HERBAL OPTIONS for POSTMENOPAUSAL WOMEN

Originally prepared by: Anne Nguyen PharmD **www.cdup.org** for the *RxFiles* - **www.RxFiles.ca** **Sept 04**

Common name ***botanical name***	**PURPORTED USE, SELECTED DOSES #, MECHANISM OF ACTION**	**TOXICITY +**	**DRUG INTERACTIONS**
Black cohosh *Actaea (Cimicifuga) racemosa* **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, cramping4 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) *Vitex agnus-castus* 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 *Angelica sinensis* 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 *Oenothera biennis*	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) *Trifolium pratense* 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 isoflavaones, 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 no 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]** **Food source may be preferred over supplements** Potential: estrogen – ?antagonize estrogen replacement therapy tamoxifen – ↓ effect of tamoxifen
Wild yam *Dioscorea villosa* Rhizome/root	↓ libido, vaginal dryness: insufficient evidence to support use[4,9] Proposed MOA: progesterone precursor; note that conversion to progesterone does not 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 *Valeriana officinalis* 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 fibroids[28] +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]

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POSTMENOPAUSAL PHARMACOTHERAPY Comparison Chart [31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46]

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	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 only47] •may start low-dose [0.3mg] to ↓side effects •+Ca^{++} &Vit.D •consider tapering estrogen when discontinuing **Combination HRT: risks exceeded benefits over 5+ years[WHI]; see note †.** Additional benefits of estrogen: prevent PMO/fractures, ↓colo-rectal cancer. Many possible benefits have been called into question following large scale randomized controlled trials (HERS, WHI, WHIMS, HABITS).	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	Estropipate (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
	synth	Ethinyl estradiol [EE] /norethindrone [NE]	**FemHRT** EE 5µg/d + NE 1mg/d tab ✗▼	1 tab po daily	335
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*	plant	Estradiol-17β **Patch**	**ESTRADERM** 25, 50, 100 µg/d ☎▼	50µg twice/wk	349
	plant	**ESTALIS-SEQUI** = **$338** ☎▼ **VIVELLE** [DC 2003] 50µg/d x14d, then **ESTALIS** 140/50 or 250/50µg/d x14d	**ESTRADOT** 25, 37.5, 50, 75, 100 µg/d ☎▼	50µg twice/wk	320
	plant		**RHOXAL-ESTRADIOL DERM** 50, 75, 100 µg/d ☎▼	50µg twice/wk	237
	plant		**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 † + estradiol dienanthate 7.5mg/1&5ml vial ✗▼	**0.5ml** IM Q4-6 wks (+/- 0.5ml DELESTROGEN †)	155 (<200)
		Testosterone 1% Gel **ANDROGEL** ✗ ⊗; ♂ 2.5-5g od $130; **data lacking in ♀**			
		Testosterone undecanoate	**ANDRIOL** 40mg cap (data lacking in ♀)	40mg po alternate days	244
		Testosterone Vag. Ointment	**T**-propionate **2**%; **M**icronized-**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 C •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 [Paget's];(5[mg tab]&70mg soln)✗ ☎✆ (PMO prevention: 5mg/day, ~35mg/wk; PMO Tx: ≥70mg/wk)	10 mg po OD am ~1hr ac 70mg po weekly ~1hr ac	560 633
		Risedronate	**ACTONEL** 5,35mg [PMO Tx] (5mg od=$797), 30 [Paget'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 C			**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 progestagen 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 83;54;55]

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

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

- **Table: Herbal Options for Postmenopausal Women**
- **Table: Postmenopausal Pharmacotherapy**

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