MIGS 26

55TH GLOBAL CONGRESS ON MIGS

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Syllabus

PG-26057

Menopause Essentials for the MIGS Surgeon: From the WHI to Hormone Therapy and Surgical Disease

HONORARY CHAIR
Charles H. Koh, MD

SCIENTIFIC PROGRAM CHAIR
Nash S. Moawad, MD

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Michael Hibner, MD, PhD



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PG-26057: Menopause Essentials for the MIGS Surgeon:
From the WHI to Hormone Therapy and Surgical Disease

Chair: Brianne D. Romeroso
Co-Chair: Barbara S. Levy
Faculty: Barbara S. Levy, Brianne D. Romeroso, James Simon

Course Description

Menopause knowledge is increasingly essential for the modern MIGS surgeon. Many patients undergoing minimally invasive gynecologic surgery are perimenopausal or postmenopausal, and surgical interventions themselves may precipitate or accelerate menopause. Yet many surgeons report limited formal training in menopause physiology, interpretation of the Women's Health Initiative (WHI), or evidence-based use of menopausal hormone therapy (MHT). The recent transition in fellowship nomenclature from Minimally Invasive Gynecologic Surgery to Complex Benign Gynecology underscores the expanding scope of surgical practice beyond operative technique alone to encompass longitudinal, multidisciplinary care across the reproductive lifespan. As this evolution emphasizes comprehensive management of benign gynecologic disease, competence in menopause care becomes even more imperative for both trainees and faculty caring for midlife patients. This postgraduate course will provide MIGS surgeons with a practical, clinically relevant foundation in menopause care, emphasizing how menopause and MHT intersect with common surgical diseases such as fibroids and endometriosis. The course will address persistent misconceptions surrounding the WHI, review current evidence-based approaches to MHT, and explore how menopausal status and hormone therapy influence symptom presentation, surgical decision-making, and postoperative management. By integrating menopause education into MIGS practice, this course addresses a critical educational gap within gynecologic surgery training while supporting AAGL's mission to advance comprehensive, evidence-based care for women undergoing minimally invasive gynecologic surgery.

Learning Objectives: *At the end of this course, the participant will be able to:* 1) Explain why menopause knowledge is essential for the MIGS surgeon, including how menopausal status and hormone therapy influence fibroids, endometriosis, surgical decision-making, and long-term patient outcomes; 2) Critically interpret evidence from the Women's Health Initiative (WHI), including its limitations, common misinterpretations, and subsequent analyses, to inform contemporary counseling and clinical decision-making regarding menopausal hormone therapy (MHT); and 3) Implement evidence-based hormonal and non-hormonal strategies for the management of menopausal symptoms such as vasomotor symptoms and sexual dysfunction, including the safe prescribing of estrogen, progestogen, and testosterone therapy.

Course Outline

2:00 pm	Welcome, Introduction and Course Overview	B. Romeroso
2:05 pm	Menopause & MIGS: Why It Matters for the Surgeon; Hormone Therapy 101: Practical Prescribing for Surgeons	B. Romeroso
2:30 pm	The Women's Health Initiative: Interpreting the Evidence for Today's Patients; Hormone Therapy 101: Practical Prescribing for Surgeons	B. Levy
2:55 pm	Testosterone Therapy and Female Sexual Dysfunction; Hormone Therapy 101: Practical Prescribing for Surgeons	J. Simon
3:20 pm	Discussion Questions & Answers	All faculty
4:00 pm	Adjourn	

ADA Statement: In accordance with the Americans with Disabilities Act (ADA), please contact CMEsupport@aagl.org should you require any special assistance.

Disclosure of Relevant Financial Relationships

As an ACCME-accredited provider, AAGL is responsible for ensuring that accredited education is fair, balanced, free of commercial bias, and supports safe, effective patient care. AAGL maintains control over all aspects of educational planning, content, faculty selection, delivery, and evaluation.

All individuals in a position to control educational content are required to disclose financial relationships with ACCME-defined ineligible companies within the past 24 months. AAGL identifies and mitigates all relevant financial relationships before individuals assume their respective roles. Educational content is also subject to independent peer review by individuals without relevant financial relationships.

Disclosure information and acknowledgment of any commercial support are provided to learners before the activity to promote transparency and maintain the independence and integrity of the education.

Asterisk (*) denotes no financial relationships with ACCME-defined ineligible companies to disclose.

PLANNER DISCLOSURES

The following members of AAGL have been involved in the educational planning and/or review of this course (listed in alphabetical order by last name).

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Ted Lee, MD – Advisory/Consultant: Johnson & Johnson, Regeneron Pharmaceuticals
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Linda D. Bradley, MD, Medical Director*
Linda Michels, Executive Director, AAGL*

COURSE CHAIR DISCLOSURE

Brianne D. Romeroso, MD*

COURSE CO-CHAIR DISCLOSURE

Barbara S. Levy, MD – Consultant: Astrin Biosciences, Channel Medsystems, Koko Medical, Natural Cycles USA, Sera Prognostics

FACULTY DISCLOSURES

The following faculty have agreed to support their presentations and clinical recommendations with the best available evidence from the medical literature (in alphabetical order by last name).

Brianne D. Romeroso, MD*
Barbara S. Levy, MD – Consultant: Astrin Biosciences, Channel Medsystems, Koko Medical, Natural Cycles USA, Sera Prognostics
James Simon, MD - Contracted Research: AbbVie, Inc., Bayer HealthCare, Madorra Inc., Mylan/Viatris Inc., Myovant Sciences, Sola Pelvic Therapy, Viking Therapeutics; Consultant: Ascend Therapeutics, Bayer HealthCare, Besins Healthcare, Biote Medical, Cosette Pharmaceuticals, Inc., Duchesnay Pharmaceutical Group Inc., Femasys, IQVIA Inc., Mayne Pharma, Inc., Organon, Pfizer Inc., Penguin Bio Corp, Vella Bioscience Inc.; Speakers Bureau: Ascend Therapeutics, Bayer HealthCare, Besins Healthcare, Lawley Pharmaceuticals Pty Ltd., Mayne Pharma, Inc., Myovant Sciencesences, Inc., Pharmavite LLC; Stock Ownership: Sermonix Pharmaceuticals

MITIGATION OF RELEVANT FINANCIAL RELATIONSHIPS

All relevant financial relationships have been mitigated.

Drs. Lee, Lemos, Mikhail, and Chaudhari's planning decisions, as part of the Scientific Program Committee (SPC), were peer reviewed by other planners on the SPC who had disclosed no financial relationships with ineligible companies, and found to be fair, balanced, and free of commercial bias. Dr. Moawad's financial relationships ended 12/2024, thus mitigating them. For most of his AAGL Professional Education Committee service, Dr. Mourad had no financial relationships to disclose. He recently disclosed a new relationship as a Proctor for Intuitive Surgical. Since then, he has not participated in activities involving control or influence over accredited educational content; therefore, no additional mitigation was necessary. Dr. Levy's role as Course Co-Chair was limited primarily to course oversight and moderation, rather than development of educational content. Any planning decisions or content under her influence were subject to independent peer review by individuals without relevant financial relationships.

The presentation content for course faculty, Drs. Levy and Simon, has been peer reviewed and found to be fair, balanced, and free from commercial bias.



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Disclosures

- None

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- For consistency with the published literature, this presentation uses "women" and female pronouns to refer to people assigned female at birth.
- Menopause can occur in anyone with ovaries, regardless of gender identity, including transgender men and non-binary people.

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Why are we talking about this?

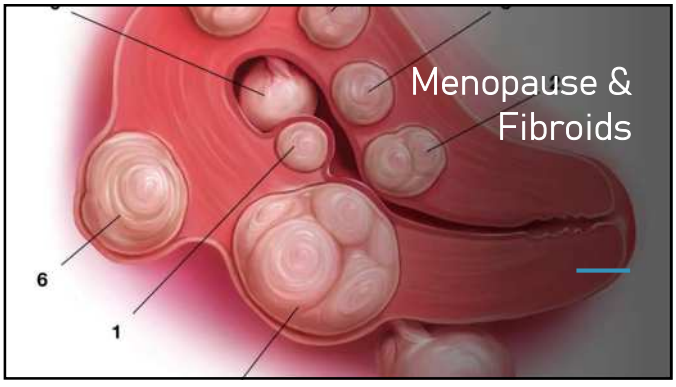
- A strong understanding of menopause and HT is essential for complex benign gynecologic surgeons
- Many of our patients are perimenopausal or postmenopausal
- Our interventions can induce or accelerate menopause
- Premenopausal patients will eventually transition through menopause, and they will look to us for guidance on how menopause and MHT affect complex benign gynecologic conditions, such as fibroids and endometriosis

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Overview

1. Perimenopause versus menopause in surgical patients
2. Surgical menopause & accelerated ovarian aging
3. Fibroids across the menopause transition and with MHT
4. Endometriosis across the menopause transition and with MHT

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Fibroids by the Numbers

- Prevalence: 70-80% of women by age 50 years
- Peak fibroid incidence: ages 45-49 years
- Peak fibroid prevalence: ages 50-54 years
- Mean age at hysterectomy for fibroids: ages 45-49 years
- Mean age at myomectomy: ages 37-41 years

Baird 2003
Yu 2016
Laughlin-Tommaso 2020
Wechter 2011
Moorman 2013

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Fibroids & Hormones

ESTROGEN

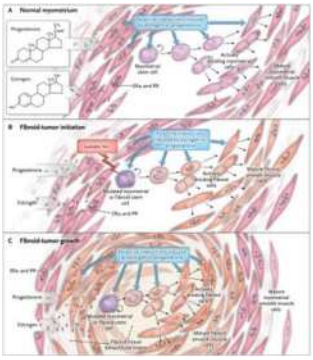
- **Mainly permissive role**
- Induces PR expression in fibroid cells
- Sources: ovary, aromatase in fibroids, placenta

PROGESTERONE

- **Primary driver of fibroid growth**
- Promotes fibroid cell proliferation
- Blocks apoptosis
- Increases ECM production
- Release paracrine signals that act on stem cells and progenitor cells
- Sources: ovary (during luteal phase), placenta

Bulun 2013

8



Bulun 2013

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Fibroids & Menopause

Image generated with ChatGPT

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True or False?

- Any fibroid that grows after menopause isn't a fibroid. It's cancer.

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Fibroids & Menopause

- Fibroids typically decrease in size after menopause, thereby becoming less symptomatic or asymptomatic and less likely to require treatment… but it's not guaranteed.
- Fibroid size and location matter.

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Fibroid Volume Change

Intervention	Volume Change
Leuprolide (no add-back)	-37%
Relugolix + E2/NETA	-12 to -17%
Elagolix + E2/NETA	?
Ulipristal	-54 to -58%
Aromatase inhibitor	-45 to -55%
Menopause	-61.4% to +184.1%

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Fibroid Volume Change After Menopause

Study	Design and population	Follow-up and measurement	Findings
Yang 2002 (Maturitas)	Prospective controlled cohort PMP women with solitary fibroids, 37 on CEE 0.625 mg + MPA 5 mg versus 35 non-users	TVUS volume yearly for 3 years	Non-users: volume rose significantly at year 1, rose insignificantly at year 2 then fell back to baseline by year 3. HT users: rose through year 2 and stayed above baseline at year 3. >25% growth in 1/34 non-users vs. 3/34 users
Shen 2021 (Menopause)	Retrospective 102 PMP women, 132 surgically confirmed (benign) fibroids	≥2 TVUS 6 months apart; ellipsoid volume	Median growth 12.9% per 6 months (range −61.4% to +184.1%). Growth rate higher by 26.6% with obesity and 15.9% with overweight. Fibroids ≥5 cm grew 30% more slowly than fibroids <3 cm
Oue 2024 (Cureus)	Retrospective cohort 97 Japanese women at a myoma clinic; dominant nodule 50–160 mm (median 81 mm); no HT or UAE; median BMI 22.4	Annual transabdominal US for ≥10 years after menopause; longest diameter of largest nodule vs. premenopausal size	Mean diameter fell ~22–23% by 10 years (~50–55% volume, estimated). About 10.5% by year 2 (fastest phase), then ~1.5%/year. Less shrinkage with BMI ≥25 (15.7% vs. 25.0%) and with ≥4 nodules (15.2% vs. 26.3% for 1 nodule). Women with ≥3 nodules had no early rapid phase. Individual results ranged from slight growth to ~74% reduction

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Why Do Some Fibroids Grow After Menopause?

- Aromatization in adipose tissue and in fibroids themselves
- Paracrine and growth-factor signaling (at least partly independent of hormones)
- Exogenous hormones

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True or False?

- Any fibroid that bleeds after menopause isn't a fibroid. It's cancer.
- 10% of submucosal fibroids present as postmenopausal bleeding.

Kumar 2022

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Fibroids & MHT: The Problem with the Data

- Few studies (only 11-ish somewhat commonly referenced studies investigating the effects of MHT on fibroids)
- They're old (newest is from 2013)
- They're small (smallest n = 27, largest n = 224)
- Short follow-up (only 2 studies with follow-up >12 months)
- They lack statistical rigor (no power analyses, no clear randomization criteria, study design not explicit, most not placebo-controlled)
- MHT regimens investigated were **all over the place**

Ang 2009
Moro 2019
Srinivasan 2018

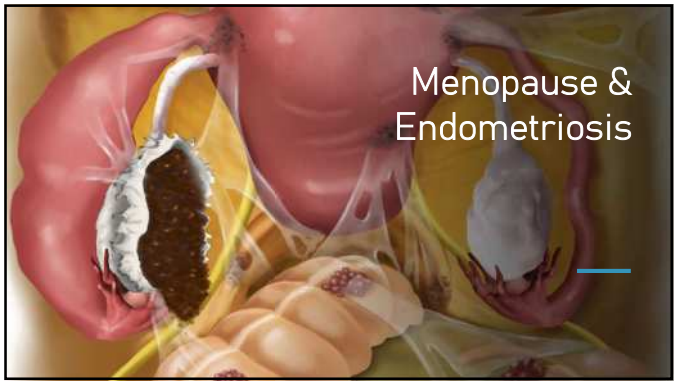
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Fibroids & MHT: Key Points

- Fibroids are **not** a contraindication to MHT
- MHT may cause fibroid growth, typically within the first 2 years of use
- **Most of this growth does not cause clinical symptoms**
- Higher risk of bleeding if fibroids are submucosal
- Fibroid growth may differ with different MHT doses/preparations
  - More growth with transdermal estrogen compared to oral estrogen
  - More growth with higher progestogen doses
- MHT may decrease uterine artery pulsatility index (PI), which indicates decreased vascular resistance and increased uterine perfusion

Yang 2002
Ang 2009
Akkad 2021
Chang 2013
Sener 1998
Polatti 2000
Palomba 2001
Cetaceri 2000

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Endometriosis by the Numbers

- Prevalence: 10% of reproductive-aged women globally
- Peak endometriosis incidence: ages 25-29 years
- Peak endometriosis prevalence: ages 30-39 years
- Mean age at conservative surgical management: ages 31-34 years
- Mean age at surgical management with hysterectomy: ages 40-47 years
- Surgical management with hysterectomy: 12-38%
  - Menopause occurs earlier in women s/p hysterectomy, even with ovarian preservation

Zondervan 2018
Missmer 2004
Shen 2024
Roman 2010
Abbott 2003
Shakiba 2008
Saavalainen 2017
Rizk 2014
Moorman 2011

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Bilateral Oophorectomy for Endometriosis

Surgical Setting	% Bilateral Oophorectomy
All endometriosis surgeries	25%
Conservative surgery only	1-2%
Hysterectomy for endometriosis	30-52%

Shakiba 2006
Long 2023

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Endometriosis & Menopause

- Endometriosis is estrogen-dependent and often improves after menopause
- However, symptomatic endometriosis after menopause does occur, accounting for 2-5% of cases
  - Includes persistent or recurrent/reactivated disease and new diagnoses

Hoek 2012
ESHRE 2022

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Endometriosis After Menopause: How?

1. Exogenous estrogen exposure (e.g., MHT)
2. Extra-ovarian estrogen production
   a. Peripheral aromatization (e.g., adipose tissue, skin, adrenal sources)
   b. Local production by the implants themselves
3. Estrogen-independent mechanisms
   a. Immune dysfunction
   b. Progesterone resistance
   c. Iron-senescence-fibrosis triad

ESHRE 2022
Wang 2025
MacLean 2022
Patel 2025

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Postmenopausal Endometriosis: Presentation

- Postmenopausal patient with:
  - Pelvic pain, and/or
  - Pelvic/adnexal mass, plus/minus
  - History of endometriosis, plus/minus
  - MHT use

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Postmenopausal Endometriosis: Evaluation

- History
  - New versus persistent/recurrent symptoms
  - Prior endometriosis (severity, management, ovarian involvement)
  - Prior hysterectomy plus/minus oophorectomy
  - MHT (type, dose, duration; estrogen-only versus combined)
  - Tamoxifen or SERMs
- Physical exam
- Imaging (transvaginal pelvic ultrasound, MRI)

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Postmenopausal Endometriosis: Medical Management

- Appropriate **only if** symptoms are mild, imaging is reassuring (i.e., no concerning mass), and patient understands limitations (i.e., no confirmatory histologic diagnosis)
- Decrease or stop estrogen
- Add a progestogen (yes, even in patients without a uterus!)
- Consider aromatase inhibitors (monitor bone health closely!)

ESHRE 2022

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The Role of Progestogen

1. Antiproliferative effect
   - Counteract estrogen-driven proliferation
   - Promote decidualization and atrophy of ectopic endometrial tissue
   - This mirrors their protective role in the eutopic endometrium
2. Reduced recurrence/reactivation
   - Combined estrogen–progestogen MHT is associated with lower rates of symptomatic recurrence than estrogen alone
3. Theoretical reduction in malignant risk
   - Suppress estrogen-induced atypia in residual implants

Erel 2025

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Postmenopausal Endometriosis: Surgical Management

- Maintain a low threshold for surgery (recommended as first-line by some groups)
- Indications:
  - Adnexal mass or any suspicion for malignancy
  - Refractory or worsening symptoms
  - Failure or intolerance of medical therapy
- Surgical principles:
  - Aim for complete excision
  - Avoid cyst drainage or partial excision
  - Send all tissue for histopathology

ESHRE 2022

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Endometriosis & Malignancy

- Rare
- 0.3–1.6% of endometriosis cases undergo malignant transformation (most commonly to endometrioid or clear cell ovarian cancer)
- Endometriosis is observed in 4–29% of patients with ovarian cancer
- Endometriosis is considered a risk factor for ovarian cancer

Adilbayeva 2024

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Endometriosis & MHT

- Endometriosis is **not** a contraindication to MHT
- MHT regimen should include a progestogen, even in patients without a uterus

ESHRE 2022

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Closing Thoughts

- A strong understanding of menopause and MHT is essential for complex benign gynecologic surgeons
- Many of our patients are perimenopausal or postmenopausal
- Our interventions can induce or accelerate menopause
- Premenopausal patients will eventually transition through perimenopause and menopause, and they will look to us for guidance on how menopause and MHT affect fibroids and endometriosis

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Thank you

TheQuietWallDesigns

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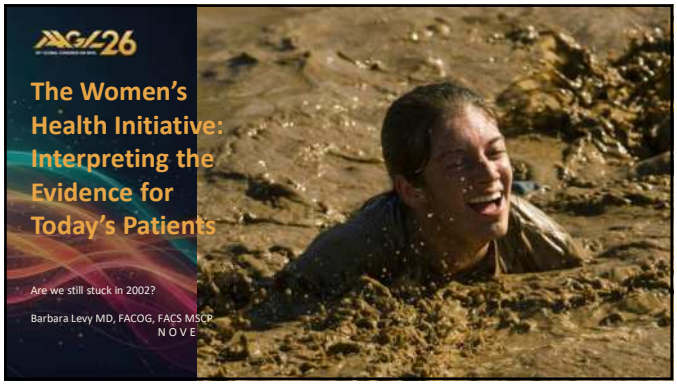
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Wechter ME, Stewart EA, Myers ER, Kho RM, Wu JM. Leiomyoma-related hospitalization and surgery: prevalence and predicted growth based on population trends. Am J Obstet Gynecol. 2011 Nov;205(5):492.e1-5. doi: 10.1016/j.ajog.2011.07.008. Epub 2011 Jul 20. PMID: 22035951; PMCID: PMC3766963.

Yu O, Schulze-Rath R, Grafton J, Hansen K, Reed SD. A US population-based study of uterine fibroid diagnosis incidence, trends, and prevalence: 2005 through 2014. Am J Obstet Gynecol. 2018 Dec;219(6):591.e1-591.e8. doi: 10.1016/j.ajog.2018.09.039. Epub 2018 Oct 3. PMID: 30291860.

Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. Nat Rev Dis Primers. 2018 Jul 19;4(1):9. doi: 10.1038/s41572-018-0008-5. PMID: 30026507.



1

Disclosures

Consultant: Channel Medsystems
Natural Cycles USA
Koko Medical
Sera
Astrin Biosciences

2

Learning Objectives

- Understand the WHI study: the good, the bad and the ugly
- Understand the current evidence regarding hormone therapy
- Know the risks, benefits and alternatives to menopausal hormone therapy

3

Epidemiological & Cohort Studies

- Framingham suggested ***CV harm*** in women on CEE+MPA (NEJM 1985)
- Nurses' Health Study, Leisure World Study, Kaiser Permanente Study – all with long term follow-up showed a substantial ***reduction in CV risk*** for the cohorts using menopausal hormone therapy.

Framingham study. N Engl J Med 1985;
313:1038–43.
Results from the Lipid
Research Clinics Program Follow-Up Study. Circulation 1987;
75:1102–9.
Noncontraceptive estrogens
and mortality: long-term follow-up of women in the Walnut
Creek Study. Obstet Gynecol 1987;70:289–93.

4

The WHI was born…

- Inconsistencies in results of the population-based studies drove controversy and discussion
- Epidemiologists attributed the positive CV outcomes to "healthy user effect"
- NIH was granted funding for large prospective randomized clinical trial to study the effects of menopausal HT on CV risk among other health and aging strategies

5

Women's Health Initiative

- Enrolled over 100,000 women at a cost of over $600 million
- Based on the low incidence of CV outcomes in younger women, researchers e enroll an older patient population to appropriately power the study
- Due to the obvious treatment effect of estrogen in managing menopausal symptoms, the investigators elected to enroll only asymptomatic patients so that treatment blinding could be preserved
- SO…we ended up with a study of hormones in 63-year-old women without symptoms!

6





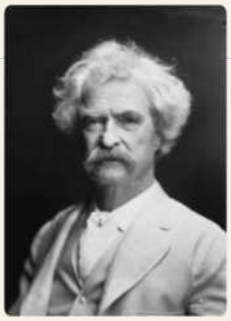




JULY 8, 2002

NIH Press Conference
Releasing WHI CEE-MPA
RCT findings

7



"It's not what you don't know that hurts you –

It's what you know for sure that just ain't so."

– Mark Twain

8

July 2002: A Sea Change in Attitude towards hormones

- Dr. Jacque Rossouw presented ***his interpretation*** of findings without discussion with the co-investigators AFTER the JAMA article had gone to press and could not be altered
- Announced the "surprising" results of preliminary analyses of the WHI combined hormone therapy randomized trial:
  - CEE+MPA increased the risk of breast cancer, heart attack, VTE and stroke

9

What the world heard Dr. Rossouw say:



10

WHI: Evidence-based Medicine and Hormone Therapy



ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

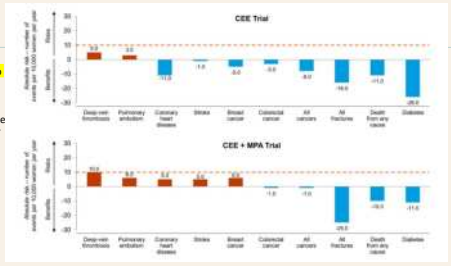
Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus

Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.

11

Fig. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (CEE + MPA), evaluated in the Women's Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line).

Adapted from Manson JE, et al. JAMA 2013;310:1353-1368.

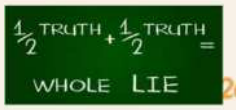


Significant harms???

12

WHI Implications

- HRT should not be continued or started to prevent heart disease
- For osteoporosis prevention, women should consult their doctor and weigh the benefits against their personal risks for heart attack, stroke, blood clots, and breast cancer; alternative treatments are available to prevent osteoporosis and fractures
- Short-term use for relief of menopausal symptoms was not studied



National Institutes of Health. National Heart, Lung, and Blood Institute. *New Facts About: Estrogen/Progestin Hormone Therapy*. July 9, 2002.

13

Consequences of the WHI publicity

- Widespread confusion and fear
- Prescriptions plummeted by 79%
- Symptomatic patients were taken off their hormones
- Physician practice patterns AND professional education on menopause and perimenopause were altered for the following decades

14

Menopause increases risk

- Cardiovascular disease
- Bone loss and osteoporotic fractures
- Sarcopenia
- Sexual dysfunction – decreased libido, pain
- Recurrent UTIs
- Cognitive decline

15

Breast cancer risk and the WHI

- It was the unusually LOW breast cancer incidence in the placebo group that had previously taken HT (25% of the study population) that created the controversial breast cancer data
- There was NO DIFFERENCE in breast cancer incidence in the cohort of never users randomized to CEE+MPA or placebo
- EVEN IN THE SHORT-TERM, CEE+MPA use had a null effect on breast cancer incidence and mortality.

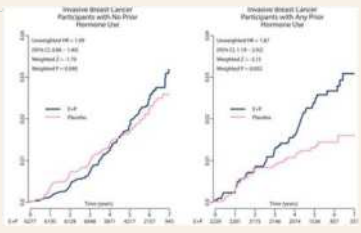




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Breast Cancer risk and hormone therapy: WHI

- Hodis HN, Sarrel PM. Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials? Climacteric 2018;21:521–8.



17



JAMA | Original Investigation

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials

JAMA 2020;324:369–80.

18

Breast cancer risk and estrogen alone

- WHI randomized 10,739 women to CEE alone or placebo
- Trend towards decreased breast cancer risk with CEE alone
- At 20 year follow up this became statistically significant
  - **22%** reduction in breast cancer incidence
  - **40%** reduction in breast cancer mortality

19

- 22% REDUCTION in Breast Ca Incidence
- 40% REDUCTION in Breast Ca Mortality
- **NO** Press Coverage



MAIN OUTCOMES AND MEASURES The primary outcome was breast cancer incidence (protocol prespecified primary monitoring outcome for harm) and secondary outcomes were deaths from breast cancer and deaths after breast cancer.

RESULTS Among 27 347 postmenopausal women who were randomized in both trials (baseline mean [SD] age, 63.4 years [7.2 years]), after more than 20 years of median cumulative follow-up, mortality information was available for more than 98%. CEE alone compared with placebo among 10 739 women with a prior hysterectomy was associated with statistically significantly lower breast cancer incidence with 238 cases (annualized rate, 0.30%) vs 296 cases (annualized rate, 0.37%; hazard ratio [HR], 0.78; 95% CI, 0.65-0.93; *P* = .005) and was associated with statistically significantly lower breast cancer mortality with 30 deaths (annualized mortality rate, 0.033%) vs 46 deaths (annualized mortality rate, 0.046%; HR, 0.60; 95% CI, 0.37-0.97; *P* = .04). In contrast, CEE plus MPA compared with placebo among 16 608 women with a uterus was associated with statistically significantly higher breast cancer incidence with 584 cases (annualized rate, 0.45%) vs 447 cases (annualized rate, 0.36%; HR, 1.28; 95% CI, 1.13-1.45; *P* < .001) and no significant difference in breast cancer mortality with 71 deaths (annualized mortality rate, 0.045%) vs 53 deaths (annualized mortality rate, 0.035%; HR, 1.35; 95% CI, 0.94-1.95; *P* = .11).

Association of menopausal hormone therapy with breast cancer incidence and mortality during long term follow-up of the Women's Health Initiative randomized clinical trials. JAMA 2020;324:369–80.

20

Breast cancer risk and CEE + MPA

AT follow-up there was **no increase in breast cancer mortality** in the cohort randomized to CEE+MPA

21

Estradiol and breast cancer risk

- Nationwide Finnish Comparative Study – large observational trial n=489,105 followed 1994-2009
- Any history of estradiol-based HT, including when combined with a progestin, associated with up to 50% reduction in breast cancer mortality.
- True for > 10 years of use and across ALL AGE GROUPS.

Mikkola TS, Savolainen-Peltonen H, Tuomikoski P, Hoti F, Vattulainen P, Gissler M, et al. Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study. Menopause 2016;23:1199–203.



22

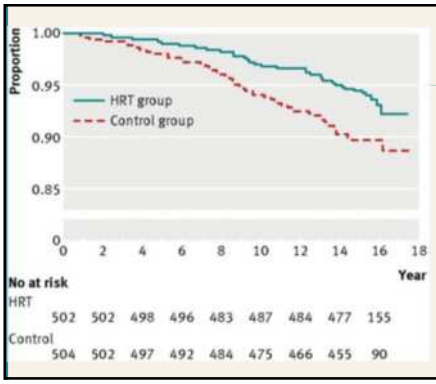
Estradiol and cardiovascular risk

- Danish Osteoporosis Study randomized recently menopausal women to 2mg oral estradiol + progestin if no hysterectomy
- 10 years of treatment
- Followed patients for 16 years
- Terminated early due to the WHI findings

Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012;345:e6409.



23



DOPS findings

- Survival curve from the Danish Osteoporosis Study showing a statistically significant reduction of cardiovascular disease by 52% (HR, 0.48; 95% CI, 0.27–0.89) after 10 years of randomized hormone therapy

24

WHI Subgroup Analysis: Estrogen and CV risk

- Confirmed that CV risk influenced by age and time since menopause
- **Initiating hormones at 50-59 resulted in a 40% reduction in MI risk and lower all-cause mortality**
- These benefits were not seen in the older cohort



Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended post stopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353–68.

25

Hormone therapy and blood clots

- ESTHER (Estrogen and Thromboembolism Risk): multi-center case-cohort study of women 45-70yrs 1999-2005. N=271 cases and 670 controls.
- OR for oral 4.2 (1.5-11.6) vs 0.9 for transdermal (0.4-2.3)
- No increased risk for micronized progesterone
- MPA and other nonpregnane progestins OR 3.9 (1.5-10)

Conclusion: VTE risk increases with age and with CEE and MPA use. **There appears to be no such association with transdermal estradiol and micronized progesterone.**

Canonicus M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 2007;115:840–5.

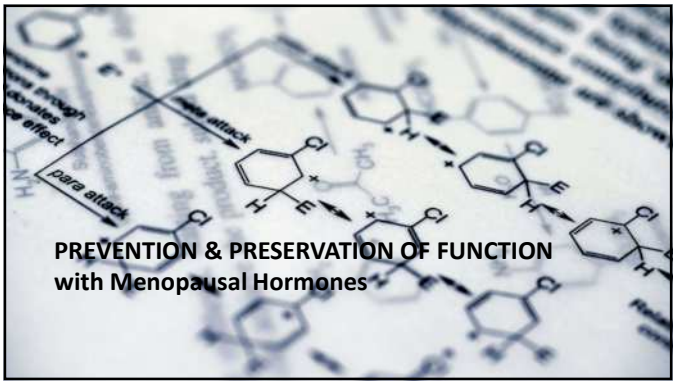
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Just published: **Increased risk** with higher dose oral estrogens

Danish National Registry – **NO increased risk** with transdermal estrogen Median age=62



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PREVENTION & PRESERVATION OF FUNCTION with Menopausal Hormones

28



JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone therapy for the primary prevention of chronic conditions in postmenopausal persons: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2022;328:1747–67.

29

Were the appropriate studies included/excluded?

menopausal symptoms (eg, vasomotor hot flashes or vulvovaginal symptoms) or for other indications is outside the scope of this recommendation.

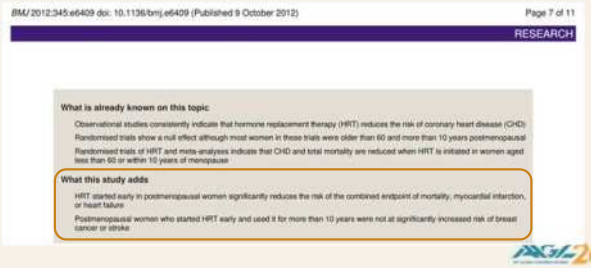
Benefits and Harms of Preventive Medication

The USPSTF found 20 randomized clinical trials that compared the effects of estrogen, either alone or in combination with progestin, vs placebo for the prevention of chronic conditions.[8,9] Of these studies, the WHI trials were the only studies powered to assess the effectiveness of hormone therapy for the primary prevention of various chronic conditions. The WHI trials enrolled postmenopausal persons aged 50 to 79 years; the mean age of participants was 63 years. The WHI compared 0.625 mg/d of oral conjugated equine estrogen, with or without 2.5 mg/d of medroxyprogesterone

jama.com

30

Evidence-based Medicine - Conclusions


BMJ 2012;345:e6409 doi: 10.1136/bmj.e6409 (Published 9 October 2012) Page 7 of 11

RESEARCH

What is already known on this topic

Observational studies consistently indicate that hormone replacement therapy (HRT) reduces the risk of coronary heart disease (CHD)

Randomised trials show a null effect although most women in these trials were older than 60 and more than 10 years postmenopausal

Randomised trials of HRT and meta-analyses indicate that CHD and total mortality are reduced when HRT is initiated in women aged less than 60 or within 10 years of menopause

What this study adds

HRT started early in postmenopausal women significantly reduces the risk of the combined endpoint of mortality, myocardial infarction, or heart failure

Postmenopausal women who started HRT early and used it for more than 10 years were not at significantly increased risk of breast cancer or stroke

31

Cochrane Systematic Review

- Trial data stratified by age or time since menopause
- 30-48% reduction in CV disease and all-cause mortality in women younger than age 60 and within 10 years of menopause
- CV disease decreased by roughly half and all-cause mortality by 30%



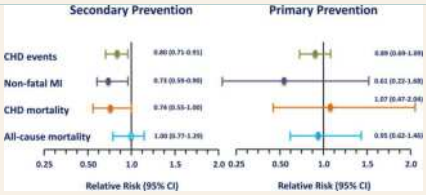
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Cochrane meta-analysis showing reduction mortality and coronary heart disease in women initiating hormone therapy, <60year old and/or,10 years since menopause relative to placebo. Nineteen randomized controlled trials of 40,410 women comparing hormone therapy of estrogen with or without progestogen with placebo.

33

Other options for CV prevention - Statins



All-cause mortality is unaffected by lipid-lowering therapy in women in secondary and primary cardiovascular disease prevention.

Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. J Am Med Assoc 2004;291:2243–2252.

34

Where do we go from here?



- Stratify all studies by age, formulation, and route of administration
- Recognize the distinction between CEE and estradiol
- Do not extrapolate results from CEE + MPA trials to conclusions regarding all hormone therapy
- To prevent ongoing public health harm, educate our colleagues and the public on the benefits of early onset menopausal treatment with hormone therapy

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Hormone Therapy 101:

- Practical Prescribing for Surgeons
- Who, what, when and why prescribe menopausal hormone therapy?

36

Hormones for health?

- Overall well-being
- Osteoporosis prevention
- Heart disease
- Dementia
- Cancer
- Genitourinary syndrome of menopause
- All cause mortality



37

The Hormone Controversy

Encourage women to communicate freely, read widely but be critical of the source of the information they receive.

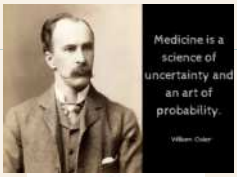
Encourage women to trust their bodies. For symptomatic women estrogen therapy is safe and effective!

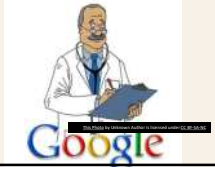


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The Hormone Controversy What do I Say to Patients?

- There is **NO** increase in incidence of or death from breast cancer in estrogen/progesterone users
- Estradiol and progesterone are the most effective treatments for symptoms AND they improve CV risk, osteoporosis risk and overall QOL
- Quality of life and individual risk factors must be considered



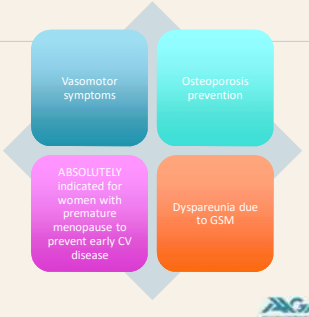


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Indications for MHT



41

Contraindications to MHT

- Hormonally sensitive malignancy
- Myocardial infarction within 6 months
- Personal hx stroke/PE/DVT not on anti-coagulation
- (transdermal estradiol may be considered with informed consent and shared decision-making)

42

The Hormone Controversy

The decision to take hormone replacement is an individual one. We must help our patients understand the data as we know it as well as the limitations of the trials.

The decision is not forever. Stay open to new data as it becomes available.



43

Tricks in prescribing MHT

- Synchronize the endometrium before initiation in perimenopausal and early menopausal women
- Women with a uterus must have uterine protection: systemic progestin, LNG-IUS, or bazedoxifene
- Combined continuous MHT WILL cause bleeding in many women within the first few months
- Alternative is cyclic MHT until no withdrawal occurs
- Consider testosterone for surgically menopausal patients with inadequate symptom resolution on estrogen alone

44

Route of administration to improve CV outcomes

- Transdermal estradiol bypasses the liver on first past
- ACOG, NAMS suggest transdermal for those at risk for CV disease BUT….
- DVT risk equivalent between transdermal and oral **estradiol** AND it is consistent with age-adjusted baseline risk
- Oral estradiol at 2mg daily reduces CV mortality by up to 40% - transdermal has less impact (no comparative studies)



45

My pearls

- **Beware extrapolating results from studies of oral conjugated equine estrogen to ALL menopausal hormone treatment**
- **Assess outcomes not surrogate endpoints**
- **Premarin is not equivalent to estradiol**
- **Provera has vastly different effects than natural progesterone**



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My pearls

- **All women are candidates for vaginal estrogen to prevent UTI and manage GSM**
- **Pre-existing CV disease is not a contraindication to transdermal estradiol**
- **No increase in breast cancer risk even in those at baseline higher risk**



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My pearls – Alternatives to MHT

VMS: **Fezolinetant**
Elinzanetant
Gabapentin
SSRIs

Osteoporosis:
Bisphosphonates
Denosumab

Cardiovascular:
Statins
PCSK9-inhibitors
?GLP-1RA



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Care over a lifetime



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CONCLUSIONS

- Current evidence supports the use of estradiol for the prevention of osteoporosis, cardiovascular disease and premature death when started within 10 years of menopause
- USPSTF and other guideline developers have allowed methodology to overtake clinical judgment in analyses of hormone therapy for prevention
- Menopausal hormone therapy with estradiol and micronized progesterone does NOT increase breast cancer incidence or mortality

50



https://www.google.com/search?q=youtube+hot+flash+havoc&tbm=isch&ved=2ahUKEwjYvuTe-hot-flash-havoc&oq=youtube+hot+flash+havoc&gs_lcrp=EgZpbWcyBggAEEUYOTIGCAEQRRg8MgYIAhBFGDwyBggDEEUYPDIGCAQQRRg8MgYIBRBFGDwyBggGEEUYPDIGCAcQRRg8MgYICBBFGDzSAQgzNjk0ajBqOagCALACAA&sclient=img&ei=UTFBaYqvE8rHptQPqPqC6Ac



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Questions?

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Non-Hormonal Treatment of Menopausal Vasomotor Symptoms And Testosterone Therapy After Menopause

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(35)

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James A. Simon, MD, CCD, MSCP, IF, FACOG Disclosures (as of 10/05/26)

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Speaker's bureaus/fees: Ascend Therapeutics, Bayer Healthcare LLC., Besins Healthcare, Lawley Pharmaceuticals Pty Ltd., Mayne Pharma, Inc., Myovant Sciences, Inc., Pharmavite LLC.

2

Learning Objectives:

Upon completion of this lecture, participants will be able to:

- Appreciate the multiple non-hormonal options (FDA-approved and off-label) for treatment of menopausal vasomotor symptoms (VMS) and the strength of data documenting their efficacy and safety
- Implement The 2023 Menopause Society evidence-based guidelines for the nonhormonal management of symptomatic VMS while eliminating the now discontinued therapies.
- Appreciate that testosterone is a female hormone with a "sweet spot" between benefits and risks.
- Understand that testosterone is present in greater quantities than estradiol in adult women of all ages.
- Apply the principal that testosterone is the hormone of sexual desire in women (like men), but with a different dose-response curve.
- Recognize the profound effects testosterone has in women extending beyond sexual function (i.e. bone, body composition, eye, etc.).
- Initiate and monitor testosterone therapy in naturally and surgically menopausal women.

3

PRESCRIPTION NON-HORMONAL THERAPY

4

SSRI/SNRI

5

FDA Approval of Paroxetine for Menopausal Hot Flushes

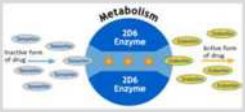
Ronald J. Orleans, M.D., Li Li, Ph.D., Myong-Jin Kim, Pharm.D., Jia Guo, Ph.D., Mahboob Sobhan, Ph.D., Lisa Soule, M.D., and Hylton V. Joffe, M.D., M.M.Sc.

The recent approval by the Food and Drug Administration (FDA) of paroxetine (Brisdelle, Noven) for the treatment of moderate-to-severe vasomotor symptoms associated with menopause was distinctive for at least two reasons. First, it offered the first nonhormonal option to women who cannot or do not want to use hormonal medications to treat their menopausal vasomotor symptoms. Second, the approval ran counter to the recommendation of the FDA Reproductive Health Drugs Advisory Committee, which had concluded, by a vote of 10 to 4, that the overall benefit–risk profile of Brisdelle did not support approval. The FDA always carefully

The New England Journal of Medicine
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Paroxetine is a Potent CYP2D6 Inhibitor



Tamoxifen

http://services.dnadirect.com/grc/patient-site/tamoxifen-response/tamoxifen-and-some-antidepressants-dont-mix.html

Tamoxifen + Paroxetine



endoxifen levels by 65%

Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

7

Efficacy of Venlafaxine

- Randomized, double-blind, placebo-controlled, 4-week study, 221 women with history breast CA or reluctance to use HT
  - Randomized to venlafaxine 37.5, 75, and 150 mg/d or placebo
  - All active groups started on 37.5 mg dose and 75 and 150 mg treatment arms were titrated up
  - Primary endpoints:
    - Frequency of hot flushes
    - Daily hot flush composite score (frequency x severity)
- Reduction in Hot Flashes:
  - Venlafaxine 37.5 mg 30% , Venlafaxine 75 mg 46%*, Venlafaxine 150 mg 58%*, Placebo 19%
  - Venlafaxine 75 and 150 mg associated with increased incidence of dry mouth, decreased appetite, nausea and constipation vs. placebo (and sweating)

Loprinzi CL, et al. *Lancet*. 2000; 356:2059-63

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Desvenlafaxine (100mg) for Hot Flashes

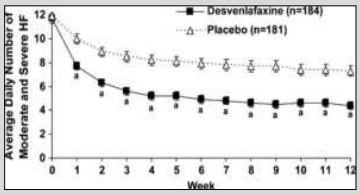


FIG. 2 . Change from baseline in the average daily number of moderate and severe hot flashes, modified intent-to-treat population (all women who took >=1 dose of study drug, had >=1 *d of baseline efficacy data, and had >=1 d of postbaseline efficacy data), last observation carried forward. Error bars indicate standard error. P* < 0.001, desvenlafaxine versus placebo. HF, hot flash.

Pinkerton J, Constantine G, Hwang E. et. al. Desvenlafaxine compared with placebo for treatment of menopausal vasomotor symptoms: a 12-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled efficacy trial. Menopause. 20(1):28-37, 2013.

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CME • Regulatory history

Why FDA did not approve desvenlafaxine for menopausal VMS

The public record supports a safety-driven nonapproval, but the 2011 Complete Response Letter did not publicly disclose FDA's specific deficiencies.

WHAT WAS CLEAR

Efficacy was demonstrated

- 100 mg/day reduced hot-flash frequency and severity vs placebo at weeks 4 and 12 **(all P<0.001).**
- Week 12 frequency reduction: **62% vs 38%.** Adverse-event discontinuation: **10.0% vs 3.7%.**
- Pfizer nevertheless received a Complete Response Letter on Sept. 8, 2011: the VMS indication could not be approved "in its present form."

Bottom line: efficacy alone was not enough for FDA approval.



Benefit–risk review

A low-mortality symptom indication demands persuasive long-term safety.

LIKELY DECISIVE ISSUE

Unresolved serious-safety signal

- A preceding trial had raised concern for potential **serious cardiovascular and hepatic events.**
- The large 1-year safety study was designed specifically to estimate ischemic cardiovascular, cerebrovascular, and hepatic events.
- It later found no evidence of increased risk vs placebo, but did observe **1 probable stroke** with desvenlafaxine and very wide confidence intervals compatible with residual uncertainty.

Interpretation: nonapproval reflected an unfavorable or insufficiently resolved benefit–risk case, not lack of VMS efficacy.

References: Pfizer. Complete Response Letterstatement, Sept 8, 2011. • Pinkerton JV, et al. Menopause. 2013;20:28–37. • Archer DF, et al. Menopause. 2013;20:47–56.

Abbreviations: FDA, US Food and Drug Administration; VMS, vasomotor symptoms.

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SSRI/SNRI and CYP2D6 Inhibition

POTENT INHIBITORS
- Fluoxetine
- Paroxetine
- Buproprion

MODERATE INHIBITORS
- Sertraline
- Duloxetine
- Fluvoxetine

WEAK INHIBITORS
- Citalopram
- Escitalopram

AVOID WITH TAMOXIFEN

NO ACTIVITY
- Venlafaxine
- Desvenlafaxine
- Mirtazepine

Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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SSRI & SNRI DOSING...

SSRI	
PAROXETINE	7.5-10 mg/day
ESCITALOPRAM	10-20 mg/day
CITALOPRAM	10-20 mg/day
SERTRALINE	not recommended due to inconsistent results
FLUOXETINE	

SNRI	
VENLAFAXINE	37.5-150 mg/day
DESVENLAFAXINE	100-150 mg/day

- Venlafaxine is the most widely used
  - Nausea, start low
  - Taper slowly

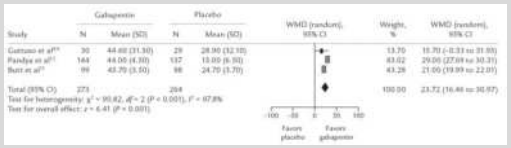
Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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GABAPENTIN & OXYBUTYNIN

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Gabapentin vs. Placebo: Frequency of Hot Flashes in Three Studies



Toulis KA, Tzellos T, Kouvelas D, Goulis DG. Gabapentin for the treatment of hot flashes in women with natural or tamoxifen-induced menopause: a systematic review and meta-analysis. Clin Ther. 2009 Feb;31(2):221-35.

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Simon JA, Gaines T, LaGuardia KD et al; Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause. 2016 Nov;23(11):1214-1221.

Oxybutynin

- Anticholinergic drug used for urinary incontinence, why are we using it for hot flashes?
- Now included in NAMS statement (not in 2015 position statement)
- 1st RCT. Presented in 2007, but not published until 2016, 175 post menopausal women with 56 or more moderate to severe VMS - oxybutynin 15 mg ER vs placebo



SEVERITY FREQUENCY

- Reduction in HF frequency and severity as early as 1-2 weeks
- 70% of patients had partial or excellent response (vs placebo 20%)
- >50% of patients had dry mouth

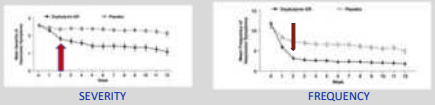
Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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Oxybutynin

Source:
- Simon, et al. Extended release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause, Vol 23. No. 11, 2016.

- Anticholinergic drug used for urinary incontinence, why are we using it for hot flashes?
- Not included in NAMS statement because new data came out after the statement was released
- 1st RCT. Presented in 2007, but not published until 2016, 175 post menopausal women with 56 or more moderate to severe VMS/w
  - Oxybutynin 15 mg ER vs placebo



SEVERITY FREQUENCY

- Reduction in HF frequency and severity as early as 1-2 weeks
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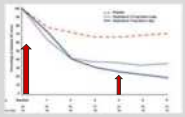
Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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Oxybutynin

2nd RCT published in 2019 looking at oxybutynin vs placebo in patients with and without breast cancer

- 3 arms, oxybutynin 5 mg BID, oxybutynin 2.5 mg BID and placebo
- 150 women enrolled, average **28 HF** per week
  - 65% of these women were on tamoxifen or AI
  - Effect was seen after 1 week, 40% reduction in HF
- Reduction in
  - HF score
  - HF frequency
  - Maximal effect seen at 4 weeks, 80% reduction
  - Dry mouth was more common in treatment groups, low discontinuation rates



Source:
- Leon-Ferre et al. Oxybutynin vs placebo for hot flashes in women with and without breast cancer: a randomized, double blind, clinical trial. *JNCI Cancer Spectrum, 2020.*

Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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Anticholinergics and Cognition

- ACh transmits messages in the brain involved in learning and memory
- Cholinergic drugs are used in the treatment of dementia
- ACh production declines with age
- Anticholinergic drugs have been associated with negative cognitive effects
- Reports linking anticholinergic drugs to dementia, though causality is not established

Source:
- Richardson, K et al. Anticholinergic drugs and risk of dementia: a case control study. BMJ, 2018.
- AUGS Consensus statement: Association of Anticholinergic Medication Use and Cognition in Women with OAB, 2020 update

Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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Anticholinergics and Cognition: THE DATA

Initial Study in JAMA 2015 (Gray et al)

- Tracked 3500 people >65 years, pharmacy record review
- Found those using anticholinergics were more likely to develop dementia
- Dementia risk increased with cumulative dose
- Taking anticholinergics for >3 years was associated with a 54% increased risk of dementia than those taking the same dose for <3 months

2016 JAMA Neurology (Risacher et al)

- Anticholinergic users showed reduced brain glucose metabolism
- Temporal lobe and whole brain atrophy was seen

- Risacher SL, McDonald BC, Tallman EF, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. JAMA Neurol 2016;73: 721–732.

Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

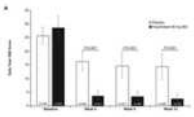
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NK3 RECEPTOR ANTAGONISTS

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Fezolinetant

- First studies in 2016, phase II trials in 2019
- Results
  - Significant reduction in VMS score (freq & severity)
    - Decrease by 93% in the 12-week study
    - Effect seen as early as first day of treatment
    - Improvement in sleep quality and decrease in daily interference symptoms
- Adverse Events
  - Most common were GI related (NK3 receptors in gut)
  - 12% of patients had transient, mild LFT elevations



Slide Courtesy of Carrie Leff, DO, FAAP, FACP, NCMP

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Double-blind, Placebo-Controlled, Multicenter, Phase 3 study (NCT04003155) SKYLIGHT 1

Inclusion criteria
Women aged 40–65 years with moderate-to-severe VMS associated with menopause (minimum average 7 moderate-to-severe hot flashes/day)

Primary objective
To evaluate the efficacy of fezolinetant vs placebo on the frequency and severity of moderate-to-severe VMS associated with menopause

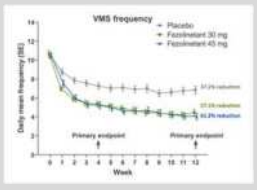
Co-primary efficacy endpoints
Mean change in frequency and severity of moderate-to-severe VMS from baseline to week 4 and 12
- Assessed daily using an electronic hot flash diary

Secondary endpoints
Mean change in frequency and severity of moderate and severe VMS each week from baseline to week 12

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Significant Improvements in VMS Frequency with Fezolinetant Through Week 12, as Early as Week 1



Week 4	Fezolinetant 30 mg	Fezolinetant 45 mg
LS mean difference vs placebo (SE)	−1.87 (0.42) **P<0.001**	−2.07 (0.42) **P<0.001**
LS mean % difference vs placebo (SE)	−16.8% (3.8%) **P<0.001**	−21.1% (3.8%) **P<0.001**
Week 12	**Fezolinetant 30 mg**	**Fezolinetant 45 mg**
LS mean difference vs placebo (SE)	−2.39 (0.44) **P<0.001**	−2.55 (0.43) **P<0.001**
LS mean % difference vs placebo (SE)	−20.1% (4.1%) **P<0.001**	−24.2 (4.1%) **P<0.001**

LS, least squares; SE, standard error; VMS, vasomotor symptoms
The LS mean difference is adjusted for means of other factors in the model; a mixed model repeated measurements analysis of covariance model was used, with change from baseline (or with percent change from baseline) as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

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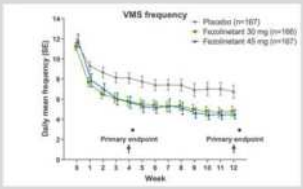
Double-blind, Placebo-controlled, Multicenter Phase 3 Study (NCT04003142) with 40-week Extension SKYLIGHT 2

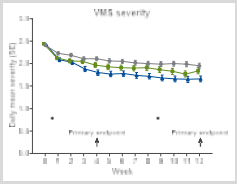
Inclusion criteria
Women aged 40–65 years, inclusive, with moderate-to-severe VMS associated with menopause (minimum average 7 moderate-to-severe hot flashes per day)

Primary objective
To evaluate the efficacy of fezolinetant vs placebo on the frequency and severity of moderate-to-severe VMS associated with menopause

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Fezolinetant Reduced VMS Frequency and Severity Across the 12-week Period





SE, standard error; VMS, vasomotor symptoms
*Statistically significant for both fezolinetant doses vs placebo.

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Original Research

OPEN

Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause

A Randomized Controlled Trial

Genevieve Neal-Perry, MD, PhD, Antonio Cano, MD, Samuel Lederman, MD, Rossella E. Nappi, MD, PhD, Nanette Santoro, MD, Wendy Wolfman, MD, Marci English, MPH, Catherine Franklin, BC, Udaya Valluri, MS, and Faith D. Ottery, MD, PhD

Long-term Treatment (52 w) of Fezolinetant in Women With Hot Flashes comparing placebo, fezolinetant 30 mg, and fezolinetant 45 mg once daily (1:1:1). (N=1,830 July 2019-January 2022)
Endometrial safety (N=599)
In the fezolinetant 45-mg group, 1 of 203 participants had endometrial hyperplasia.
No cases in the placebo (0/186) or fezolinetant 30 mg (0/210) group.
Endometrial malignancy (1 of 210) in the fezolinetant 30-mg group with no other cases.
Liver enzyme elevations (> 3x upper limit of normal) occurred in 6 of 583 placebo, 8 of 590 fezolinetant 30mg, and 12 of 589 fezolinetant 45 mg.
Changes in BMD and trabecular bone score were similar across groups.

Neal-Perry G, Cano A, Lederman S, Nappi RE, Santoro N, Wolfman W, English M, Franklin C, Valluri U, Ottery FD. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A Randomized Controlled Trial. Obstet Gynecol. 2023 Apr 1;141(4):737-747.

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TEAEs Were Similar for Fezolinetant and Placebo

TEAE, n (%)	Fezolinetant 30 mg (n=174)	Fezolinetant 45 mg (n=173)	Placebo (n=175)
TEAE	65 (37.4)	75 (43.4)	78 (44.6)
Drug-related TEAE	17 (9.8)	13 (7.5)	22 (12.6)
Serious TEAE	2 (1.1)	2 (1.2)	1 (0.6)
Drug-related serious TEAE	2 (1.1)	0	0
TEAE leading to permanent discontinuation of study drug	10 (5.7)	4 (2.3)	9 (5.1)
Drug-related TEAE leading to permanent discontinuation of study drug	6 (3.4)	3 (1.7)	7 (4.0)

TEAE, treatment-emergent adverse event (an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state)

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12/16/2024

FDA Adds Warning About Rare Occurrence of Serious Liver Injury with Use of Veozah (fezolinetant) for Hot Flashes Due to Menopause. Stop Medicine if Signs and Symptoms of Liver Injury Occur - Drug Safety Communication

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Elinzanetant

(a NK1 and NK3 Antagonist)

- **Bayer's elinzanetant meets all primary and key secondary endpoints in pivotal OASIS 1 and 2 Phase III studies**
- OASIS 1 and 2 pivotal studies evaluating investigational compound elinzanetant met all primary endpoints demonstrating a statistically significant reduction in frequency and severity of moderate to severe vasomotor symptoms (VMS) compared to placebo in postmenopausal women
- Both studies also showed superiority over placebo for all key secondary endpoints with a statistically significant reduction in frequency of VMS at week 1, as well as improvement of sleep disturbances and menopause-related quality of life
- The safety profile observed in both studies is overall consistent with previously published data on elinzanetant
- OASIS 1 and 2 are two of three Phase III clinical studies investigating the efficacy and safety of elinzanetant, a first dual neurokinin-1,3 (NK-1,3) receptor antagonist, as a non-hormonal treatment of moderate to severe VMS associated with menopause, administered orally once daily

Business wire January 8, 2024

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JAMA | Original Investigation

Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause

OASIS 1 and 2 Randomized Clinical Trials

JoAnn V. Pinkerton, MD, MSCP; James A. Simon, MD, MSCP; Hadine Joffe, MD, MSc; Pauline M. Maki, PhD; Rossella E. Nappi, MD, PhD; Nick Panay, BSc, MBBS; Claudio N. Soares, MD, PhD, MBA; Rebecca C. Thurston, PhD; Cecilia Caetano, MD; Claudia Haberland, PhD; Nazanin Haseli Mashhadi, MSc(Statistics); Ulrike Krahn, PhD; Uwe Mellinger, Dipl-Math; Susanne Parke, MD; Christian Seitz, MD; Lineke Zuurman, MD, PhD

Pinkerton JV, Simon JA, Joffe H, Maki PM, Nappi RE, Panay N, Soares CN, Thurston RC, Caetano C, Haberland C, Haseli Mashhadi N, Krahn U, Mellinger U, Parke S, Seitz C, Zuurman L. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618.

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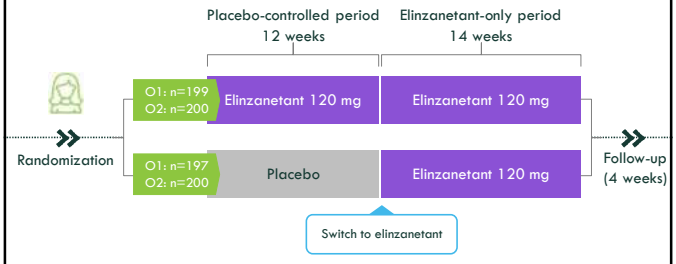
NK1/NK3 Receptor blocker Elinzanetant

- Similar mechanism of action, has greater potency at NK1 receptor
- Antagonism of the NK1 receptor alone is not effective in the treatment of HF
- NK1/NK3 receptors antagonist likely will have more significant benefit on mood and sleep disturbance vs NK3 selective medications
- Recently completed their Phase II trial (SWITCH-1 Trial)
  - Rapid and sustained reductions in frequency and severity of VMS symptoms with improvement in QoL scores
- Well tolerated, phase II trial did not reveal LFT elevations
- Most common SE was somnolence which was mild

Simon, J. , Anderson, R. , Ballantyne, E. , et. al. (2023). Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). *Menopause, 30* (3), 239-246. as Modified from: Carrie Leff, DO, FAAP, FACP, NCMP

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OASIS-1 and -2 were twin Phase III studies that compared elinzanetant with placebo for the treatment of VMS



32 O1, OASIS-1; O2, OASIS-2; VMS, vasomotor symptoms
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54

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Study endpoints assessed reductions in frequency and severity of VMS, reductions in sleep disturbances, and improvements in QoL

Endpoints[1]

Primary*
- Mean change in **frequency** of moderate-to-severe VMS from baseline to **week 4** and **week 12**
- Mean change in **severity**† of moderate-to-severe VMS from baseline to **week 4** and **week 12**

Key secondary
- Mean change in **frequency** of moderate-to-severe VMS from baseline to **week 1**
- Mean change in **PROMIS SD-SF-8b** total score from baseline to week 12
- Mean change in **MENQOL** total score from baseline to week 12

Study endpoints were selected and discussed with women experiencing menopause symptoms to assess appropriateness and to ensure that affected women were at the center of study design[2]

*Primary endpoints are used to assess the efficacy of elinzanetant for the treatment of moderate-to-severe VMS associated with menopause;†Reduction in VMS severity was a primary endpoint for US regulatory submissions but a key secondary endpoint for all other regions. MENQOL, Menopause-Specific Quality of Life questionnaire; PROMIS SD-SF-8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b; QoL, quality of life; VMS, vasomotor symptoms
1. Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials; 2. Pinkerton JV, Simon J, Panay N et al. Menopause 2024;31:522–9

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All primary and key secondary endpoints were met in both studies

	Endpoint	OASIS-1 *P*-value	OASIS-2 *P*-value	Outcome vs placebo
Primary*	VMS **frequency** week **4**	<0.001	<0.001	Elinzanetant superior
	VMS **frequency** week **12**	<0.001	<0.001	Elinzanetant superior
	VMS **severity** week **4**†	<0.001	<0.001	Elinzanetant superior
	VMS **severity** week **12**†	<0.001	<0.001	Elinzanetant superior
Key secondary	VMS **frequency** week **1**	<0.001	0.001	Elinzanetant superior
	Sleep disturbances (PROMIS SD-SF-8b) week **12**	<0.001	<0.001	Elinzanetant superior
	Quality of life (MENQOL) week **12**	<0.001	0.006	Elinzanetant superior

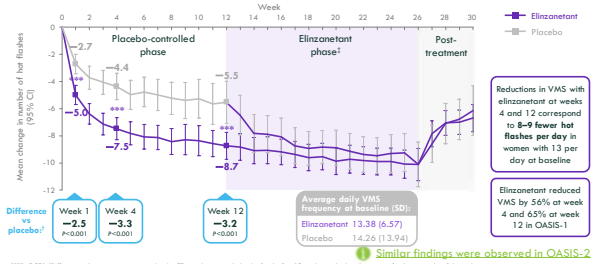
†Reduction in VMS severity was a primary endpoint for US regulatory submissions but a key secondary endpoint for all other regions. MENQOL, Menopause-Specific Quality of Life questionnaire; PROMIS SD-SF-8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b; VMS, vasomotor symptoms
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials

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Elinzanetant significantly and rapidly reduced the frequency of VMS from baseline to weeks 4 and 12, and from as early as week 1

OASIS-1: Change in mean daily VMS frequency from baseline



Reductions in VMS with elinzanetant at weeks 4 and 12 correspond to **8–9 fewer hot flashes per day** in women with 13 per day at baseline

Elinzanetant reduced VMS by 56% at week 4 and 65% at week 12 in OASIS-1

Similar findings were observed in OASIS-2

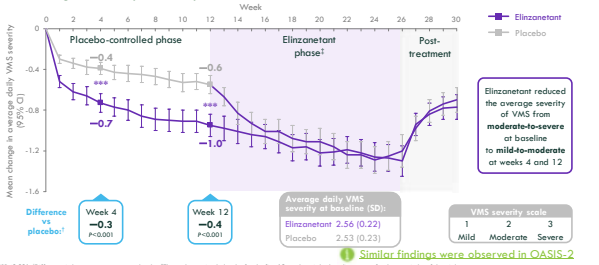
***P<0.001; †Difference in least square means vs placebo; ‡Those who received placebo for the first 12 weeks switched to elinzanetant for the remainder of the trial
CI, confidence interval; SD, standard deviation; VMS, vasomotor symptoms
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials

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Elinzanetant significantly reduced the severity of VMS from baseline to weeks 4 and 12 compared with placebo

OASIS-1: Change in mean daily VMS severity from baseline



Elinzanetant reduced the average severity of VMS from **moderate-to-severe** at baseline to **mild-to-moderate** at weeks 4 and 12

Similar findings were observed in OASIS-2

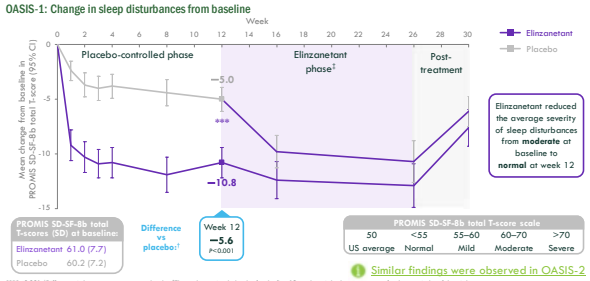
***P<0.001; †Difference in least square means vs placebo; ‡Those who received placebo for the first 12 weeks switched to elinzanetant for the remainder of the trial
CI, confidence interval; SD, standard deviation; VMS, vasomotor symptoms
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials

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Elinzanetant significantly reduced sleep disturbances from baseline to week 12 compared with placebo

OASIS-1: Change in sleep disturbances from baseline



Elinzanetant reduced the average severity of sleep disturbances from **moderate** at baseline to **normal** at week 12

PROMIS SD-SF-8b total T-scores (SD) at baseline:	
Elinzanetant	61.0 (7.7)
Placebo	60.2 (7.2)

Difference vs placebo†: Week 12 −5.6 P<0.001

PROMIS SD-SF-8b total T-score scale

50	<55	55–60	60–70	>70
US average	Normal	Mild	Moderate	Severe

Similar findings were observed in OASIS-2

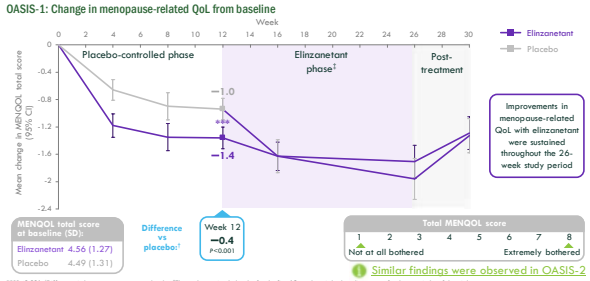
***P<0.001; †Difference in least square means vs placebo; ‡Those who received placebo for the first 12 weeks switched to elinzanetant for the remainder of the trial
CI, confidence interval; PROMIS SD-SF-8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b; SD, standard deviation
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials

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Elinzanetant provided statistically significant improvements in menopause-related QoL from baseline to week 12 vs placebo

OASIS-1: Change in menopause-related QoL from baseline



Improvements in menopause-related QoL with elinzanetant were sustained throughout the 26-week study period

MENQOL total score at baseline (SD):	
Elinzanetant	4.56 (1.27)
Placebo	4.49 (1.31)

Difference vs placebo†: Week 12 −0.4 P<0.001

Total MENQOL score

1	2	3	4	5	6	7	8
Not at all bothered							Extremely bothered

Similar findings were observed in OASIS-2

***P<0.001; †Difference in least square means vs placebo; ‡Those who received placebo for the first 12 weeks switched to elinzanetant for the remainder of the trial
CI, confidence interval; MENQOL, Menopause-Specific Quality of Life questionnaire; QoL, quality of life; SD, standard deviation
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials

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Fatigue and headache were also the most commonly reported drug-related TEAEs

OASIS-1: TEAEs assessed by the investigator as related to study drug (≥2% in any treatment arm)

n (%)	Elinzanetant Week 1–12 (n=199)	Placebo Week 1–12 (n=194)	Elinzanetant Week 13–26 (n=171)
Fatigue	12 (6.0%)	2 (1%)	0 (0.0%)
Headache	9 (4.5%)	4 (2.1%)	0 (0.0%)
Gastroesophageal reflux disease	4 (2.0%)	1 (0.5%)	2 (1.2%)
Nausea	4 (2.0%)	5 (2.6%)	1 (0.6%)
Diarrhea	4 (2.0%)	3 (1.5%)	1 (0.6%)
Arthralgia	4 (2.0%)	3 (1.5%)	0 (0.0%)
Somnolence	4 (2.0%)	0	0 (0.0%)

Similar findings were observed in OASIS-2

TEAE, treatment-emergent adverse event
Pinkerton JV, Simon JA, Joffe H et al. JAMA 2024;332:1343–54, including supplementary materials

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer

F. Cardoso,[1,2] S. Parke,[3] D.J. Brennan,[4] P. Briggs,[5] G. Donders,[6,7] N. Panay,[8] N. Haseli-Mashhadi,[9] M. Block,[10] C. Caetano,[11] M. Francuski,[3] C. Haberland,[3] K. Laapas,[12] C. Seitz,[13] and L. Zuurman[13]

CONCLUSIONS

Elinzanetant led to a significantly lower frequency of vasomotor symptoms associated with endocrine therapy than placebo. (Funded by Bayer; OASIS-4 ClinicalTrials.gov number, NCT05587296.)

Cardoso F, Parke S, Brennan DJ, Briggs P, Donders G, Panay N, Haseli-Mashhadi N, Block M, Caetano C, Francuski M, Haberland C, Laapas K, Seitz C, Zuurman L. Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer. N Engl J Med. 2025 Aug 21;393(8):753-763.

40

40

Side-by-Side Comparison of Adverse Effects (Not From Head-to-Head Trials)

Category	Fezolinetant (VEOZAH)	Elinzanetant (LYNKUET)
Common adverse effects	Abdominal pain, diarrhea, insomnia, back pain, hot flush	Headache, fatigue, dizziness, somnolence, abdominal pain, diarrhea
Central nervous system effects	Insomnia reported in trials	Somnolence, daytime impairment, dizziness, fatigue
Gastrointestinal effects	Diarrhea, abdominal pain	Diarrhea, abdominal pain, nausea
Liver-related effects	ALT/AST elevations; rare serious hepatotoxicity with boxed warning	Mild ALT/AST elevations; no Hy's law cases observed
Other notable risks	Back pain	Rash, muscle spasms, seizure risk in predisposed patients

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Comparison of Liver Function Test Monitoring

Monitoring Parameter	Fezolinetant	Elinzanetant
Baseline liver tests	**Required prior to initiation (ALT, AST, bilirubin)**	**Required prior to initiation (ALT, AST, bilirubin)**
Early monitoring	**Monthly for first 3 months**	**Single follow-up at ~3 months**
Ongoing monitoring	**Additional tests at 6 and 9 months**	**No routine monitoring beyond 3 months**
Discontinuation thresholds	**>5× ULN ALT/AST or >3× ULN with bilirubin >2× ULN**	**ALT/AST ≥2× ULN or symptoms of liver injury**

As of 4/1/26

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What the 2026 ACP Guideline Actually Recommends

A GRADE-based outpatient pharmacologic sequence for perimenopausal and postmenopausal patients seeking VMS treatment

FIRST LINE — **Menopausal hormone therapy** — **STRONG • HIGH**
Estrogen + progestogen (uterus) | Estrogen alone (no uterus)

SECOND LINE — **SNRI: desvenlafaxine or venlafaxine** — **CONDITIONAL** — **MODERATE**

THIRD LINE — **SSRI: escitalopram, paroxetine, gabapentin , NK antagonist: elinzanetant or fezolinetant** — **CONDITIONAL** — **LOW • MOD.**

Key distinction: **The guideline's sequencing is not a rank-order of mechanism specificity: NK antagonists carry moderate-certainty evidence, yet are placed after SNRIs and alongside lower-certainty SSRIs/gabapentin.**

References: Qaseem A, et al. Ann Intern Med. 2026. doi:10.7326/ANNALS-26-01205. • ACP Newsroom. Published October 5, 2026.

43

Why mandatory SSRI/SNRI "step therapy" before NK antagonists is: Categorically Wrong

It confuses lower acquisition cost and historical familiarity with evidence quality, indication specificity, and patient-centered value

REPURPOSED CNS DRUGS: SSRIs / SNRIs	VMS-TARGETED DRUGS: NK3 / NK1,3 antagonists
Evidence hierarchy — SNRI: moderate certainty; SSRI: low certainty in ACP	**Evidence hierarchy** — Moderate certainty in ACP, the same certainty assigned to SNRIs
Target — Serotonergic/noradrenergic systems, not the VMS thermoregulatory pathway	**Target** — Neurokinin signaling within the thermoregulatory circuitry implicated in VMS
Common treatment burdens — Nausea, sleep disturbance or somnolence, dizziness, blood-pressure effects (SNRIs), discontinuation symptoms, and sexual dysfunction	**Regulatory fit** — Fezolinetant (VEOZAH) and elinzanetant (LYNKUET) are FDA-approved specifically for moderate-to-severe menopausal VMS
Regulatory fit — Only low-dose paroxetine is FDA-approved for VMS; venlafaxine, desvenlafaxine and escitalopram use is off-label for VMS	**Real safety trade-off** — Not risk-free: labeling requires attention to hepatic risk/monitoring; elinzanetant also has CNS effects. These risks should be compared, not used to erase choice

1 Delays mechanism-matched care → 2 Privileges off-label use over VMS approvals → 3 Weakens the R&D signal in women's health*

References: Qaseem A, et al. Ann Intern Med. 2026; Moss SY, Lee A, Simon JA. Drugs. 2025;85:1363–1379; FDA VEOZAH and LYNKUET reviews/labels.
*Policy/economic inference, not a clinical-trial endpoint.

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Conclusions

- Hormone therapy remains the most effective treatment for VMS in menopausal women within 10 years of their final menstrual periods and under age 60.
- For women who are not good candidates for HT because of contraindications (e.g., estrogen-dependent cancers or cardiovascular disease) or personal preference, it is important for healthcare professionals to be well informed about nonhormonal treatment options for reducing VMS that are supported by the evidence.
- Evidence-based review of the literature resulted in several nonhormonal options for the treatment of VMS.

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Recommended

- Cognitive-behavioral therapy (Level I)
- Clinical hypnosis (Level I)
- Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (Level I)
- Gabapentin (Level I)
- Oxybutynin (Levels I-II)
- Fezolinetant (Level I)
- Elinzanetant (Level I)
- Weight loss (Levels II-III)
- Stellate ganglion block (Levels II-III).

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Not Recommended

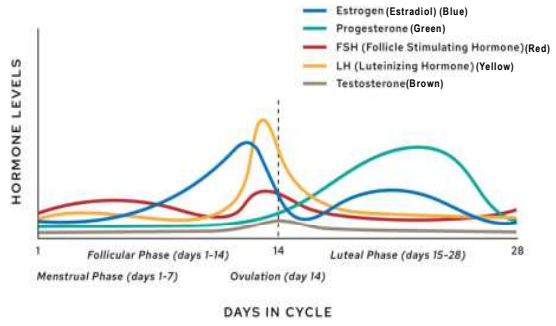
- Paced respiration (Level I)
- Supplements/Herbal remedies (Levels I-II)
- Cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, suvorexant, soy foods and soy extracts, soy metabolite equol, cannabinoids, acupuncture, calibration of neural oscillations (Level II)
- Chiropractic interventions (Levels I-III)
- Clonidine (Levels I-III)
- Dietary modification (Level III)
- Pregabalin (Level III)

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TESTOSTERONE THERAPY AFTER MENOPAUSE

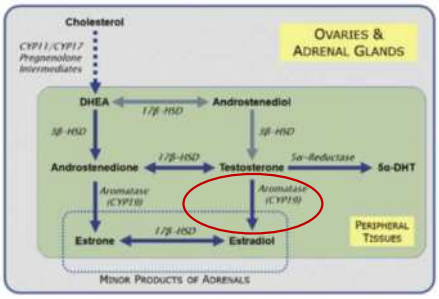
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Hormones of the Normal Menstrual Cycle



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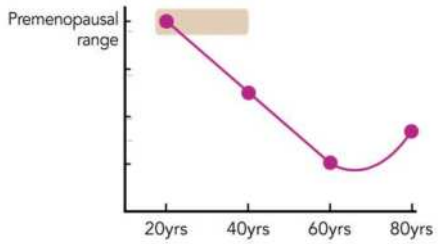
Synthesis of Androgens



Traish AM, Vignozzi L, Simon JA, Goldstein I, Kim NN. Role of Androgens in Female Genitourinary Tissue Structure and Function: Implications in the Genitourinary Syndrome of Menopause. Sex Med Rev. 2018 Oct;6(4):558-571.

50

Lifespan of Testosterone in Women



References: 1. Davison, S. L. et al. J Clin Endocrinol Metab 2005;90:3847-3853.

51

Periovulatory and Midluteal Estradiol and Testosterone Concentrations: Normally Cycling Women

Mean Peak Periovulatory Concentration (pg/ml or pmol/L)		Mean Peak Midluteal Concentration (pg/ml or pmol/L)	
Estradiol*	Testosterone**	Estradiol*	Testosterone**
≈250–300 pg/mL	≈ 400–450 pg/mL	≈ 150–250 pg/mL	≈ 300–400 pg/mL
≈920–1,100 pmol/L	≈ 1,400–1,600 pmol/L	≈ 550–920 pmol/L	≈ 1,000–1,400 pmol/L

*Simon JA, Bustillo M, Thorneycroft IH, Cohen SW, Buster JE. Variability of midcycle estradiol positive feedback: evidence for unique pituitary responses in individual women. J Clin Endocrinol Metab. 1987 Apr;64(4):789-93., World Health Organization, Task Force on Methods for the Determination of the Fertile Period, Special Programme of Research, Development and Research Training in Human Reproduction. Temporal relationships between ovulation and defined changes in the concentration of plasma estradiol-17 beta, luteinizing hormone, follicle-stimulating hormone, and progesterone. I. Probit analysis. Am J Obstet Gynecol. 1980 Oct 15;138(4):383-90.

**Goebelsmann U, Arce J, Thorneycroft I, Mishell D. Serum testosterone concentrations in women throughout the menstrual cycle and following HCG administration. American Journal of Obstetrics & Gynecology, 1974:119 (4), 445-452., Huang G, Bhasin S, Pencina K, Cheng M, Jasuja R. Circulating dihydrotestosterone, testosterone, and free testosterone levels and dihydrotestosterone-to-testosterone ratios in healthy women across the menstrual cycle. Fertil Steril. 2022 Dec;118(6):1150-1158.

52

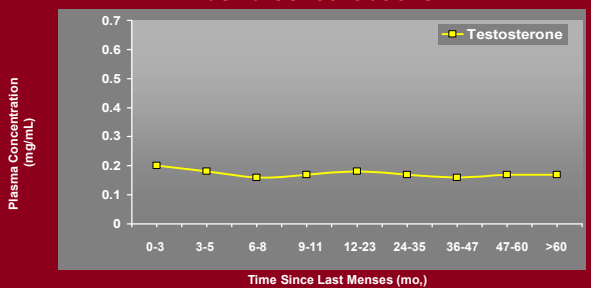
Mean Steroid Levels in Women (pg/ml)

	Reproductive Age	Natural Menopause	Surgical Menopause
Estradiol	150	10-15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
DHEA	5000	2000	1800
DHEAS	3,000,000	1,000,000	1,000,000

Buster J. In Lobo R. *Treatment of Postmenopausal Women*. Boston, MA.; Lippocott:1999.
Judd HL, et. al. J Endocrinol Metab. 1974:39:1020-1024.

53

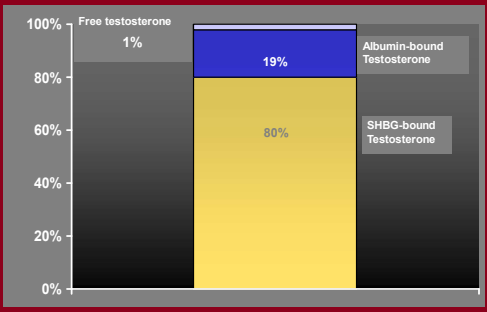
Time Since Last Menses: Testosterone Plasma Concentrations



Longcope C. *Ann NY Acad Sci.* 1990;592:21-30.

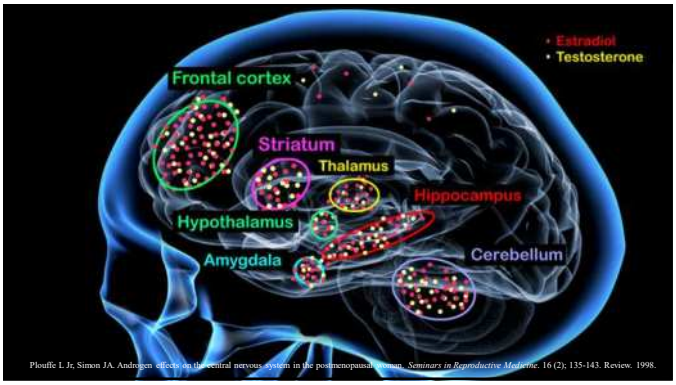
54

Physical State of Testosterone in Plasma



Vermeulen A, Verdonck L, van der Straeten M, et al. *J Endocrinol Metab.* 1969:29:1470-1480.

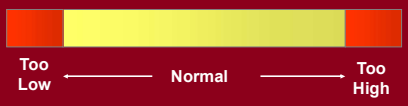
55



Plouffe L Jr, Simon JA. Androgen effects on the central nervous system in the postmenopausal woman. *Seminars in Reproductive Medicine.* 16 (2); 135-143. Review. 1998.

56

All Hormones Have a Physiologic Window Outside Which There Is Deficiency or Excess



Testosterone deficiency in women is a valid clinical entity which merits diagnosis and treatment

57

So, what does all this mean clinically?

58

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Documented Changes Following Oophorectomy Greatest Changes >60 Years Olds

Clinical Expression of Androgen Deficiency
May be subtle
Traditionally Accepted as "Aging"

Adrenarche

Increase in:

- Sexual hair
- Libido
- Bone density
- Stature
- Muscle Mass
- Immune function

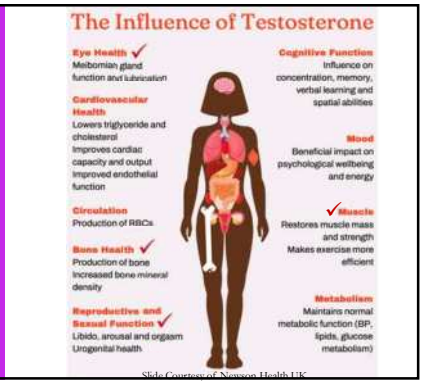
Menopausal Senescence

Decrease in:

- Sexual hair
- Libido
- Bone density
- Stature
- Muscle Mass
- Immune function

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Testosterone



Slide Courtesy of Newson Health UK

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Androgens in Women: Testosterone
The Short List for Today

- Reproductive and sexual function: a focus on:
  - a) urogenital effects (i.e. the vestibule) Covered in GSM Lecture
  - b) sexual desire (libido) Case covered by Dr. Alyse Kelly-Jones
- Bone Health
- Lean Muscle Mass/Body Composition
- Dry Eye Disease (DED)
- Cognitive Function? Mood?

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Sexual Desire (Libido)

Libido: a concept originated by Dr. Sigmund Freud in the early 20th century: from the Latin, literally 'desire, lust.' Used to signify the instinctual physiological or psychic energy associated with sexual urges and, in his later writings, with all constructive human activity.

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THE JOURNAL OF SEXUAL MEDICINE

SOCIETY PAPER

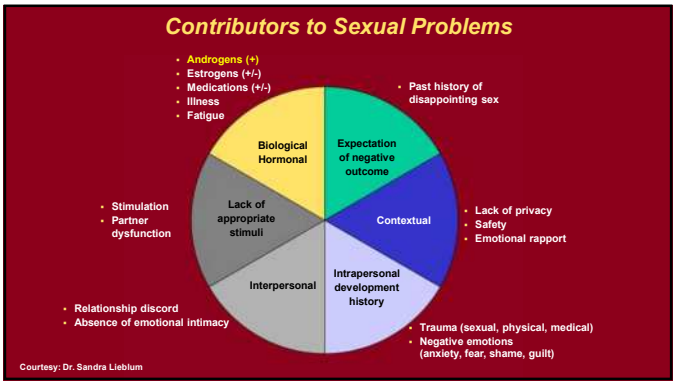
Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Susan R. Davis, MBBS, PhD,[1,A] Rodney Baber, BPharm, MBBS, FRANZCOG,[2,A,B] Nicholas Panay, BSc, FRCOG, MFSRH,[3,A] Johannes Bitzer, MD,[4,C] Sonia Cerdas Perez, MD,[5,D] Rakibul M. Islam, MPH, PhD,[1,A] Andrew M. Kaunitz, MD,[6,E] Sheryl A. Kingsberg, PhD,[7,F] Irene Lambrinoudaki, MD, PhD,[8,G] James Liu, MD,[9,E] Sharon J. Parish, MD,[10,H] JoAnn Pinkerton, MD,[11,I] Janice Rymer, MBBS,[12,J] James A. Simon, MD,[13,H] Linda Vignozzi, MD,[14,C] and Margaret E. Wierman, MD[15,J]

This Statement is being simultaneously published in the journals *Climacteric*, *Maturitas*, *Journal of Sexual Medicine*, and *Journal of Clinical Endocrinology and Metabolism* on behalf of the International Menopause Society, The European Menopause and Andropause Society, The International Society for Sexual Medicine, and The Endocrine Society, respectively. This Position Statement has been endorsed by the International Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The International Society for Sexual Medicine, The International Society for the Study of Women's Sexual Health, The North American Menopause Society, The Federacion Latinoamericana de Sociedades de Climaterio y Menopausia, The Royal College of Obstetricians and Gynaecologists, The International Society of Endocrinology, The Endocrine Society of Australia, and The Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

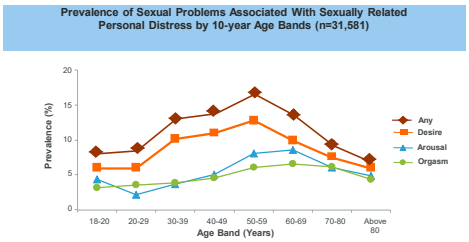
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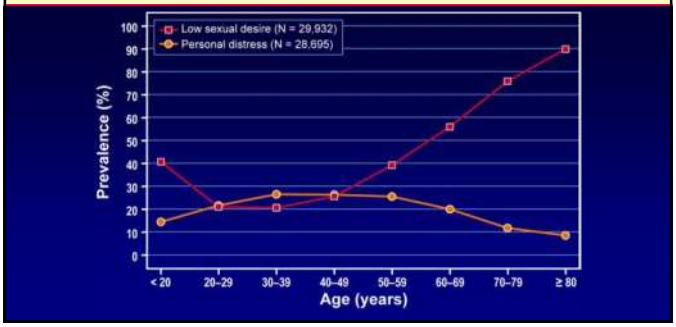
Decreased Sexual Desire With Distress Occurs in Adult Women*



*Sexual pain was not measured in this survey.
Shifren JL, et al. Sexual problems and distress in United States Women. *Obstet Gynecol.* 2008;112(5):970-978.
Figure reproduced with permission from the publisher.

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Prevalence of Low Sexual Desire and Sexually Related Personal Distress



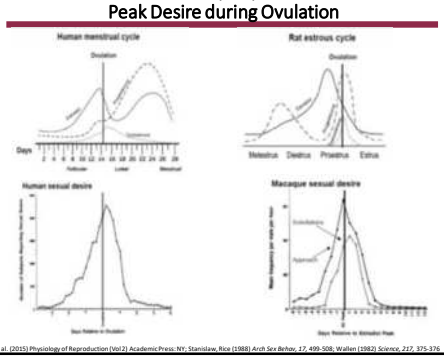
66

Reproductive Aged, Normal, Ovulating Women (All have normal testosterone levels)

67

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Evolutionary Imperative: Peak Desire during Ovulation



Pfaus et al. (2015) Physiology of Reproduction (Vol 2) Academic Press: NY; Stanislaw, Rice (1988) *Arch Sex Behav, 17*, 499-508; Wallen (1982) *Science, 217*, 375-376

68

Transdermal Testosterone Patch Development Program: Comprehensive & Robust

- 9 Pharmacokinetic Studies
  - Range of doses/dosing durations
- 3 Instrument Validation Studies
  - Followed by a Confirmatory Validation Study
- 3 Phase II studies
  - Dose-ranging, different routes of E administration
- 6 Phase III studies: well-controlled / comparable
  - 2 in surgical menopausal women (SM)
  - 2 in natural menopausal women (NM)
  - 1 Testosterone-only (SM & NM, no estrogen)
  - 1 in natural menopausal women, transdermal estrogen



- Alcohol-free, translucent, matrix patch
- Twice-a-week application to abdomen
- Contains 8.4 mg testosterone
- Delivers 300 mcg/day testosterone

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Study	Population / Design	Shorthand Findings
Shifren 2000 (proof of concept cross-over)	Crossover RCT; surgical menopause on estrogen	✅ Proof-of-concept: ↑ sexual activity & orgasm; 300 µg/day established
Braunstein 2005 (Phase II dose-ranging)	Dose-ranging RCT (150 / 300 / 450 µg/day)	✅ Only 300 µg/day effective → optimal dose
Simon 2005 (SM1)	Phase III RCT (surgical menopause)	✅ ↑ desire + ↑ satisfying sexual events
Buster 2005 (SM2)	Parallel Phase III RCT	✅ Reproducible efficacy across trials
Davis 2006	RCT on transdermal estrogen	✅ ↑ desire + multi-domain improvement; well tolerated
Shifren 2006 (NM1)	Large RCT (natural menopause on HT)	✅ ↑ SSE (2.1 vs 0.5; p<0.0001)
Davis 2008 (APHRODITE)	Phase III RCT (no estrogen; n=814) (150 / 300 µg/day)	✅ ↑ SSE (2.1 vs 0.7; p<0.001); largest trial; durable efficacy (300 µg/day only)
Panay 2010 (ADORE)	RCT (natural menopause; minimal HT)	✅ ↑ SSE, ↑ desire, ↓ distress (all stat significant)

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Hormone Concentrations in the Intrinsa Trials

TABLE 2. *Serum hormone values at baseline and during the study for placebo and testosterone treatment groups*

Hormone [reference range]	Treatment group	n	Baseline	n	Week 12	n	Week 24
Free testosterone [0.9-7.3 pg/mL]	Placebo	34	1.3 [0.9, 2.0]	30	1.1 [0.8, 1.7]	30	1.3 [0.8, 2.1]
	300 µg/day	33	1.2 [1.0, 1.5]	29	6.5 [5.0, 7.7]	23	4.8 [2.6, 6.7]
Total testosterone [12-50 ng/dL]	Placebo	34	17 [13, 23]	30	15 [12, 18]	30	17 [11, 22]
	300 µg/day	33	15 [13, 18]	29	76 [41, 97]	24	63 [38, 84.5]
Bioavailable testosterone [0.8-8.6 ng/dL]	Placebo	24	1.08 [0.76, 1.78]	23	0.93 [0.76, 1.30]	22	1.13 [0.72, 2.62]
	300 µg/day	25	1.39 [0.85, 1.64]	22	5.80 [3.29, 9.88]	15	4.79 [3.17, 8.46]
Sex hormone-binding globulin [13-98 nmol/L]	Placebo	34	54 [46, 74]	30	56 [45, 83]	30	55 [40, 78]
	300 µg/day	33	49 [40, 78]	29	48 [33, 64]	26	55 [38, 65]
Estradiol [12-101 ng/dL; follicular phase]	Placebo	34	56 [27, 75]	29	40 [27, 61]	27	47 [22, 71]
	300 µg/day	32	57 [31, 102.5]	29	49 [24, 98]	25	69 [46, 81]
Estrone [15-150 ng/dL; early follicular phase]	Placebo	34	52.5 [38, 75]	30	46.5 [31, 58]	29	42 [30, 69]
	300 µg/day	33	50 [40, 85]	29	42 [36, 63]	25	54 [41, 63]
Total dihydrotestosterone [6-31 ng/dL]	Placebo	31	8 [5, 12]	29	7 [5, 11]	25	9 [6, 14]
	300 µg/day	31	6 [4, 8]	27	19 [14, 27]	22	17.5 [13, 23]

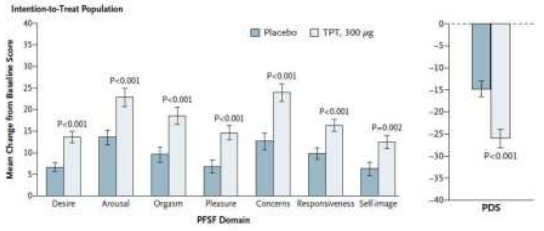
Values are medians [25th, 75th percentile ranges].
Reference ranges for serum free, total, and bioavailable testosterone, total dihydrotestosterone, and SHBG levels were established using measurements from 161 regularly cycling, healthy women aged 18 to 49 years who were not taking any medications or hormone therapies. Estradiol and estrone reference ranges are standard values from Quest Diagnostics, Inc.

Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarege A, Studd J; APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008 Nov 6;359(19):2005-17.

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Transdermal Testosterone for HSDD Postmenopausal Women *Not* Taking Estrogen

Changes from Baseline Scores at Week 24



TPT: testosterone patch treatment
PFSF: Profile of Female Sexual Function
PDS: Personal Distress Scale
Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarege A, Studd J; APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008 Nov 6;359(19):2005-17.

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US Transdermal Testosterone Study 12 Month AEs of Special Interest

Adverse Events	% of Patients Placebo n =36	150µg/d n =44	300µg/d n =37	450µg/d n =38
Alopecia	0%	7%	0%	3%
Hirsutism	3%	5%	5%	16%
Breast Pain	19%	14%	14%	16%
Hot Flushes	6%	5%	5%	0%
Acne	19%	11%	27%	24%

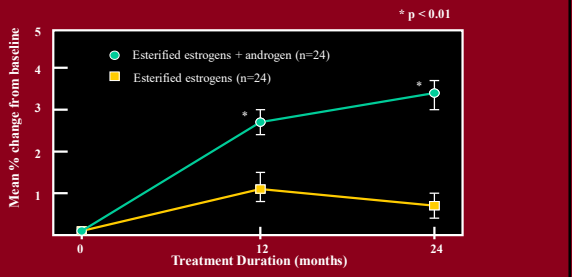
Modified from: Simon JA et al NAMS 2003

73

Bone Health

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Bone Mineral Density, L1-L4



Watts NB, Notelovitz M, Timmons MC, Addison WA, Wilts B, Downey LJ. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. Obstet Gynecol. 1995 Apr;85(4):529-37. Erratum in: Obstet Gynecol 1995 May;85(5 Pt 1):868.

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Body Composition

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Effect of Androgens on Body Composition (DEXA)

- Postmenopausal women lose 4% muscle mass in first 3 years of menopause; increase in body fat by 20%
- 1.25 mg EE/2.5 mg methyltestosterone
  - 4 months treatment
  - Decrease in fat: 2%-4%
  - Increase in lean muscle: 4%-6%
- 1.25 mg EE only: no significant changes

From Dobs AS et al. J Clin Endocrinol & Metab 2002;87:1509-1516.

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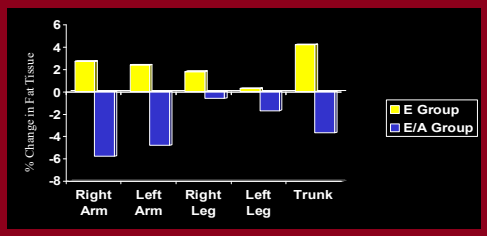
Changes in Lean Body Mass



Adapted from Dobs AS et al. J Clin Endocrinol & Metab 2002;87:1509-1516.

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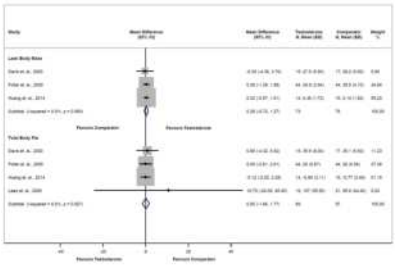
Changes in Fat Tissue



Adapted from Dobs AS et al. J Clin Endocrinol & Metab 2002;87:1509-1516.

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Testosterone Effects on Lean Muscle Mass



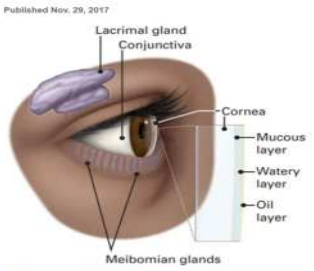
From: Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol. 2019 Oct;7(10):754-766. Supplemental Materials p. 38.

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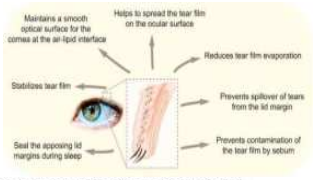
Perimenopausal and Menopausal Dry Eye Disease (DED)

81

The Tear Film is Androgen Dependent



The meibomian gland originates from the surface ectoderm, specifically during the "sealed-lid phase" of eyelid development in the embryo. It develops from the same embryonic layer as the skin and hair follicles, occurring between the third and seventh months of gestation in humans.



Tears are made up of three layers: the oily layer on the outside, the watery layer in the middle, and the inner, mucus layer. The three layers together are known as the tear film.

Downloaded: Tear Film - American Academy of Ophthalmology 2024

82

A pilot randomized controlled trial of topical androgen treatment in dry eye.
Jiang JR, Khankan R, Ridder WH 3rd, Nguyen AL, Paugh JR. Ocul Surf. 2025 Oct;38:56-63.

Conclusions: Eyelid androgen gel application, 4.5 % wt./wt., was effective in improving tear fTBUT, symptoms, TMH and meibomian secretion grade in dry eye patients. Future research requires a larger sample size, outcome measure variability reduction and formulation optimization for absorption, androgen type, and dosing regimen.

tear meniscus height (TMH), fluorescein tear breakup time (fTBUT)

83

Mood and Cognitive Function

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Testosterone Impact on Mood and Cognitive Symptoms

ORIGINAL ARTICLE

Effect of transdermal testosterone therapy on mood and cognitive symptoms in peri- and postmenopausal women: a pilot study

Sarah Glynne[1] · Aini Kamal[1] · Ahmed M. Kamel[2] · Dan Reisel[3,4] · Louise Newson[5]

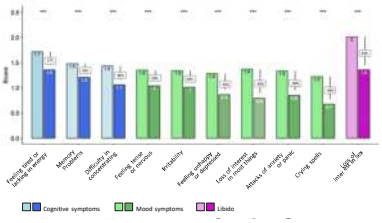
Received: 22 April 2024 / Accepted: 27 August 2024
© The Author(s) 2024

The purpose of this study was to assess the impact of testosterone therapy on mood and cognitive symptoms in perimenopausal and postmenopausal women.

Glynne S, Kamal A, Kamel AM, Reisel D, Newson L. Effect of transdermal testosterone therapy on mood and cognitive symptoms in peri- and postmenopausal women: a pilot study. Arch Women's Ment Health. 2024 Sep 16.

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Mood and Cognitive Symptoms in Peri and Postmenopausal Women



- The findings of this pilot study suggest that transdermal testosterone therapy has a beneficial effect on cognitive and mood-related symptoms in peri- and postmenopausal women.
- **All nine cognitive and mood symptoms significantly improved across the study period.** Mood improved more than cognition (47% of women reported an improvement in mood vs. 39% reported an improvement in cognition; 34% vs. 22% decrease in mean symptom scores, respectively). Regarding libido, 52% of women reported an improvement; mean symptom score decreased by 33%.

Glynne S, Kamal A, Kamel AM, Reisel D, Newson L. Effect of transdermal testosterone therapy on mood and cognitive symptoms in peri- and postmenopausal women: a pilot study. Arch Women's Ment Health. 2024 Sep 16.

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Dosing, Prescribing, and Monitoring

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What Is The Target Blood Level?

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What is the Target Testosterone Level In Postmenopausal Women: A Look to Premenopausal Women

= SI
= Conventional

Age	20-29 (n=17)	30-39 (n=23)	40-49 (n=20)
DHEAS ug/dL	176.9-214.3	139.0-170.8	124.7-156.1
SHBG nmol/L	43.6-58.6	44.6-52.4	47.0-58.4
Total T nmol/L	1.57-1.99	.95-1.38	.93-1.33
Total T ng/dL	45.5-57.5	27.6-39.8	27.0-38.6
Free Androgen Index (FAI)	3.72-4.96	2.04-2.96	1.98-2.94
Calculated Free T pmol/L	21.5-27.2	13.4-19.5	12.4-17.8
Calculated Free T ng/dL	0.6 - 0.8	0.4 - 0.6	0.4 - 0.6

SI Units in nmol/L (Conventional Units in ng/dL × 0.0347)

Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20-49 years with no complaints of sexual dysfunction.

Slide Courtesy of Dr. Sharon Parish

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Testosterone Summary and Key Understandings RE: Administration and Monitoring

1) Total testosterone concentration is the best practical assay.
2) Total testosterone and SHBG should be measured before initiating therapy to rule out:
   a) individuals with levels of testosterone in the upper ½ of the normal premenopausal range and to,
   b) determine if SHBG is >170 ng/dl or <0.19 ng/dl (JAS personal opinion) as the former are frequent non-responders to testosterone treatment for HSDD, and the later group may suffer androgen excess symptoms at normal total testosterone concentrations.
3) Proper dosing should attain and maintain total testosterone levels in the premenopausal physiological range.
4) If an approved female formulation is not available, one-tenth of a standard male dose of 1% transdermal testosterone product or about 300 mcg/day can usually achieve the normal premenopausal physiological range.
5) Compounded testosterone, pellets, IM injections, and oral formulations are not recommended.
6) Additional testing and alternative strategies may be required to assess failure to respond to typical testosterone treatment, particularly when testosterone or SHBG levels are high.

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Therapeutic Choices for Women: Pills, Patches, Pellets, Pastes

- **Pills**: Esterified Estrogens + Methyltestosterone (Estratest® and Estratest-HS® [EEMT]) Doses .625/1.25 mg EEMT-HS or 1.25/2.5 EEMT[1]
- **Patches**: Testosterone patches (Intrinsa®)[2-5] Not currently commercially available despite the source of RTC data
- **Pellets**: Biote®, Sottopelle®, Qualgen, Pro-Pell, etc. Not recommended due to unknown pharmacodynamics. compounded (Doses not clearly known)
- Injections: Testosterone Cypionate, Testosterone Enanthate. Not recommended due to dosing and excess side effects (available in 100mg and 200mg/cc; Typical female doses 1/10th weekly male dose of 100 mg)
- **Paste: 1% w/v testosterone (10 mg testosterone per 1 mL) in almond oil (Androfeme-1®). Approved for use in women (Australia) 0.5 or 1 ml topically/day[6]**
- **Gel: 1% w/v testosterone in hydroalcolic gel (Available for men—multiple dosage forms) ISSWSH recommended generic form of Testim® (1/10th tube/day or 4-6 drops/d and assess)[7]**

[1]Simon J, Klaiber E, Wiita B, et. al. Menopause. 1999;6(2):138-46. [2]Simon JA, Braunstein G, Nachtigall L, et. al. J Clin Endocrinol Metab 2005;90(9):5226-33. [3]Buster JE, Kingsberg SA, Aguirre O, et al. Obstet Gynecol. 2005 May;105(5 Pt 1):944-52. [4]Shifren JL, Davis SR, Moreau M, et al. Menopause. 2006 Sep-Oct;13(5):770-9. [5]Davis SR, Moreau M, Kroll R, et al. N Engl J Med. 2008 Nov 6;359(19):2005-17.[6]El-Hage G, Eden JA, Manga RZ. Climacteric. 2007 Aug;10(4):335-43. [7]Parish SJ, Simon JA, Davis SR, et al. ISSWSH Clinical Practice Guideline for the Use of Systemic Testosterone for HSDD. J Sex Med. 2021 May;18(5):849-867.

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THE JOURNAL OF SEXUAL MEDICINE

SOCIETY REPORT

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

Sharon J. Parish, MD,[1] James A. Simon, MD,[2] Susan R. Davis, MBBS, PhD,[3] Annamaria Giraldi, MD, PhD,[4,5] Irwin Goldstein, MD,[6,7] Sue W. Goldstein, BA, CSE,[7] Noel N. Kim, PhD,[8] Sheryl A. Kingsberg, PhD,[9] Abraham Morgentaler, MD,[10] Rossella E. Nappi, MD, PhD,[11] Kwangsung Park, MD, PhD,[12] Cynthia A. Stuenkel, MD,[13] Abdulmaged M. Traish, PhD,[14] and Linda Vignozzi, MD[15,16]

Parish SJ, Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Sex Med. 2021 Mar 29:51743-6095(20)30982-6. doi: 10.1016/j.jsxm.2020.10.009. Epub ahead of print. PMID: 33814355.

Parish SJ, Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Womens Health (Larchmt). 2021 Apr;30(4):474-491. doi: 10.1089/jwh.2021.29037. Epub 2021 Apr 1. PMID: 33797277; PMCID: PMC8064950.

Parish SJ, Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. Climacteric. 2021 Apr 1:1-18. doi: 10.1080/13697137.2021.1891773. Epub ahead of print. PMID: 33792440.

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Testosterone Therapy – Off Label For Women

Testosterone Preparation	Daily Dose	Mode of Delivery
FDA approved male products Gel, 1-2% Underarm solution	**1/10 male dose** ½ cc in 5 cc syringe 0.3 cc (4-6 drops, 1%)	**Transdermal:** **Back of calf, thigh*** Underarm
Testosterone enanthate/cypionate	50 mg/ml 0.1 ml	IM injection into vastus lateralis thigh muscle, 27g needle
Testosterone pellet	75 mg 1 pellet	Subcutaneous implantation Q4-6 months
Testosterone compounded cream 1%, meter-dosed dispenser	5 mg	Transdermal – arms, legs, abdomen; avoid transfer
Testosterone cream, 1% (Australia)	**5 mg**	**Transdermal: thigh and buttock**

*hair bearing area

- Measure total testosterone in 3-4 and 6-8 weeks, then 6 months when at goal.
- Compounded products have no regulation and no black box warning.
- Intramuscular injections and implants/pellets – risk of supra-physiological dosing

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Testim® (Brand) and Testosterone 1% (Generics: Prasco, Perrigo, Teva, Upsher-Smith) Are Available in Multiple Formats (Buyer Beware! Format Counts! No "Ketchup" Packets)



Tubes in a yellow box-OK



Tubes in a blue box-OK



Tubes in a blue box-OK



Tubes in a box by Upsher-Smith-OK



Tubes in a box by Prasco, Teva, Perrigo, etc.-OK



Sachet/"Ketchup" packets in a box-No!

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Dosing Recommendations

- Men use **30 tubes** or packets per month
- **1/10th** of a tube or packet/day; **3 tubes/month**
- **Resealable** tubes, room temp. (4 drops, 5cc syringe)
- Apply **gel** to **skin** surface, back of calf or thigh, upper outer thigh, or buttock (to avoid transference).
- Patients should be counseled that on average efficacy emerges **6 to 8 weeks** after initiation of therapy.
- Many women feel improvement after **4 weeks**, including reductions in distress, with maximal efficacy in **12 weeks**.

- Generally not covered by commercial insurance
- Cost saving apps may be recommended:
  - GoodRx (www.goodrx.com)
  - SingleCare (www.singlecare.com)

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AndroFeme® 1 1% Testosterone Cream





ANDROFEME 1 contains 1% w/v testosterone (10 mg testosterone per 1 mL) in almond oil Immediately apply to clean dry skin on the upper outer thigh or buttock. The cream should be massaged evenly until absorption is complete (typically around 30 seconds).

Approved for use in women in all of Australia as of November 23, 2020

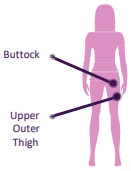
www.lawleypharm.com.au

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Prescribing AndroFeme®1



Starting dose	**0.5mL (5mg) once daily**
Maximum dose	**1mL (10mg)**
Dose adjustment	**Titrate up or down by 0.25mL increments**
Pack size	**50mL tube. 100 days using 0.5mL once daily**



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Monitoring and Follow-up

- **Baseline total testosterone** should be measured before initiating therapy with **repeat level** in **3–6 weeks**.
- Check T levels **6 weeks** after dose increase and **2-3 weeks** after supraphysiological level and dose decrease.
- Monitor for clinical response, assess for signs of **androgen excess**, and decrease dose if side effects occur.
- Check **serum total testosterone** level every **4-6 months** to screen for overuse and androgenic consequences.
- If no benefit by **6 months**, treatment should be ceased.
- If testosterone therapy results in improvement of HSDD, consider continuing for **6–12 months** and then taking a drug holiday to see if further treatment is required.

*In most cases, **ongoing testosterone therapy** is needed to maintain the improvement in HSDD.

Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.

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Monitoring and Follow-up

- **Measurement of SHBG and assessing free T may contribute to understanding lack of response.**
  - Women whose blood levels are in physiologic range and not experiencing improvement of HSDD symptoms
  - **High SHBG**: healthy women, high dose oral estrogens, estrogen-containing hormonal contraceptives, untreated hyper- and hypothyroidism, thyroid replacement
- **Androgenic side effects** may occur despite standard dosing or normal levels of total testosterone or both.
  - May occur with **low concentrations of SHBG**, associated with **type 2 diabetes, metabolic syndrome, and/or obesity**

Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.

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Potential for Skin-to-Skin Transfer

It has been reported that high dose transdermal testosterone preparations used in men can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and, with repeated contact, possibly adverse effects.

While the ISSWSH recommended doses of testosterone for women are very low by comparison to male doses, close skin contact with the area of application by a partner, child, or pet should be avoided.

Patients should be made aware of the consequences of making sustained long-term close physical contact with infants, young children and pets.

Long-term continual exposure may result in passive absorption and may have adverse effects, including virilization, in infants, and young children, and sexual behavior in pets.

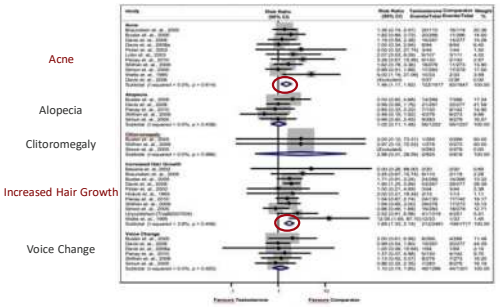
The risk of transfer is substantially reduced by wearing clothes covering the application site. The majority of residual testosterone is removed from the skin surface by washing with soap and water prior to close contact.

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Safety-Short Term

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META-ANALYSIS: Testosterone vs Comparator: Androgenic Events



Islam RM et al.
Lancet D&E ePub July 25, 2019

Weill Cornell Medicine

Slide Courtesy of Dr. Sharon Parish; Modified

NewYork-Presbyterian

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Safety Summary Across All Intrinsa Trials

Domain	Finding
Androgenic effects	Mild acne and hair growth (dose-dependent)
Virilization	No alopecia, clitoromegaly, or voice change at physiologic doses/levels
Lipids	Adverse effects with oral route only; non-oral routes appear safe
Cardiovascular	No increase in BP, glucose, or HbA1c; insufficient long-term data
Breast	No change in mammographic density or Ki67; no increase in breast cancer
Endometrium	No increase in endometrial thickness
Serious AEs	None reported across all RCTs
Long-term safety	Data lacking beyond 24 months

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Safety of Transdermal Testosterone Over 48 Months (1092 patient-years exposure)*

- **No clinically relevant changes in:**
  - Lipids
  - Liver function
  - Hematology
  - Carbohydrate metabolism
- **Small weight gain of 1.7 kg (p<0.05)**
- **Small increase in blood pressure (<2mmHg) (p>0.05)**
- **Rate of invasive breast cancer consistent with age-appropriate expected rates (SEER)**

*Open Label Extension

Nachtigall L, Casson P, Lucas J, Schofield V, Melson C, Simon JA. Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. Gynecol Endocrinol. 2011 Jan;27(1):39-48.

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Safety Overview (RCT + Meta-analysis)

What We Know
- No ↑ serious adverse events
- AE rates ~ placebo
- Well tolerated at physiologic dosing

Observed
- Acne ↑
- Hirsutism ↑
- Dose-related

Evidence
- No major safety signal detected
- Meta-analysis confirms short-term safety
- Transdermal preferred

Key Limitation
- Trials ≤12–24 months
- Not powered for rare events
- Long-term safety uncertain

Not Observed
- Voice deepening (rare)
- Clitoromegaly (not seen)
- Severe virilization absent

Critical Unknown
- CV events (MI, stroke)
- Breast cancer risk
- >24-month exposure

Jayasena CN et al. Clin Endocrinol 2019; Islam RM et al. Lancet Diabetes Endocrinol 2019

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Long Term Safety

- Jayasena CN, Alkaabi FM, Liebers CS, Handley T, Franks S, Dhillo WS. **A systematic review of randomized controlled trials** investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women. Clin Endocrinol (Oxf). 2019 Mar;90(3):391-414.
- Islam RM, Bell RJ, Green S, et al. Safety and efficacy of testosterone for women: **a systematic review and meta-analysis of randomised controlled trial data**. Lancet Diabetes Endocrinol. 2019 Oct;7(10):754-766.

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JAMA Network

From: **Illicit Anabolic Steroid Use and Cardiovascular Status in Men and Women**

JAMA Netw Open. 2025;8(8):e2526636. doi:10.1001/jamanetworkopen.2025.26636

Table 3. Atherosclerotic Stigmata and Their Association With Cumulative Lifetime Duration of AAS Use

Dependent variable	OR (95% CI) per unit increase in cumulative lifetime duration of AAS use, y[a]			
	Univariable logistic regression	P value	Multivariable logistic regression	P value
Coronary NCPs	1.17 (1.09-1.26)	<.001	1.17 (1.05-1.30)	.004
CAC score >0[b]	1.18 (1.09-1.27)	<.001	1.23 (1.09-1.39)	.001
Femoral artery plaque	1.05 (1.00-1.10)	.04	0.98 (0.92-1.05)	.63
Carotid artery plaque	1.10 (1.03-1.17)	.002	1.08 (0.99-1.18)	.09

Abbreviations: AAS, androgenic anabolic steroids; CAC, coronary artery calcium; NCP, noncalcified plaque; OR, odds ratio.

[a] Univariable and multivariable logistic regression analyses of the entire population (N = 164) were performed with cumulative lifetime duration of AAS use in years as the independent variable for atherosclerotic measures. The multivariable model included the following covariables: age, body fat percentage, family history of coronary artery disease, blood pressure, total cholesterol, use of recreational drugs, tobacco smoking status, alcohol consumption, and hours of hard exercise and strength training per week.

[b] The CAC variable was dichotomized (CAC = 0 vs CAC>0).

Table Title:
Atherosclerotic Stigmata and Their Association With Cumulative Lifetime Duration of AAS Use Abbreviations: AAS, androgenic anabolic steroids; CAC, coronary artery calcium; NCP, noncalcified plaque; OR, odds ratio.

[a] Univariable and multivariable logistic regression analyses of the entire population (N = 164) were performed with cumulative lifetime duration of AAS use in years as the independent variable for atherosclerotic measures. The multivariable model included the following covariables: age, body fat percentage, family history of coronary artery disease, blood pressure, total cholesterol, use of recreational drugs, tobacco smoking status, alcohol consumption, and hours of hard exercise and strength training per week.

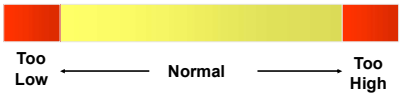
[b] The CAC variable was dichotomized (CAC = 0 vs CAC>0).

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Finding the Sweet Spot
(Sometimes too much of a good thing!)

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All Hormones Have a Physiologic Window Outside Which There is Deficiency or Excess



Proposal:

Testosterone deficiency in women is a valid clinical entity which merits diagnosis and treatment

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Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 4, pp. 462–470
DOI: 10.1097/GME.0000000000000863
© 2017 by The North American Menopause Society

PERSONAL PERSPECTIVE

A sex-specific dose-response curve for testosterone: could excessive testosterone limit sexual interaction in women?

Jill M. Krapf, MD, FACOG,[1] and James A. Simon, MD, CCD, NCMP, IF, FACOG[2,3]

Abstract

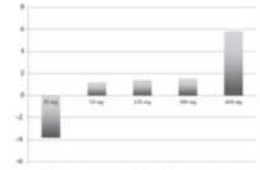
Testosterone treatment increases sexual desire and well-being in women with hypoactive sexual desire disorder; however, many studies have shown only modest benefits limited to moderate doses. Unlike men, available data indicate women show a bell-shaped dose-response curve for testosterone, wherein a threshold dosage of testosterone leads to desirable sexual function effects, but exceeding this threshold results in a lack of further positive sexual effects or may have a negative impact. Emotional and physical side-effects of excess testosterone, including aggression and virilization, may counteract the modest benefits on sexual interaction, providing a possible explanation for a threshold dose of testosterone in women. In this commentary, we will review and critically analyze data supporting a curvilinear dose-response relationship between testosterone treatment and sexual activity in women with low libido, and also explore possible explanations for this observed relationship. Understanding optimal dosing of testosterone unique to women may bring us one step closer to overcoming regulatory barriers in treating female sexual dysfunction.

Key Words: Dose-response curve – Female aggression – Female sexual dysfunction – Hypoactive sexual desire disorder – Testosterone – Virilization.

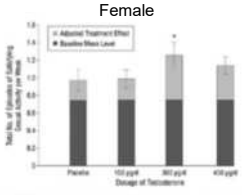
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Male vs Female Dose Response to Testosterone

Male



Female



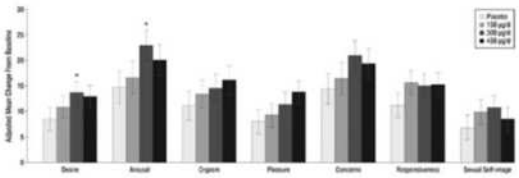
Gray PB, Singh AB, Woodhouse LJ, et al. Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. J Clin Endocrinol Metab 2005;90:3838-3846

Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 2005;165:1582-1589.

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Female Dose Response to Testosterone Across Multiple Domains of Sexual Function



Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 2005;165:1582-1589.

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Key Take Home Points

- Transdermal testosterone is **moderately effective** for HSDD in late reproductive age and post-menopausal women.
- Start1% testosterone cream in almond oil, 0.5 ml (5 mg) once daily
- Titrate in 0.25 ml increments with 1 ml (10 mg) maximum dose
- Maintain **total** testosterone levels in the **physiological premenopausal range** to diminish adverse events and optimise CNS and peripheral sexual responses.
- **Compounded** testosterone, pellets, IM injections and oral formulations are **not recommended.**
- ***If*** an approved female formulation is not available, **one-tenth of a standard male dose of 1% transdermal testosterone** can be considered for use.
- Future directions include exploration of testosterone in women regarding **urogenital effects, body weight, lean muscle mass, skeletal composition, plus mood** and **cognitive symptoms.**

References: 1. Parish et al. J Sex Med 2021;18:849-867. 2. Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.

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CULTURAL AND LINGUISTIC COMPETENCY & IMPLICIT BIAS

The California Medical Association (CMA) outlines standards for Cultural Linguistic Competency and Implicit Bias in CME. The goal of the standards is to support the role of accredited CME in advancing diversity, health equity, and inclusion in healthcare. These standards are relevant to ACCME-accredited, CMA-accredited, and jointly accredited providers located in California. AAGL is ACCME-accredited and headquartered in California.

CMA developed the standards in response to California legislation (Business and Professions (B&P) Code Section 2190.1), which directs CMA to draft a set of standards for the inclusion of cultural and linguistic competency (CLC) and implicit bias (IB) in accredited CME.

The standards are intended to support CME providers in meeting the expectations of the legislation. CME provider organizations physically located in California and accredited by CMA CME or ACCME, as well as jointly accredited providers whose target audience includes physicians, are expected to meet these expectations which began on January 1, 2022. AAGL has been proactively adopting processes that meet and often exceed the required expectations of the legislation.

CMA CME offers a variety of resources and tools to help providers meet the standards and successfully incorporate CLC & IB into their CME activities, including FAQ, definitions, a planning worksheet, and best practices. These resources are available on the CLC and IB standards page on the CMA website.

Important Definitions:

Cultural and Linguistic Competency (CLC) – The ability and readiness of health care providers and organizations to humbly and respectfully demonstrate, effectively communicate, and tailor delivery of care to patients with diverse values, beliefs, identities and behaviors, in order to meet social, cultural and linguistic needs as they relate to patient health.

Implicit Bias (IB) – The attitudes, stereotypes and feelings, either positive or negative, that affect our understanding, actions and decisions without conscious knowledge or control. Implicit bias is a universal phenomenon. When negative, implicit bias often contributes to unequal treatment and disparities in diagnosis, treatment decisions, levels of care and health care outcomes of people based on race, ethnicity, gender identity, sexual orientation, age, disability and other characteristics.

Diversity – Having many different forms, types or ideas; showing variety. Demographic diversity can mean a group composed of people of different genders, races/ethnicities, cultures, religions, physical abilities, sexual orientations or preferences, ages, etc.

Direct links to AB1195 (CLC), AB241 (IB), and the B&P Code 2190.1:

Bill Text – AB-1195 Continuing education: cultural and linguistic competency.
Bill Text – AB-241 Implicit bias: continuing education: requirements.
Business and Professions (B&P) Code Section 2190.1

CLC & IB Online Resources:

Diversity-Wheel-as-used-at-Johns-Hopkins-University-12.png (850×839) (researchgate.net)
Implicit Bias, Microaggressions, and Stereotypes Resources | NEA
Act, Communicating, Implicit Bias (racialequitytools.org)
https://www.contemporaryobgyn.net/view/overcoming-racism-and-unconscious-bias-in-ob-gyn
https://pubmed.ncbi.nlm.nih.gov/34016820/
https://hr.ucdavis.edu/departments/learning/certificate/implicit-bias
https://pmc.ncbi.nlm.nih.gov/articles/PMC7011228/