

POSTMENOPAUSAL PHARMACOTHERAPY

September, 1999

As Canada's baby boomers age, more and more women will face the option of Hormone Replacement Therapy (HRT). The decision can be a difficult one given the conflicting pros and cons. This *RxFiles* examines the role and use of HRT, as well as newer SERMS and bisphosphonates in post-menopausal (PM) patients.

HRT

HRT is indicated for the treatment of PM symptoms such as vasomotor disturbances and urogenital atrophy, and is considered primary therapy for prevention and treatment of postmenopausal osteoporosis (PMO).¹ Contraindications are reviewed in **Table 2**. Although HRT is contraindicated in women with active breast or uterine cancer, note that a prior or positive family history of these does not necessarily preclude women from receiving HRT.¹

Estrogen Replacement Therapy (ERT)

Naturally secreted estrogens include:²

- ♦ **estrone** (E1): acts as natural reservoir for E2 with which it easily intraconverts *in vivo*; the main estrogen after menopause
- ♦ **estradiol** (E2): the predominant, most potent, and physiologically important estrogen produced by the ovary in the reproductive years
- ♦ **estriol** (E3): a metabolite of E1 and E2

Estrogens cause proliferation of breast tissue and vaginal and uterine mucosa, inhibit rate of bone resorption, and have positive effects on skin, the cardiovascular, immune system, and CNS. Drug interactions may be seen with anticoagulants, hypoglycemics, antihypertensives and drugs that affect the CYP₄₅₀ enzyme system.

Comparative Efficacy: The most common estrogens prescribed for HRT are the conjugated estrogens containing primarily estrone and equilin from either equine urine (CEE, i.e. Premarin[®]) or plant sources (CES[®]). Estradiol, also from plant sources, is contained in many of the other oral and topical products. Regardless of their source, equivalent doses of oral estrogen products produce similar estradiol/estrone plasma levels because of rapid conversion to these forms *in vivo*.³ There is no objective data to suggest any product is more efficacious than others. All are effective in the short-term management of PM symptoms. Long-term therapy is beneficial in preventing PMO and possibly Alzheimer's. In some cases, lower-dose ERT (e.g. CEE 0.3mg po daily) given with calcium supplements may also prevent of osteoporosis.^{4,5}

Cardiovascular benefits have also been demonstrated⁶; however, due to a lack of benefit in patients with existing coronary heart disease (CHD) in the HERS trial, HRT is not currently recommended for the secondary prevention of CHD.^{7,8,1} Several large-scale, long-term prospective studies are ongoing.

The best route of administration depends on indication and patient preference. Transdermal therapy is preferred in women unable to take oral products due to intolerance or contraindications such as liver dysfunction or elevated triglycerides. Local vaginal therapies in the form of creams or a vaginal ring (Estring[®]) are effective for urogenital PM symptoms. They have variable, dose-related systemic absorption (levels up to 25% of equivalent oral dosing).

HIGHLIGHTS

- ♦ Long term HRT carries several major benefits but also risks which should be evaluated on an individual and ongoing basis
- ♦ Continuous ERT is appropriate for women without a uterus
- ♦ Women with a uterus should receive progestagen (at least 12 days per month or continuous low-dose) as part of their HRT
- ♦ Low-dose ERT (CEE 0.3mg) + Ca⁺⁺ appears to prevent PMO
- ♦ Bisphosphinates (e.g. alendronate, etidronate) and raloxifene are alternatives to HRT in treating and preventing PMO
- ♦ "Natural" HRT regimens can be compounded but data is lacking

Comparative Safety: Because of differences between products, some side effects may be alleviated by switching from one product to another, particularly from equine to plant sources or from oral to topical (see **Table 3** - Side Effects & Their Management).

Unopposed oral or transdermal ERT increases the risk of endometrial hyperplasia and uterine cancer. Women with an intact uterus must receive progestagen therapy either sequentially or continuously to minimize this risk. Despite its many benefits, long term ERT also carries an increased risk of breast cancer of 2% per year of use over 5 years.⁹ Addition of progestagen does not appear to protect against this risk. (See **Table 4**- Risks vs. Benefits)

Progestagen Replacement Therapy (PRT)

Naturally occurring progesterone transforms an estrogen-primed proliferative endometrium into a secretory endometrium. PRT is indicated to prevent the endometrial hyperplasia caused by unopposed estrogen therapy in women with intact uteri. Available **progestagens include** the natural plant-derived **progesterone** (Prometrium[®]) and the **synthetic progestins**, medroxyprogesterone acetate (MPA/Provera[®]) and norethindrone (in Estracomb[®] patch).

Comparative Efficacy: Oral progestagens are effective in preventing endometrial hyperplasia but do not reduce the long term risk of breast cancer with HRT. Although synthetic progestins seem to attenuate the beneficial lipid effects of estrogens (↓HDL-C), combination HRT appears to confer the same cardioprotective effect as ERT.³

Comparative Safety: Side effects are more problematic with the synthetic progestins, higher dose PRT, and sequential therapy (Table 3). Sedation is more prevalent with Prometrium[®] which may require dividing the dose and/or administration at bedtime. C₁₉ derivatives (norethindrone) tend to produce more androgenic side effects and greater lowering of HDL-C than MPA.¹⁰

Androgen Replacement

Women who have undergone oophorectomy may require androgen therapy. Decreased libido and loss of energy or sense of well-being may be caused by androgen deficiency and require supplementation. Data is limited as to optimal regimens. Climacteron[®] injection contains testosterone enanthate in

combination with estradiol dienanthate. **Climacteron® 0.5ml** injection can be given IM every 4-6 weeks. If a larger estrogen component is desired, Delestrogen® 0.5ml injection may be added to the same syringe. The recent SOGC consensus stated that 1ml dose of Climacteron® used in the past should be avoided due to the problems of hirsutism, virilization, and long term habituation.¹

Oral testosterone undecanoate (Andriol®) 40mg EOD is most commonly used but data is lacking. Vaginal ointments of either testosterone propionate¹ or micronized testosterone¹¹ can be compounded in select pharmacies, although data is limited.

Testosterone is partly metabolized to estrogen and thus women with an intact uterus will require progestagen opposition. Women taking androgens should be monitored for potential adverse effects on lipids and symptoms of androgen excess (hirsutism, voice changes, and clitoromegaly).

SELECTING AN HRT REGIMEN

Considerations: Although many women would benefit from HRT¹², only 15-25% of eligible women avail themselves of it. Compliance is poor, estimated at <30%. Of 1st time users, 20-30% will never fill their script, 20% will discontinue therapy within 9 months, and 10% will take their pills intermittently.¹³ Common reasons for refusing HRT include side effects, non-acceptance of bleeding, complicated regimens, and fear of cancer.¹⁴ Patient education and careful individualization of therapy can significantly boost compliance rates.

Women with hysterectomies may receive **unopposed ERT** as addition of progesterone is not required to protect the uterus.

Continuous ERT is now recommended as cyclic regimens (i.e. Days 1-25) often resulted in the uncomfortable return of menopausal symptoms in the withdrawal period.

Women with intact uteri should receive **continuous estrogen combined with a progestagen** to prevent endometrial hyperplasia. The progestagen may be given either sequentially for a minimum of 12-14 days per month or continuously. Common regimens are compared in Table 1.

"Natural" or "Bioidentical" HRT is an evolving alternative approach to HRT which attempts to mimic the physiological pattern of estrogens (E1,E2,E3), progesterone, and testosterone. Commercial preparations are not available thus requiring compounding of products (e.g. Tri-est cream, progesterone cream) at select pharmacies. Many questions remain as data on efficacy and safety is limited.¹⁵ There is no evidence that percutaneous progesterone creams offer protection against endometrial cancer.¹⁶

SERMS

Selective estrogen receptor modulators (SERMs) have recently been developed in an attempt to gain the skeletal and cardioprotective benefits of the estrogens without increasing the risk of breast or endometrial cancer. Raloxifene (Evista®) 60mg daily is indicated for the prevention of PMO. Bone density is maintained or slightly increased in both the spine and the hip.¹⁷ Recent data also shows a reduction in vertebral, but not nonvertebral fractures, after one year.¹⁸ It also lowers LDL cholesterol. Raloxifene does not stimulate uterine or breast tissue, and may even reduce the risk of breast cancer.¹⁹ Disadvantages include its high cost relative to HRT, a risk of thromboembolism similar to ERT, and its lack of benefit in relieving MP symptoms which may actually worsen in some women.

BISPHOSPHONATES

Bisphosphonates are the most effective agents to reduce bone loss. They are valuable agents in preventing PMO when HRT is otherwise not indicated or undesirable. Cyclic etidronate and calcium (e.g. Didrocal®) and alendronate (Fosamax®) 10mg are indicated for treatment of osteoporosis. Low-dose alendronate (5mg daily) has recently been approved for the prevention of PMO. It maintains bone mass in more than 85% of treated women when started within 5 years of MP.²⁰ In Saskatchewan, only the 10mg alendronate currently has drug plan (EDS) coverage.

MISCELLANEOUS AGENTS

Calcium and Vitamin D is essential in preventing PMO. It is recommended that PM women get at least 1,000 mg (1,500 mg if not on HRT) of calcium and 400-800 IU of Vitamin D per day.¹ Calcium carbonate is a preferred form and a variety of supplements are available (e.g. TUMs®, Apo®-Cal). Multivitamins are often the most convenient and economical source of Vitamin D.

Calcitonin Salmon Nasal (Miacalcin®) is effective in controlling pain related to OP fracture. It is available free through the HPB - *Special Access Program* for "severe refractory PMO".

Replens® Vaginal Moisturizer is an excellent alternative to vaginal estrogen in treating urogenital PM symptoms.²¹ It is usually applied vaginally at HS three times weekly.

Herbal Products: Black Cohosh (Remifemin®) has been useful in the treatment of PM related hot flashes and mood changes.¹ It may be suitable for short-term symptom relief in patients not on ERT. Phytoestrogens from various foods, especially soybean and linseed products, may also have some positive estrogen-like effects on PM symptoms although results vary widely and data is limited.

Table 1: Comparison of HRT Regimens

♀	REGIMEN	USUAL STARTING DOSE	COMMENTS
without uterus	CONTINUOUS ESTROGEN (ERT)	♦0.3-0.625 mg conjugated estrogen daily or equivalent (refer to Comparative chart); ↑dose as needed (0.3mg q3months) ♦begin with 0.3 mg in elderly and ↑	♦no need for addition of progestagen ♦avoids return of PM symptoms during withdrawal period ♦ 0.625 mg considered <u>minimum effective dose</u> for prevention of CHD and PMO ²² (0.3mg + Ca⁺⁺ <u>may be</u> effective for PMO ^{4,23})
with uterus	SEQUENTIAL HRT Continuous Estrogen Progestagen days 1-12	♦Estrogen as above ♦ Progestagen dose should be in proportion to estrogen dose. May adjust for age and effects. ²⁴ (e.g. MPA or equivalent ~ 5mg OD)	♦compliance best if progestagen given on 1 st 12 days/month vs last ♦disadvantages: withdrawal bleeds, cyclic PMS-like symptoms, complicated pill pattern ♦produces more regular bleeding pattern than continuous therefore often preferred in recent menopause ♦some evidence that sequential therapy <u>may be</u> more advantageous to overall health, particularly in women under 55 years old ²⁵
	CONTINUOUS HRT Continuous Estrogen & Progestagen	♦As above, but progestagen dose should be halved or lower (e.g. MPA 2.5mg OD)	♦will cause irregular bleeding in 1 st 6 months, especially in recent menopause, but results in amenorrhea in >80% within 12 months ²⁶ ♦advantages: regimen easy to remember; lower progestagen doses better tolerated; avoids withdrawal bleeds

Table 2: HRT Contraindications and Precautions ¹
ABSOLUTE CONTRAINDICATIONS:
<ul style="list-style-type: none"> •unexplained vaginal bleeding •active liver disease •active thrombosis
RELATIVE CONTRAINDICATIONS - caution if hx of:
<ul style="list-style-type: none"> •endometrial cancer - may consider use following tx if low risk (e.g. Stage 1 disease); unknown if progestagen ↓ risk of recurrence •breast cancer - HRT does not appear to further ↑ risk in pts with +ve family hx and does not affect long term survival in those with previously treated localized disease²⁷; ♦may consider: Replens[®] Vag. Moisturizer or estrogen cream/ring for vaginal symptoms; clonidine or higher-dose progestagen for vasomotor symptoms •liver dysfunction - advantageous to use non-oral routes •gall bladder disease - oral ERT ↑ risk 1.5-2x; effect persists >5yrs •thromboembolism - oral HRT may ↑ risk of VTE 3x²⁸ •endometriosis - addition of progestagen may be required for women with residual disease (recurrence of pain/symptoms) following definitive surgery/hysterectomy •migraine headache - low-dose continuous combined HRT may be better tolerated due to less fluctuation in hormone levels; discontinue if symptoms worsen •hypertriglyceridemia - potentiated by oral ERT; topical preferred

Table 3: HRT Side Effects & Their Management
Estrogen related
<ul style="list-style-type: none"> ♦5-10% incidence; often resolve within first 6 months! ♦reducing dose, changing route or type of estrogen may help Nausea - take with meals or at bedtime; use topical tx Headache - continuous oral or topical better tolerated Breast tenderness - start with low dose and titrate ↑ Bloating - add diuretic prn
Progestagen related
<ul style="list-style-type: none"> ♦dose and duration dependent (start low and titrate ↑ as needed) ♦consider alternate route, reducing dose & continuous regimen ♦"natural" Prometrium[®] may be better tolerated than synthetics ♦MPA less androgenic than norgestrel/norethindrone Mood swings, depression Breast tenderness Bloating/fluid retention Sedation: > with Prometrium[®] (take at hs) vs Provera[®]
Withdrawal bleeding
<ul style="list-style-type: none"> ♦with sequential regimens, should occur after Day 9 of progestagen therapy, usually 1-3 days after last dose; bleeding should be lighter, shorter duration, less symptomatic than regular menses ♦if bothersome, use continuous vs cyclical progestagen at lower dose (amenorrhea should result in 80-90% of women within 12 months vs. 30% with sequential regimens²⁹)
Irregular bleeding
<ul style="list-style-type: none"> ♦should be investigated if occurrence is after HRT amenorrhea established or prior to Day 9 of sequential progestagen therapy ♦often responds to ↑ progestagen dose and/or ↓ estrogen dose ♦with continuous progestagen treatment, should resolve in 6-12 months although will persist in 10% of women ♦conversion back to sequential treatment should produce predictable bleeding which may be preferable
Skin irritation with topical therapy
<ul style="list-style-type: none"> ♦10% of alcohol reservoir patch users (Estraderm, Estracomb) ♦5% of matrix system patch users (Vivelle, Climara) ♦avoid moisture trapping and rotate sites ♦try gel or cream ♦may try Beconase Aq[®] -spray skin area, allow to dry & apply patch

Table 4: Benefits versus Risks of HRT
BENEFITS: may improve quality of life & longevity via:
Relief of PM symptoms
<ul style="list-style-type: none"> •relieves vasomotor symptoms in up to 90% of patients with maximal effect in 3 months³⁰ (higher doses may be required) •improves urogenital symptoms within weeks but optimal relief may take months and regular maintenance therapy •improves mood and energy levels (progestagen may ↑ depression and irritability and oppose some of ERT's positive effect)
Disease Prevention: lifelong tx for proposed lifelong benefits
<ul style="list-style-type: none"> •Reduces <u>long-term</u> risk of CHD by up to 50%; women at greatest risk derive greater benefit than those at low risk^{31,32} -MPA (Provera[®]) but not progesterone (Prometrium[®]) attenuates estrogen's beneficial effect on HDL³³ -despite reduction in HDL with progestins, most studies suggest cardioprotection with combined HRT similar to ERT^{34,35} •Prevents loss of bone density and osteoporosis - risk of osteoporotic fractures ↓ by up to 50% (observational data, as opposed to randomized clinical trials)³⁶ •Appears to confer additional protection against colon cancer³⁷, Alzheimer's³⁸, other age-related dementias, & periodontal disease
RISKS:
<ul style="list-style-type: none"> •Endometrial cancer - baseline risk = 1:1000 -risk is related to dose and duration of estrogen therapy -unopposed ERT ↑ risk 8x over baseline but this = 1 new case per 1000 women/year³⁹. Adding a progestagen for >12days/month reduces (to near baseline), but does not eliminate the risk^{1,40,41} •Breast cancer- baseline risk = 1:9 (based on cumulative 11% incidence of breast cancer to age 85)⁴² -no increased risk if ERT taken <5yrs -relative risk ↑ 2% per year of use = extra 2-6-12 cases/1000 users after 5-10-15 years respectively⁴³ -risk returns to baseline within 5 years of discontinuing HRT -addition of progestagen does <u>not</u> affect risk one way or the other -morbidity may ↑ but mortality may not as breast cancer in HRT users generally less advanced with better prognosis than in non-users (possible surveillance bias in data)⁴² •Thromboembolism -<u>absolute effect is small</u>, only 1 extra case/5000 users/year so likely most significant for those with <u>predisposing risks</u> -HRT may ↑ risk of VTE 2-3x⁴⁴. -topical therapies may not ↑ clotting factors as much as oral

SO WHAT DOES THIS REALLY MEAN FOR AN AVERAGE 50 YR OLD ♀ PATIENT ON HRT UNTIL AGE 75? ⁴⁵									
<p>She will face a lifetime risk of:</p> <ul style="list-style-type: none"> 8% for breast cancer (B.Ca) 15% for hip fracture (H.Fr) 45% for CHD 	<table border="1"> <caption>Lifetime Risks for Average 50 Yr Old Female Patient on HRT until Age 75</caption> <thead> <tr> <th>Risk Category</th> <th>Lifetime Risk (%)</th> </tr> </thead> <tbody> <tr> <td>Breast Cancer (B.Ca)</td> <td>8%</td> </tr> <tr> <td>Hip Fracture (H.Fr)</td> <td>15%</td> </tr> <tr> <td>Coronary Heart Disease (CHD)</td> <td>45%</td> </tr> </tbody> </table>	Risk Category	Lifetime Risk (%)	Breast Cancer (B.Ca)	8%	Hip Fracture (H.Fr)	15%	Coronary Heart Disease (CHD)	45%
Risk Category		Lifetime Risk (%)							
Breast Cancer (B.Ca)	8%								
Hip Fracture (H.Fr)	15%								
Coronary Heart Disease (CHD)	45%								
<p>With HRT, she will:</p> <ul style="list-style-type: none"> ↑ risk of breast cancer to 12% ↓ risk of hip fracture to <10% ↓ risk of CHD to 20-25% 									

We wish to acknowledge those who have assisted in the development and review of this newsletter: Dr. T. Smith (Obs/Gyne), Dr. M. Schubert (Obs/Gyne), Dr. W.P. Olszynski (Rheum), Dr. M. Lyon (Pharmacol) Dr. Z. Tymchak (FM), Dr. M. Jutras (FM) Dr. Shannan Neubauer (UofS-Pharm), Dr. J. Richardson (SDH-Pharm), & the SDH-CDUP Advisory Committee.

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POSTMENOPAUSAL PHARMACOTHERAPY - COMPARISON CHART

Prepared by: Loren Regier, Sharon Downey - *The Rx Files* – August /2000

	Source	Name	Brand Name / Strength	Equivalent / Usual Dose	\$/Year
ESTROGENS - ORAL ♦↓MP symptoms; prevention of PMO & CHD ♦preferred route if dyslipidaemia (other than hypertriglyceridemia) {↓LDL, ↑HDL, & ↑TGs} ♦low-dose (+ Ca ⁺⁺ & Vit.D) <u>may</u> also prevent PMO	equine	Conjugated estrogens (CEE)	PREMARIN 0.3, 0.625, 0.9, 1.25, 2.5 mg ✓	0.625mg po OD	96
	plant	Conjugated estrogen sulfate	C.E.S. 0.3, 0.625, 0.9, 1.25 mg ✓	0.625mg po OD	85
	plant	Micronized estradiol-17β	ESTRACE 0.5, 1, 2 mg (scored tab) ✓	1mg po OD	130
	synth	Ethinyl estradiol	ESTINYL 20X, 50mcg✓ Avoid high dose ^{HSt}	10-20mcg po OD (or EOD)	150
	plant	Estropipate (estrone sulfate)	OGEN 0.625, 1.25, 2.5mg (scored tab) ✓	0.625mg po OD	112
ESTROGENS - TRANSDERMAL / TOPICAL ♦↓MP symptoms; appears to prevent PMO ♦alternative if unable to tolerate po estrogens; may be preferred over oral if liver dysfunction or hypertriglyceridaemia {↓LDL, ↔HDL, ↓TGs} ♦ patch : rotate sites (abdomen/thighs/buttocks) ♦ gel : do not rotate sites (arm, abdomen, thigh) ♦Tri-est Cr. -controversial: promoted as "bio-identical"; SOGC: <i>no advantages and expensive</i> ¹	plant	Estradiol-17β Patch	ESTRADERM 25, 50, 100 mcg/d ☹	50mcg twice/wk	320
	plant		VIVELLE 37.5, 50, 75, 100 mcg/d ☹	50mcg twice/wk	320
	plant		OESCLIM 25, 50 mcg/d ☹	50mcg twice/wk	335
	plant		CLIMARA 50, 100 mcg/d ☹	50mcg weekly	320
	plant / synth	Estradiol-17β /norethindrone Patch (estrogen/progestin)	ESTRACOMB E2 50mcg/d alone x 14d, then with NE 250mcg/d x14d ☹	apply twice/wk (cyclic regimen)	337
			ESTALIS E2 50mcg/d + NE 140mcg OR 250mcg ☹	(continuous regimen)	355
	plant	Estradiol-17β Topical Gel	ESTROGEL 1mg/1.25g to <u>each</u> arm OD ☹	2.5g daily (as directed)	298
	plant	Estriol/Estrone/Estradiol Cr.	TRI-EST Cr. 2.5mg/g compounded 80%/ 10%/ 10% ✗	~ 1g daily	230
ESTROGENS - VAGINAL ♦effective for urogenital symptoms (atrophy/dryness) ♦less systemic effect (both benefits and risks)	equine	Conjugated estrogens	PREMARIN Vag. Cr 0.625mg/g ✓	2-4g pv HS (cyclic ✱)	25
	synth	Dienestrol	ORTHO DIENESTROL Vag. Cr 0.1mg/g ✗	5-10g pv HS (cyclic ✱)	28
	plant	Estradiol-17β	ESTRING Vag. Ring 7.5mcg/day ✓	vaginally X 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 ♦progesterone <u>cream</u> 2.5, 5, & 10% can be <u>compounded</u> but lack data on serum levels and efficacy (apply to thigh, inside of upper arm, abdomen)	synth	Medroxyprogesterone (MPA) ♦may ↓HDL	PROVERA 2.5, 5, 10 mg tab ✓	2.5mg po OD	73
			PROCLIM 2.5,5,10 mg (carousel mate for Oesclim)	5-10mg po X12-14 d/mo	70-90
	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	265-450 200-300
				(Apply 1.25-2.5ml daily)	90-180
ANDROGENS (T=testosterone) ♦effective for symptoms of androgen deficiency post bilateral oophorectomy & post-menopause; ↓ abdom. fat & TBW. ⁴⁶ ♦studies re. optimal prep, dose, & long-term safety are lacking		Testosterone & Estradiol Inj.	CLIMACTERON INJ testosterone enanth. 150mg + estradiol diananthathe 7.5mg per 1ml vial † ✗	0.5ml IM Q4-6 wks (+/- 0.5ml Delestrogen †)	155 (<80)
		Testosterone undecanoate	ANDRIOL 40mg cap (data lacking in ♀) ✓	40mg po alternate days	25
		Testosterone Vag. Ointment ^{1,11}	T-propionate 2%; Micronized-T 0.125% (compounded) ✗	M-T 0.125%: 0.2-0.4ml per vag. OD	??
SERMs (2nd generation) ♦prevent PMO; does <u>not</u> stimulate breast or endometrial tissue; ↓risk of breast ca?; <u>small</u> ↑risk of VTE similar to estrogen ⁴⁷		Raloxifene	EVISTA 60mg tab ✗	60mg po OD	710
BISPHOSPHONATES ♦effective in preventing PMO; side effects - <u>minimal</u> (altered taste, GI irritation, & bone pain); <u>no effect</u> on MP symptoms, CHD, lipids, breast & endometrial tissue; lack long-term data		Etidronate & Calcium ♦lack long-term fracture data	DIDROCAL etidronate 400mg po x14 days, then calcium 500mg po x76 days ✓	daily (cyclic regimen as directed)	203
		Alendronate ♦↑risk of esophageal irritation	FOSAMAX 5mg tab (PMO prevention) ✗ 10mg tab (PMO treatment) ☹ 40mg tab (PMO treatment) ☹	5mg po OD AM ac 10mg po OD AM ac 80mg po weekly	677 837 495
MISC		Vaginal Moisturizer REPLENS ® ♦useful alternative to vaginal estrogen for urogenital symptoms (vag. dryness) ⁴⁸ ; Apply HS ~3X/week; Cost: 8pack = \$20	Oral Contraceptive combinations ♦perimenopause option when standard estrogen-progestagen regimens may be associated with irregular bleeding; use low-dose (~20mcg ethinyl estradiol)		
		Calcitonin (Salmon) Nasal MIACALCIN ® ♦available through EDS for crush fractures with bone pain (alternate to subcutaneous); Dose: <u>200</u> I.U. OD (alternating nostrils); \$786 per year	Calcium 1000-1500mg daily. Vitamin D 400-800 I.U. daily ♦often included in multivitamin & Ca ⁺⁺ products; recommend 800-1000 I.U. in elderly / dietary deficiency ⁴⁹		

MP =menopausal; PMO =postmenopausal osteoporosis; CHD =coronary heart disease; VTE =venous thromboembolism; ✓ =formulary coverage in SK; ☹ =Exception Drug Status; ✗ =non-formulary in SK; † may add 0.5ml of estradiol valerate inj. (Delestrogen®) in same syringe to ensure adequate estrogen component; partly metabolized to estrogen ∴ requires progestagen opposition in a woman with a uterus; ✱after initial, short-term treatment of ~1-2 weeks, dosage usually tapered or reduced to lowest effective maintenance dose (e.g. 1-3Xper wk); \$ Cost = approximate retail cost to consumer in SK (includes markup and dispensing fee); TBW =total body weight; GI =gastrointestinal; SE =side effects; HSt =causes hepatic stimulation; **Other notes:** Estrogen in HRT regimens generally contain 1/6 - 1/3 the estrogen amounts found in oral contraceptives

References:

- ¹ Society of Obstetricians and Gynaecologists of Canada (SOGC). The Canadian Consensus Conference on Menopause and Osteoporosis. *J Soc Obstet Gynaecol Can* 1998;20(13):1243-72.
- ² Depiro JT et al. *Pharmacotherapy* (3rd ed.). Appleton and Lange; Stamford, CT, 1997, p.1636.
- ³ Witt DM and Louisberg TR. Controversies surrounding estrogen use in PM women. *Ann Pharmacother*. 1997;31:745-55.
- ⁴ Genant HK, Lucas J, Weiss S, et al. Low-Dose Esterified Estrogen Therapy: Effects on bone, plasma estradiol concentrations, endometrium, and lipid levels, Estratab/Osteoporosis Study Group. *Arch Intern Med* 1997; 157(22):2609-15.
- ⁵ Recker RR et al. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. *Ann Intern Med*. 1999;130:897-904.
- ⁶ Mendelsohn ME, Karas RH. The protective effects of the estrogen on the cardiovascular system. *N Eng J Med* 1999;340(23):1801-1811.
- ⁷ Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-13.
- ⁸ Petitti DB. Editorial: Hormone therapy and heart disease prevention: Experimentation trumps observation. *JAMA* 1998;280:650-52.
- ⁹ Collaborative Group on Hormone Factors in Breast Cancer. Breast cancer and HRT. *Lancet*. 1997;350:1047-59.
- ¹⁰ Lobo RA. Effects of hormone replacement on lipids and lipoproteins in post-menopausal women. *J Clin Endocrinol Metab*. 1991;73:925-30.
- ¹¹ Medical Arts Pharmacy, Saskatoon. Booklet: Natural Hormones, The latest approach to hormone replacement Therapy. August, 1999.
- ¹² Col NF et al. Patient specific decisions about HRT in PM women. *JAMA*. 1997;277(14): 1140-47.
- ¹³ Ravnika VA. Compliance with HRT. *Am J Obstet Gynecol*. 1987;156:1332-4.
- ¹⁴ Mattson LA et al. What do women really want? *Br J Obstet Gynaecol*. 1996;103 suppl(13):104-6.
- ¹⁵ Taylor M. Alternatives to conventional hormone replacement therapy. *Comp Ther* 1997;23(8):514-32.
- ¹⁶ Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstet Gynecol* 1999;180(6):1504-11.
- ¹⁷ Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337:1641-7.
- ¹⁸ Ettinger B, Black D, Mitlak B, et al. Reduction of Vertebral Fracture Risk in Postmenopausal Women with Osteoporosis Treated with Raloxifene. *JAMA* 1999;282(7):637-645.
- ¹⁹ Cummings SR et al. The effect of raloxifene on risk of breast cancer in PM women- results from the MORE randomized trial. *JAMA*. 1999;281:2189-97.
- ²⁰ Hosking D, Chilvers CED, Christiansen C et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. *N Engl J Med* 1998;338:485-92.
- ²¹ Bygdeman M, Swahn ML. Replens versus dienestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas* 1996;23(3):259-63.
- ²² Society of Obstetrics and Gynecology Policy Statement. The Canadian menopause consensus conference. *J SOGC*. 1994;16:4-40.
- ²³ Recker RR et al. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. *Ann Intern Med*. 1999;130:897-904.
- ²⁴ Farrell B. Understanding osteoporosis. CCCEP Home Study Program. 1999;Vol.XXI, lesson 2:25
- ²⁵ Gambrell RD. Management of HRT side effects. *Menopause*. 1994;1:67-72
- ²⁶ Archer DF et al. Bleeding patterns in women taking continuous combined or sequential regimens of conjugated estrogens with MPA. *Obstet Gynecol*. 1994;83:686-92.
- ²⁷ Collaborative Group on Hormone Factors in Breast Cancer. Breast cancer and HRT. *Lancet*. 1997;350:1047-59.
- ²⁸ Oger E and Scarabin P. Assessment of the risk of VTE among users of HRT. *Drugs and Aging*. 1999;14(1):55-61.
- ²⁹ Greendale G et al. The menopause. *Lancet*. 1999;353:571-80.
- ³⁰ Andrews WC. The transitional years and beyond. *Obstet Gynecol* 1995;85:1-5.
- ³¹ Chow SS. Benefit/risk of estrogen therapy in cardiovascular disease; current knowledge and future challenges. *J Clin Pharmacol*. 1995;35 (suppl): 11s-7s.
- ³² Grodstein F et al. Postmenopausal hormone therapy and mortality. *N Engl J Med*. 1997;336:1769-75.
- ³³ The writing group for PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in PM women. *JAMA*. 1995;273:199-208.
- ³⁴ Grodstein F et al. Post-menopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med*. 1996;335:453-61. (**Nurses' Health Study)
- ³⁵ Nabulsi AA et al. Association of HRT with various cardiovascular risk factors in PM women. *N Engl J Med*. 1993;328:1069-75.
- ³⁶ Grady D et al. Hormone therapy to prevent disease and prolong life in PM women. *Ann Intern Med*. 1992;117:1016-37.
- ³⁷ Newcomb PA and Storer BE. Postmenopausal hormone use and risk of large bowel cancer. *J Natl Cancer Inst*. 1995;87:1067-70.
- ³⁸ Tang M et al. Effect of estrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet*. 1996;348:429-32.
- ³⁹ Grady D et al. HRT and endometrial cancer risk : a meta-analysis. *Obstet Gynecol*. 1995;85:304-13.
- ⁴⁰ Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 1997;349(9050):458-61.
- ⁴¹ Whitehead MI, Townsend PT, Pryse Davies J, et al. Effects of various types and dosages of progestogens on the postmenopausal endometrium. *J Reprod Med* 1982;27(8) Suppl: 539-48.
- ⁴² SOGC. Hormone Replacement Therapy: an update...the benefits of HRT and counseling issues related to breast cancer. SOGC Clinical Practice Guidelines. Policy statement no.73, May 1998.
- ⁴³ Collaborative Group on Hormone Factors in Breast Cancer. Breast cancer and HRT. *Lancet*. 1997;350:1047-59.
- ⁴⁴ Oger E and Scarabin P. Assessment of the risk of VTE among users of HRT. *Drugs & Aging*. 1999;14(1):55-61.
- ⁴⁵ Gibaldi M. HRT: estrogen after menopause. *Pharmacother*. 1996;16:366-75.
- ⁴⁶ Gruber DM, Sator MO, Kirchengast S. Effect of percutaneous androgen replacement therapy on body composition and body weight in postmenopausal women. *Maturitas* 1998;29(3):253-9.
- ⁴⁷ Mitlak BH, Cohen FJ. Selective Estrogen Receptor Modulators: A look ahead. *Drugs* 1999;57(5):653-663.
- ⁴⁸ Bygdeman M, Swahn ML. Replens versus dienestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas* 1996;23(3):259-63.
- ⁴⁹ Utiger RD. The need for more vitamin D. *N Engl J Med* 1998;338(12):828-829.