HRT Therapy – An evidence based review and summary of treatment options in Canada

Created by Jasmine Stroeder PharmD student. Dec 6, 2021
Reviewed by Trudy Huyghebaert PharmD, Dr. Mary Cedeno

ESTROGEN						
Type of estrogen		**Dosing**	**Efficacy**	**Safety (adverse effects)**		**Comments**
Oral	Conjugated estrogen **Premarin**: 0.3, 0.625, 0.125mg tablets	One tablet daily	Effective for VMS (Decrease by 60-100%) NNT = 2 Decrease total fracture risk HR 0.66 NNT=48/5.2yrs ARR 2.08% Decreased colorectal cancer risk HR 0.63 NNT 333/5.2yrs ARR 0.3% Decreased endometrial cancer risk HR 0.83 NNT 1667/5.2yrs ARR 0.06%	Hypertension 2% Peripheral edema 3% Abdominal pain 13% Flatulence 4% Nausea 5% Headache 20% Depression 6% Breast pain 12%	Increased risk of stroke HR 1.31 ARI 0.45% NNH = 222/5.2yrs Increased risk of CHD HR 1.29 ARI 0.42% NNH 238/5.2yrs (if >60 yrs or > 10 yrs since menopause) Increased risk of VTE HR 2.11 ARI 0.94% NNH= 103/5.2yrs Increase risk of invasive breast cancer HR 1.26 ARI 0.42% NNH 238/5.2yrs Women >65 years: Increased risk of dementia Increased gallbladder disease (33/ 10 000)	VMS symptoms occur in 80% of women during menopause Decreased dose = decreased side effects Progesterone required if intact uterus
	17β estradiol **Estrace**: 0.5, 1, 2mg tablets					
Transdermal patches	17β estradiol patch **Estradot**: 25, 37.5, 50, 75, 100ug patches **Sandoz Estradiol Derm**: 50, 75, 100ug patches **Oesclim**: 25, 50ug patches	Twice weekly application	Equal efficacy for vasomotor symptoms and in preserving bone density.	Avoids 1st pass effect; bypass liver entering directly into the circulation. Less nausea compared to oral. Application site erythema 7%	No increase in VTE risk Decreased risk of gallbladder disease (Transdermal RR 1.17 Vs. Oral RR 1.74). Same risk as oral estrogen for breast cancer, stroke.	Rotate sites (abdomen/ thigh/buttocks)
	17β estradiol patch **Climara**: 25, 50, 75, 100ug patches	Once weekly application				
Transdermal gel	17β estradiol patch **Estrogel**: 0.75mg estradiol per 1.25g metered dose. (=one actuation) **Divigel**: 0.25, 0.5, 1mg individual packets	Daily application				Consistent application site (thigh/ abdomen/arms)
Vaginal cream	Conjugated estrogen **Premarin**: 0.625mg/g	0.5g vaginally daily x 14days, then 0.5g 2-3x/week	Effective for genitourinary symptoms. Less systemic effect; still effective for reducing VMS (decrease 30-80%) Vaginal preparations have favorable effects on bone density.	Pruritus 3% Rash 3% Breast pain 3%	Low dose vaginal estrogen not associated with a higher risk of CV disease or cancer.	Low dose vaginal estrogen does not require progesterone for endometrial protection. Low dose vaginal estrogen is considered: vaginal cream 2-3x/week, vaginal ring every 3m, Vaginal tablet 2x/week.
	Estrone **Estragyn** 0.1% vaginal cream:1mg/g	0.5-4g daily cyclic (3 weeks on, 1 week off) or 2-3x /week				
Vaginal ring	17β estradiol **Estring**: 2mg/vaginal ring	Inserted every 3 months		Vaginitis 5% Vaginal discomfort 5% Vulvovaginal pruritus 12%		
Vaginal insert	17β estradiol **Vagifem**: 10ug vaginal tablets	1 tab vaginally x 14 days, then 1 tab twice weekly				

HRT Therapy – An evidence based review and summary of treatment options in Canada

Created by Jasmine Stroeder PharmD student. Dec 6, 2021
Reviewed by Trudy Huyghebaert PharmD, Dr. Mary Cedeno

PROGESTERONE						
	Type of progesterone	**Dosing**	**Efficacy**	**Safety (adverse effects)**		**Comments**
Oral	Micronized progesterone **Prometrium**: 100mg capsule	Continuous regimen: 1 capsule (100mg) daily (most common) Cyclic regimen: 200mg daily for 12-14 days/month	Effective for VMS (Decrease by 60%) Reduces the risk of endometrial hyperplasia and carcinoma, when oral estrogen is used.	Cramps 29% Abdominal pain 20% Bloating 12% Tired/lethargy 7% Dizziness 6% Breast tenderness 21% Weight gain 7-38%	Required if intact uterus and on systemic estrogen. No conclusive evidence to suggest a differential effect on breast cancer risk.	Prometrium contains peanut oil; caution with allergies. Cyclical progesterone therapy usually produces regular withdrawal bleeding in 80-90% of women. Cyclic regimen increased bleeding and bloating vs continuous. Continuous progesterone therapy usually results in amenorrhea after several months.
	Medroxyprogesterone acetate **Provera**: 2.5, 5, 10mg tablets	1 tablet daily 2.5mg daily continuous regimen. 5mg daily for 12-14 days/month cyclic regimen.				
	Norethindrone acetate **Norlutate**: 5mg tablet	*1 tab daily				
Levonorgestrel intrauterine system	Levonorgestrel intrauterine system **Mirena**: 52mg/IUS	1 IUS/5 years	Provides adequate endometrial protection, as effective as oral progesterone.	Metrorrhagia >10% Hypomenorrhea >10%		*Off label use Need to replace every 5 years.
COMBINATION HORMONE THERAPY						
	Type of Combo Product	**Dosing**	**Efficacy**	**Safety (adverse effects)**		**Comments**
Oral - estrogen + progesterone	17β estradiol/ norethindrone acetate **Activelle**: 1mg/0.5mg **Activelle LD**: 0.5mg/0.1mg	One tablet daily	Effective for VMS symptoms (60-100% reduction) Decrease total fracture risk (46/10 000)	Increased CHD risk (7/ 10 000) Increased stroke risk (8/10 000) Increased VTE risk (8/10 000) Increased risk of invasive breast cancer (8/10 000)		Expected CHD reduction not seen. Not indicated for use as contraception. If contraception needed use low dose OCP.
	17β estradiol/ drospirenone **Angeliq**: 1mg estradiol/1mg drospirenone	One tablet daily				
Transdermal - estrogen + progesterone	17β estradiol/ norethindrone acetate **Estalis patch**: 50mcg/140mcg, 50mcg/250mcg	Twice weekly application		Application site reaction >10% Rash 1-10%		
Tissue selective estrogen complex (TSEC): Estrogen and selective estrogen receptor modulator	Conjugated estrogen/ bazedoxifene **Duavive**: 0.45mg CE/20mg bazedoxifene	One tablet daily	Reduces hot flashes by 23% (ARR) compared to placebo. Bazedoxifene provides adequate endometrial protection. Increased BMD by 1.5% at 12 months; fracture risk not assessed.	Diarrhea 3% Nausea 3% Hypertension 2%	Same risks as estrogen therapy. No breast tenderness or uterine bleeding as seen in progesterone therapy.	Do not recommend use in obese women (BMI >30), as a greater reduction of bazedoxifene seen and may be associated with ↓ protection of endometrial hyperplasia. Option for those who cannot tolerate progesterone.
Low dose oral contraceptive	Ethinyl estradiol/norethindrone **Lolo** 10mcg/1mg	One tablet daily	Low dose estrogen oral contraceptive effective for relief of menopausal symptoms and for those who also want contraception.	Increased risk of VTE (8-10/10 000)		Perimenopause options for symptomatic patients. Re-evaluate at ~50 years. Consider stopping the pill or changing to postmenopausal estrogen regimen if needed for symptoms.

HRT Therapy – An evidence based review and summary of treatment options in Canada

Created by Jasmine Stroeder PharmD student. Dec 6, 2021
Reviewed by Trudy Huyghebaert PharmD, Dr. Mary Cedeno

Compounded estrogen and progesterone: Promoted as 'bioidentical' or safer options. There are quality control issues, they lack evidence and are more expensive. Compounded progesterone creams also do not provide endometrial protection.
Dosing Estrogen - Start with a lower dose and titrate up based on symptom relief: can start on 0.5mg/day oral estrogen, 0.625mg CES or 0.025mg/d transdermal estrogen. - Usual therapeutic/effective dose of 17β estradiol: oral 1 mg/day or transdermal 0.05mg/day (adequate for symptom relief). Progesterone - First choice of progesterone is micronized progesterone: 100mg/day - Cyclic regimen: 200mg/d x 12 days. Daily: 100mg - Intact uterus needs 2400mg progesterone/month
Legend: VMS= vasomotor symptoms. CHD= coronary heart disease. HRT= hormone replacement therapy. MRT= menopausal hormone therapy. CES= conjugated estrogen. TSEC= tissue selective estrogen complex. OCP = oral contraceptive pill. ARI= Absolute Risk Increase. ARR= Absolute Risk Reduction.

Starting Treatment

- Starting therapy: start when age <60 or <10 years from the start of menopause. Increased CV harm when started late (10+ years post menopause).
- If using HRT after age 60, using lowest effective dose important due to gradually increasing risk.

WHAT TO CHOSE WHEN		
	Options	**Comments**
Without an intact uterus	Estrogen alone	Choice of oral/transdermal/vaginal based on patient preference.
With an intact uterus	Estrogen + Progesterone	Higher doses of estrogen often require higher doses of progesterone.
Genitourinary syndrome	Vaginal estrogen > systemic estrogen	Increased efficacy of local symptoms and decreased side effects.
Hypertension	Estrogen +/- Progesterone Transdermal > oral estrogen	Consider lowest dose of estrogen.
Breast Cancer Risk	Low risk: Estrogen +/- Progesterone, TSEC Moderate to high risk: non-hormonal therapies	Estrogen has minimal effect on the risk of breast cancer. Small increase in invasive breast cancer risk (8/10 000)
Cardiovascular Risk	Low risk (<5%): HRT an option Moderate risk (5-10%): transdermal > oral estrogen Micronized progesterone > medroxyprogesterone High risk (>10%): avoid HRT	Can use HRT in patients with risk factors for CHD if risk is low-moderate and <10 years since start of menopause. >10 years post-menopause or age > 60 years: increased risk of CHD CV risk assessment as per Framingham.
VTE Risk	Non oral form of estrogen at the lowest effective dose. Progesterone	HRT contraindicated if active VTE.
Hepatic dysfunction	Progesterone Estrogen: caution in dosing, can accumulate in liver dysfunction	Patients who have previously had liver disorders such as liver adenomas should be monitored closely as this can recur.
Osteoporosis	Estrogen +/- Progesterone	HRT is the most appropriate therapy for fracture prevention in early menopause. Reduction of overall fracture risk (HR 0.66, NNT 48)
Contraindication to estrogen	Progesterone	Progesterone alone can control VMS symptoms (60% reduction).
Breakthrough bleeding occurs	Switch to continuous progesterone. Reduce dose of estrogen Switch to use of TSEC	
Clinical Indications for initiation of systemic HRT: vasomotor symptoms and night sweats, prevention of bone loss, reduction in fracture risk in women at increased risk of osteoporosis, early menopause (<45y), sleep disturbance.		

HRT Therapy – An evidence based review and summary of treatment options in Canada

Created by Jasmine Stroeder PharmD student. Dec 6, 2021
Reviewed by Trudy Huyghebaert PharmD, Dr. Mary Cedeno

CONTRAINDICATIONS TO HRT	
Estrogens	**Progestogens**
Unexplained vaginal bleeding Acute liver dysfunction Estrogen-dependent cancer Endometrial hyperplasia Coronary heart disease Previous history of stroke History of thromboembolic disease	Unexplained vaginal bleeding Active or past history of arterial thromboembolic disease (ie: stroke, MI) Active or past history of venous thromboembolism (ie: DVT, PE) Hypersensitivity to peanuts/peanut oil (used in some preps of micronized progesterone, okay to use medroxyprogesterone in these patients).

Duration of Treatment

- Individualized based on symptom control and effect on quality of life and the woman's risk of cancer, coronary heart disease, and VTE.
- For women who undergo early menopause (before age 45) it is recommended to use hormone therapy, at least until the average age of menopause, due to proven health benefits for menopause symptoms, prevention of bone loss, cognition, and mood issues.
- Guidelines recommend 3-5 years duration of therapy. Decision to continue systemic HRT should be assessed annually and take into account patient symptoms and preferences. Extended use of HRT (>5 years or age beyond 60 years), consider restarting estrogen at lowest possible dose.
- Low dose vaginal estrogen therapy can be used life-long.

Clinical Pearls

- Contraception remains important during perimenopause, as women cannot be certain of infertility until they reach menopause (i.e. 1 year without menses). Can continue low dose OCP until menopause reached.
- If last menstrual period < 1yr prior, a sequential combined regimen recommended (i.e. continuous estrogen with 12-14 days progestogen/month) as it produces more regular bleeding pattern than continuous therefore often preferred in recent menopause. However, if patient prefers continuous can start anytime, would start with 14 days progesterone treatment to induce initial bleeding episode.
- If last menstrual period > 1yr prior, may start continuous combined regimen if wanting to avoid monthly withdrawal bleeding.
- Progesterone regimen most tolerated and used in clinical practice: continuous regimen > cyclic regimen.
- If breakthrough bleeding occurs following switch to continuous combined, and if does not resolve within 3-6months, consider switching back to sequential for 1 or more years.
- Persistent bleeding beyond 6 months warrants investigations.

Limitations

- Clinical trials have fixed dosing regimens and no evaluation of other forms of estrogen or reduction of dosing.
- Hard to confer risks and benefits to other agents that have not been studied.
- HRT is no longer recommended for the prevention of chronic disease such as CHD, cognitive function, or prevention of dementia.

HRT Therapy – An evidence based review and summary of treatment options in Canada

Created by Jasmine Stroeder PharmD student. Dec 6, 2021
Reviewed by Trudy Huyghebaert PharmD, Dr. Mary Cedeno

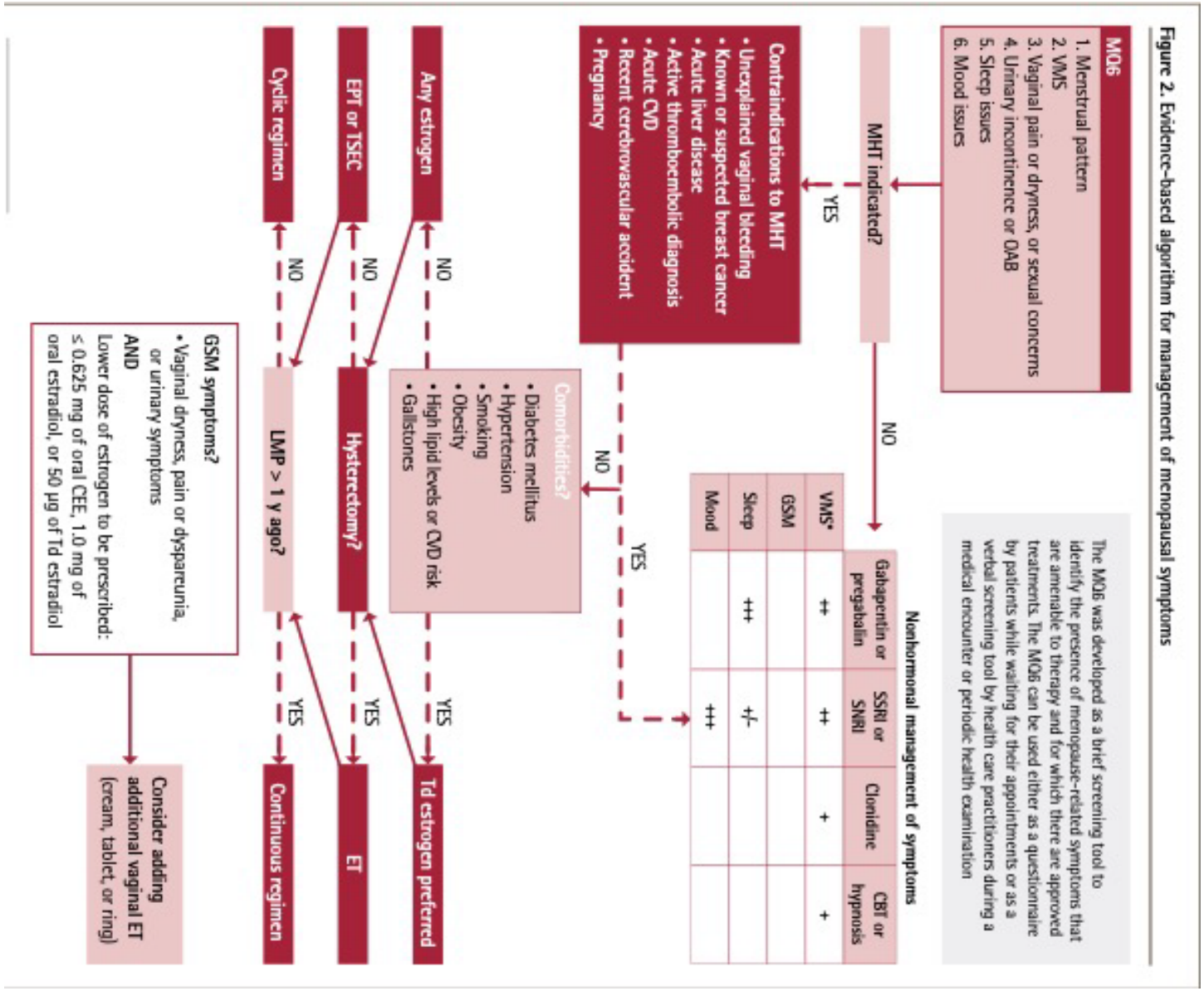

Figure 2. Evidence-based algorithm for management of menopausal symptoms

Goldstein S., An efficient tool for the primary care management of menopause. Can Fam Physician 2017; 63:285-8. Available from: https://www.cfp.ca/content/cfp/63/4/295.full.pdf

HRT Therapy – An evidence based review and summary of treatment options in Canada

Created by Jasmine Stroeder PharmD student. Dec 6, 2021
Reviewed by Trudy Huyghebaert PharmD, Dr. Mary Cedeno

References:

1. Baumgardner SB, Condrea H, Daane TA, Dorsey JH, Jurow HN, Shively JP, et al. Replacement estrogen therapy for menopausal vasomotor flushes. Comparison of Quinestrol and conjugated estrogens. Obstetrics and Gynecology 1978;51(4):445-52. [MEDLINE: 78200565]
2. Canadian Menopause Society. Pocket guide menopause management. https://www.sigmamenopause.com/sites/default/files/pdf/publications/Final-Pocket%20Guide.pdf
3. 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.
4. Cintron D, Lahr BD, Bailey KR, et al. Effects of oral versus transdermal menopausal hormone treatments on self-reported sleep domains and their association with vasomotor symptoms in recently menopausal women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). Menopause. 2017 Aug 21.
5. Goodwin JW, Green SJ, Moinpour CM, Bearden JD, Giguere JK, Jiang CS, et al. Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. J Clin Oncol 2008;26:1650–6.
6. 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.
7. 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.
8. Journal of Midwifery & Women's Health, Volume: 63, Issue: 2, Pages: 168-177, First published: 09 March 2018, DOI: (10.1111/jmwh.12737)
9. Liu B, Beral V, Balkwill A, et al. Gallbladder disease and use of
transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. BMJ. 2008;337:
a386.
10. Steingold K, Laufer L, Chetkowski R, et al. Treatment of Hot Flashes with transdermal estradiol administration.
11. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev*. 2004;2004(4):CD002978. Published 2004 Oct 18. doi:10.1002/14651858.CD002978.pub2
Mirkin S, Pickar JH. Management of osteoporosis and menopausal symptoms: focus on bazedoxifene/conjugated estrogen combination. *Inj J Womens Health* 2013;5:465-75.
12. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA 2004;291(13):1610-20.
13. Notelovitz M, Cassel D, Hille D, Furst KW, Dain MP, VandePol C, et al. EGicacy of continuous sequential transdermal estradiol and norethindrone acetate in relieving vasomotor symptoms associated with menopause. American Journal of Obstetrics and Gynecology 2000;182(1 Pt 1):7-12. [MEDLINE: 20114933]
14. Pinker ton JV, Utian WH, Constantine GD, et al. Relief of vasomotor symp- toms with the tissue-selective estrogen complex containing bazedoxifene/ conjugated estrogens: a randomized, controlled trial. [SMART-2] *Menopause* 2009;16(6):1116–1124.
15. RxFiles. Hormonal Therapy for Menopause. https://www.rxfiles.ca/RxFiles/uploads/documents/members/CHT-Postmenopausal-RxandHerbal.pdf
16. Shelley N. Dolitsky, MD,[1] Christina N. Cordeiro Mitchell, MD,[2] Sarah Sheehan Stadler, MD,[3] and James H. Segars, MD. Efficacy of progestin-only treatment for the management of menopausal symptoms: a systematic review. Menopause: The Journal of The North American Menopause Society Vol. 28, No. 2, pp. 217-224
17. 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.
18. Somboonporn, Woraluk MD; Panna, Sunida MD; Temtanakitpaisan, Teerayut MD; Kaewrudee, Srinaree MD; Soontrapa, Sukree MD Effects of the levonorgestrel-releasing intrauterine system plus estrogen therapy in perimenopausal and postmenopausal women, Menopause: October 2011 - Volume 18 - Issue 10 - p 1060-1066 doi: 10.1097/gme.0b013e31821606c5
19. Vickers MR, MacLennan AH, Lawton B, et al. Main morbidities recorded in the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM): a randomized controlled trial of hormone replacement therapy in postmenopausal women. BMJ 2007; DOI:10.1136/bmj.39266.425069
20. 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.
Lexi-Comp. eCPS. RxTx.