

# Genitourinary Syndrome of Menopause and Black Box Warnings

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NAMS 2023

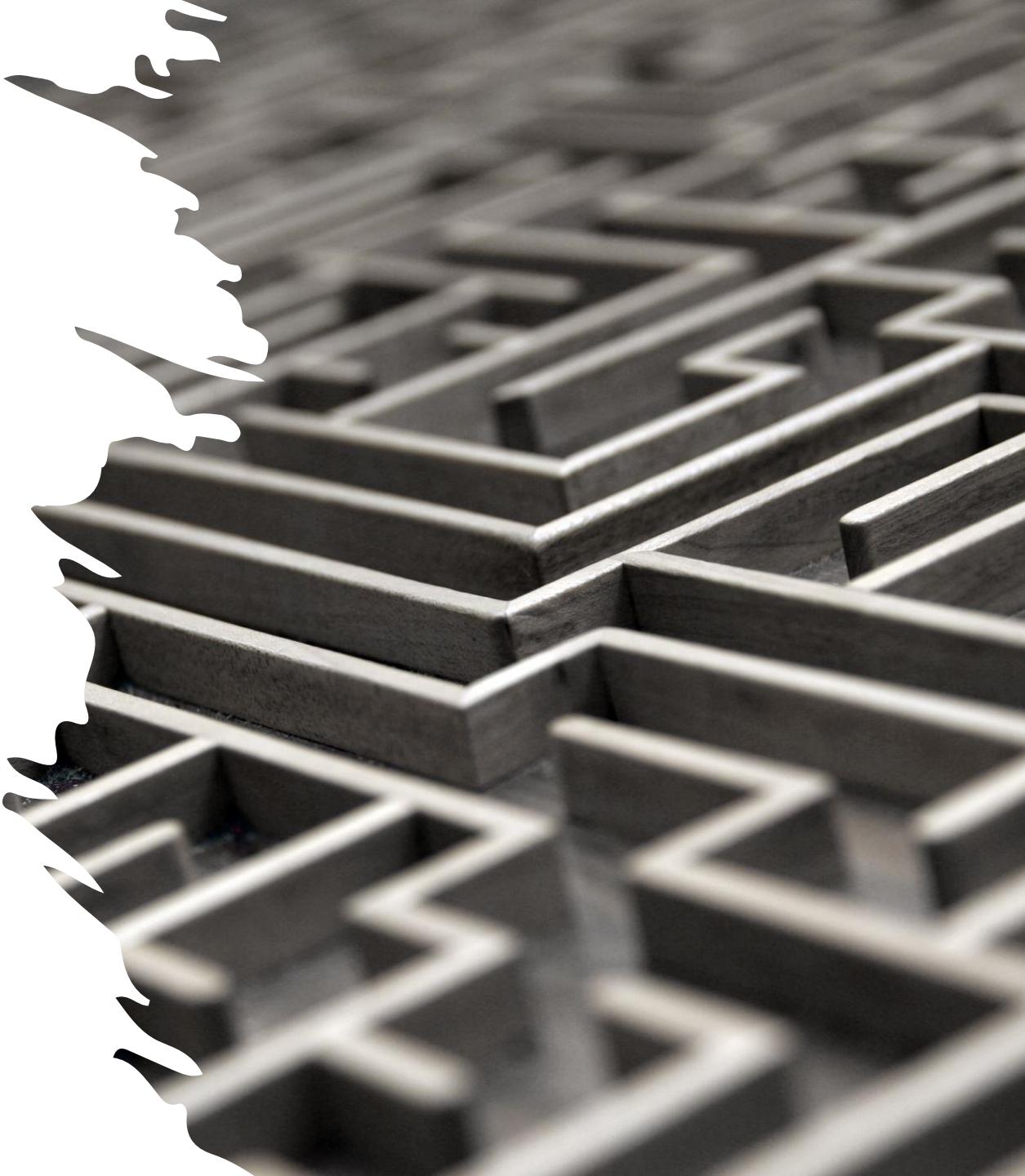


# Disclosures

- 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 $\beta$ -estradiol <sup>†</sup>	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 <sup>‡</sup>
Vaginal cream	Conjugated equine estrogen	<ul style="list-style-type: none"> <li>Evidence-based regimen: twice weekly administration of 0.5 g intravaginally (eg, Monday and Thursday) for treatment of moderate-to-severe dyspareunia</li> <li>Dosage regimens of 1 g every night for 2 weeks, then twice a week or 0.5 g twice a week are commonly used<sup>§\$</sup></li> </ul>
Vaginal ring	17 $\beta$ -estradiol	7.5 micrograms/day for 90 days
Vaginal tablet or insert	Estradiol hemihydrate	<ul style="list-style-type: none"> <li>10 micrograms/day for 2 weeks, then 10 micrograms/day 2 times a week</li> <li>A vaginal insert containing 4 micrograms is available, although not used in included studies</li> </ul>
Vaginal cream	Testosterone	<ul style="list-style-type: none"> <li>300 micrograms or 150 micrograms applied daily for 28 days</li> <li>300 micrograms or 150 micrograms applied daily for 2 weeks, then 3 times a week</li> </ul>

\*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.

<sup>†</sup>Known, suspected, or history of breast cancer is listed as a contraindication in the product label.

<sup>‡</sup>U.S. Food and Drug Administration-approved dosages of conjugated estrogen and estradiol creams may be higher than dosages commonly used in clinical practice.

# 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*

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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.

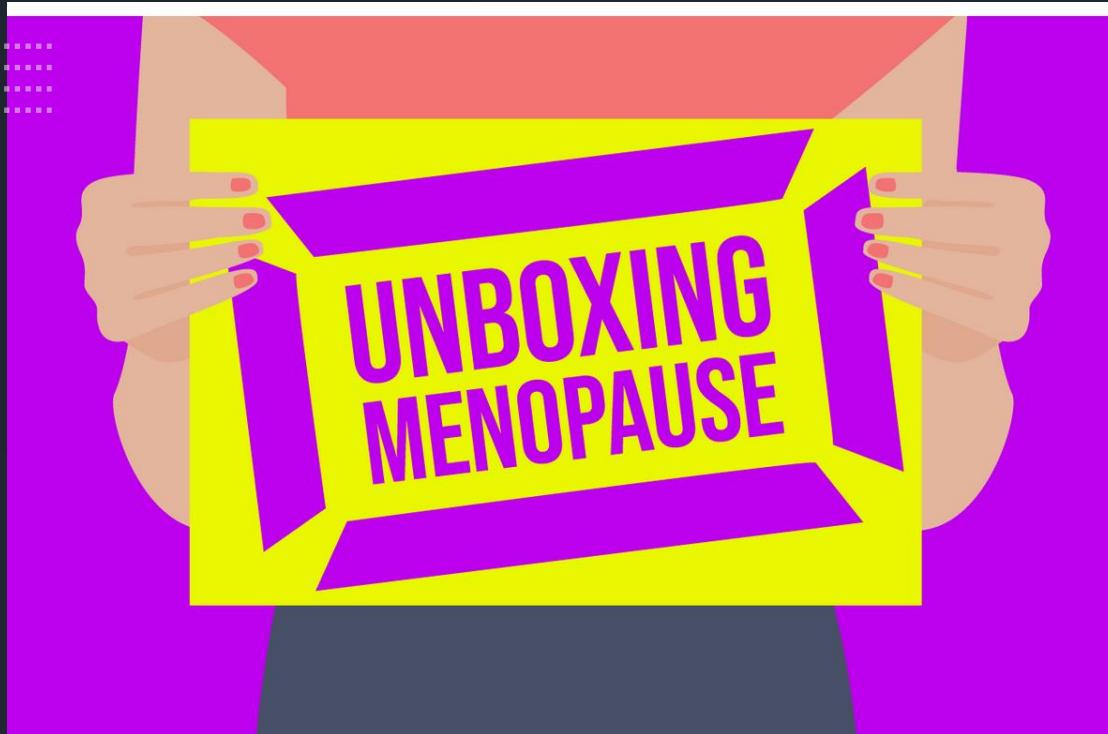
The agency said that since a large federal study concluded last summer that Prempro, a drug made by Wyeth, slightly increased

# What do They See When They Open the Rx?

What is the most important information I should know about [REDACTED] 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 [REDACTED] 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 [REDACTED] 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

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

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?

BRIEF REPORT

FREE

November 2, 2023

## Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer

Lauren McVicker, PhD<sup>1</sup>; Alexander M. Laheij, PhD<sup>1</sup>; Carol A. C. Coupland, PhD<sup>2,3</sup>; et al

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<sup>1,2</sup>, Francine Grodstein, ScD<sup>1,3</sup>, Meir J Stampfer, DrPH<sup>1,2,3,6</sup>, Walter C Willett, MD, DrPH<sup>1,2,3</sup>, Carolyn J Crandall, MD, MS<sup>4</sup>, Janet E. Stanford, PhD<sup>5</sup>, and JoAnn E Manson, MD, DrPH<sup>1,3,6</sup>

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

JOURNAL ARTICLE

## Vaginal estradiol use and the risk for cardiovascular mortality

Tomi S. Mikkola, MD, 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

# 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.<sup>158</sup> 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.<sup>158,159</sup> 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.<sup>160</sup> Treating dyspareunia secondary to vaginal atrophy and stenosis with vaginal dilators or pelvic floor relaxation techniques may be helpful.<sup>76</sup>



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<sup>1</sup>, M. Dowsett<sup>1</sup>, E. Folkard<sup>1</sup>, I. Smith<sup>2</sup>

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FEEDBACK

It's more  
than just  
Breast  
Cancer

But since that's what  
we usually have as the #1  
fear:  
**Let's Hear From an  
ACTUAL  
ONCOLOGIST**