for osteoporosis over five years.
Methods: In this randomized trial, 8556 women aged 59 to 80 years with femoral neck or spine bone mineral density T-scores $\leq$-2.5 received lasofoxifene 0.25 mg/d, 0.5 mg/d, or placebo for five years.
Results: Endometrial cancer was confirmed for seven subjects (two subjects in each lasofoxifene group and three placebo subjects). Endometrial hyperplasia was confirmed for five subjects: three subjects in the lasofoxifene 0.25 mg/d group, two subjects in the lasofoxifene 0.5 mg/d group, and no subjects in the placebo group. Vaginal bleeding occurred in 2.2% ($p = 0.012$), 2.6% ($p = 0.001$), and 1.3% of patients treated with 0.25 mg/d lasofoxifene, 0.5 mg/d lasofoxifene, and placebo, respectively; the excess in vaginal bleeding observed with lasofoxifene treatment were attributed to the benign endometrial effects of lasofoxifene. Lasofoxifene treatment was associated with a small increase in endometrial thickness compared to placebo (LS mean change -0.72 mm, 1.19 mm [$p=0.001$], and 1.43 mm [$p<0.001$] for placebo, 0.25 mg/d, and 0.5 mg/d lasofoxifene). The number of subjects requiring surgery for pelvic organ prolapse or urinary incontinence was similar between subjects treated with placebo and 0.5 mg/d lasofoxifene (1.2% vs 1.6%, $p=0.224$).
Conclusions: These findings indicated that lasofoxifene treatment over five years did not increase the risk for endometrial cancer or hyperplasia in postmenopausal women.
Keywords: SERM, lasofoxifene, osteoporosis, endometrial cancer or hyperplasia.

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EQUOL BUT NOT GENISTEIN IMPROVES FRACTURE HEALING IN SEVERE EXPERIMENTAL OSTEOPOROTIC BONE

L. Kolios, S. Sehmisch, F. Daub, T. Rack, M. Tezval, K.M. Stuermer, E.K. Stuermer. *University of Goettingen, Department of Trauma and Reconstructive Surgery, Göttingen, Germany*

Objectives: Healing of predominantly metaphyseal fractures in postmenopausal osteoporosis is delayed and comparatively poor. HRT could improve fracture healing, but, because of potential side effects, natural alternatives are appealing. The study examined if the soy metabolites equol and genistein, in comparison to 17-β-estradiol, improve metaphyseal fracture healing in postmenopausal osteoporotic bone.
Methods: Forty-eight 12-week-old rats developed severe osteoporosis eight weeks after ovariectomy. After a metaphyseal tibial osteotomy and standardized stable internal fixation, changes in callus morphology were evaluated biomechanically, qualitatively and quantitatively (in histological sections and microradiographies) in ovariectomized rats (C) and under standardized 17-β-estradiol- (E), equol- (EQ) and genistein (G)-supplemented diets over a period of five weeks.
Results: Estrogen and equol improve the stiffness of callus formation significantly in postmenopausal osteoporotic bone (S[N/mm]C: 121.4±47.08, E: 147.9±39.38, EQ: 167.8±59.9). The effects of estrogen are evident in trabecular bone (N.Nd [abs] of E: 6.47±7.68, EQ: 4.25±3.96). But in terms of the whole body, equol induces a less adverse reaction than estrogen (bodyweight of C: 342.2±19.91g, E: 280.25±12.05g EQ: 308.75±24.28g). Genistein as an osteoclast inhibitor influences callus stiffness (G: 144.5±61.52 N/mm) and negatively impacts trabecular structure (N.Nd [abs] of G: 0.59±1.01) in severely osteoporotic bone.
Conclusions: Estrogen and equol improve fracture healing in postmenopausal osteoporotic bone, and the extent of callus formation plays only a minor role. Genistein negatively influences fracture healing. The metaphyseal osteotomy model in ovariectomized rats allows researchers to accurately study the therapeutic effects of antiosteoporotic substances.
Keywords: Fracture healing - osteoporosis - estrogen - phytoestrogen - equol - genistein.

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PSYCHOBIOLOGICAL PREDICTORS OF EXERCISE BEHAVIOUR IN POSTMENOPAUSAL WOMEN

F. Barnett. *James Cook University, Townsville, Australia*

Objectives: Weight gain and obesity-related diseases are associated with the postmenopausal period. Moderate intensity exercise may be protective through attenuation of weight gain, however, many postmenopausal women do not engage in regular exercise. This study investigated the exercise behaviour of postmenopausal women in regional Queensland to determine whether differences existed for personal, physiological and psychological variables and if so, which of these variables may predict future exercise behaviour.
Methods: Participants were postmenopausal women (N=101) resident in North Queensland. A self-report questionnaire, the Self-efficacy for Exercise Scale and the Health Belief Model Scale were completed.
Anthropometric and physiological measures were obtained. Participants also completed a 20 minute moderate intensity exercise bout on a cycle ergometer; measures of affect were obtained using the Subjective Exercise Experience Scale. Participants were then categorised as exercisers (n=53) or non-exercisers (n=48).
Results: Compared to the exercisers, the non-exercisers had a lower level of

education (U=971.5, p=0.03), cardio respiratory fitness ($F_{1,99}$=21.57, p=0.00) and exercise self-efficacy ($F_{1,99}$=39.56, p=0.00) and higher resting diastolic blood pressure ($F_{1,99}$=7.57, p=0.01) and BMI ($F_{1,99}$=33.63, p=0.00).
The barrier items of perceived lack of time, difficulty getting to an exercise location and the weather provided the greatest discrimination between exercisers and non-exercisers. However, the acute exercise bout produced higher positive well-being postexercise compared to pre and during exercise for both groups.
Conclusions: Identification of the differences in exercise behaviour between exercisers and non-exercisers may provide information for future health promotion policy directions for this population and allow for the formulation of guidelines for exercise professionals.
Keywords: Postmenopausal women, exercise behaviour.

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EVALUATION OF THE HYPERLIPIDEMIA AND HYPERGLYCEMIA IN PROGESTERONE ONLY PILL (POP) USERS

M. Kashanian, M. Fekrat. *Iran University of Medical Sciences, Obstetrics and Gynecology, Tehran, Iran, Islamic Republic of*

Objectives: Evaluation of the hyper lipidemia and hyperglycemia in the progesterone only pill (POP) users.
Methods: A semi-experimental study was performed on 170 women, who were 20-45 years old and used lynesterenol (POP), as a contraceptive. Fasting blood sugar (FBS), serum cholesterol, serum triglyceride (TG), serum HDL-Cholesterol, serum LDL-Cholesterol, were measured at the beginning of lynesterenol use and again 6 months after its use.
Results: FBS was 65.3±5.2 mg/dl and 88±6.1mg/dl before and after the treatment respectively, which showed a statistically significant difference, ($p<0.001$, pair t test), but the values after treatment, were in the normal range. Cholesterol was 161.5±20.2 mg/dl and 169±10.5 mg/dl before and after the treatment respectively, which showed a statistically significant difference ($p<0.001$, pair t test), and again values after treatment were in the normal range. TG was 73.7±8.7 and 76.4±7.1 mg/dl before and after the drug use, respectively, without a statistically significant difference. LDL-C was 108±10.2 and 111±8.5 mg/dl, and HDL-C was 41.4±3.5 and 39.1±4.2 mg/dl before and after the treatment respectively, without a statistically significant difference.
Conclusions: Regarding to the small effects of POPs on lipid profile and blood sugar, it can be offered as an effective method for contraception in patients who are at risk for cardiovascular disease and also diabetese and in women who can not use combined pills, and also in women older than 40 years old, because in this group of patients, unwanted estrogen effects are dangerous.
Keywords: Contraception, perimenopause, progesterone only pill (POP).

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SMART-2: A PHASE III STUDY OF THE EFFICACY AND SAFETY OF BAZEDOXIFENE/CONJUGATED ESTROGENS (BZA/CE) FOR TREATMENT OF MENOPAUSAL VASOMOTOR SYMPTOMS

J. Pinkerton[1], W. Utian[2], G. Constantine[3], S. Olivier[3], J. Pickar[3]. *[1]University of Virginia, Charlottesville, United States; [2]Case Western Reserve University, Cleveland, United States; [3]Wyeth Research, Collegeville, United States*

Objective: Bazedoxifene (BZA) partnered with conjugated estrogens (CE) is a novel tissue selective estrogen complex (TSEC). In a prior 2-year, double-blind trial, BZA 20 mg/CE 0.45 or 0.625 mg was shown to significantly increase bone mineral density and reduce the frequency and severity of hot flushes (HFs) compared with placebo without endometrial stimulation in postmenopausal women. The SMART-2 (Selective estrogens, Menopause And Response to Therapy-2) trial evaluated the efficacy and safety of BZA/CE versus placebo for treatment of moderate-to-severe vasomotor symptoms.
Methods: This 12-week trial randomized 332 postmenopausal women with ≥7 moderate-to-severe HFs daily (or ≥50 per week) to receive BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, or placebo. Subjects recorded the number and severity of HFs daily. Transvaginal ultrasound was performed at baseline and 12 weeks.
Results: BZA 20 mg/CE 0.45 and 0.625 mg showed significantly greater reductions in number of moderate-to-severe HFs at weeks 4 and 12 versus placebo ($P<0.001$), achieving 74% and 80% reductions from baseline at week 12, respectively. Statistically significant improvements over placebo were observed in daily number of moderate-to-severe HFs with BZA 20 mg/CE 0.45 mg from week 3 onward and with BZA 20 mg/CE 0.625 mg from week 2 onward. There were no differences in incidence of adverse events or changes in endometrial thickness among groups.
Conclusion: BZA/CE, the first TSEC, effectively and safely reduced the number and severity of HFs in this study of symptomatic postmenopausal women with no evidence of endometrial stimulation.
Keywords: TSEC, menopause, vasomotor symptoms.

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SMART-3: EFFECTS OF BAZEDOXIFENE/CONJUGATED ESTROGENS (BZA/CE) ON VULVAR/VAGINAL ATROPHY (VVA) AND SEXUAL FUNCTION IN POSTMENOPAUSAL WOMEN

R. Kagan[1], M. Gass[2], R. Williams[3], S. Olivier[4], J. Pickar[4]. *[1]Foundation for Osteoporosis Research and Education, Oakland, United States; [2]University of Cincinnati College of Medicine, Cincinnati, United States; [3]University of Florida College of Medicine, Gainesville, United States; [4]Wyeth Research, Collegeville, United States*

Objective: The first tissue selective estrogen complex (TSEC), bazedoxifene (BZA) with conjugated estrogens (CE), was shown to prevent bone loss with favorable endometrial, tolerability, and safety profiles in postmenopausal women in the 2-year SMART-1 (Selective estrogens, Menopause And Response to Therapy-1) trial. The SMART-3 trial assessed the efficacy and safety of BZA/CE versus placebo for treatment of vulvar/vaginal atrophy (VVA) and impact on sexual function.
Methods: In this 12-week double-blind phase 3 study, 652 postmenopausal women aged 40-65 years with moderate-to-severe VVA, vaginal pH >5.0, and ≤5% superficial cells were randomized to receive BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, BZA 20 mg, or placebo daily. Primary endpoints were percentage of vaginal superficial and parabasal cells, vaginal pH, and severity of most bothersome VVA symptom at week 12; secondary endpoints included Arizona Sexual Experiences Scale (ASEX) and Menopause-Specific Quality of Life (MENQOL) total and sexual function scores.
Results: At week 12, BZA 20 mg/CE 0.45 and 0.625 mg significantly increased the percentage of superficial cells and decreased the percentage of parabasal cells compared with placebo ($P<0.001$ and $P\leq0.01$, respectively). Vaginal pH and most bothersome symptom scores were significantly improved with BZA 20 mg/CE 0.625 mg versus placebo ($P<0.001$ and $P<0.05$, respectively). ASEX lubrication and MENQOL total and sexual function scores were significantly improved over placebo in both BZA/CE groups ($P<0.05$ for all).
Conclusion: TSECs containing BZA/CE improved biologic markers of VVA and sexual function in postmenopausal women.
Keywords: TSEC, menopause, VVA, sexual functionl.

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EUROPEAN UNION STANDARDS IN MENOPAUSE SERVICE: A ROLE FOR EMAS

S. Sharma, C.A. Pop, J. Pitkin. *Northwick Park & St Mark's Hospitals, Menopause Clinical and Research Unit, Harrow, United Kingdom*

Objectives: To explore a possible role for the European Menopause and andropause society (EMAS) for standards setting in menopause which, could be tailored to individual European Union countries needs.
Methods: An e-mail questionnaire survey of menopause specialists from twenty-seven European Union countries and Switzerland was undertaken in September to November 2008.

Table 1. National gynaecological society recommendation

Recommendations	
Areas covered	Yes %
Standards for menopause	75%
Hormone replacement therapy recommendations	50%
Non-hormonal therapy	50%
Bone density scans for osteoporosis	50%
Breast screening	75%
Multi-disciplinary approach	75%
Gynaecology standards	75%