

Genitourinary Syndrome of Menopause and Black Box Warnings

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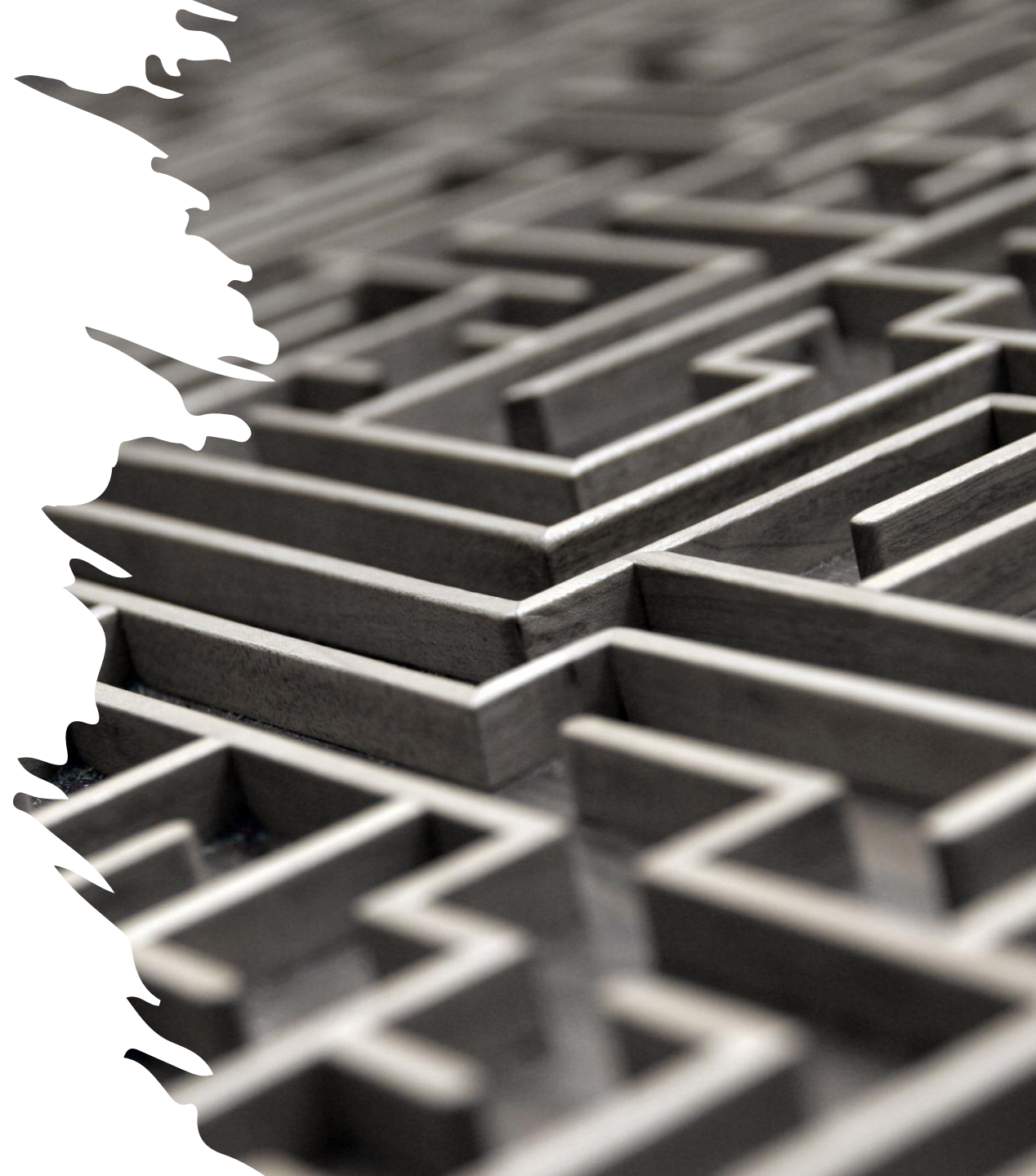
Disclosures

- Consultant/content provider
 - MCG Health, Roon Health, Endo



Outline


- Scope of the Problem
- Treatment Options
- What the data actually shows
- Addressing patient fears
- Addressing provider fears





How Common is GSM?



- Exact prevalence is unknown, >50% in general population
 - some data suggested upwards of 75% of breast CA pts will experience GSM
 - GSM is related to
 - Age of patient
 - Menopausal status
 - Natural vs medical vs surgical menopause
 - Cancer treatment with hormone therapies
 - Sexual Activity
- 

GSM options

Not all Products
are the Same!!!

	polycarbophil-based products	
Moisturizers	Hyaluronic acid Polyacrylic acid Polycarbophil-based vaginal moisturizer	5 mg daily for 2 weeks, then 3–5 times per week 3 g daily 2.5 g 3 times/week
Vaginal suppositories	Vitamin E Vitamin D	30–200 international units 1,000 international units
Lidocaine	4% aqueous lidocaine	Fully saturated cotton ball applied to the vulvar vestibule for 3 minutes
Hormonal options		
Vaginal insert	Prasterone*	One 6.5-mg vaginal insert once daily
Vaginal cream	17 β -estradiol [†]	The usual dosage range is 1 to 4 g (marked on the applicator) daily for 1 or 2 weeks, then gradually reduced to one-half initial dosage for a similar period; a maintenance dosage of 1 g, 1 to 3 times a week, may be used after restoration of the vaginal mucosa has been achieved [‡]
Vaginal cream	Conjugated equine estrogen	<ul style="list-style-type: none"> Evidence-based regimen: twice weekly administration of 0.5 g intravaginally (eg, Monday and Thursday) for treatment of moderate-to-severe dyspareunia Dosage regimens of 1 g every night for 2 weeks, then twice a week or 0.5 g twice a week are commonly used^{‡§}
Vaginal ring	17 β -estradiol	7.5 micrograms/day for 90 days
Vaginal tablet or insert	Estradiol hemihydrate	<ul style="list-style-type: none"> 10 micrograms/day for 2 weeks, then 10 micrograms/day 2 times a week A vaginal insert containing 4 micrograms is available, although not used in included studies
Vaginal cream	Testosterone	<ul style="list-style-type: none"> 300 micrograms or 150 micrograms applied daily for 28 days 300 micrograms or 150 micrograms applied daily for 2 weeks, then 3 times a week
<p>*The product label contains the following warning and precaution for those with a current or past history of breast cancer: “Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. [It] has not been studied in women with a history of breast cancer.” Additional data have been published on this population since the U.S. Food and Drug Administration approval of this medication.</p> <p>[†]Known, suspected, or history of breast cancer is listed as a contraindication in the product label.</p> <p>[‡]U.S. Food and Drug Administration–approved dosages of conjugated estrogen and estradiol creams may be higher than dosages commonly used in clinical practice.</p>		

Why is Any of This Controversial?



U.S.

The New York Times

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F.D.A. Orders Warning on All Estrogen Labels



Share full article



By **Gina Kolata**

Jan. 9, 2003

The Food and Drug Administration announced yesterday that all companies making drugs that contain estrogen or estrogen and progestin for menopausal women must include a boxed warning on labels stating that the drugs may slightly increase the risk of heart attacks, strokes, blood clots and breast cancer.

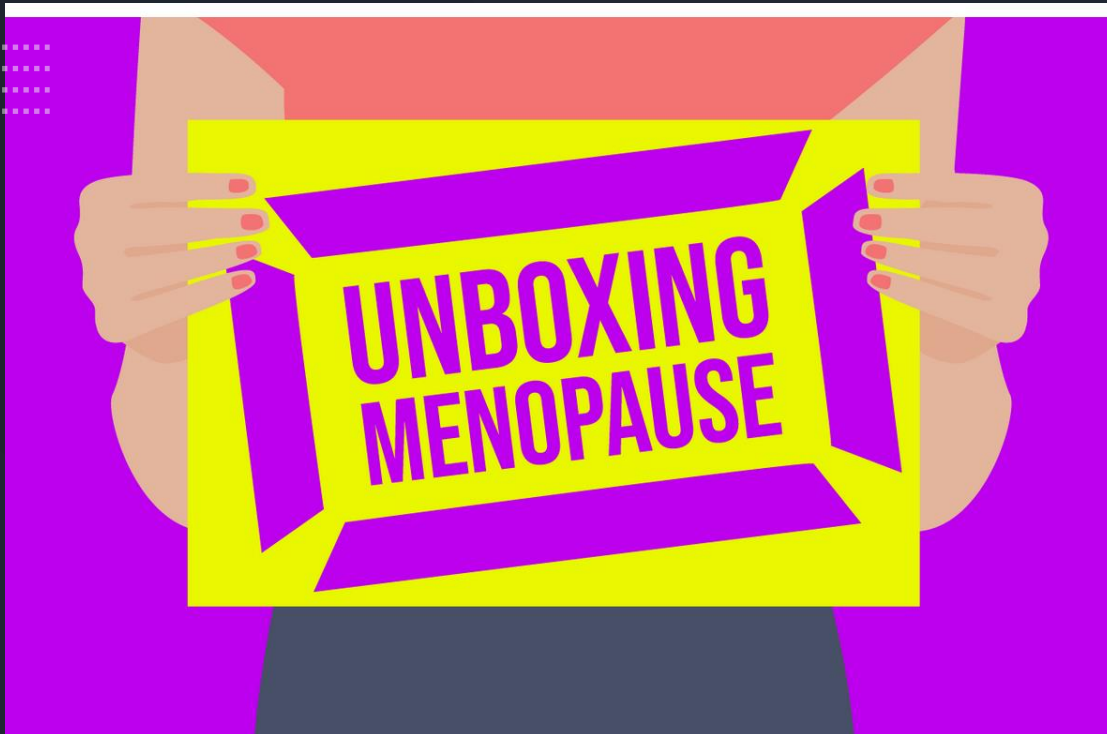
The agency said that since a large federal study concluded last summer that Prempro, a drug made by Wyeth, slightly increased

What do They See When They Open the Rx?

What is the most important information I should know about ~~PREMIRON~~ Vaginal Cream (an estrogen mixture)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb) Report any unusual vaginal bleeding right away while you are using ~~PREMIRON~~ Vaginal Cream. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in brain function)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years of age or older
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women age 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with ~~PREMIRON~~ Vaginal Cream

So Where are WE now?



[Medscape Medical News > Features](#)

Clinicians Call for Easing FDA Warnings on Low-Dose Estrogen

Kerry Dooley Young
May 14, 2024

A graphic with a dark blue background. At the top, it lists FDA warnings: "WARNINGS: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCERS AND PROBABLE DEMENTIA" in white and yellow text, followed by three yellow question marks. Below this, the text "WHY YOU SHOULD STILL USE VAGINAL ESTROGEN DESPITE" is in white. A red banner in the center contains the title "THE BOX LABEL" in white. At the bottom left, it identifies "Rachel Rubin, MD" and her "Washington, D.C. area office" in white text. On the right side of the graphic is a portrait of a woman with brown hair, wearing a white lab coat over a blue shirt, with her arms crossed.

"WARNINGS: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCERS AND PROBABLE DEMENTIA" ? ? ?

WHY YOU SHOULD STILL USE VAGINAL ESTROGEN DESPITE

THE BOX LABEL

Rachel Rubin, MD
Washington, D.C. area office

Does This Translate into Clinical Risk?

Short Report

November 2, 2023

Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer

Lauren McVicker, PhD¹, Alexander M. Labeit, PhD¹, Carol A. C. Coupland, PhD^{2,3}, et al

FREE

Published in final edited form as:

Menopause. 2018 December 17; 26(6): 603–610. doi:10.1097/GME.0000000000001284

Vaginal estrogen use and chronic disease risk in the Nurses' Health Study

Shilpa N Bhupathiraju, PhD^{1,2}, Francine Grodstein, ScD^{1,3}, Meir J Stampfer, MD, DrPH^{1,2,3,6}, Walter C Willett, MD, DrPH^{1,2,3}, Carolyn J Crandall, MD, MS⁴, Janice K Buring, MD, DrPH^{1,3,6}, and JoAnn E Manson, MD, DrPH^{1,3,6}

GYNECOLOGY: ORIGINAL RESEARCH

Safety of Vaginal Estrogen Therapy for Genitourinary Syndrome of Menopause in Women With a History of Breast Cancer

Agrawal, Pranjal BA; Singh, Sajya M. BS; Able, Corey BS; Dumas, Kathryn MD; Kohn, Jaden MD, MPH; Kohn, Taylor P. MD, MPhil; Clifton, Marisa MD

Author Information ☺

Obstetrics & Gynecology 142(2):p 660-668, September 2023. | DOI: 10.1097/

JOURNAL ARTICLE

Vaginal estradiol use and the risk for cardiovascular mortality FREE

Tomi S. Mikkola ✉, Pauliina Tuomikoski, Heli Lyytinen, Pasi Korhonen, Fabian Hoti, Pia Vattulainen, Mika Gissler, Olavi Ylikorkala

Human Reproduction, Volume 31, Issue 4, April 2016, Pages 804–809, doi.org/10.1093/humrep/dew014

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Important Considerations of Local Hormones

- Absorption of local ET varies by the active ingredient
 - potency: conjugated equine estrogens (CEE)>estradiol>estrone>estriol
- Creams absorbed to higher surface area than ring/tablets
- Vulva less vascular/less absorption compared to the vagina, esp upper third
- Consider most sx are on vulva/entrance to vagina, keep cream there
- Consider vaginal DHEA(prasterone)
 - Why no black box?
- Also oral options (ospemefine)

Other Resources/Controversies to be Aware Of



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NCCN Guidelines

Treatment by Cancer Type

Breast Cancer

Detection, Prevention,

It is important to counsel patients concerning possible sexual dysfunction remedies, including treatments for vaginal dryness. Nonhormonal, water-based lubricants and moisturizers remain the primary treatment.¹⁵⁸ Silicone-based products may last longer than water-based or glycerin-based products. A combination of therapies may provide additional short-term comfort. Hormonal therapies, such as a low-dose estrogen vaginal tablets or an estradiol vaginal ring, may be recommended for vaginal dryness because of urogenital atrophy, although results commonly take approximately 6 to 12 weeks.^{158,159} The safety of these therapies in women with a history of breast cancer is not well established at this time. The level of estrogen absorption is variable, which raises concerns in patients who have a history of breast cancer. Use of hormonal therapies for women on aromatase inhibitors is not recommended.¹⁶⁰ Treating dyspareunia secondary to vaginal atrophy and stenosis with vaginal dilators or pelvic floor relaxation techniques may be helpful.⁷⁶



Annals of Oncology
Volume 17, Issue 4, April 2006, Pages 584-587



Original article
breast cancer

Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors

[A. Kendall](#)¹, [M. Dowsett](#)¹, [E. Folkard](#)¹, [J. Smith](#)²

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Outline Share Cite

FEEDBACK

It's more
than just
Breast
Cancer

But since that's what
we usually hear as the #1
fear:

Let's Hear From an
ACTUAL
ONCOLOGIST