

# Case Reviews: Hormone Therapy & Over the Counter Supplements for Treating Menopausal Symptoms

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# Disclosures

- Clark Professional Pharmacy – Pharmacist & Owner
  - Scope of practice includes compounded and traditional hormone therapy, nutritional supplements, and hormone consulting
- Ann Arbor Professional Pharmacy – Owner
- Wayne Professional Pharmacy – Owner
  - Scope of practice includes psychiatric medications, group home and assisted living settings



# Objectives

- Overview of the major symptoms that bring women into your office
- Discuss why and how women are making choices regarding menopause
- Case Study review:
  - DHEA suppositories (RX)(OTC)
  - Hyaluronic Acid suppositories (RX)
  - Black Cohosh (OTC)
  - Soy Isoflavones (OTC)
  - Siberian Rhubarb (OTC)
  - Progesterone cream (OTC)



# Making the decision– It's a jungle out there

- Different opinions from different doctors
  - Family medicine vs gynecologist
- Influences from family and friends
  - Stop or continue HT based on experience of others
- What therapies she has tried in the past
- Continuation of work
- How she feels as of now
- Marketing of supplements is a billion dollar business
  - Most marketing tactics are deceiving
  - Limited in supportive studies
  - Dismissive of published literature that may rebuke product claims



## Example of Deceptive Marketing Patients are Exposed to



Add to circles

**Emily Butler**  
Research Herbalist

(product) Reviews - What Is It?

**WARNING: DO NOT BUY (product) Until You Read This Review!**

Is it a Scam? Does It Really Work?  
Check Ingredients, Side Effects and More!

So, what side effects can Rhubarb cause? One can suffer from stomach and intestinal pain, uterine contractions, and watery diarrhea. Long-term use or use in higher doses can lead to bone loss, muscular weakness, irregular heart rhythm, and potassium loss. One customer reported of kidney failure after using rhubarb. There are also some special precautions concerning this component. Rhubarb is unsafe for children. There is information that one 4-year-old boy died after eating rhubarb leaves. The latter contain a lot of oxalic acid, which can have lethal consequences if consumed in large doses. Rhubarb is also dangerous for pregnant and breast-feeding women. Rhubarb can easily make constipation or diarrhea worse, that is why you should avoid this compound if you are prone to any of these conditions. Rhubarb is prohibited to usage by people who suffer from appendicitis; a bowel obstruction; unexplained stomach pain; Crohn's disease, irritable bowel syndrome (IBS) and colitis. People with kidney disease should also avoid rhubarb as that might be harmful for the kidneys and even be a reason for kidney failure. Patients with kidney stones are also highly recommended to avoid taking rhubarb. Liver problems can be another restriction to using Rhubarb which can worsen liver function even more.



### My Final Summary

I do not think that (PRODUCT) can help you to get rid of menopause symptoms. The claims of the manufacturer are not based on any unbiased clinical trial. Future studies are needed to confirm benefits of the supplement. The effect of (PRODUCT) is under doubt, as there are numerous users' reviews saying that the product does not work at all. At the same time, this supplement can cause a number of side effects. It can stimulate estrogen receptors and contribute to the development of breast cancer. Do not try (PRODUCT) but better stay on the safe side. **Look for a safer and more effective alternative.**

### Affordable Alternative

A lot of doctors are sure that the main symptoms of menopause problem can be perfectly solved with the combination of such natural products as Theobromine, Ginseng, Ginkgo Biloba, red raspberry and Licorice root. I completely agree with them because I study many products of the kind. I can say with confidence that there is such a product on the modern market! It is called **(Product #2)**. Isn't it great? I recommend you **reading my review about (Product #2)**. I hope it will be helpful for your sexual life.

# Why are Peri-and Post- Menopausal Women are Seeking Hormone Replacement and OTC Alternatives

## Quality of Life Symptoms

- Hot Flash relief
- Night sweats
- Disrupted sleep
- Vaginal Dryness
- Sexual Dysfunction
- Change in mental acuity
- Low libido
- Weight gain
- Joint pain
- Depression
- Anxiety

## Disease Prevention

- Osteoporosis – FDA approved use
- Macular degeneration prevention
- Colon cancer prevention
- Alzheimer's/Memory preservation
- Heart Disease prevention



# Case Review – Hyaluronic Acid Suppositories

- Patient JH is a 62 year old female reporting a chief complaint of chronic vaginal and perianal burning and itching. She has been to multiple OB/GYN's and dermatologist since age 55 to seek treatment. Cultures for fungal and bacterial vaginitis have consistently been negative. Despite negative cultures she has undergone several treatments with fluconazole, metronidazole, topical clotrimazole, and clindamycin without success. Autoimmune conditions have also been ruled out, she has also undergone topical and oral steroid therapy without success.

# Case Review – Hyaluronic Acid Suppositories

- She reports that several gynecologist have recommended vaginal or systemic hormone therapy to treat severe vaginal dryness. Patient states that she has a sister with breast cancer (non-specified) and did not feel comfortable taking any type of hormone therapy.
- She is not sexually active and is not taking any medications
- It was recommend that she try using a non-hormonal vaginal suppository containing 5 mg of Hyaluronic Acid nightly for 14 days and 3 times per week thereafter.

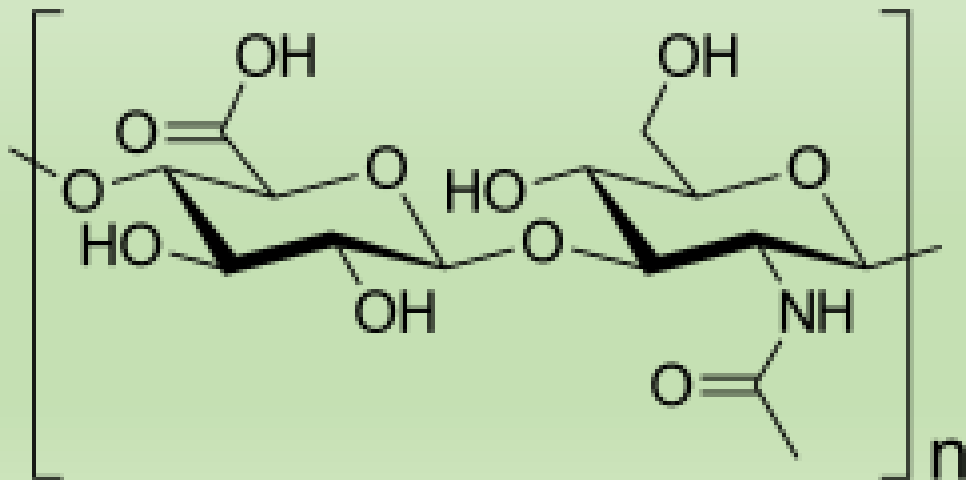


# Case Review – Hyaluronic Acid Suppositories

- Follow up
  - Patient reported a significant improvement in perianal and vaginal itching within 3 weeks of therapy.
  - Within 6 weeks patient reported a significant improvement in vaginal dryness and complete resolution of burning and itching symptoms.
  - Patient has continued with therapy and has been consistently filling the prescription for 4 years with no notable side effects.

# Hyaluronic Acid

- Hyaluronic acid is a major component of connective tissue
- Major component of synovial fluid
- Stimulates cell proliferation
- Can retain 1000 times its molecular weight in water



# Hyaluronic Acid Suppositories

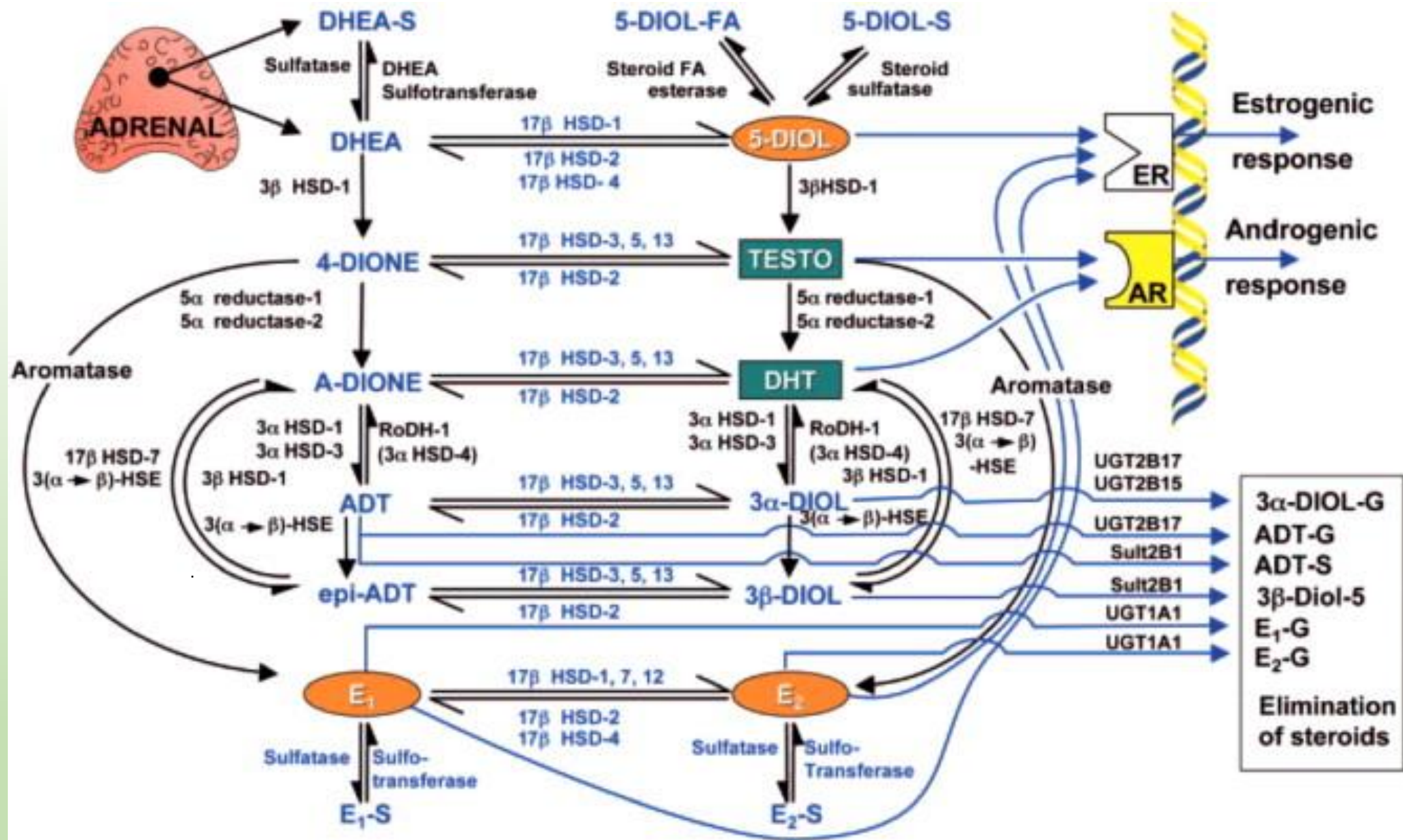
- UK, hyaluronic acid vaginal gel (Hyalofemme) is used to ease vaginal dryness
- Italy, hyaluronic acid 5 mg suppositories with vitamin A & E were found to be a safe and effective alternative to estrogen
  - Primary End point: Visual Analogue Scale
  - Secondary End points: itching, burning, dyspareunia, irritation

# Hyaluronic Acid Suppositories- Dosing

- Suppositories:
  - Hyaluronic Acid 5 mg suppositories: Insert 1 suppository vaginally once daily at bedtime for 14 days then use 2 to 3 times weekly
- Vaginal Gel:
  - Hyaluronic Acid gel: Insert 1 gram vaginally once daily at bedtime for 14 day, then use 2 to 3 times weekly

# DHEA (Dihydroepiandrosterone)

- DHEA – is a sex steroid precursor that is converted to Estradiol and Testosterone in sex steroid responsive peripheral tissues. (**with the exception of the endometrium**)
- It is known as a “pro-hormone” or “precursor” since it is converted into the end hormones of estrogen and testosterone
  - Dependent on the tissue type and cellular need
- DHEA is also known as the “mother hormone”, “fountain of youth hormone”, “master hormone”, “adrenal hormone”
- DHEA does not have a specific receptor
  - Exerts its effect by conversion to Estrogen and Testosterone



# DHEA (Dihydroepiandrosterone)

- DHEA is available over the counter in the United States
  - Grandfathered in as a dietary supplement in 1994
- DHEA is considered an anabolic steroid in several other countries-
  - Canada classifies DHEA as a C-III controlled substance and only available by prescription
- DHEA is a banned for athletic competition by the World Anti-Doping Agency

# DHEA has effects on so many end organ sites there are several proposed uses:

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- Aging skin
- Depression
- Aging
- Physical performance
- Psoriasis
- Rheumatoid arthritis
- Withdrawal symptoms
- Cognitive function
- Sjogren's Syndrome
- Addison's disease
- Adrenal insufficiency
- Atrichia pubis
- Cervical dysplasia
- Lupus
- Weight loss
- COPD
- Chronic fatigue syndrome
- Chronic fatigue syndrome
- COPD
- Coronary heart disease
- Exercise induced muscle damage
- Fibromyalgia
- HIV/AIDS
- Infertility
- Inflammatory bowel disease
- **Menopausal symptoms**
- Metabolic syndrome
- Myotonic dystrophy
- Osteoporosis
- Partial androgen deficiency
- Parturition
- Schizophrenia
- **Sexual dysfunction**
- **Vaginal atrophy**



# DHEA – Use in Menopause

- DHEA metabolites: Estrogen and Testosterone act directly on ER-alpha, ER-beta, and androgen receptors.
- Hot flashes:
  - Some evidence suggest 10 to 25 mg orally can reduce vasomotor symptoms and psychological symptoms
  - Some studies show lack of effect
- Vaginal atrophy
  - Vaginal administration of 6.25 mg to 13 mg **daily** improved vaginal atrophy symptoms as well as estrogen
- Sexual function
  - Single po 300 mg dose appears to improve sexual response
  - 50mg to 100 mg po daily appears to improve sexual desire
  - Some studies show lack of effect

# DHEA – Regimens and Doses

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- DHEA 5 to 50 mg capsules: Take 1 capsule orally once daily in the morning
- DHEA 300 mg capsule: Take 1 capsule orally one hour prior to intercourse
- DHEA 13 mg suppositories: Insert 1 suppository vaginally at bedtime daily. May use 2 to 3 times per week. (most effective if used daily)
- DHEA 6.25 & 13 mg/gm vaginal gel: Insert 1 gram vaginally at bedtime daily. May use 2 to 3 times per week. (most effective if used daily)
- DHEA 1% cream: Apply topically to skin once daily at bedtime for wrinkles and dry skin

# DHEA – Safety

- Considered safe when 50 mg or less is used daily for up to 6 months
  - No long term studies but has traditionally been used longer in practice
- Side effects: Generally very well tolerated. More commonly androgenic side effects such as acne, aggression, facial hair, menstrual irregularities
- Drug interactions: should not be used with estrogen blockers (SERM's or aromatase inhibitors)
- Should not be used in hormone dependent cancers
  - Production of estrogen can stimulate estrogen sensitive cancers

# DHEA- Case Study

- 67 year female with significant vaginal dryness and lack of sexual desire. Patient was previously on hormone replacement starting at age 50. She discontinued all HRT at 62 for concerns of cardiovascular and breast cancer concerns. Within 8 months of discontinuing therapy she reported to her physician severe vaginal dryness and loss of sexual function. She was prescribed DHEA 13 mg suppositories to use 3 times per week. Within 6 weeks she reported almost complete resolution of dryness and some improvement in sexual function. She has not reported any significant side effects and is continuing with therapy.
  - Studies show no increases in estradiol or testosterone levels with the vaginal administration of DHEA

# DHEA – Case Study

- 58 year old female was recently diagnosed with DCIS. She had been on a combination of DHEA, estradiol, progesterone since age 48. She was advised to discontinue all hormone therapy and to start a 5 years course letrozole. Within eight weeks she reported a significant decline in her quality of life due to medication side effects. She did her own research and decided to restart her DHEA 5 mg over the counter to help with symptoms. She asked the pharmacist about taking a higher dosage for a better effect.
- Resolution: Patient was advised not to take DHEA since it will counter act letrozole and may activate estrogen receptors in cancer tissue. She was advised to continue letrozole therapy and seek a second opinion about long term treatment.

# Case Study – OTC Herbal

- 76 year female history of severe hot flashes in early 50's. She describes her self as a “super flasher” and reported hot flashes as debilitating.
- History - Late onset menopause, started Vivelle (estradiol patch) 0.025 mg at age 58 and Estrace vaginal cream. She had complete hysterectomy at age 61 due to endometrial hyperplasia and continual spotting. She continued estrogen therapy to control hot flashes for 18 years. In December 2016 she had acute swelling and fluid retention in her right lower leg with a dull ache. She presented to a local urgent care and was diagnosed with a blood clot.

# Case Study – OTC Herbal

- She was referred to two specialist that confirmed the diagnosis of peripheral blood clots. Both specialist agreed that it was not a DVT and did not require anticoagulant therapy but strongly advised that she discontinue all estrogen products including vaginal estrogen cream.
- She is now reporting significant hot flashes, vaginal dryness, joint pain that have worsened over the last 8 weeks. She has set up a consult to discuss non-hormonal OTC options to help and would like to avoid medications such as antidepressants. She wants to try Progesterone cream or Rhubarb extract she read about on-line.

# Case Study – OTC Herbal

- Current meds:
  - Synthroid
  - Tramadol as needed for migraine
  - Imodium for IBS flare up
  - Tylenol for joint pain
- Supplements:
  - Vitamin D3
  - Biotin
  - Omega-3
  - Co-Q-10
  - Multi-vite
  - Ocuville



# Black Cohosh

- Undetermined mechanism of action, theory is through serotonergic system
- Available forms: capsules, tablets, liquid tincture, extracts
- Dosage: 20 – 80 mg daily
- Current literature:
  - Systematic review involving 2,027 patients did not find evidence to support the use of black cohosh for menopausal symptoms
  - 2010 review found reduction in hot flashes and night sweats by 26%
- Safety:
  - AE: abdominal pain, shortness of breath, diarrhea, dizziness, headaches, joint pain, nausea
  - Reports of liver toxicity
  - Unknown long-term effects

Vasomotor Symptoms	Quality of life	Psychological symptoms	Sexual function	Urogenital atrophy	Sleep disturbances
Low strength (6.7)	Insufficient strength (5.9)	Insufficient strength	--	Two studies reported significant improvements	--

# Soy Isoflavones

- Plant compounds demonstrating estrogen-like activity
  - **Genistein** most abundant isoflavone and strong activator ER-beta
- Mild estrogenic effects have been observed
- Dosage: 60 – 350 mg daily
- Current literature:
  - Systematic review: correlation with a reduction in the number of daily hot flashes & increasing genistein levels
- Safety:
  - Adverse effects: constipation, bloating, nausea
  - Avoid in women with a history of breast cancer
  - **Reduces thromboxane levels and lowers the risk of clotting**

Vasomotor Symptoms	Quality of life	Psychological symptoms	Sexual function	Urogenital atrophy	Sleep disturbances
Low strength (5.9)	Low strength (5.1)	Low strength-improved depression, moderate strength-improvement of anxiety	Low strength- two trials reported improvement in pain	Low strength	Low strength

# Rhubarb

- Siberian Rhubarb, Rhapontic rhubarb extract ERr 731
- Exact extract of ERr 731 has been used from hot flashes since 1993.  
Originally developed in Germany
  - This specific extract does not contain anthraquinones and therefore does not have a laxative effect for which rhubarb is known for
  - Anthraquinones also activate both Estrogen Receptors in breast and endometrium ER-alpha and ER-beta
  - The ERr 731 extract selectively binds to ER-Beta which is thought reduce hotflashes and treat other menopausal symptoms such depression and anxiety

# Rhubarb

- Published data is primarily from the manufacture
  - Shows improvement in several menopausal symptoms after 12 weeks of therapy
  - Does not appear to stimulate endometrial tissue
  - Toxicity studies have not shown any proliferative effectiveness
  - Safety: there is no data on clotting or activating breast cancer cells
- Recommendation:
  - Good alternative for low risk women without a cancer history
  - Unknown effect on clotting
  - May take several weeks for effect
  - Typical dosage 4 mg once daily

# Progesterone Cream - OTC

- Prescription strength Micronized Progesterone has been FDA approved in oral dosage forms, injectable, and vaginal delivery products for several years
  - Has been found to be safe & effective protection of endometrial hyperplasia, cervical ripening, and maintaining pregnancy
- OTC topical progesterone is sold as a cosmetic
  - Made popular by John Lee MD “What your Doctor May not Tell you About Menopause” in 1996
  - Basic premise is that Progesterone needs to be in balance with estrogen production and androgen production.
  - Women with medical conditions such as PCOS, diabetes, and premenopausal are not making enough progesterone and become “estrogen dominant”
  - According to Dr. Lee, progesterone can be used to treat PMS, hot flashes, and osteoporosis among several other conditions.

# Progesterone Cream - OTC

- Recommendations:
  - Few large scale trials fail to demonstrate any benefit on vasomotor symptoms and bone turn over
  - Small study published in Obstetrics and Gynecology 1999 “Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss”
    - Found 25 of 30 women studied had significant improvement in hot flashes
    - No change in bone density
  - No long term studies regarding safety particularly in regards to breast cancer
  - Studies show that serum progesterone level do not increase sufficiently to protect against Endometrial Hyperplasia- **particularly when estrogen is used**
  - OTC progesterone has been used for over 20 years – limited negative reports to FDA concerning it use.

# Progesterone Cream - OTC

- Recommendation based on clinical experience:
  - Progesterone cream seems to be more beneficial for younger women going through the peri-menopausal transition.
  - Primary benefit is improvement in mood, sleep, and hot flashes
  - Has been used OTC for over 20 years without major concerns reported to the FDA
    - Most complaints to FDA stem from unethical marketing
  - Progesterone does not seem to increase clotting factors like estrogen
  - Most likely not very effective in women who are 5 years past menopause
  - Would limit use to six months unless properly monitored for long term therapy
    - Monitor: Progesterone serum levels (controversial since levels fluctuate), breast exam, breast density, mammograms, spotting, bleeding, cramping, fluid retention, blood pressure

# Case Study – OTC Herbal Recommendations

## Lifestyle

- Avoid sugar
- Avoid all alcohol
- Dress lightly
- Increase exercise
- Try to lose weight

- Over the Counter/RX changes
  - Consider DHEA vaginal cream
  - Black Cohosh/Soy Isoflavones
    - Try for 6 to 8 weeks
  - Siberian Rhubarb
    - Did not recommend because of unknown safety concerns
  - Progesterone cream
    - Did not recommend, generally not effective in older women
  - Reevaluate medications if no success



Thank you

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