MENOPAUSE TREATMENT: UPDATE

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ACCLAIM WOMEN'S SERVICES DEPARTMENT

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DISCLOSURES

- LUPIN SPEAKER BUREAU: SOLOSEC
- THERAPEUTICS MD: ADVISORY COMMITTEE FOR IMVEXXY
- PFIZER: MENOPAUSE TOOL PANELIST
- (NAMS) NATIONALLY CERTIFIED MENOPAUSE PROVIDER



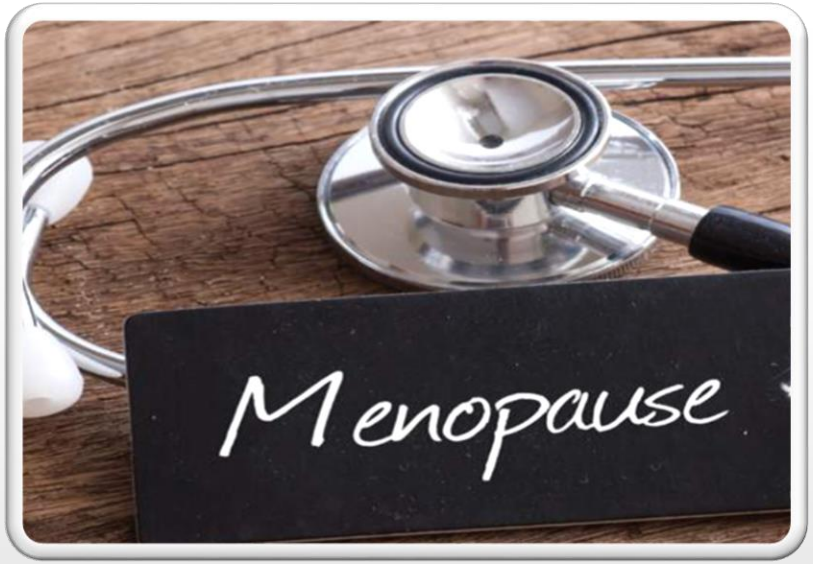
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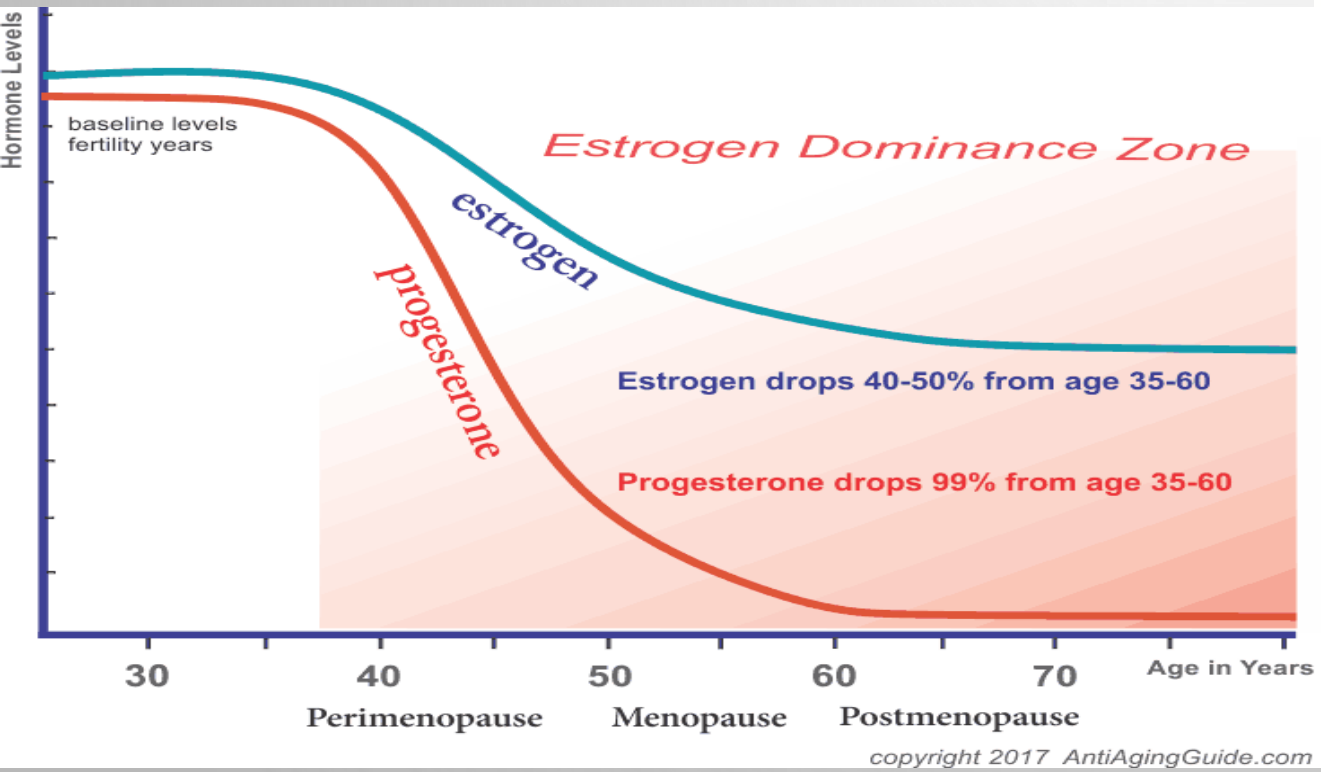
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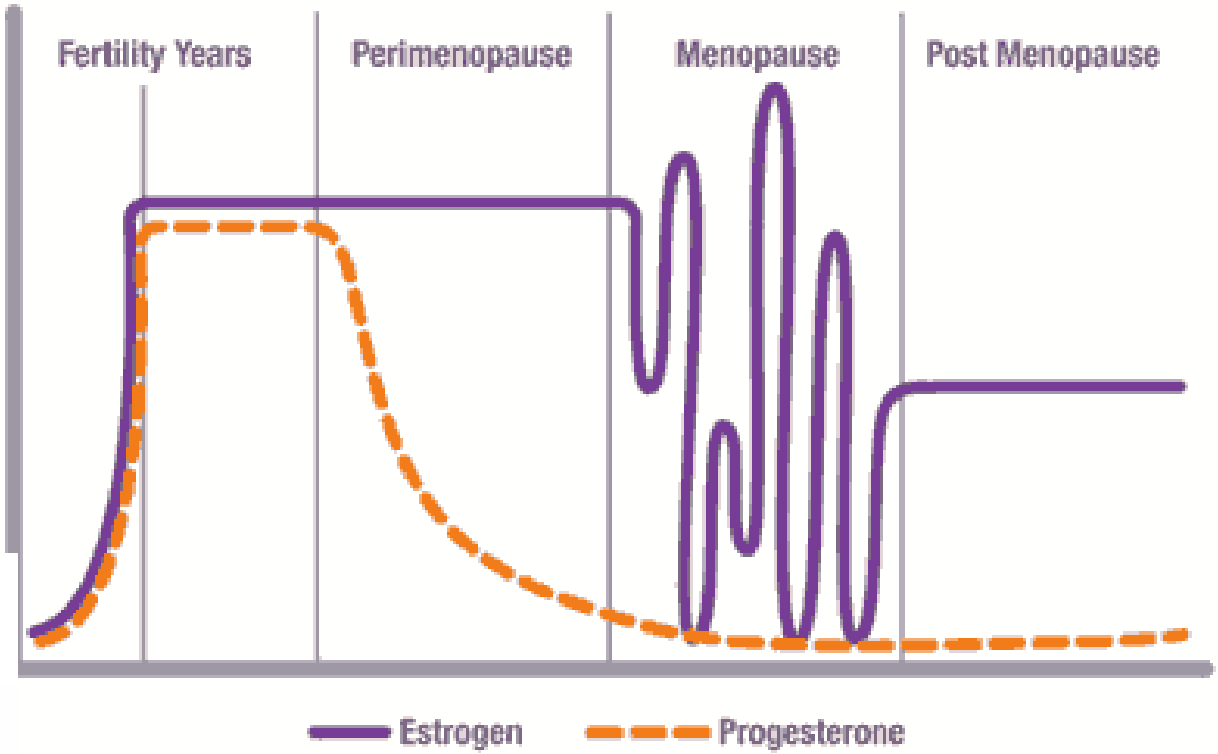
THE NORTH AMERICAN MENOPAUSE SOCIETY



- IS A NORMAL PHYSIOLOGIC EVENT, DEFINED AS THE FINAL MENSTRUAL PERIOD (FMP) AND REFLECTING LOSS OF OVARIAN FOLLICULAR FUNCTION
- SPONTANEOUS OR NATURAL MENOPAUSE IS RECOGNIZED AFTER 12 MONTHS OF AMENORRHEA
- AVERAGE AGE IS 52 YEARS, BUT CAN VARY FROM AGE 45 TO 55
- BY THE YEAR 2025, THE NUMBER OF POSTMENOPAUSAL WOMEN IS EXPECTED TO RISE TO 1.1 BILLION, WORLDWIDE

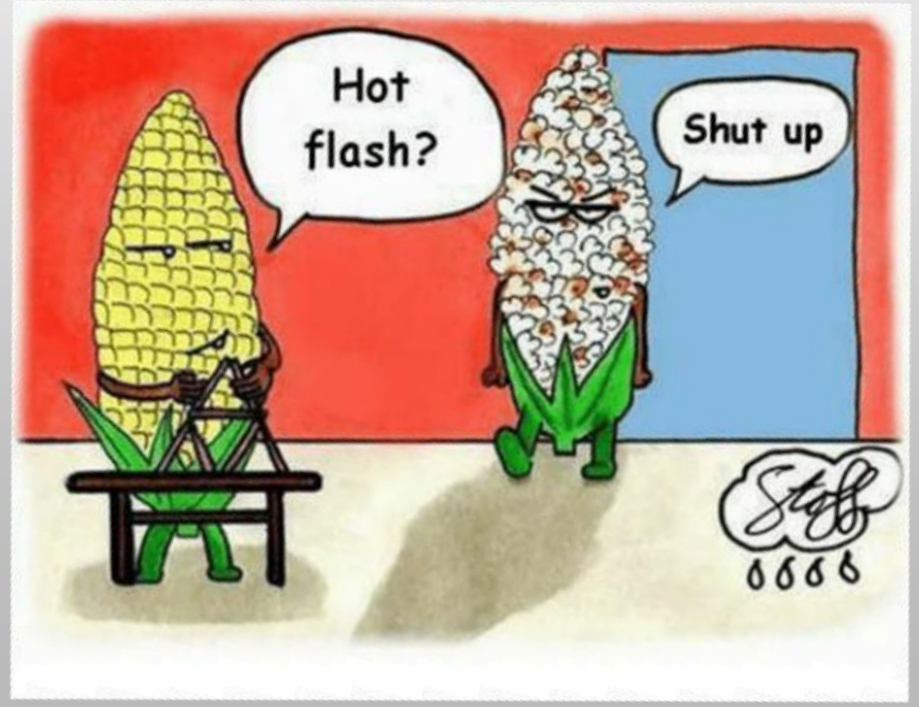
Approximately 90% of women experience 4 to 8 years of menstrual cycle changes before natural menopause, which may include heavier flow of longer duration resulting in anemia, avoidance of activities (including sex), and diminished quality of life.

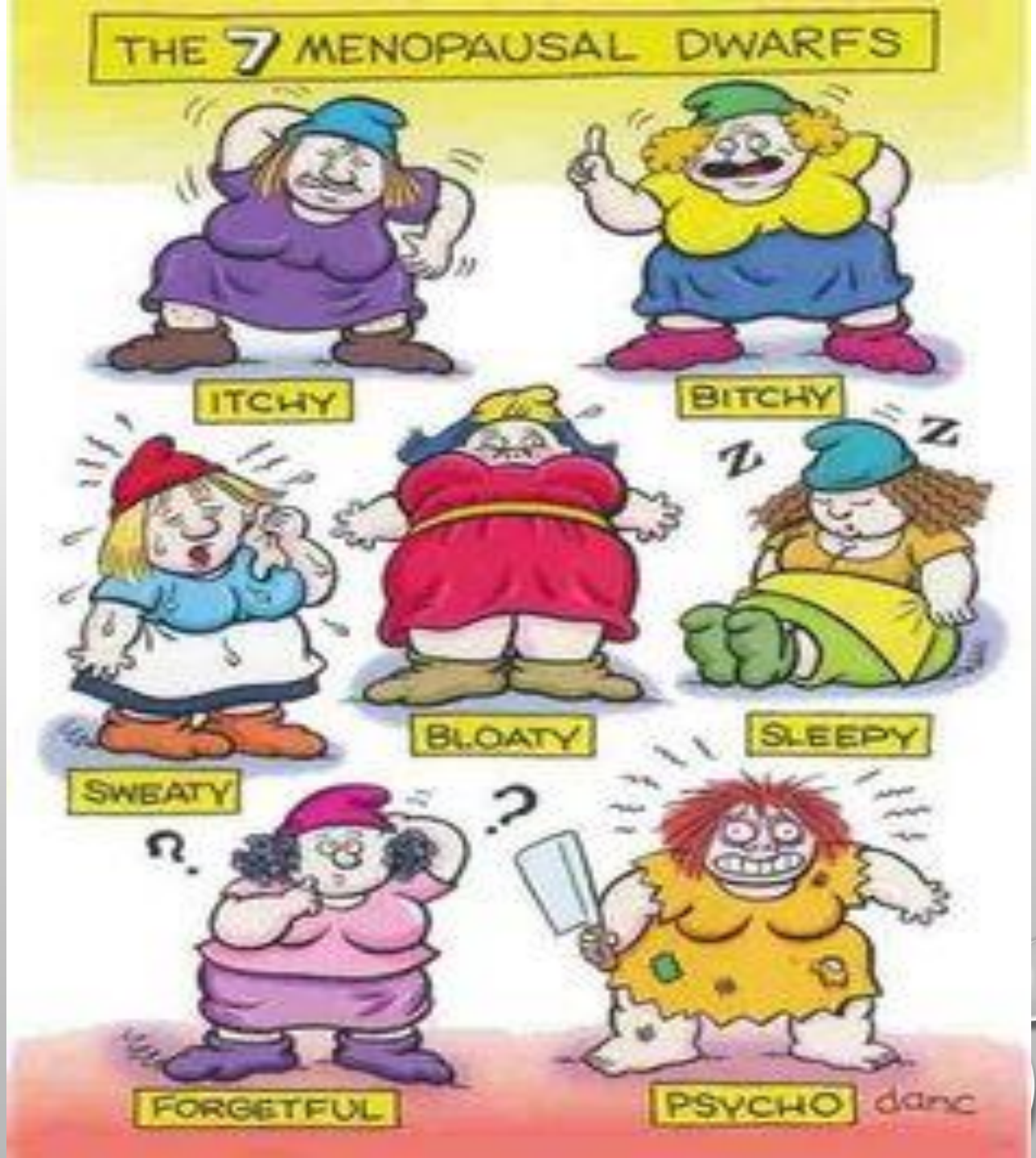




- In healthy nonsmokers, low-dose oral contraceptives may be considered for the treatment of heavy or irregular bleeding during the menopause transition.
- These improve bleeding in part by reducing wide excursions in HPO hormone secretion.
- Contraception is recommended until women have experienced 12 months of amenorrhea

THERE'S YOUR SIGN…





A List of Menopause Symptoms

- Hot Flashes *
- Night Sweats *
- Irregular Periods *
- Loss of Libido *
- Vaginal Dryness *
- Mood Swings
- Fatigue
- Hair Loss or Thinning
- Sleep Disorders
- Difficulty Concentrating
- Disturbing Memory Lapses
- Dizziness
- Weight Gain
- Incontinence
- Bloating
- Increase in Allergies
- Changes in Fingernails (weakening)
- Changes in Body Odor
- Irregular Heartbeat
- Depression
- Anxiety
- Irritability
- Feelings of Dread
- Breast Pain
- Headaches
- Aching Joints and Muscle Problems
- Burning Tongue
- Electric Shock Sensation
- Digestive Problems
- Gum Problems
- Increased Tension in Muscles
- Itchy, Crawly Skin
- Tingling Extremities
- Osteoporosis (After Several Years)

* most common symptoms



... of women say their symptoms interfere with their lives; 12% say they interfere “a great deal” or are debilitating.

The most common symptoms of menopause for women:

50% Hot flashes

42% Night sweats

38% Vaginal dryness



... say they’ve never discussed menopause with a health provider.



Only 1 in 5 women received a referral to a menopause specialist.

SYMPTOMS OF THE MENOPAUSE TRANSITION

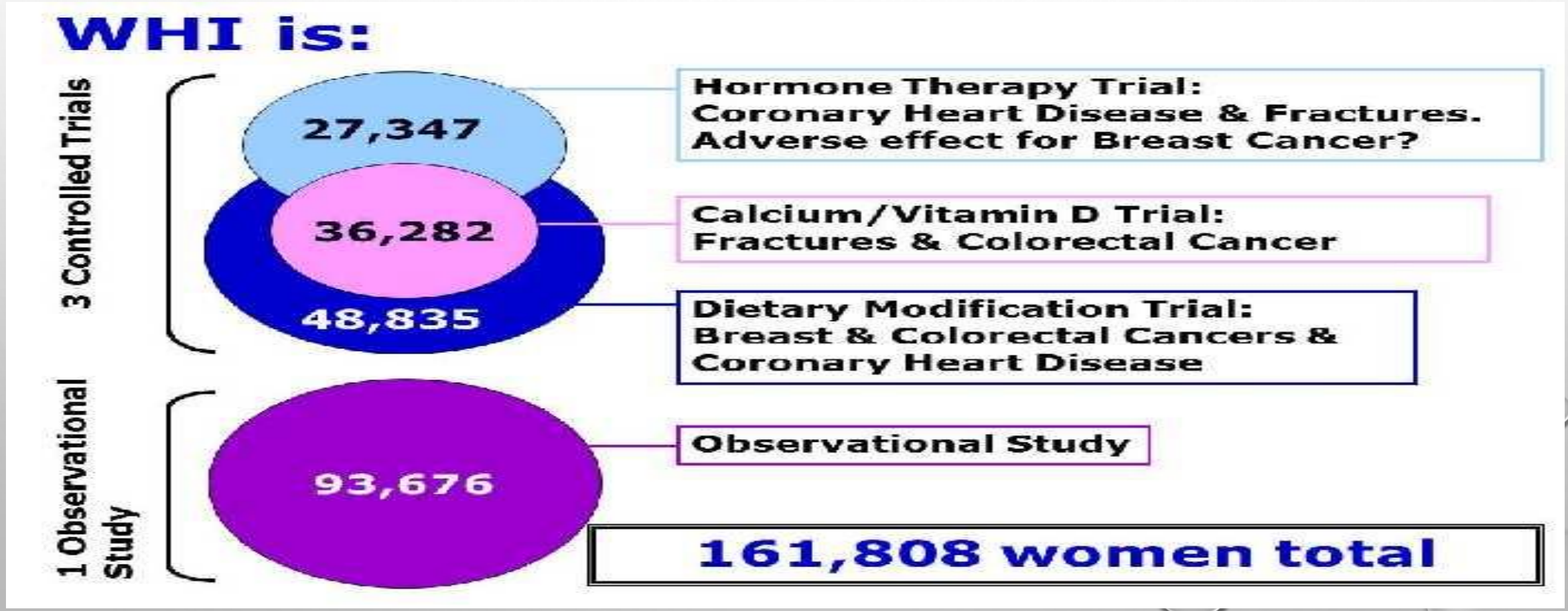


- PRIMARILY VASOMOTOR SYMPTOMS (VMS), START 2-4-YEARS IMMEDIATELY BEFORE AND AFTER THE FMP, BUT MAY CONTINUE FOR 10 YEARS IN SOME WOMEN
- GIVEN THE ERRATIC NATURE OF OVARIAN FUNCTION DURING THIS TIME, HORMONAL MEASUREMENTS ARE DIFFICULT TO INTERPRET AND, IN MOST INSTANCES, SHOULD BE AVOIDED.
- LEVELS OF ANTIMULLERIAN HORMONE (AMH), CYCLE DAY-3 FSH AND ESTRADIOL, AND OVARIAN ANTRAL FOLLICLE COUNT, ARE BEST CONFINED TO COUNSELING WOMEN SEEKING FERTILITY RATHER THAN PREDICTING TIME TO MENOPAUSE.
- AS BOTHERSOME VMS MAY BEGIN WELL BEFORE THE FMP, PROVIDERS SHOULD ASK ABOUT VMS AND PROVIDE INFORMATION REGARDING THERAPEUTIC OPTIONS, EVEN IF THEY ARE STILL CYCLING.
- GIVEN THAT OVULATORY CYCLES OCCUR DURING THE MENOPAUSE TRANSITION, CONTRACEPTION IS RECOMMENDED UNTIL WOMEN HAVE EXPERIENCED 12 MONTHS OF AMENORRHEA
- ENDOMETRIAL PATHOLOGY IS INCREASED AT THE MENOPAUSE TRANSITION BECAUSE SERUM ESTROGEN CONCENTRATIONS ARE INTERMITTENTLY ELEVATED AND OVARIAN PROGESTERONE PRODUCTION IS DIMINISHED. ANY HEAVY OR IRREGULAR BLEEDING AT MIDLIFE SHOULD BE THOROUGHLY EVALUATED.

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

VULVOVAGINAL CHANGES:
GENITOURINARY SYNDROME OF MENOPAUSE (GSM),

- COLLECTION OF SYMPTOMS AND SIGNS ASSOCIATED WITH A DECREASE IN ESTROGEN AND OTHER SEX STEROIDS INVOLVING CHANGES TO THE LABIA MAJORA/MINORA, CLITORIS, VESTIBULE/INTROITUS, VAGINA, URETHRA, AND BLADDER.
- MAY INCLUDE BUT IS NOT LIMITED TO GENITAL SYMPTOMS OF DRYNESS, BURNING, AND IRRITATION; SEXUAL SYMPTOMS OF LACK OF LUBRICATION, DISCOMFORT OR PAIN, AND IMPAIRED SEXUAL FUNCTION; AND URINARY SYMPTOMS OF URGENCY, DYSURIA, AND RECURRENT URINARY TRACT INFECTIONS (UTIS).
- POSTMENOPAUSAL ESTROGEN LOSS AND AGING ACCOMPANIED BY PHYSIOLOGIC, VASCULAR, NEUROLOGIC, AND HISTOLOGIC CHANGES MAY RESULT IN VULVOVAGINAL SYMPTOMS,
- INCLUDING IRRITATION, BURNING, ITCHING, VAGINAL DISCHARGE, POSTCOITAL BLEEDING, AND DYSPAREUNIA
- ALL PERIMENOPAUSAL AND POSTMENOPAUSAL WOMEN SHOULD BE ASKED ABOUT VULVOVAGINAL AND URINARY SYMPTOMS AT EVERY COMPREHENSIVE VISIT
- WOMEN OF ANY AGE WITH LOW ESTROGEN LEVELS, INCLUDING WOMEN WITH POI, PREMATURE MENOPAUSE, HYPOTHALAMIC AMENORRHEA, DURING LACTATION; DEPO PROVERA OR OTHER HORMONAL BCM OR AFTER TREATMENT WITH GONADOTROPIN-RELEASING HORMONE (GNRH) AGONISTS/ ANTAGONISTS OR AROMATASE INHIBITORS, MAY EXPERIENCE SYMPTOMS OF GSM/VVA
- UNLIKE VASOMOTOR SYMPTOMS, WHICH IMPROVE OVER TIME, SYMPTOMS OF GSM ARE CHRONIC AND PROGRESSIVE AND WILL GENERALLY NOT RESOLVE WITHOUT A THERAPEUTIC INTERVENTION.


WHI is:
3 Controlled Trials
27,347
36,282
48,835
Hormone Therapy Trial:
Coronary Heart Disease & Fractures.
Adverse effect for Breast Cancer?
Calcium/Vitamin D Trial:
Fractures & Colorectal Cancer
Dietary Modification Trial:
Breast & Colorectal Cancers &
Coronary Heart Disease
1 Observational Study
93,676
Observational Study
161,808 women total

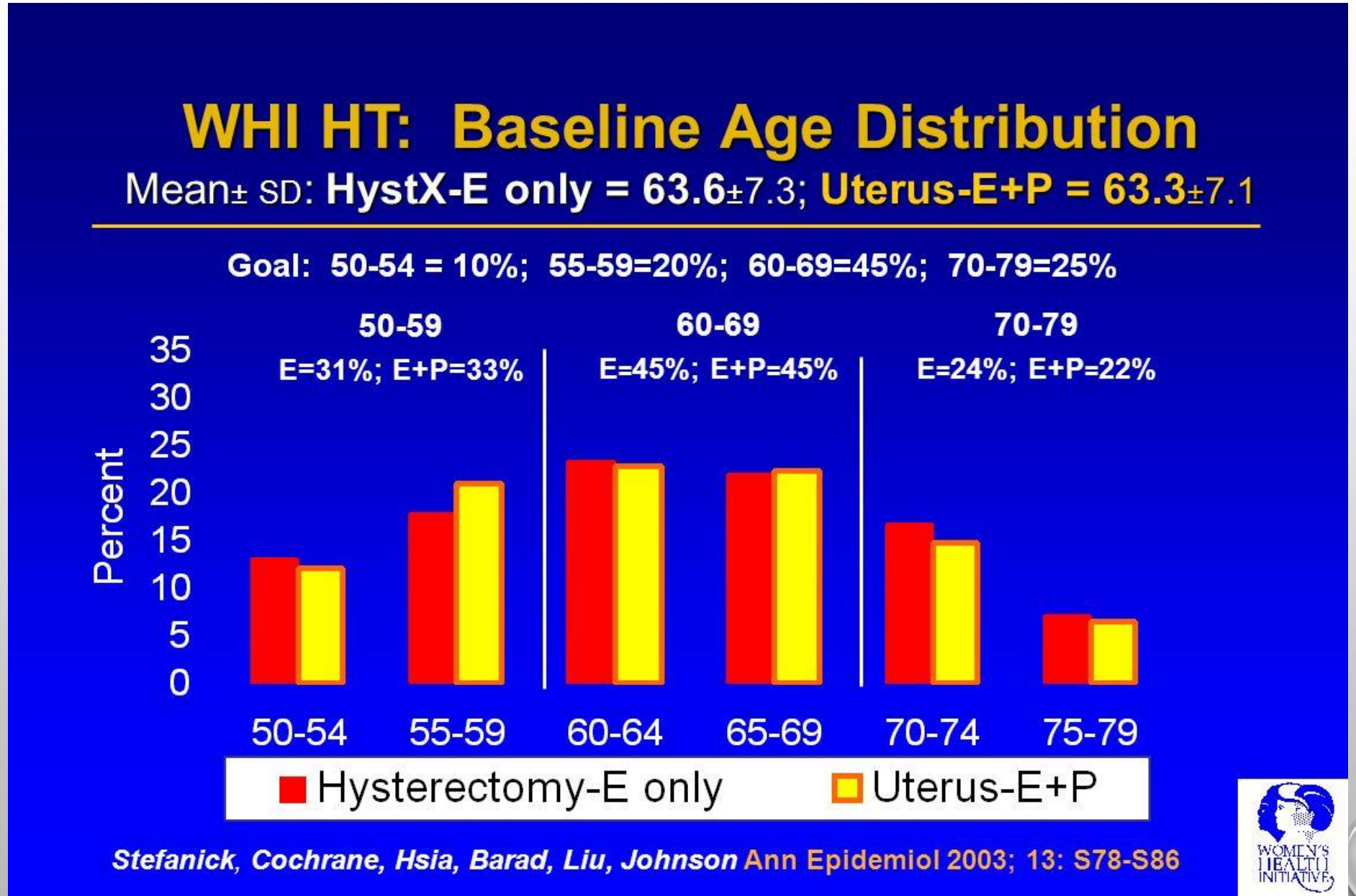
Wyeth

Women's Health Initiative (WHI)

- 15-year study to of ways to prevent heart disease, breast and colorectal cancer, and osteoporosis by NIH.
- Designed in 1991 and enrolled over 161,809 women between 1993-1998; it was scheduled to end in 2005.
- The Prempro arm of the study involved 16,608 women who took either Prempro (combination HRT) or placebo.
- In May 2002, The DSMB recommended that the Prempro arm of the trials be stopped.
- Research stopped due to high risks:
  - 26% increase in breast cancer
  - 41%increase in strokes
  - 29% increase in heart attacks
  - Doubled rates of blood clots



WHI: AGE


WHI HT: Baseline Age Distribution
Mean± SD: HystX-E only = 63.6±7.3; Uterus-E+P = 63.3±7.1
Goal: 50-54 = 10%; 55-59=20%; 60-69=45%; 70-79=25%
50-59
E=31%; E+P=33%
60-69
E=45%; E+P=45%
70-79
E=24%; E+P=22%
Percent
35
30
25
20
15
10
5
0
50-54
55-59
60-64
65-69
70-74
75-79
Hysterectomy-E only
Uterus-E+P
Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WOMEN'S HEALTH INITIATIVE

THE WORLD WAS MISLED ABOUT HT RISK

- A RESEARCHER INVOLVED IN THE TRIAL SAID THAT THE LINK TO HRT AND BREAST CANCER AND HEART DISEASE RESULTS WERE EXAGGERATED TO THE PUBLIC
- TWO PROBLEMS
  - THE STUDY WAS STOPPED IN EARLY 2002 CITING INCREASE IN BREAST CANCER AND HEART ATTACKS BUT THESE WERE *NOT* SIGNIFICANTLY SIGNIFICANT
  - THE STUDY (2/3) FOCUSED ON WOMEN OLDER THAN 60 BUT GENERALIZED TO YOUNGER WOMEN
  - FALLOUT: PROVIDERS AND PATIENT BELIEVED HRT TO BE DANGEROUS, EVEN THOUGH THE RISK FOR THE YOUNGER WERE LOW
  - HRT USAGE PLUMMETED BY AS MUCH AS 80%
  - HIP FRACTURES RATES INCREASED BY 55%
  - 18,601-91,610 AMERICAN WOMEN DIED PREMATURELY BETWEEN 2002-2012 AS A RESULTS OF AVOIDING ET

WHI: LIMITATIONS

IS THE ONLY LARGE, LONG-TERM RCT OF HT IN WOMEN AGED 50 TO 79 YEARS

- FINDINGS GIVEN PROMINENT CONSIDERATION
  - NOT DESIGNED TO ADDRESS RISKS & BENEFITS OF HORMONES GIVEN FOR RELIEF OF VMS OR IMPROVEMENT IN QOL, BUT WHETHER POSTMENOPAUSAL WOMEN SHOULD CONSIDER HT TO *PREVENT CHRONIC DISEASE,* OVER WIDE RANGE OF AGES 50-79
- LIMITATIONS INCLUDED:
  - ONE ROUTE OF ADMINISTRATION (ORAL)
  - ONE FORMULATION OF ESTROGEN (CONJUGATED EQUINE ESTROGENS [CEE], 0.625 MG)
  - ONE PROGESTOGEN (MEDROXYPROGESTERONE ACETATE [MPA], 2.5 MG)
  - HAD LIMITED ENROLLMENT OF WOMEN WITH BOTHERSOME VMS WHO WERE AGED <60 YEARS OR WHO WERE <10 YEARS FROM MENOPAUSE ONSET—THE GROUP OF WOMEN FOR WHOM HT IS PRIMARILY INDICATED.
  - 2/3 OF ENROLLMENT WERE OLDER THAN 60.

- FINDINGS FROM THE INTERVENTION AND EXTENDED POST-INTERVENTION FOLLOW-UP OF 2 WHI HT TRIALS *DO NOT* SUPPORT USE OF HT FOR CHRONIC DISEASE PREVENTION (LEVEL I)

(Manson et al (2013).Menopausal Hormone Therapy and Health Outcomes During Intervention and Extended Post stopping Phases of the Women's Health Initiative Randomized Trials. JAMA.)

WHI: REST OF THE STORY…



ESTROGEN ALONE SHOWED A NONSIGNIFICANT REDUCTION IN BREAST CANCER RISK AFTER AN AVERAGE OF 7.2 YEARS OF RANDOMIZATION, **WITH 7 FEWER CASES OF INVASIVE BREAST CANCER PER 10,000 PERSON-YEARS,** REMAINED FOR UP TO A MEDIAN 13 YEARS'

THE ATTRIBUTABLE RISK OF BREAST CANCER (MEAN AGE, 63 Y) RANDOMIZED TO **CEE & MPA IS <1 ADDITIONAL CASE OF BREAST CANCER DIAGNOSED PER 1,000 USERS ANNUALLY**

- **A RISK SLIGHTLY GREATER THAN THAT OBSERVED WITH ONE DAILY GLASS OF WINE, LESS THAN WITH TWO DAILY GLASSES,**
- ***SIMILAR* TO THE RISK REPORTED WITH OBESITY, LOW PHYSICAL ACTIVITY, AND OTHER MEDICATIONS**

- Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353-1368
- Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 2006;166:1027-1032.
- Li CI, Daling JR, Tang MT, Haugen KL, Porter PL, Malone KE. Use of antihypertensive medications and breast cancer risk among women aged 55 to 74 years. JAMA Intern Med 2013;173:1629-1637

THE WHI: 2017 UPDATE

- Among postmenopausal women, hormone therapy with
  - CEE plus MPA for a median of 5.6 years or
  - CEE alone for a median of 7.2 years was

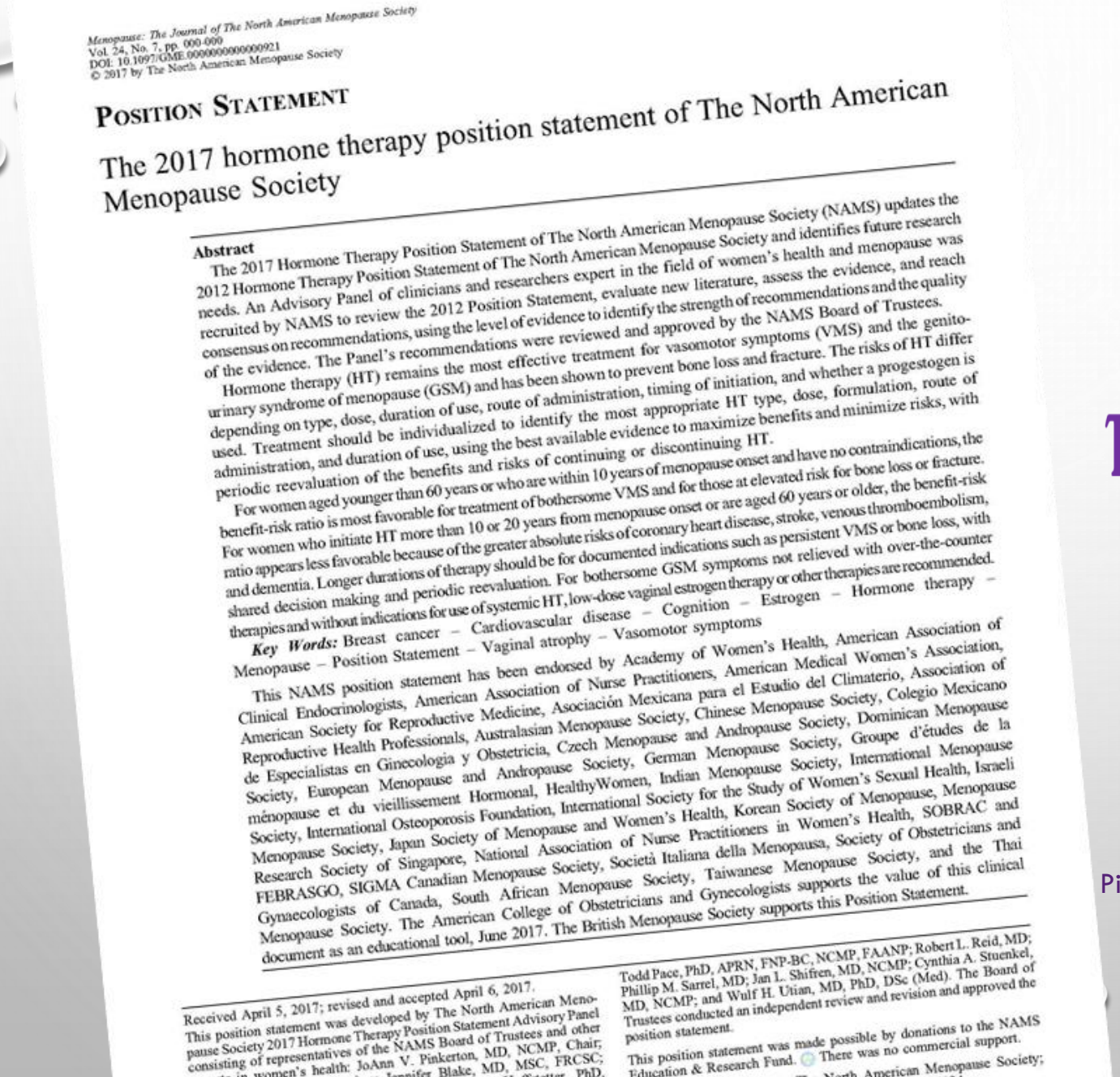
not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.

Manson, J.E., Aragaki, A.K., Jacques E. Rossouw, J.E.,et al, 2017

THE IMPACT OF LONG-TERM USE OF SYSTEMIC HT ON ALZHEIMER DISEASE (AD) RISK

- TENTATIVE OBSERVATIONAL DATA SUPPORT FOR A "CRITICAL WINDOW" HYPOTHESIS, LEAVING OPEN THE POSSIBILITY THAT INITIATING SYSTEMIC HT SOON AFTER MENOPAUSE ONSET AND CONTINUING IT LONG TERM MAY REDUCE THE RISK OF AD.
- UP TO 5 YEARS OF HT USE WAS NOT ASSOCIATED WITH A RISK OF BEING DIAGNOSED WITH AD.
- FIVE TO 10 YEARS OF HT USE WAS ASSOCIATED WITH A HAZARD RATIO (HR) OF 0.89, AN 11% RISK REDUCTION THAT DID NOT ACHIEVE STATISTICAL SIGNIFICANCE. BY CONTRAST,
- HOWEVER, MORE THAN 10 YEARS' USE OF SYSTEMIC HT WAS ASSOCIATED WITH AN HR OF 0.53, A STATISTICALLY SIGNIFICANT 47% REDUCTION IN RISK OF AD.[1]

Andrew M. Kaunitz MD, NCMP JoAnn V. Pinkerton, MD, NCMP JoAnn E. Manson, J.E, 2018 Update on menopause. OBG Manag. 2018 June;30(6):28-33
What's the impact of long-term use of systemic HT on Alzheimer disease risk? *Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study. Neurology. 2017;88(11):1062-1068.*



Menopause: The Journal of The North American Menopause Society
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POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic reevaluation. For bothersome GSM symptoms not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal estrogen therapy or other therapies are recommended.

Key Words: Breast cancer – Cardiovascular disease – Cognition – Estrogen – Hormone therapy – Menopause – Position Statement – Vaginal atrophy – Vasomotor symptoms

This NAMS position statement has been endorsed by Academy of Women's Health, American Association of Clinical Endocrinologists, American Association of Nurse Practitioners, American Medical Women's Association, American Society for Reproductive Medicine, Asociación Mexicana para el Estudio del Climaterio, Association of Reproductive Health Professionals, Australasian Menopause Society, Chinese Menopause Society, Colegio Mexicano de Especialistas en Ginecologia y Obstetricia, Czech Menopause and Andropause Society, Dominican Menopause Society, European Menopause and Andropause Society, German Menopause Society, Groupe d'études de la ménopause et du vieillissement Hormonal, HealthyWomen, Indian Menopause Society, International Menopause Society, International Osteoporosis Foundation, International Society for the Study of Women's Sexual Health, Israeli Menopause Society, Japan Society of Menopause and Women's Health, Korean Society of Menopause, Menopause Research Society of Singapore, National Association of Nurse Practitioners in Women's Health, SOBRAC and FEBRASGO, SIGMA Canadian Menopause Society, Società Italiana della Menopausa, Society of Obstetricians and Gynaecologists of Canada, South African Menopause Society, Taiwanese Menopause Society, and the Thai Menopause Society. The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017. The British Menopause Society supports this Position Statement.

Received April 5, 2017; revised and accepted April 6, 2017.
This position statement was developed by The North American Menopause Society 2017 Hormone Therapy Position Statement Advisory Panel consisting of representatives of the NAMS Board of Trustees and other women's health: JoAnn V. Pinkerton, MD, NCMP, Chair; Jennifer Blake, MD, MSC, FRCSC; Todd Pace, PhD, APRN, FNP-BC, NCMP, FAANP; Robert L. Reid, MD; Phillip M. Sarrel, MD; Jan L. Shifren, MD, NCMP; Cynthia A. Stuenkel, MD, NCMP; and Wulf H. Utian, MD, PhD, DSc (Med). The Board of Trustees conducted an independent review and revision and approved the position statement.

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North American Menopause Society;

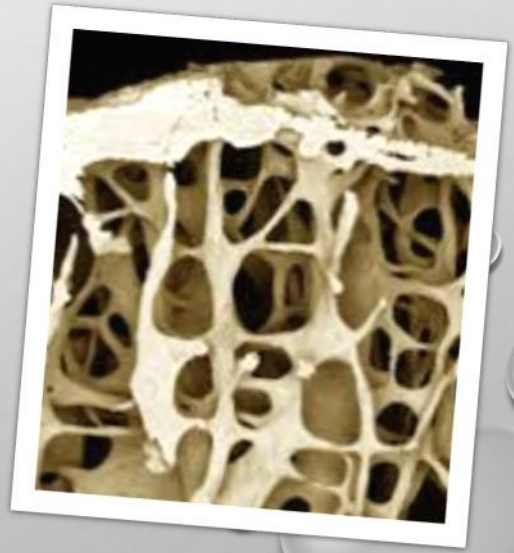
The 2017 Hormone Therapy Position Statement of The North American Menopause Society

Pinkerton, J. A. V., Aguirre, F. S., Blake, J., Cosman, F., et al. (2017).

FDA APPROVED INDICATIONS FOR HORMONE THERAPY

- VASOMOTOR SYMPTOMS
- PREVENTION OF BONE LOSS & FRACTURE
- PREMATURE HYPOESTROGENISM
- GENITOURINARY SYMPTOMS





WHAT'S NEW

- "APPROPRIATE DOSE, DURATION, REGIMEN, AND ROUTE OF ADMINISTRATION."
- THERE ARE NO DATA TO SUPPORT ROUTINE DISCONTINUATION IN WOMEN AGED 65 YEARS.
- BENEFITS ARE MOST LIKELY TO OUTWEIGH RISKS FOR SYMPTOMATIC WOMEN WHO INITIATE HT WHEN AGED <60 YEARS OR <10 YEARS OF MENOPAUSE ONSET.
- SURVIVORS OF BREAST AND ENDOMETRIAL CANCER, USE OF LOW-DOSE VAGINAL ET FOR THOSE WHO FAIL NONHORMONE THERAPY APPEARS SAFE AND GREATLY IMPROVES QOL FOR MANY, DISCUSS WITH ONCOLOGIST

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

AGE AND TIME SINCE MENOPAUSE ONSET: *TIMING HYPOTHESIS*

- THE EFFECTS OF HORMONE THERAPY (HT) ON CORONARY HEART DISEASE (CHD) MAY VARY DEPENDING ON A WOMAN'S AGE AND TIME SINCE MENOPAUSE ONSET
- DATA SHOW REDUCED CHD IN WOMEN WHO INITIATE HT AGED YOUNGER THAN 60 YEARS AND/OR WITHIN 10 YEARS OF MENOPAUSE ONSET
- THERE IS CONCERN OF INCREASED RISK OF CHD IN WOMEN WHO INITIATE HT MORE THAN 10 OR 20 YEARS FROM MENOPAUSE ONSET

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THE *NEW AND IMPROVED GUIDELINES*

- BENEFITS ARE MOST LIKELY TO OUTWEIGH RISKS FOR SYMPTOMATIC WOMEN WHO *INITIATE* HT WHEN AGED <60 YEARS OR <10 YEARS OF MENOPAUSE ONSET.
- PREVIOUS POSITION STATEMENT: THE LOWEST DOSE USED FOR THE SHORTEST DURATION NEEDED TO MANAGE MENOPAUSAL SYMPTOMS.

NEW STATEMENT: **MANAGEMENT SHOULD BE *INDIVIDUALIZED* AND PATIENT PREFERENCE CONSIDERED TO IDENTIFY THE MOST APPROPRIATE:**

- **HT TYPE**
- **DOSE**
- **FORMULATION**
- **ROUTE OF ADMINISTRATION**
- **DURATION OF USE**

- USING THE BEST AVAILABLE EVIDENCE TO MAXIMIZE BENEFITS AND MINIMIZE RISKS
- PERIODIC REEVALUATION OF THE BENEFITS AND RISKS OF CONTINUING OR DISCONTINUING HT

SHOULD BE INDIVIDUALIZED TO IDENTIFY THE MOST APPROPRIATE:

- HT TYPE: ET, E+PT, SERM, DHEA
- DOSE: NOT NECESSARILY THE LOWEST
- FORMULATION: BIOIDENTICAL, COMPOUNDS
- ROUTE OF ADMINISTRATION: TRANSDERMAL, PO, SUPPOSITORY
- DURATION OF USE: ***NO*** INDICATION OF DISCONTINUATION
- USING THE BEST AVAILABLE EVIDENCE TO MAXIMIZE BENEFITS AND MINIMIZE RISKS,
- PERIODIC REEVALUATION OF THE BENEFITS AND RISKS OF CONTINUING OR DISCONTINUING HT.

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ESTROGEN THERAPY AND ESTROGEN-PROGESTOGEN THERAPY

- ESTROGEN AS A SINGLE SYSTEMIC AGENT IS APPROPRIATE IN WOMEN AFTER HYSTERECTOMY, BUT ADDITIONAL PROGESTOGEN (OR USE OF CEE WITH BAZEDOXIFENE) IS REQUIRED IN THE PRESENCE OF A UTERUS.

- PROGESTOGEN THERAPY (PROGESTERONE AND SYNTHETIC PROGESTOGENS) IS AN OPTION TO TREAT HOT FLASHES, BUT NOT AS EFFECTIVE AS ESTROGEN
  - LONG-TERM SAFETY DATA ARE LIMITED.
  - PRIMARY USE IN POSTMENOPAUSAL WOMEN IS TO REDUCE RISK OF ENDOMETRIAL CANCER ASSOCIATED WITH UNOPPOSED ESTROGEN THERAPY (ET).

"HORMONES WILL GIVE YOU BREAST CANCER!"

- NO LINK BETWEEN HT AND ALL-CAUSE MORTALITY IN THE OVERALL STUDY POPULATION (AGES 50-79) IN EITHER TRIAL.
- HOWEVER, THERE WAS A TREND TOWARD LOWER ALL-CAUSE MORTALITY AMONG THE YOUNGER WOMEN IN BOTH TRIALS. IN WOMEN AGED 50 TO 59,
- THERE WAS A STATISTICALLY SIGNIFICANT 31% LOWER RISK OF MORTALITY IN THE POOLED TRIALS AMONG WOMEN TAKING ACTIVE HT COMPARED WITH THOSE TAKING PLACEBO,
- BUT NO REDUCTION IN MORTALITY WITH HT AMONG OLDER WOMEN



Mason, JE. 2018. 18 Years of WHI follow-up data on menopausal HT and all-cause mortality provide reassurance. **2018 Update on menopause.** *OBG Manag*. 2018 June;30(6):28-33

UNIQUE CONCERNS ABOUT SAFETY SURROUND USE OF COMPOUNDED BIOIDENTICAL HORMONE THERAPY

- LACK OF REGULATION AND MONITORING
- POSSIBILITY OF OVERDOSING OR UNDER-DOSING
- LACK OF SCIENTIFIC EFFICACY AND SAFETY DATA
- LACK OF A LABEL OUTLINING RISKS

- NO EVIDENCE TO SUPPORT USE OF ROUTINE SERUM OR SALIVARY HORMONE TESTING

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ESTROGEN

Approved Prescription Products for Menopausal Symptoms in the United States and Canada

Oral estrogen products

Revised: February 2016

(Providers should check the full prescribing information for appropriate dosages for the indication and any updates or information that is not provided here, such as warnings and contraindications.)

Active Ingredient(s)	Product Name(s)	Dosages (mg/d)
17β-estradiol*	Estrace† Generic(s) available	0.5, 1.0, 2.0
Conjugated estrogens	Premarin	0.3, 0.45‡, 0.625, 0.9‡, 1.25
Synthetic conjugated estrogens, B	Enjuvia‡	0.3, 0.45, 0.625, 0.9, 1.25
Conjugated estrogens, CSD‡ (synthetic)	C.E.S. pms-Conjugated estrogens, CSD	0.3, 0.625, 0.9, 1.25
Esterified estrogens	Menest‡ Estragyn†	0.3, 0.625, 1.25, 2.5 (administer cyclically) 0.3, 0.625
Estropipate	Generic(s) available‡	0.625 (0.75 estropipate), 1.25 (1.5), 2.5 (3.0)

*Bioidentical: defined as compounds that have the same chemical and molecular structure as hormones that are produced in the body
† Available in Canada but not the United States
‡ Available in the United States but not Canada
Product names not marked are available in both the United States and Canada.

Transdermal estrogen products

Revised: February 2016

(Providers should check the full prescribing information for appropriate dosages for the indication and any updates or information that is not provided here, such as warnings and contraindications.)

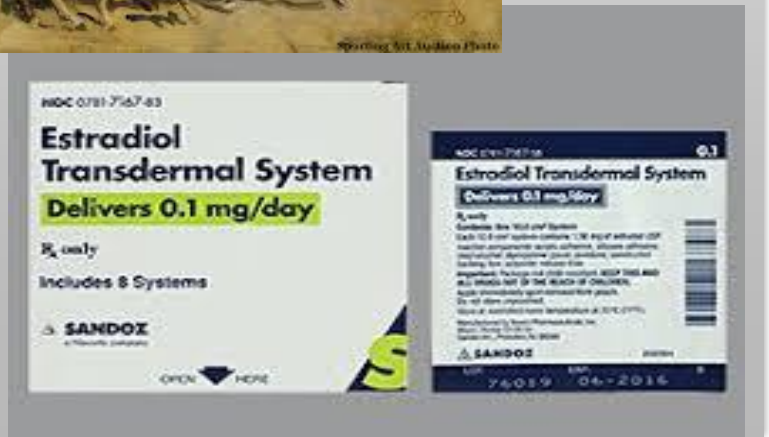
Active Ingredient(s)	Product Name	Dosage (mg E_2/day)
Patch, Film		
17β-estradiol*	Alora†	0.025, 0.05, 0.075, 0.1 twice/wk
	Climara	0.025, 0.0375,† 0.05, 0.06,† 0.075, 0.1 once/wk
	Estraderm†	0.05, 0.1 twice/wk
	Estradot‡	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Minivelle†	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Oesclim‡	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Vivelle-Dot†	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Generic(s) available	
Transdermal gel		
17β-estradiol*	Divigel	0.25, 0.5, 1.0
	EstroGel	0.75 (*US:* single approved dose, *Canada:* adjust to control symptoms)
	Elestrin†	0.52 (adjust based on clinical response)
Transdermal spray		
17β-estradiol*	Evamist†	1.53 (1 spray/d initially, adjust dosage by clinical response)

*Bioidentical: defined as compounds that have the same chemical and molecular structure as hormones

http://www.menopause.org/docs/default-source/professional/nams-ht-tables.pdf

DIFFERENCE BETWEEN CEE AND E2





Both CEE and estradiol are rapidly metabolized into weaker estrogens such as estrone

Meta-analysis of FDA-approved estrogen trials found no evidence of a significant difference in effectiveness between estradiol and CEE in treating VMS

There were differences in cognitive outcomes between types of estrogen and the brain serotonergic system, with estradiol providing more robust anxiolytic and antidepressant effects

Without RCTs, data for one agent should be generalized to all agents within same hormonal family



Pharmacokinetic Differences Between Oral and Transdermal Hormone Therapy

Oral

Stomach/ Intestines

Liver

Liver protein/lipid synthesis (eg, ↑TGs, ↑CRP)

First-pass metabolism

Transdermal

No first-pass metabolism
More stable circulating levels
Less variability
Lower administered doses

Bloodstream

Cells of target tissues

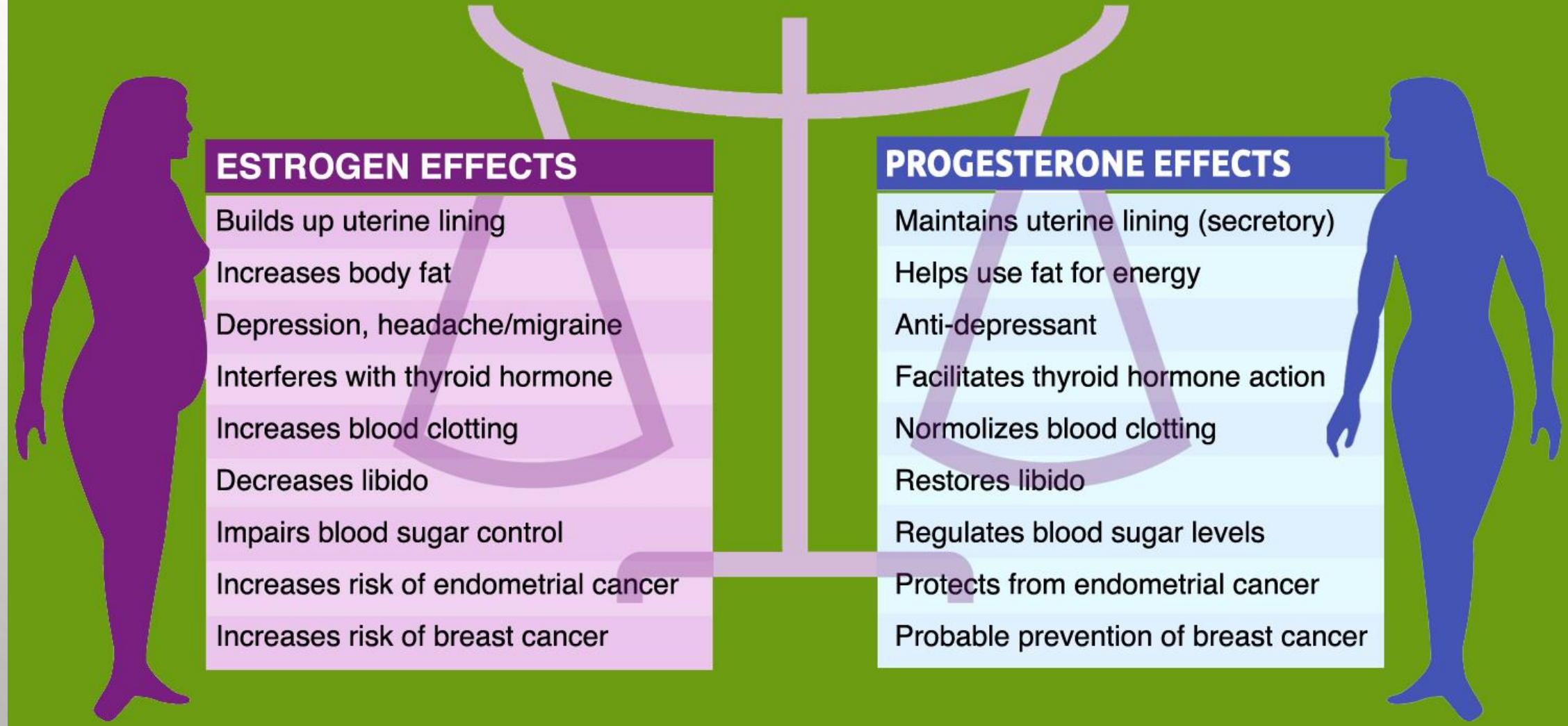
Minkin MJ. *J Reprod Med*. 2004; 49: 311-320

ORAL OR TRANSDERMAL

- ORAL ESTROGEN INCREASES THE LIVER'S PRODUCTION OF SEX HORMONE–BINDING GLOBULIN, RESULTING IN LOWER FREE (BIOAVAILABLE) TESTOSTERONE.
- TRANSDERMAL ESTROGEN DOES NOT PRODUCE THIS EFFECT.
- SEXUALITY CONCERNS MAY REPRESENT A REASON TO PREFER THE USE OF TRANSDERMAL AS OPPOSED TO ORAL ESTROGEN.
- RECENT STUDIES SUGGEST THAT PO A ESTROGEN MAY EXERT A PROTHROMBOTIC EFFECT, BUT TRANSDERMAL ESTROGEN HAS LITTLE OR NO EFFECT IN ELEVATING PROTHROMBOTIC SUBSTANCES AND MAY HAVE BENEFICIAL EFFECTS ON PROINFLAMMATORY MARKERS.
- TRANSDERMAL THERAPY CAN ALSO BE CONSIDERED FOR WOMEN WITH METABOLIC SYNDROME, HYPERTRIGLYCERIDEMIA, AND FATTY LIVER, SINCE THIS ROUTE AVOIDS FIRST-PASS HEPATIC METABOLISM.

Taylor HS, Tal A, Pal L, et al. Effects of oral vs transdermal estrogen therapy on sexual function in early post menopause: ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). JAMA Intern Med. 2017;177(10):1471–1479

The Role of Estrogen and Progesterone



ENDOMETRIAL PROTECTION

- FOR SYSTEMIC ESTROGEN, ENDOMETRIAL PROTECTION REQUIRES AN ADEQUATE DOSE AND DURATION OF A PROGESTOGEN OR USE OF THE COMBINATION CONJUGATED EQUINE ESTROGEN WITH BAZEDOXIFENE (LEVEL I)
- PROGESTOGEN THERAPY IS ***NOT*** RECOMMENDED WITH LOW-DOSE VAGINAL ESTROGEN—LEVEL I-YEAR SAFETY DATA
- APPROPRIATE EVALUATION OF THE ENDOMETRIUM SHOULD BE PERFORMED FOR VAGINAL BLEEDING (LEVEL I)

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753

PROGESTOGEN "PRO-PREGNANCY"

- **SYNTHETIC PROGESTIN** WITH CEE
- 0.3MG/1.5MG
- 0.45MG/1.5MG
- 0.625MG/5MG



- **OTHER:**

SUGGEST OFF-LABEL USE OF THE LOWER DOSE LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE WHEN NO OTHER ORAL PROGESTOGEN IS TOLERATED



- ***MICRONIZED PROGESTERONE***

NATURAL PROGESTERONE



- *IN PEANUT OIL*
- *HELPS W HOT FLASHES, INSOMNIA AND BONE HEALTH*
- *200-400 MG HS*
- *INCREASED DEEP SLEEP BY APPROXIMATELY 15 %*
- *STIMULATES FORMATION OF NEW BONE*

OTHER HORMONES EFFECT

- THERE IS EBM LITERATURE THAT NATURAL PROGESTERONE IS NOT ASSOCIATED WITH AN INCREASED RISK OF VENOUS THROMBOEMBOLISM. CONVERSELY, THERE IS EVIDENCE THAT BY COMPARISON, SYNTHETIC PROGESTINS (EG, MEDROXYPROGESTERONE ACETATE) DO INCREASE THE RISK OF VENOUS THROMBOEMBOLISM
- TESTOSTERONE CAN RAISE BLOOD PRESSURE AND CONTRIBUTE TO INSULIN RESISTANCE, WHICH ARE HARMFUL EFFECTS, WHEREAS ESTROGEN RELAXES BLOOD VESSELS AND LOWERS BAD CHOLESTEROL LEVELS, WHICH TEND TO BE GOOD THINGS FOR THE HEART AND VASCULAR SYSTEMS.

https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Postmenopausal-Estrogen-Therapy?IsMobileSet=false#10

FAMILY HISTORY OF BREAST CANCER

- BRCA+ WITHOUT BREAST CANCER ARE AT HIGHER GENETIC RISK OF BREAST CANCER, PRIMARILY ER-NEGATIVE. BENEFITS OF ESTROGEN TO DECREASE HEALTH RISKS CAUSED BY PREMATURE LOSS OF ESTROGEN NEED TO BE CONSIDERED. (LEVEL II).
- NO INCREASED RISK WAS SEEN IN AN OBSERVATIONAL TRIAL OF SURVIVORS OF BREAST CANCER ON TAMOXIFEN OR AI THERAPY WITH LOW-DOSE VAGINAL ET FOR 3.5 YEARS' MEAN FOLLOW-UP.
- OBSERVATIONAL EVIDENCE SHOWS USE OF HORMONE THERAPY DOES NOT ALTER RISK FOR BREAST CANCER IN WOMEN WITH A FAMILY HISTORY OF BREAST CANCER
- FAMILY HISTORY *IS ONE RISK AMONG MANY* THAT SHOULD BE ASSESSED WHEN COUNSELING WOMEN ON THE USE OF HORMONE THERAPY (LEVEL II)

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

BREAST CANCER CONNECTION

- **NO EVIDENCE FOR BEERS CRITERIA TO RECOMMEND DISCONTINUATION OF HORMONE THERAPY AFTER AGE 65 IF INDICATION TO CONTINUE REMAINS AND NO CONTRAINDICATIONS**

- **BREAST CANCER RISK DOES NOT INCREASE APPRECIABLY WITH SHORT-TERM USE OF ESTROGEN-PROGESTOGEN THERAPY AND MAY BE DECREASED WITH ESTROGEN ALONE (CONJUGATED EQUINE ESTROGEN IN THE WOMEN'S HEALTH INITIATIVE)**

- **NO INCREASED RISK OF BREAST CANCER IN WOMEN WHO ARE *BRCA*-POSITIVE ON HORMONE THERAPY AFTER RISK-REDUCING BILATERAL SALPINGO-OOPHORECTOMY (OBSERVATIONAL STUDIES)**

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

TRIALS OF HORMONE THERAPY AND CORONARY HEART DISEASE



- **META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS (BOARDMAN HM, ET AL. *COCHRANE DATABASE SYST REV*. 2015.)**

HORMONE THERAPY INITIATED LESS THAN 10 YEARS OF MENOPAUSE ONSET:

REDUCED CORONARY HEART DISEASE

RELATIVE RISK (RR), 0.52; 95% CONFIDENCE INTERVAL (CI), 0.29-0.96

- ***SIGNIFICANT INCREASED RISK OF VENOUS THROMBOEMBOLISM*** **RR, 1.74; 95% CI, 1.11-2.73**
- THE ABSOLUTE RISK OF VENOUS THROMBOEMBOLISM IS AGE DEPENDENT.

- ***DEATH WAS SIGNIFICANTLY REDUCED***
  - **RR, 0.70; 95% CI, 0.52-0.95**

BONE HEALTH

- HORMONE THERAPY EFFECTIVELY PREVENTS POST MENOPAUSE OSTEOPOROSIS AND FRACTURES
- WOMEN IN THE ESTROGEN-ALONE AND ESTROGEN-PROGESTOGEN THERAPY OVERALL COHORTS IN THE WOMEN'S HEALTH INITIATIVE (WHI) HAD SIGNIFICANT 33% REDUCTIONS IN HIP FRACTURE
- AFTER TREATMENT DISCONTINUATION IN THE WHI, BENEFICIAL EFFECTS ON BONE DISSIPATED RAPIDLY, BUT NO REBOUND WAS SEEN
- WOMEN IN THE WHI SHOWED LESS JOINT PAIN OR STIFFNESS

TISSUE-SELECTIVE ESTROGEN COMPLEX "T SEC"



- **CEE + BAZEDOXIFENE (DUAVEE®)**
  - TREAT MODERATE TO SEVERE HOT FLASHES AND OTHER SYMPTOMS OF MENOPAUSE AND TO PREVENT OSTEOPOROSIS
  - PROVIDE ENDOMETRIAL PROTECTION WITHOUT THE NEED FOR A PROGESTOGEN

ONE TABLET DAILY (20 MG BAZEDOXIFENE AND 0.45 MG OF CEE)

- IF DOSE NOT SATISFACTORY TO RELIEVE VMS, DO NOT ADD ADDITIONAL ESTROGEN. ****CHANGE RX*****.
- BREAST TENDERNESS, BREAST DENSITY, AND BREAST CANCERS WERE NOT INCREASED WITH ORAL CEE

GSM: MEDICAL MANAGEMENT

- WOMEN WITH GSM/VVA SHOULD CONSIDER NONHORMONAL VAGINAL LUBRICANTS AND MOISTURIZERS AS INITIAL THERAPY. (LEVEL II).
- LOW-DOSE VAGINAL ET (AVAILABLE AS A CREAM, TABLET, OR RING) IS A HIGHLY EFFECTIVE TREATMENT FOR PERSISTENT SYMPTOMS OF GSM/VVA. (LEVEL I)
- THE ESTROGEN AGONIST/ANTAGONIST OSPEMIFENE IS AN ORAL AGENT FOR THE TREATMENT OF MODERATE TO SEVERE DYSPAREUNIA DUE TO GSM/VVA. (LEVEL I)
- PROGESTOGEN THERAPY FOR ENDOMETRIAL PROTECTION IS *NOT* RECOMMENDED WITH THE USE OF LOW-DOSE VAGINAL ET. (LEVEL I)
- POSTMENOPAUSAL WOMEN WITH RECURRENT UTI'S MAY CONSIDER TREATMENT WITH LOW-DOSE VAGINAL ET OR PROPHYLACTIC ANTIBIOTICS. (LEVEL I)
- ANY BLEEDING IN A POSTMENOPAUSAL WOMAN, INCLUDING POST-COITAL BLEEDING, REQUIRES A THOROUGH EVALUATION. (LEVEL I)

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

Current FDA-Approved VVA Products

Product	Estrace® Cream (estradiol vaginal cream, USP, 0.01%)[1]	Premarin Cream® (conjugated estrogens vaginal cream)[2]	Estring® (estradiol vaginal ring)[3]	Vagifem® (estradiol vaginal inserts)[4]	IMVEXXY (estradiol vaginal inserts)[5,6]	Intrarosa® (prasterone vaginal inserts)[7]	Osphena® (ospemifene tablets)[8]
							
	Allergan	Pfizer	Pfizer	novo nordisk	TherapeuticsMD For Her. For Life.	amag	DUCHESNAY USA
FDA approval	1984	1978	1996	1999	2018	2016	2013
TRx Dollars 2017[9]	$583,612,698	$533,386,029	$120,499,734	$525,321,410[a]	-	$4,187,571	$75,683,654
Method of administration	Vaginal Cream	Vaginal Cream	Vaginal Ring	Vaginal Tablet	Vaginal Softgel	Vaginal Bullet	Oral Tablet
Application	Reusable vaginal applicator	Reusable vaginal applicator	90-day ring	Vaginal applicator	No applicator needed	Vaginal applicator	Oral daily SERM
Active ingredient	100 µg estradiol	625 µg/g conjugated equine estrogens	2,000 µg estradiol	10 µg estradiol	4 µg or 10 µg estradiol	6,500 µg prasterone	60,000 µg ospemifene
Average maintenance dose	100 µg 2x/week	312.5 µg 2x/week	7.5 µg daily	10 µg 2x/week	4 µg or 10 µg 2x/week	6,500 µg daily	60,000 µg daily
Onset of action* dyspareunia	Approved without dyspareunia and dryness data	Week 4+	Approved without dyspareunia and dryness data	Week 8	Week 2	Week 6	Week 12
Onset of action* dryness		Not demonstrated			Week 2	Week 12	Not demonstrated
WAC 30-day supply (2018)[10]	$104.96	$118.59	$143.78	$170.16	$180.00	$198.75	$203.80

*Onset of action = first efficacy observation.

There have been no head-to-head trials between IMVEXXY and any of the products listed above.
All trademarks are the property of their respective owners.
Abbreviations: SERM, selective estrogen receptor modulator; WAC, wholesale acquisition cost.

References: 1. Estrace Vaginal Cream [package insert]. Irvine, CA: Allergan USA, Inc.; 2017. **2.** Premarin Vaginal Cream [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.; 2017. **3.** Estring [package insert]. New York, NY: Pharmacia & Upjohn Company LLC, a subsidiary of Pfizer Inc.; 2017. **4.** Vagifem [package insert] Plainsboro, NJ: Novo Nordisk Inc.; 2017. **5.** IMVEXXY [package insert]. **6.** Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause*. 2017;24(4):409-416. **7.** Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2017. **8.** Osphena [package insert]. Florham Park, NJ: Shionogi Inc.; 2015. **9.** Symphony Health Solutions PHAST Data powered by IDV; Annual 2017 [a. 2017 Vagifem, Yuvafem (authorized generic of Vagifem), and Teva generic]. **10.** Price RX March 2018.

TherapeuticsMD®
For Her. For Life.

NEW KIDS ON THE BLOCK

OSPHENA® (OSPEMIFENE)

- IS THE ONLY FDA-APPROVED ***ORAL*** PILL FOR THE TREATMENT OF MODERATE-SEVERE DYSPAREUNIA DUE TO MENOPAUSE. IT IS NOT AN ESTROGEN BUT HELPS IMPROVE SPECIFIC VAGINAL TISSUES* AND RELIEVES MODERATE TO SEVERE PAINFUL SEX DUE TO MENOPAUSE.
- **INCREASES SUPERFICIAL CELLS, DECREASES PARABASAL CELLS AND REDUCES VAGINAL PH.*
- THE DOSE OF OSPHENA IS A 60 MG TABLET, TAKEN ONCE DAILY WITH FOOD. OSPHENA MAY INTERACT WITH FLUCONAZOLE (DIFLUCAN), RIFAMPIN (RIFADIN), AND ESTROGENS.

INTRAROSA (PRASTERONE)

- TO TREAT WOMEN EXPERIENCING MODERATE TO SEVERE PAIN DURING SEXUAL INTERCOURSE (DYSPAREUNIA), A DUE TO MENOPAUSE.
INTRAROSA IS THE FIRST FDA APPROVED PRODUCT CONTAINING THE ACTIVE INGREDIENT PRASTERONE, ALSO KNOWN AS DEHYDROEPIANDROSTERONE (DHEA).

IMVEXXY (ESTRADIOL)

- MOFERATE TO SEVERE DYSPAREUNIA DUE TO MENPAUSE
- available as 4mcg and 10mcg strength vaginal inserts in 8- and 18-count packs; the 4mcg dose represents the lowest approved dose of vaginal estradiol available.
- The softgel capsule is administered vaginally without an applicator once daily for 2 weeks, followed by 1 insert twice weekly.

HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD)

IS A DEFICIENCY OR ABSENCE OF SEXUAL FANTASIES AND DESIRE FOR SEXUAL ACTIVITY. CONSIDERED A DISORDER IF IT CAUSES DISTRESS FOR THE PATIENT OR PROBLEMS IN THE PATIENT'S RELATIONSHIPS.

FLIBANSERIN (ADDYI)

- TREAT DECREASED SEXUAL DESIRE IN WOMEN WHO HAVE NOT GONE THROUGH MENOPAUSE AND WHO HAVE NEVER HAD LOW SEXUAL DESIRE IN THE PAST.
- ONLY AVAILABLE THROUGH A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM DUE RISK OF EXPERIENCING SEVERE LOW BLOOD PRESSURE AND FAINTING (LOSS OF CONSCIOUSNESS) WITH ALCOHOL USE. YOU CAN ONLY GET THIS MEDICINE FROM PHARMACIES THAT ARE ENROLLED IN THE ADDYI REMS PROGRAM.
- 100 MG ORALLY ONCE PER DAY AT BEDTIME
- DURATION OF THERAPY: THIS DRUG SHOULD BE DISCONTINUED AFTER 8 WEEKS IF THE PATIENT DOES NOT REPORT AN IMPROVEMENT IN SYMPTOMS.
- THIS DRUG IS NOT INDICATED TO ENHANCE SEXUAL PERFORMANCE
- SKIP YOUR BEDTIME DOSE IF YOU HAVE CONSUMED ALCOHOL LESS THAN 2 HOURS EARLIER.

BREMELANOTIDE (VYLEESI)

- TREATMENT OF PREMENOPAUSAL WOMEN WITH ACQUIRED, GENERALIZED (HSDD), AS CHARACTERIZED BY LOW SEXUAL DESIRE THAT CAUSES MARKED DISTRESS OR INTERPERSONAL DIFFICULTY AND IS **NOT** DUE TO A CO-EXISTING MEDICAL OR PSYCHIATRIC CONDITION, PROBLEMS WITH THE RELATIONSHIP, OR THE EFFECTS OF A MEDICATION OR DRUG SUBSTANCE
- CONTRAINDICATIONS: HIGH BLOOD PRESSURE THAT IS NOT CONTROLLED (UNCONTROLLED HYPERTENSION) AND KNOWN HEART (CARDIOVASCULAR) DISEASE
- COMES IN AN AUTOINJECTOR; GIVEN AS A SUBCUTANEOUS INJECTION IN YOUR THIGHS OR ABDOMEN
- INJECT AT LEAST 45 MINUTES BEFORE YOU THINK THAT YOU WILL BEGIN SEXUAL ACTIVITY.
- DO NOT INJECT MORE THAN ONE DOSE WITHIN 24 HOURS OF YOUR LAST DOSE OR MORE THAN 8 DOSES WITHIN A MONTH
- SIDE EFFECTS
  - TEMPORARY INCREASE IN BLOOD PRESSURE AND DECREASE IN HEART RATE,
  - DARKENING OF THE SKIN ON CERTAIN PARTS OF THE BODY (FOCAL HYPERPIGMENTATION) INCLUDING THE FACE, GUMS (GINGIVA) AND BREAST.
  - NAUSEA IS COMMON AND CAN ALSO BE SEVERE



The Cat In The Hat On Aging

I cannot see
I cannot pee
I cannot chew
I cannot screw
Oh, my God, what can I do?
My memory shrinks
My hearing stinks
No sense of smell
I look like hell
My mood is bad -- can you tell?
My body's drooping
Have trouble pooping
The Golden Years have come at last
The Golden Years can kiss my ass