

HERBAL OPTIONS for POSTMENOPAUSAL WOMEN

Originally prepared by: Anne Nguyen PharmD www.cdup.org for the *RxFiles* - www.RxFiles.ca

Sept 04



Common name <i>botanical name</i>	PURPORTED USE, SELECTED DOSES, MECHANISM OF ACTION	TOXICITY	DRUG INTERACTIONS
Black cohosh <i>Actaea (Cimicifuga) racemosa</i> NUFEM, generics, (REMIFEMIN not available in Can.) rhizome/root	vasomotor symptoms: • limited studies show comparable efficacy to estrogen; one study, showed better efficacy ¹ . Not effective in breast cancer survivors. ² • Onset of action: 2-4 weeks Dose: 20mg po bid (20mg tablet = 1mg triterpene glycoside. Improved manufacturing processes of some products permits this lower dosing instead of 40-80mg po bid.) ^{3,4} Proposed MOA: uncertain; may or may not have estrogenic effects ¹	Has been used safely in trials up to 6 months ^{1,4} (2 months in women with history of breast cancer ² ; does not cause proliferation of breast tissue in vitro ⁵) Documented: headache, dizziness, GI upset, weight gain, heaviness in legs, cramping ⁴ Potential: contains salicylic acid; short term data (12-24 wk) did not show endometrial thickening ^{3,6}	Documented: black cohosh with chasteberry & evening primrose oil – nocturnal seizures ⁷ Potential: tamoxifen, antihypertensive – ↑ drug effects ¹ ; Iron – may ↓ absorption of iron ⁸ Note: Some Black Cohosh products have DINs (Drug Identification Numbers) and are subject to regulations by Health Canada
Chasteberry (chaste tree berry) <i>Vitex agnus-castus</i> fruit ⁴	↓ libido, vaginal dryness, dyspareunia (difficult/painful coitus) • although possibly effective for PMS, insufficient evidence to support use in postmenopausal women ^{4,9} Proposed MOA: various effects on FSH, LH, dopamine ⁴	Generally well tolerated ⁴ ; used safely in trials up to 1.5yr ⁴ Documented: headache, GI upset, itching, urticaria, rash, acne, intermenstrual bleeding ⁴ Potential: avoid in hormone sensitive conditions ⁴	Documented: black cohosh with chasteberry & evening primrose oil – nocturnal seizures ⁷ Potential: neuroleptics, metoclopramide, oral contraceptives, hormone replacement therapy – interfere with effect
Dong quai <i>Angelica sinensis</i> root	vasomotor symptoms: not better than placebo ¹⁰ Proposed MOA: estrogenic effects ⁴	Generally well tolerated ⁴ Potential: photosensitization ¹¹ , carcinogenic, mutagenic ⁴ antiarrhythmic ¹² ; avoid in hormone sensitive conditions ⁴	Documented: warfarin – ↑ drug effects ^{13,14} Potential: anticoagulant, antiplatelet – ↑ drug effects ⁴
Evening primrose oil <i>Oenothera biennis</i>	vasomotor symptoms: not better than placebo ¹⁵ Proposed MOA: An essential fatty acid, gamma-linolenic acid (GLA) is thought to be the active ingredient, however no good scientific rationale exists for benefit in postmenopausal women. ¹⁵	Generally safe ⁴ Documented: headache, indigestion, nausea, soft stools ⁴ Potential: unknown	Documented: phenothiazine neuroleptic, anesthesia – seizures ⁴ ; black cohosh with chasteberry & evening primrose oil – nocturnal seizures ⁷ Potential: anticoagulant, antiplatelet – ↑ drug effects ⁴
Red clover (isoflavone source) <i>Trifolium pratense</i> Flower top	vasomotor symptoms: no better than placebo to ↓ hot flashes ^{JAMA Jul03} cardiovascular disease: ↑HDL; insufficient evidence to support use ^{9,16} bone loss: may ↑ BMD ^{4,16} ; Dose: 4g flower tops po tid, ⁴ PROMENSIL 40mg od (vasomotor); RIMOSTIL 1 tablet od (bone/heart) Proposed MOA: contains isoflavones, has weak estrogenic effect ⁴	Documented: rash ⁴ Potential: avoid in hormone sensitive conditions ⁴	Potential: anticoagulant, antiplatelet – ↑ risk of bleeding estrogen, oral contraceptives – interfere with effect fexofenadine, itraconazole, ketoconazole, lovastatin, triazolam – may see ↑ effects of these medications ⁴
Soy (a phytoestrogen; 25g soy protein =50mg isoflavones) ipriflavone =synthetic isoflavone derivative)	vasomotor symptoms: conflicting results whether better than placebo for hot flashes. ^{17,18} Not effective in breast cancer survivors. ¹⁸ heart disease: Lipids: no benefit ^{JAMA July7/04; prev ↓cholesterol, LDL&TG 19} Dose: 20-50g po od soy protein ⁴ (up to 60g for hot flashes) bone loss: no benefit ^{JAMA July7/04} ; previous results ↑lumbar BMD ²⁰ ; but ipriflavone <u>no</u> effect on fracture ²¹ Proposed MOA: contains isoflavones, has weak estrogenic effects; may block production of thyroid hormone ⁴	Has been used safely in trials up to 2 months ⁴ Documented: constipation, bloating, nausea ⁴ Potential: conflicting results, thus best to avoid use in patients with breast cancer ⁴ (preliminary studies did not show endometrial effects ^{22,23}) • 240ml (1 cup) soy milk contains ~ 6-9g soy protein • 100g tofu contains ~8-14g soy protein (16-28mg isoflavone)	Documented: theophylline - ↑ theophylline by ipriflavone (semisynthetic isoflavone soy derivative) ¹¹ thyroxine – ↓ thyroxine levels ²⁴ Potential: estrogen – ?antagonize estrogen replacement therapy tamoxifen – ↓ effect of tamoxifen
Wild yam <i>Dioscorea villosa</i> Rhizome/root	↓ libido, vaginal dryness: insufficient evidence to support use ^{4,9} Proposed MOA: progesterone precursor; note that conversion to progesterone does <u>not</u> occur in the human body, ∴ may not be of value. Less useful than compounded progesterone cream. ^{3,4}	Generally well tolerated Documented: emesis (large doses) ⁴ Potential: avoid in hormone sensitive conditions ⁴	none reported ⁴
VALERIAN <i>Valeriana officinalis</i> root ²⁵	insomnia: ²⁶ {NYTOL NATURAL SOURCE, UNISOM NATURAL SOURCE} Dose: 400-800mg po hs Proposed MOA: mediate release of GABA. ²⁴	Has been used safely in trials up to 28 days. ⁴ Documented: Withdrawal symptoms (cardiac failure, delirium) ²⁷ , ataxia, hallucination, ↑ muscle relaxation, hypothermia ²³ , restlessness & palpitations (paradoxical) ²³	Documented: none ²⁵ Potential: alcohol, barbiturates, benzodiazepines, opiates – ↑ CNS effects ²⁵

BMD=bone mineral density **MOA**=mechanism of action **hormone sensitive conditions** = breast, uterine or ovarian cancer, endometriosis & uterine fibroids²⁸ **+**Avoid herbal products in pregnancy/lactation.

Doses have been provided only for products which may be more effective than placebo. **Purity** of compounds a concern & may affect dosing. **Purported uses bolded** when substantiated by evidence.



Ginkgo biloba: not included as not efficacious for memory enhancement in a 6 week trial.²⁹ A longer 5-year study is being conducted by the National Institute of Aging. REMEMBER to check back in ~5 yrs ©.


Kava kava: not included as it was pulled off the Canadian market in August 2002 due to liver toxicity.

St. John's Wort: sometimes for mild-moderate depression (not major depression ^{JAMA APR01 & APR02}), but has many drug interactions.

Review: Kronenberg F, Complementary & alternative medicine for menopausal symptoms -a review of evidence. Ann Intern Med. Nov 2002.³⁰


Additional Reviewers: **Janet Webb** BSc(Pharm), MSc(Med) (drug information pharmacist,BC); **Brent Jensen** BSP (The RxFiles); **Suzanne Montemuro**, MD, CCFP (FM Vancouver, BC)

	Source	Generic Name	TRADE Name / Strength	Equivalent / Usual Dose	\$/Yr		
ESTROGENS - ORAL ♦↓MP symptoms & ↓ hip fracture risk ♦↑stroke ^{HR1,4} ; ↔CHD or breast cancer ^{WHI estrogen only} ♦may start low-dose ^{0.3mg} to ↓side effects ♦+Ca ⁺⁺ & Vit.D ♦consider tapering estrogen when discontinuing	equine	Conjugated equine est. (CEE)	PREMARIN 0.3, 0.625 ^{WHI} estrogen only, 0.9, 1.25 mg tab	0.625mg po OD	94		
	plant	Conjugated estrogens	PMS Conj. Estrogens 0.625, 1.25 mg tab	0.625mg po OD	74		
	plant	Conjugated estrogen sulfate	C.E.S. 0.3, 0.625, 0.9, 1.25 mg tab	0.625mg po OD	84		
	plant	Micronized estradiol-17β	ESTRACE 0.5, 1 ^{WELL-HART 48} , 2 mg (scored tabs)	1mg po OD	136		
	plant	Estropiate (estrone sulfate)	OGEN 0.625, 1.25, 2.5mg (scored tabs)	0.625mg po OD	109		
	equine	CEE + MPA (Blister-card) †	PREMPLUS 0.625mg tab + 2.5mg tab (or 5mg tab)	1 tab of each OD	142		
ESTROGENS -TRANSDERMAL/TOPICAL ♦↓MP symptoms; prevent PMO; ?less VTE than oral ♦alternative to po estrogens; may be preferred over oral if liver dysfunction or hypertriglyceridemia (↓LDL, ↔HDL, ↓TGs); unknown if safer than po; ♦patch: rotate sites (abdomen/thighs/buttocks) ♦gel: do not rotate sites (arm, abdomen, thigh) ♦TRI-EST Cr. -controversial: promoted as "bio-identical"; SOGC ⁹⁸ : no advantages & expensive	synth	Ethinyl estradiol ^{EE} /norethindrone ^{NE}	FemHRT EE 5µg/d + NE 1mg/d tab	✗ ▼	1 tab po daily	335	
	plant	Estradiol-17β Patch	ESTRADERM 25, 50, 100 µg/d	☞ ▼	50µg twice/wk	349	
	plant	ESTALIS-SEQUI = \$338 ☞ ▼	ESTRADOT 25, 37.5, 50, 75, 100 µg/d	☞ ▼	50µg twice/wk	320	
	plant	VIVELLE ^{DC 2003} 50µg/d x14d, then	RHOXAL-ESTRADIOL DERM 50, 75, 100 µg/d	☞ ▼	50µg twice/wk	237	
	plant	ESTALIS 140/50 or 250/50µg/d x14d	OESCLIM 25, 50 µg/d	☞ ▼	50µg twice/wk	320	
	plant		CLIMARA 25, 50, 75, 100 µg/d	☞ ▼	50µg weekly	320	
	pl/syn	Combination Patch	ESTRACOMB E2 50µg/d x14d; E2+NE 250µg/d x14d	☞ ▼	twice/wk (cyclic)	348	
	pl/syn	Estradiol-17β/norethindrone	ESTALIS E2 50µg/d + NE 140µg or 250µg	☞ ▼	twice/wk (continuous)	354	
	plant	Estradiol-17β Topical Gel	ESTROGEL 1mg/1.25g {to each arm OD}	☞ ▼	2.5g daily (as directed)	321	
	plant	Estriol/Estrone/Estradiol Crm.	TRI-EST Cr 2.5mg/g compounded 80/10/10%	✗ ⊗	Apply ~ 1g daily	~ 285	
ESTROGENS - VAGINAL ♦for urogenital symptoms: atrophy/dryness/stress incont. ♦less systemic effect (but creams may require progesterone)	equine	Conjugated estrogens	PREMARIN Vag. Cr 0.625mg/g	2-4g pv HS (cyclic ^{3wk/1wk} *)	252		
	plant	Estradiol-17β	VAGIFEM Vag. Tab 25µg {initial: 1tab vag OD x2wks}	1 tab per vag twice/wk	272		
	plant	Estradiol-17β	ESTRING Vag. Ring 2mg (7.5µg/day)	vaginally every 90 days	314		
PROGESTAGENS - ORAL ♦for endometrial protection in women on ERT with an intact uterus; dose required depends on ERT ♦if continuous regimen, will prevent bleeding	synth	Medroxyprogesterone (MPA) ♦may ↓HDL; †	PROVERA 2.5, 5, 10 mg scored tabs	2.5mg po OD 5-10mg po X12-14 d/mo	75 70-95		
	plant	Micronized progesterone ♦less breakthrough bleeding	PROMETRIUM 100mg cap ♦has peanut oil ♦sedating (give doses ≥200mg at HS); ?less SE's	100-200mg po OD 200-300mg po X12-14 d/mo	394-747 324-465		
♦Progesterone cream 2.5, 5, & 10% can be compounded but lack data on absorption, serum levels & efficacy (apply to thigh, inside of upper arm, abdomen)				✗ ⊗	Apply ~ 1g daily	~ 260	
ANDROGENS (T=testosterone) ♦for symptoms of androgen deficiency post bilateral oophorectomy & post-menopause; ↓ abdom. fat & TBW. ⁴⁹ ♦studies re. optimal prep, dose & long-term safety are lacking	Testosterone & Estradiol Inj.		CLIMACTERON INJ testosterone enanth. 150mg	✗ ▼	0.5ml IM Q4-6 wks (+/- 0.5ml DELESTROGEN )	155 (<200)	
	Testosterone 1% Gel ANDROGEL ✗ ⊗; ♂ 2.5-5g od \$130; data lacking in ♀ + estradiol dienanthate 7.5mg/1&5ml vial		Testosterone undecanoate	ANDRIOL 40mg cap (data lacking in ♀)		40mg po alternate days	244
			Testosterone Vag. Ointment	T-propionate 2%; Micronized-T 0.125% (compounded)	✗ ⊗	M-T 0.125%: 0.2-0.4ml per vag. OD	500
SERMs (2nd generation) ♦prevent/treat PMO; no stimulation of breast or endometrium	Raloxifene		EVISTA 60mg tab	☞ ⊗	60mg po OD	785	
	♦does not control MP symptoms & may worsen them in some ♀ ♦no breakthrough bleeding ♦↓LDL, ↔HDL or TGs; small ↑ VTE like estrogen ♦?↓CV events in ♀ at high CV risk; ?↓ breast ca MORE trial		☞ ⊗ for pts unable to tolerate, or not responding in 1yr to etidronate & calcium - DIDROCAL				
Parathyroid hormone ?osteosarcoma in rats; leg cramps, ↑Ca ⁺⁺ , ↓BP	Teriparatide		FORTEO 750ug/3 ml pen stored in fridge	✗ ⊗	20ug SC OD	9,000	
BISPHOSPHONATES  ♦most effective agents in preventing/treating PMO ♦minimal SE (altered taste, GI irritation & bone pain; rare: ocular disorders) ♦no effect on MP symptoms, CHD, lipids, breast, endometrium ♦long term data: alendronate in PMO trials up to 10 yrs ⁵⁰	Etidronate & Calcium		DIDROCAL etidronate 400mg x14d; then Ca ⁺⁺ 500mg x76d		po daily (hs or ~1hr ac)	203	
	Alendronate	♦risk of esophageal irritation	FOSAMAX 10&70mg tab, 40mg tab ^{Pager's} ; (5mg tab & 70mg soln) ^X	☞ ⊗	10 mg po OD am ~1hr ac 70mg po weekly ~1hr ac	560 633	
			(PMO prevention: 5mg/day, ~35mg/wk; PMO Tx: ≥70mg/wk)				
	Risedronate		ACTONEL 5,35mg ^{PMO Tx} (5mg od=\$797), 30 ^{Pager's} mg tab	☞ ⊗	35mg po weekly ~1hr ac	633	
Pamidronate		AREDIA Inj. 30, 90mg Inj	☞ ▼	30mg IV ^{2hr D5W} q3month	470		
MISC	Vaginal Moisturizer REPLENS ♦useful alternative to vaginal estrogen for urogenital symptoms (vag. dryness) ⁵¹ ♦Apply HS ~3X/week; Cost: 8pack = \$20		Oral Contraceptives (low-dose) ♦perimenopause option for symptomatic, healthy non-smokers ^{level I} evidence, HRT also used to control symptoms ^{level III} evidence (less effective for cycle control/contraception)				
	Calcitonin (Salmon) Nasal MIACALCIN ☞ ⊗ pts unable to tolerate/not responding in 1yr to bisphosphonates. ♦also ↓vertebral fracture pain. ♦Dose: 200 I.U. OD (alternating nostrils) \$646/yr		Calcium ▼ 1000-1500mg daily. Vitamin D 400-800 I.U. daily ♦often included in multivitamin & Ca ⁺⁺ products; recommend 800-1000 I.U./day in elderly / dietary deficiency ⁵²				

☞ =Exception Drug Status ✗ =non-formulary Sask ⊗ prior approval NIHB BP=blood pressure CHD=coronary heart disease CV=cardiovascular E2=estradiol 17β GI=stomach MP=menopausal PMO=postmenopausal osteoporosis SE=side effect TBW=total body weight VTE=venous thromboembolism  may add 0.5ml estradiol valerate inj. (Delestrogen) in same syringe to ensure adequate estrogen component; requires progesterone opposition in ♀ with a uterus.

* after initial, short-term treatment of ~1-2 weeks, dosage usually tapered/reduced to lowest effective maintenance dose (e.g. 1-3Xper wk); Cost=retail cost to consumer in Sask including markup & dispensing fee.

Other: Estrogen in HRT regimens generally contain 1/6-1/3 the estrogen amounts found in oral contraceptives † Combination HRT (CEE 0.625mg+MPA 2.5mg od): ↑MI, stroke, clots & breast ca ^{Womens Health Initiative: JAMA July 02 2002}

Drug induced osteoporosis: aluminum antacids, antineoplastics, corticosteroids, heparin-chronically for > 1 month, levothyroxine (↑ dose) & phenytoin. ⊗not covered by NIHB ▼covered by NIHB  = ↓ dose for renal dysfx 23

References: *The Rx Files* HRT Options in Light of the WHI

◆Table: Herbal Options for Postmenopausal Women

◆Table: Postmenopausal Pharmacotherapy

- ¹ Pepping J. Black cohosh: Cimicifuga racemosa. Am J Health Syst. Pharm. 1999;56:1400-02.
- ² Jacobson JS, Troxel AB, Evans J et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19:2739-45.
- ³ The Canadian consensus conference on menopause and osteoporosis. J Obstet Gynaecol Can 2001;23:1-90.
- ⁴ Therapeutic Research Faculty. Natural Database Mongraphs. Natural Database . 2002. Ref Type: Electronic Citation
- ⁵ Amato P, Christophe S, Mellon P. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause 2002;9:145-50.
- ⁶ Liske E, Hanggi W, et al. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosa rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based. Med 2002;11:163-74.
- ⁷ Shuster J. Black cohosh root? Chasteberry tree? Seizures! Hospital Pharmacy 1996;31:1553-4.
- ⁸ Facts and comparisons. The review of natural products (formerly the Lawrence Review of natural products). In: DerMarderosian A, editor. St. Louis MO, 2002.
- ⁹ Morelli V, Naquin C. Alternative therapies for traditional disease states: menopause. Am. Fam. Physician 2002;66:129-34.
- ¹⁰ Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. Fertil. Steril. 1997;68:981-6.
- ¹¹ Scott GN, Elmer GW. Update on natural product--drug interactions. Am J Health Syst. Pharm 2002;59:339-47.
- ¹² Chandler F. Herbs: everyday reference for health professionals. Ottawa, Canadian Pharmacists Association & Canadian Medical Association. 2000.
- ¹³ Page RL, Lawrence JD. Potentiation of warfarin by dong quai. Pharmacotherapy 1999;19:870-876.
- ¹⁴ Fugh-Berman A. Herb-drug interactions. Lancet 2000;355:134-8.
- ¹⁵ Chenoy R, Hussain S, Tayob Y, O'Brien PMS, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. BMJ 1994;308:501-3.
- ¹⁶ Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery ML, Moreton T. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. Menopause. 2001;8:259-65.
- ¹⁷ Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flashes. Obstet. Gynecol 1998;91:6-11.
- ¹⁸ Quella SK, Loprinzi CL, Barton DL et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. J Clin Oncol 2000;18:1068-74.
- ¹⁹ Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995;333:276-82.
- ²⁰ Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman JW, Jr. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. Am J Clin Nutr. 1998;68:1375S-1379S.
- ²¹ Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. JAMA. 2001 Mar 21;285(11):1482-8.
- ²² Duncan AM, Underhill KE, Xu X, Lavallee J, Phipps WR, Kurzer MS. Modest hormonal effects of soy isoflavones in postmenopausal women. J Clin Endocrinol. Metab 1999;84:3479-84.
- ²³ Balk J, Whiteside D, Naus, G et al. A pilot study of the effects of phytoestrogen supplementation on postmenopausal endometrium. J Soc Gynecol Invest 2002;9:238-42.
- ²⁴ Brinker F. Herb contraindications and drug interactions, 3rd ed. Eclectic Medical Publishing. 2001. 177-178.
- ²⁵ O'Hara M, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. Arch. Fam. Med 1998;7:523-36.
- ²⁶ Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. Am J Health Syst. Pharm 1999;56:125-38.
- ²⁷ Garges HP, Varia I, Doraiswamy PM. Cardiac complications and delirium associated with valerian root withdrawal. JAMA 1998;280:1566-7.
- ²⁸ Bedard M. Dong quai for women. Canadian Pharmaceutical Journal 2002;135:20-1.
- ²⁹ Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002;288:835-40.
- ³⁰ Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med. 2002 Nov 19;137(10):805-13.
- ³¹ Micromedex 2004
- ³² Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, et al.; **WHI** Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA. 2003 May 28;289(20):2673-84.
- ³³ Rapp SR, Espeland MA, et al.; **WHIMS**. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2663-72.
- ³⁴ Shumaker SA, Legault C, et al.; **WHIMS**. Estrogen plus progestin & the incidence of dementia & mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2651-62.
- ³⁵ Khan MA, Hlatky MA, Liu MW, Lin F, Rogers WJ, Shlipak MG; **HERS** Investigators. Effect of postmenopausal hormone therapy on coronary heart disease events after percutaneous transluminal coronary angioplasty. Am J Cardiol. 2003 Apr 15;91(8):989-91, A7.
- ³⁶ Hays J, Ockene JK, Brunner RL, Kotchen JM, et al.; **WHI** Investigators. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med. 2003 May 8;348(19):1839-54. Epub 2003 Mar 17
- ³⁷ Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. Am J Med. 2002 Nov;113(7):543-8.
- ³⁸ Byington RP, Furberg CD, Herrington DM, Herd JA, et al.; Heart and Estrogen/Progestin Replacement Study Research Group. Effect of estrogen plus progestin on progression of carotid atherosclerosis in postmenopausal women with heart disease: **HERS B-mode substudy**. Arterioscler Thromb Vasc Biol. 2002 Oct 1;22(10):1692-7.
- ³⁹ Hulley S, Furberg C, Barrett-Connor E, Cauley J, et al.; HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (**HERS II**). JAMA. 2002 Jul 3;288(1):58-66.
- ⁴⁰ Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA; Heart and Estrogen/Progestin Replacement Study (**HERS**) Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. JAMA. 2002 Feb 6;287(5):591-7.
- ⁴¹ Simon JA, Hunninghake DB, et al. Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2001 Oct 2;135(7):493-501.
- ⁴² Cauley JA, Black DM, Barrett-Connor E, Harris F, et al. Effects of hormone replacement therapy on clinical fractures and height loss: The Heart and Estrogen/Progestin Replacement Study (**HERS**). Am J Med. 2001 Apr 15;110(6):442-50.
- ⁴³ Chelebowski R, Hendrix S, Langer R, Stefanick M, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. The Women's Health Initiative (**WHI**) Randomized Trial. JAMA 2003;289:3243-53.
- ⁴⁴ **Treatment Guidelines:** Drugs for Prevention & Treatment of Postmenopausal Osteoporosis. **The Medical Letter:** November, 2002; (3) pp. 13-18.
- ⁴⁵ Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004 Jan 7;291(1):47-53.
- ⁴⁶ Holmberg L., Anderson H., for the HABITS steering and data monitoring committees; **HABITS** (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped; Published online February 3, 2004.
- ⁴⁷ Women's Health Initiative (**WHI**). Effects of Conjugated Equine **Estrogen** in Postmenopausal Women with Hysterectomy. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2004;291:1701-1712.
- ⁴⁸ Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, Faxon DP, Cashin-Hemphill L, Sanmarco ME, French WJ, Shook TL, Gaarder TD, Mehra AO, Rabbani R, Sevanian A, Shil AB, Torres M, Vogelbach KH, Selzer RH; Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial Research Group (**WELL-HART**). Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med. 2003 Aug 7;349(6):535-45.
- ⁴⁹ Gruber DM, Sator MO, Kirchengast S. Effect of percutaneous androgen replacement therapy on body composition and body weight in postmenopausal women. Maturitas 1998;29:253-9.
- ⁵⁰ Bone H.G., Hosking D, et al., for the Alendronate Phase III Osteoporosis Treatment Study Group Ten Years' Experience with Alendronate for Osteoporosis in Postmenopausal Women N Eng J Med 2004;350:1189-1199.
- ⁵¹ Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996;23:259-63.
- ⁵² Utiger RD. The need for more vitamin D. N Eng J Med 1998;338:828-9.
- ⁵³ Women's Health Initiative (**WHI**). Risks and benefits of estrogen plus progestin in health postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288:321-33.
- ⁵⁴ Manson JE, Hsia J, Johnson KC, Rossouw JE, et al; Women's Health Initiative Investigators (**WHI**). Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003 Aug 7;349(6):523-34.
- ⁵⁵ Wathen CN, Feig DS, Feightner JW, et al. Hormone replacement therapy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ. 2004 May 11;170(10):1535-1537.