Menopause Symptom Management: Hormonal and Non-Hormonal Approaches

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Objectives

- Identify common symptoms of menopause
- Demonstrate familiarity with available hormonal and non-hormonal treatments for menopause related vasomotor symptoms
- Display understanding of when to use a progestin as part of hormone therapy

This presentation includes “off-label” discussion of products.

When the speaker mentions use of medications for purposes other than what is included in their FDA label they will be identified as such.

Abbreviations/Definitions

Abbreviation	Definition
E	Estrogen
E_2	Estradiol
CEE	Conjugated Equine Estrogen
P	Progesterone
P	Progestin
P	Progestogen (refers to either progesterone or progestin)

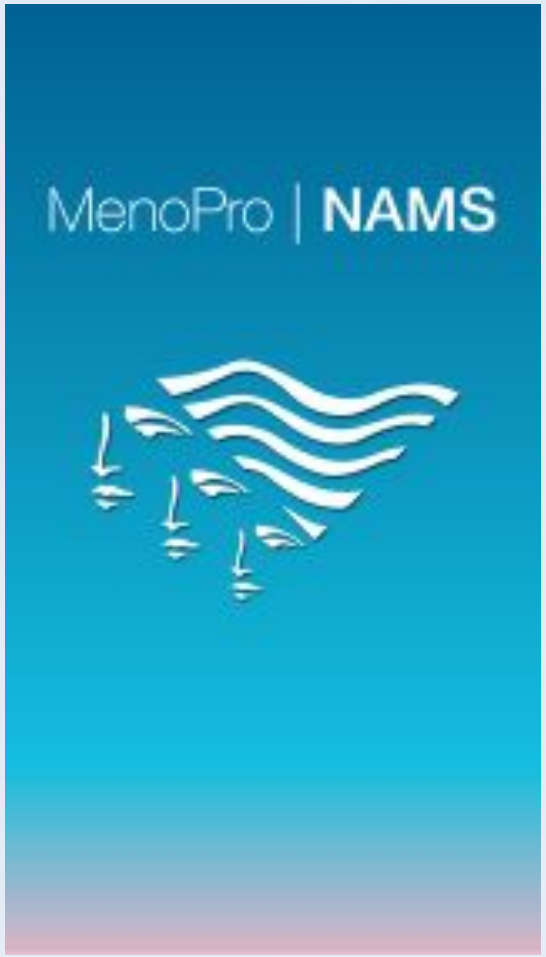
Abbreviation	Definition
ET	Estrogen Therapy
EPT	Combined E and P therapy
HT	Hormone therapy (ET or EPT)
MHT	Menopausal Hormone Therapy
HRT*	Hormone Replacement Therapy

* Not a term in general use anymore

Abbreviation	Definition
VMS	Vasomotor Symptoms
VVA*	Vulvovaginal Atrophy
GSM	Genitourinary syndrome of menopause

* Not a term in general use anymore

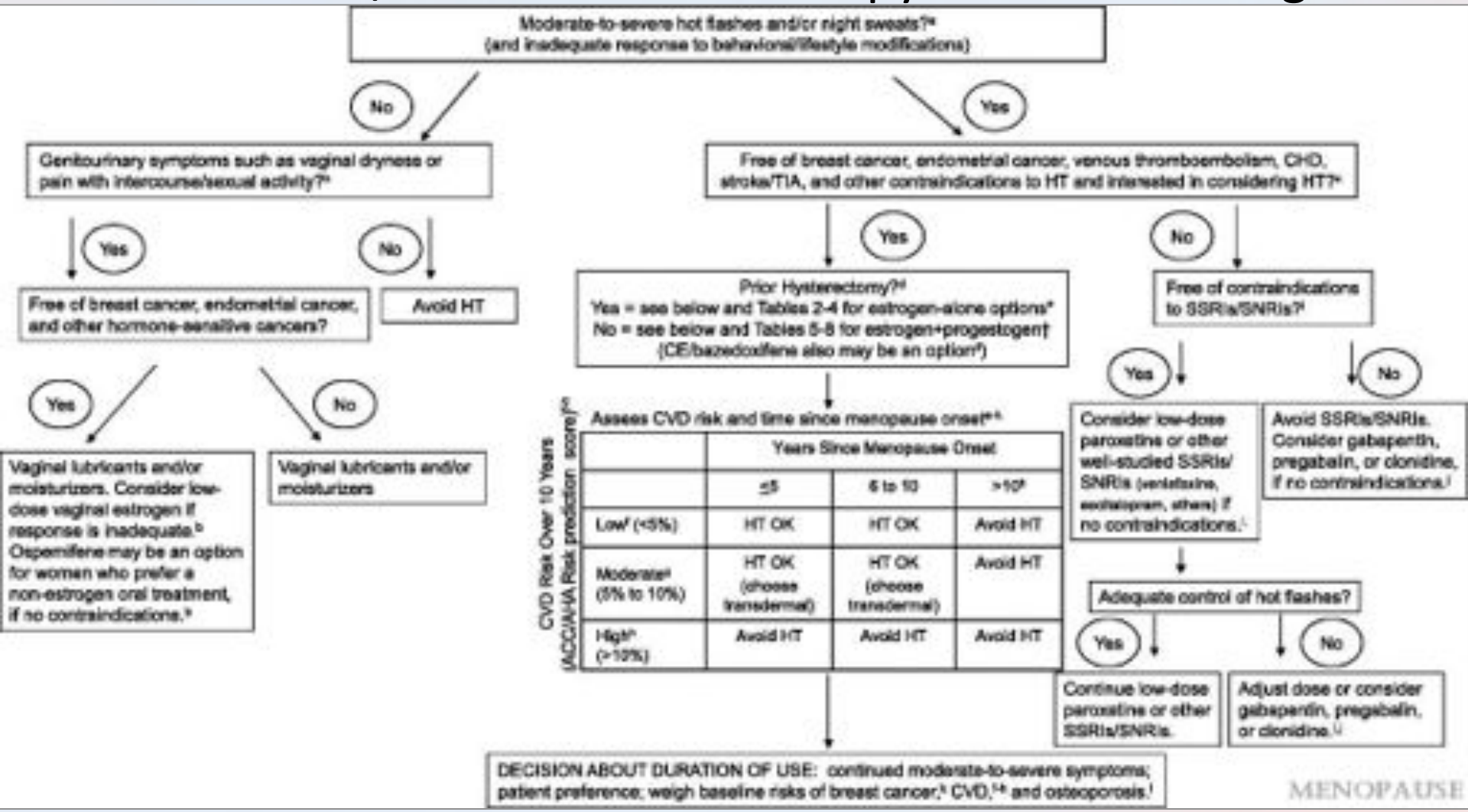
MenoPro by The North American Menopause Society



Available for ipad, iphone and android


AT&T M-Cell 10:20 AM 100%
The MenoPro app from The North American Menopause Society (NAMS) has 2 modes: one for clinicians and one for women/patients, to support shared decision making.
Are you a Health Care Provider or Woman/Patient?
Health Care Provider
Woman/ Patient
Calculator
About

FIG. 1. Algorithm for menopausal symptom management and hormonal/non-hormonal therapy decision making.



(Manson et al., 2015)

Premature Ovarian Failure
Primary Ovarian Insufficiency (POI)

- Approx 1%
- Waxes and wanes
- Prolonged and unique amenorrhea-related symptoms
- Menopausal symptoms may not diminish across time

(Stuenkel et al., 2015)
(Benetti-Pinto et al., 2015)
(Allshouse et al., 2015)

POI

- Depression is very common
- Depression may precede diagnosis of POI
- Hypothyroidism >3X the population mean
- Desire and arousal complaints are more common

(Stuenkel et al., 2015)
(Benetti-Pinto et al., 2015)
(Allshouse et al., 2015)

Global Consensus Statement


A decade after the Women's Health Initiative—the experts do agree

Cynthia A. Stuenkel, M.D., N.C.M.P.,[a] Margery L. S. Gass, M.D., N.C.M.P.,[b] JoAnn E. Manson, M.D., Dr.P.H., N.C.M.P.,[c] Rogerio A. Lobo, M.D.,[d] Lubna Pal, M.B.B.S., M.R.C.O.G., M.Sc., N.C.M.P.,[e] Robert W. Rebar, M.D.,[f]

- Recommend systemic MHT for women with premature ovarian insufficiency at least to age 51
- The use of custom-compounded hormone therapy is not recommended

How Much Calcium and Vitamin D?

Goal: reduce fractures and avoid increase in kidney stones

- Combine with HT/ET
- Total daily calcium intake of 1,200 mg
- Vitamin D intake of and 600 to 800 IU

Genitourinary Syndrome Of Menopause (GSM)

Vulva
Vagina
Cervix
Urinary tract

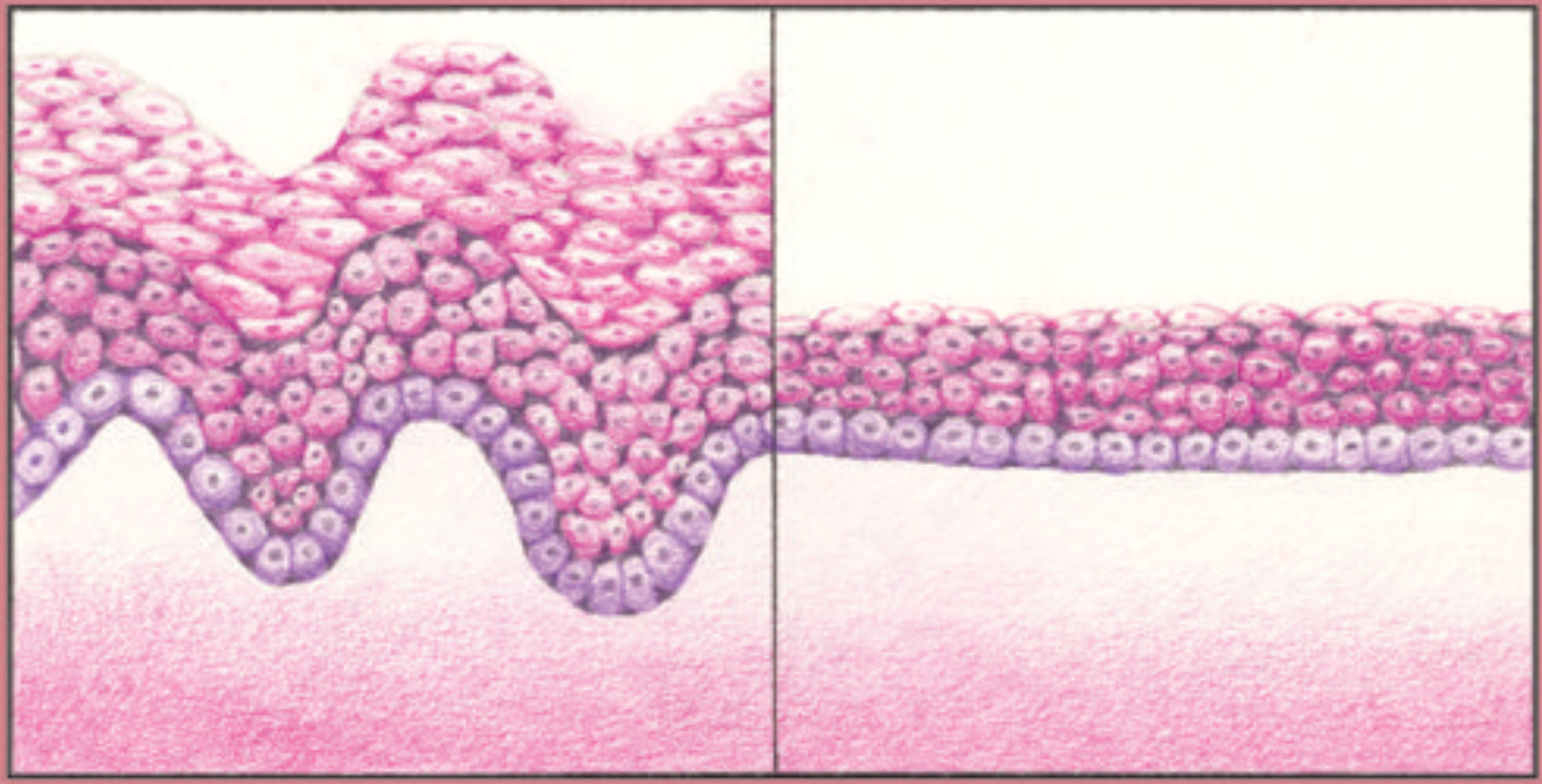
Genitourinary Syndrome Of Menopause (GSM)

- The terms vulvovaginal atrophy (VVA) and atrophic vaginitis inadequately describe the range of menopausal symptoms associated with physical changes of the vulva and vagina.

- Neither term includes reference to the lower urinary tract.

Genitourinary Syndrome Of Menopause (GSM)

- The word atrophy has negative connotations for midlife women
- The word vagina is not a generally accepted term for public discourse or for the media.



Well-Estrogenized
Premenopausal State

Low-Estrogen
Postmenopausal State

Goals:

- Alleviate symptoms
- Preserve sexual function
- Clarify diagnosis

Vulvar Symptoms

- Irritation
- Dyspareunia
- Diagnostic confusion

Consider

- Lichen sclerosis
- VIN
- Biopsy after E_2

Vulvar Changes

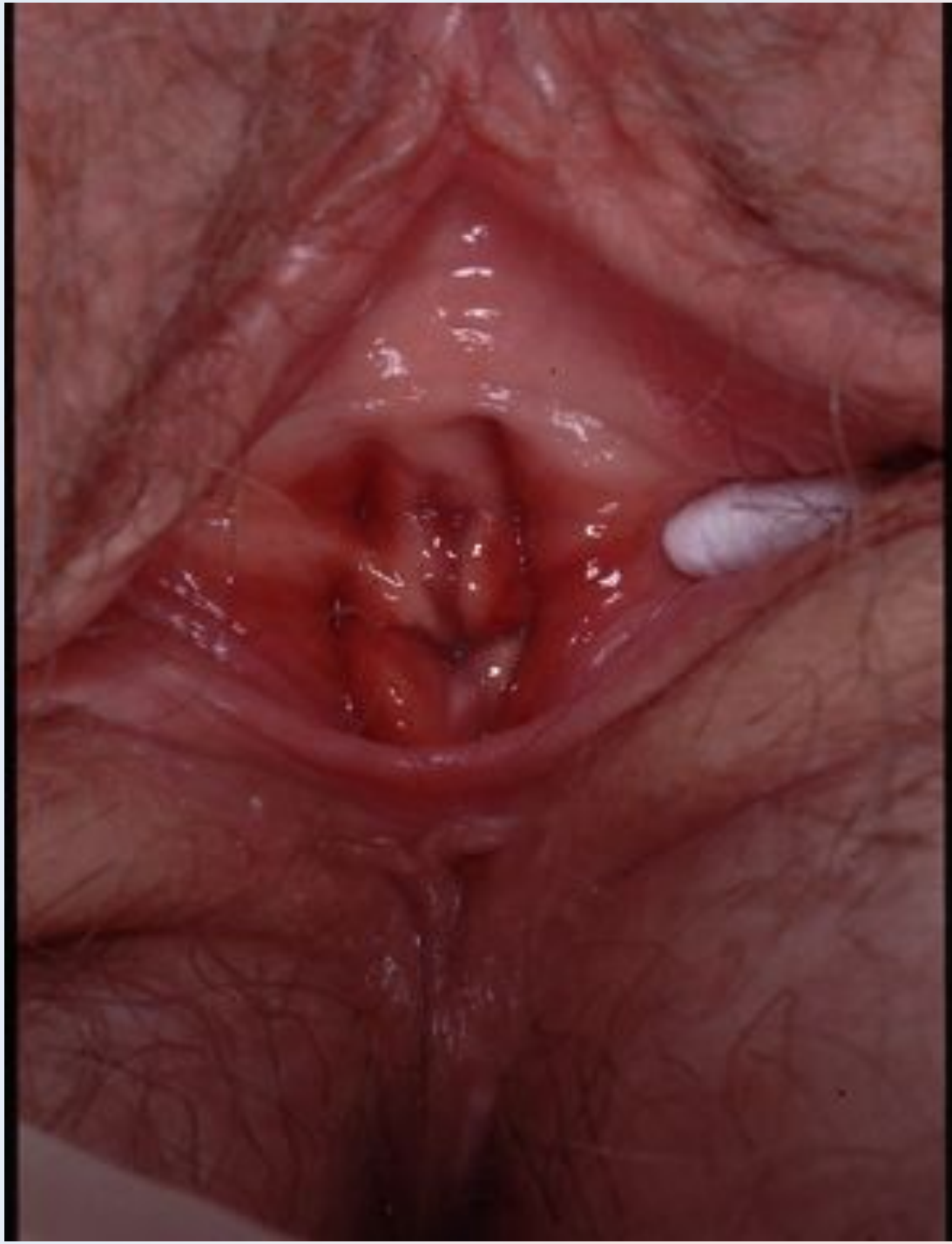


Photo courtesy of
Dr. Hope Haefner

Care of the vulva/perineum

No Products

- Wash with water after urinating or defecating
- Hand held shower sprayer
- Non-alcohol hypo-allergenic baby wipe *if no access to water*
- No soap, body wash, body creams
- No residue of detergent or fabric softener on underwear

Natural Beauty Cleansing Bar

- pH of 4.5
- No soap or detergent
- Made by Nature's Plus

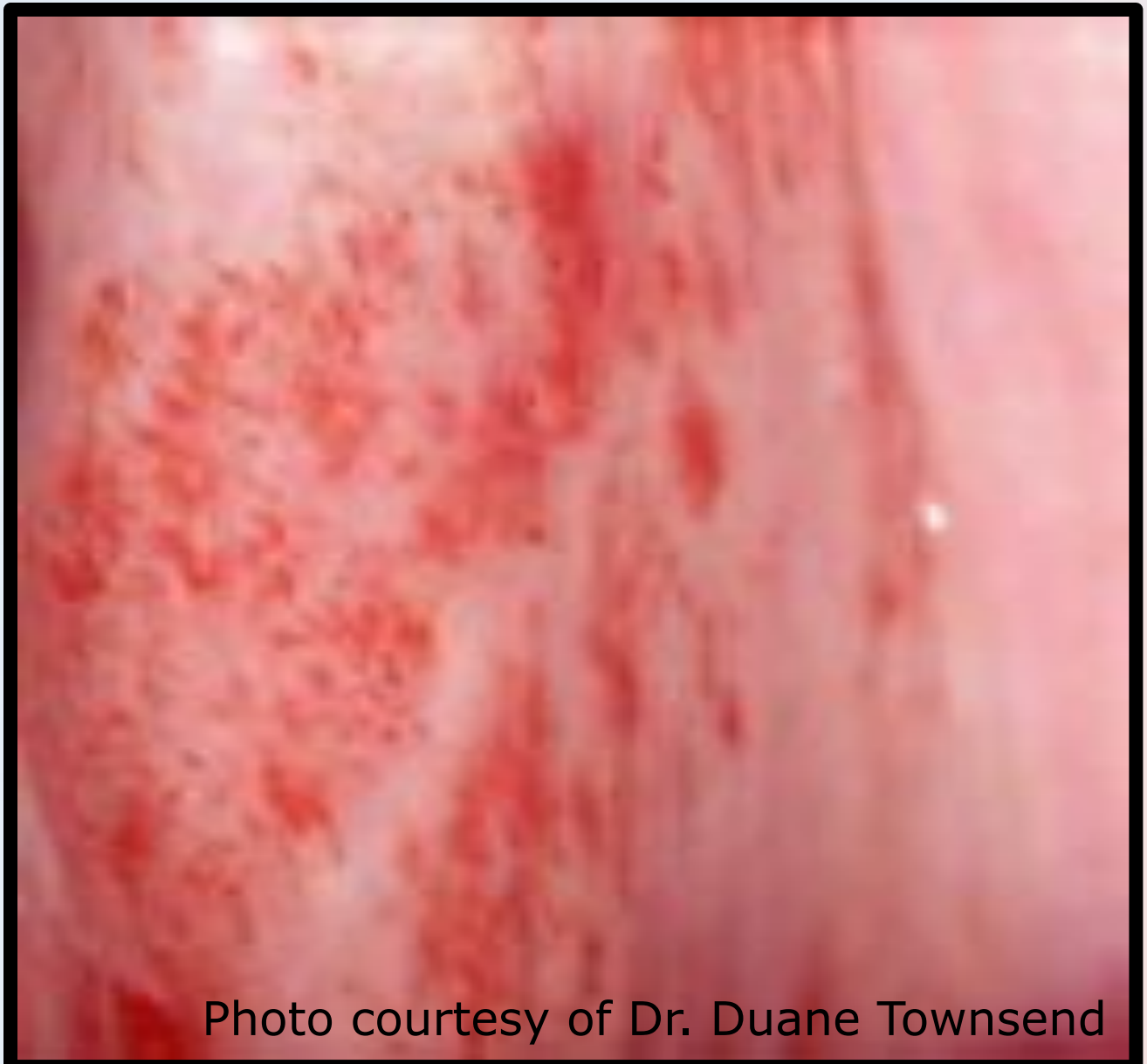
Vaginal Symptoms

- Dryness
- Dyspareunia
  - Decreased lubrication
  - Less vaginal elasticity
  - Skin irritation
  - Introital shrinkage
- Spotting or bleeding
- Discharge/vaginitis
  - Yellow creamy
  - Bloody

(Kingsberg et al., 2013)

Vaginal Epithelium

- Thin, friable epithelium
- Petechiae
- Low maturation index
- pH > 4.6



Cervix

- Thin, friable epithelium
- May be over-diagnosed as LSIL or ASC-US
- Colposcopy may be confusing
- Vaginal E_2 4-6 weeks prior to pap or colposcopy (expert opinion)

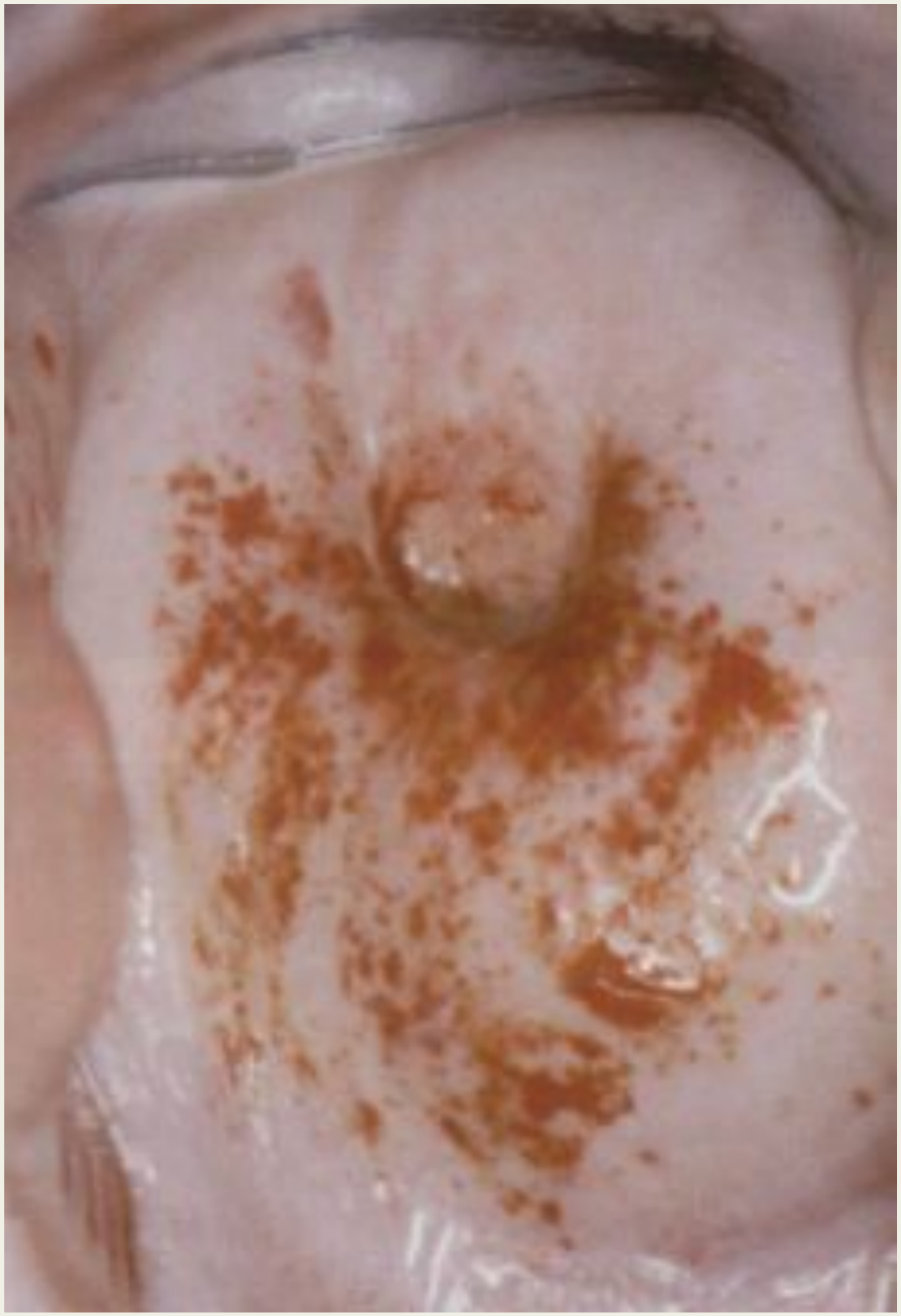


Photo courtesy of Dr. Barbara Apgar

Urinary Tract Thinning

- Urinary tract infection
- Urge incontinence
- Irritative symptoms:
  - Urgency
  - Frequency
  - Dysuria
- Less effect on stress incontinence

Non-prescription Treatments

- Moisturizers, lubricants first line
- Hyaluronic acid gel, prebiotic
- Encourage resumption of penetrative sex (as appropriate for given patient)

(Chen et al., 2013)
(Nappi & Lachowsky, 2009)
("Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society," 2013)

Drugs@FDA
FDA Approved Drug Products

Local or Systemic Estrogen Therapy

Oral Ospemiphene

PRESCRIPTION TREATMENTS

Topical/ Vaginal Estrogen

Composition	Brand Name	Dose and sig
Vaginal cream 17β-Estradiol	Estrace® Vaginal Cream	Initial: 2.0-4.0g/d for 1-2 wk Maintenance: 1.0g/d (0.1 mg/g)
Vaginal cream conjugated estrogens	Premarin® Vaginal Cream	0.5-2.0 g/d or twice/wk (0.625 mg/g) Use lowest effective dose
Vaginal ring 17β-estradiol	Estring®	Ring contains 2 mg releases 7.5 mcg/d for 90 d
Vaginal ring Estradiol acetate	Femring® (**Systemic dose and indication**)	Systemic dose ring for 90 d 12.4mg releases 50mcg/d 24.8mg releases 100mcg/d
Vaginal tablet Estradiol hemihydrate	Vagifem® 10mcg (25mcg no longer available)	Initial: 1 tablet/d for 2 wk Maintenance: 1 tab 2x /wk

NAMS Position Statement Menopause. 2013:20(9)

Systemic Absorption

- Low-dose vaginal estrogen increased plasma estradiol levels during chronic administration
- Not above the normal range of ≤ 20 pg/ml.
- Each preparation associated with peaks at 8 h and return to baseline at 12 h

(Santen RJ. 2015)

Topical Vs. Systemic E_2

Preferred mode of delivery when vulvar or vaginal symptoms are the only complaint

- Topical more effective than systemic oral ET
- Evidence of lower risk

(Nappi & Lachowsky, 2009)
("Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society," 2013)
(Cody, Richardson, Moehrer, Hextall, & Glazener, 2009)

Urinary Tract Symptoms
Local Vaginal E_2

- Provides greater benefit than nonhormonal interventions
- Improves, may cure:
  - Overactive bladder
  - Incontinence
  - Urinary tract infections
  - Urethritis (irritative) symptoms

(Nappi & Lachowsky, 2009)
("Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society," 2013)
(Cody, Richardson, Moehrer, Hextall, & Glazener, 2009)

Vaginal ET and Endometrial Carcinoma

- P not indicated with low-dose local ET

- Closer surveillance if:
  - Using a higher dose of vaginal ET
  - At high risk for endometrial cancer
  - Symptoms of spotting or bleeding

North American Menopause Society. *Menopause*. 2013;20(9):886-904.

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Vaginal ET for GSM With Breast Cancer

- Nonhormone dependent cancer: management is similar to that for women without cancer
- Hormone-dependent cancer: management depends on the woman's preference ***in consultation with her oncologist***

(North American Menopause Society. *Menopause*. 2013)

Ospemiphene (Osphena)

- 60mg ORAL
- Estrogen agonist/antagonist
- Selective estrogen-receptor modulator (SERM)

Ospemiphene: Effectiveness

Improvement in:

- Dyspareunia
- Vaginal maturation index
- Vaginal pH
- Vaginal dryness

(Cui et al., 2014)
("Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society," 2013)

Ospemiphene

Prescribing information similar to estrogens and other SERMs

Contraindicated in

- Genital bleeding unknown etiology
- Estrogen-dependent neoplasia
- DVT, PE, CVA, MI history or current

Ospemiphene: Questions

- Antitumor effect in experimental breast cancer models
- Data in women with breast cancer or at high risk of developing breast cancer are lacking
- Positive effects on bone turnover

(Cui et al., 2014)
("Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society," 2013)
(Ylikorkala et al., 2003)
(Komi et al., 2004)

Vasomotor Symptoms
VMS

Hot Flushes

Hot Flashes

Night Sweats

VMS Definition

A relatively sudden, discrete episode of intense heat that starts at the chest and travels upward toward the neck and face, causing flushing.

“Women with hot flashes have more sensitive thermostats in their brain, so are comfortable only in a small range of temperatures”

VMS can:

- last for several seconds to several minutes.
- be followed by sweating and heart palpitations.
- happen repeatedly throughout the day and night.

- Experienced by up to 75% percent of menopausal women
  - May start during peri-menopause
  - Last <2 to 10 years, then wane
  - 25% have VMS > 5 years after menopause
- Smoking, obesity, depression are risk factors

(Stuenkel et al., 2015)
(Avis et al., 2004)
(Mirkin et al., 2015)
(Järvstråt et al., 2015)
(Gallicchio et al., 2015)

VMS Mimics

- Anxiety disorders
- Alcohol, spicy food, food additives (MSG, sulfites)
- Thyroid hormone excess
- Chronic infection, TB
- Postgastric surgery dumping syndrome
- Mastocytosis and mast cell disorders

VMS Mimics

- Carcinoid syndrome (flushing without sweating)
- Lymphoma, thyroid, pancreatic, renal cell CA
- Pheochromocytoma (hypertension, flushing, sweating)

Medications

- Thyroid hormone excess
- Opioid use or withdrawal
- SSRIs
- Nicotinic acid (intense warmth, itching lasting up to 30 min)
- Calcium channel blockers
- Medications that block estrogen action

Estrogen

HORMONE THERAPY

VMS and Hormone Therapy

ET with or without progestogen is the most effective treatment of menopause-related VMS

(Schmidt, 2012)

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The North American Menopause Society

E Contraindications

- Unexplained vaginal bleeding
- Liver dysfunction or disease
- Hx of CHD, CVA, TIA, DVT, PE
- Known clotting disorder, thrombophilia
  - protein C, protein S, or antithrombin deficiency,
- Untreated hypertension
- Hx of breast, endometrial cancer, or other estrogen-dependent tumor

Exercise Caution

- Gallbladder disease (oral ET)
- Hypertriglyceridemia (400 mg/d) (oral ET)
- Migraine with aura (oral ET)
- Diabetes
- Hypoparathyroidism (risk hypocalcemia)
- Benign meningioma
- High risk of heart disease

Consider Non Hormonal Therapy

- ≥ One 1st degree relative(s) with breast CA
- Otherwise at increased risk of breast CA

- Breast Cancer Risk Score:

http://www.cancer.gov/bcrisktool/

Choice of HT Regimen

If no uterus: ET estrogen only

“First Line” Transdermal Estrogen

- Women needing “steady state” drug release
  - Daily mood swings
  - Migraine headaches
- May be less likely to reduce libido than oral
- Difficulty taking a pill
- Obesity, diabetes, or metabolic syndrome

Choice of Estrogens

- Start *low dose* transdermal; oral or vaginal
- If suboptimal response, modify by
  - Increase the estrogen dose
  - Change the estrogen preparation
  - Change delivery systems:

    Transdermal $\rightleftarrows$ Oral

    Gel $\leftrightarrows$ Patch

    Patch $\leftrightarrows$ Ring

Choice of Estrogens

Injectable estrogen not recommended

- Dosage equivalencies are not known
- Estrogen cannot be discontinued easily

Consideration

Women taking thyroid medication may need dose adjustments

Estrogen Dose Equivalents

17-β-estradiol (E_2) is the only formulation considered bioidentical*

Estrogen	Standard	Low Dose	Ultra-Low Dose
Conjugated equine estrogen (CEE)	0.625	0.3	
Oral E_2	1mg	0.5mg	
Transdermal E_2	0.05mg	0.025mg	0.014 mg
Ethinyl estradiol	5mcg	0.025mg	

*2015 Position Statement of the Endocrine Society.

Oral	Brand	Source	Dose Equivalents
Conjugated equine estrogen	Premarin	Pregnant mares urine	0.625mg
Synthetic conjugated estrogen	Cenestin, Enjuvia	Plant derived: Soy/ Yams	0.625mg
Esterified estrogens	Menest	Plant derived: Soy/ Yams	0.625mg
E_2 micronized	Estrace	Plant derived: Soy/ Yams	1mg
Estropipate	Ogen, Ortho-Est	Plant derived: Yams	0.625mg

Transdermal Patch	Brand	Source: Plant derived	Dose Equivalents
E_2 matrix	Alora Climara Vivelle Vivelle-Dot Menostar	Soy/Yams	0.05mg
	E_2 is embedded in the adhesive layer that is applied directly to the skin.		
E_2 reservoir	Estraderm	Soy/Yams	0.05mg
	E_2 is contained in a drug reservoir and its release is controlled by a copolymer membrane; contains more layers than matrix patch		

Transdermal Gel	Brand	Source: Plant derived	Dose Equivalents
E_2 gel No direct comparison trials. Dose equivalents are estimates	Divigel	Soy/Yams, Sunflower seeds, Rapeseed, Poppy seeds, Pine trees	1g packet
	Elestrin	Soy, Rapeseed, Pine tree wood	2-3 pumps
	Estrogel	Oil seed, Soy, Pine tree wood	.035mg
E_2 emulsion	Estrasorb	Soy	2 packets
E_2 spray	Evamist	Soy/ Yams	just over 3 sprays

Systemic/ Vaginal Estrogen

Composition	Brand Name	Dose and sig
Vaginal ring Estradiol acetate	Femring ®	Systemic dose ring for 90 d 12.4mg releases 50mcg/d
Vaginal ring Estradiol acetate	Femring ®	Systemic dose ring for 90 d 24.8mg releases 100mcg/d

Estrogen and Progestogen

HORMONE THERAPY

Choice of HT Regimen

If uterus present:

- Goal is to avoid vaginal bleeding entirely
- Or if using progestin cyclically, make the bleeding predictable
- Consider LNG IUD 20mcg

Choice of HT Regimen

Choose based on bleeding pattern

- Recent spontaneous or induced bleeding
  - Use sequential 14 out of 28 days
- No bleeding for >2-3 cycles
  - Use continuous combined
  - Transition to continuous as soon as possible

Continuous P Better Than Sequential

- Oral and transdermal similar risk
- Type of progestin similar risk
- Continuous EP →76% reduction in endometrial cancer risk compared to background population
- Sequential EP:
  - –69% risk elevation if P was used monthly
  - –276% risk elevation if P was used q 3-mos

(Jaakkola, Pukkala, K.Lyytinen, & Ylikorkala, 2012)

Lowest Effective Progestogen Doses

- Oral
  - Medroxyprogesterone 2.5 mg
  - Micronized progesterone 100 mg
  - Norethindrone acetate 0.1 mg
  - Drosperinone 0.5 mg
- Transdermal
  - Norethindrone acetate 0.14 mg
  - Levonorgestrel 0.015 mg

Lowest Effective Progestogen Doses

- 20mcg levonorgestrel IUDs (Mirena, Liletta)
- Lower dose levonorgestrel IUDs (Skyla) no data

(Stuenkel et al., 2015)
(Wildemeersch D, et al., 2007)
(Orbo A, et al. 2014)
(Morelli M, et al.,2013)

Indication for Androgen?

- Add to estrogen if moderate to severe VMS not improved by estrogen alone
- Not strong correlations between endogenous androgen levels & overall well-being or mood
- Not recommended to check androgen levels
- Used off-label for sexual complaints, anti-aging, well being

(Guerrieri et al., 2014)
(Flores-Ramos, Moreno, Heinze, Aguilera-Perez, & Pellicer Graham, 2014)

E plus Testosterone

Moderate to severe VMS not improved by estrogen alone

- Previously Estratest
- COVARYXT®
  - 1.25 mg of Esterified Estrogens, and 2.5 mg of Methyltestosterone
- COVARYX® H.S.
  - 0.625 mg of Esterified Estrogens, and 1.25 mg of Methyltestosterone

Bazedoxifene 10mg with CE 0.45 mg Duavee®

- FDA approved tissue selective estrogen receptor modulator (SERM) plus CE
- Progestin-free
- Reduces VMS frequency and severity
- Prevents loss of bone mass

(Taylor & Ohleth, 2012)

Bazedoxifene 10mg with CE 0.45 mg Duavee®

- No increase in endometrial hyperplasia
- Amenorrhea, breast tenderness adverse event rates and overall safety similar to placebo

(Taylor & Ohleth, 2012)


Non-Hormonal Interventions

Use of nonhormonal therapies is high

- 50% to 80% of North American women use nonhormonal therapies for VMS at midlife

North American Menopause Society. *Menopause*. 2015;22(11).

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Selective Seratonin Reuptake Inhibitor's (SSRIs)

Seratonin Norepinephrine Reuptake Inhibitor's (SNRI's)

Gabapentin, Clonidine

NON ESTROGEN PHARMACOLOGIC TREATMENTS

Recommend: Prescription therapies

- FDA-approved low-dose paroxetine salt
- Other SSRIs and SNRIs yielding significant VMS reductions in large RCTs
- Gabapentin and pregabalin

Stuenkel et al. Endocrine Society Guideline on Menopause 2015 North American Menopause Society. *Menopause*. 2015;22(11).

ENDOCRINE SOCIETY

NAMS THE NORTH AMERICAN MENOPAUSE SOCIETY

BRISDELLE™

Drugs@FDA
FDA Approved Drug Products

Paroxetine 7.5 mg

- Commonly used SSRI Paroxetine (Paxil)
- Brisdelle™ is the only FDA-approved **nonhormonal** therapy to treat VMS
- The most common adverse reactions compared to placebo:
  - Headache
  - Fatigue/malaise/lethargy
  - Nausea/vomiting

(Manson et al., 2015)
(Portman et al., 2014)

Other SSRIs, SNRIs

- Large RCTs show significant VMS reductions with
  - —Paroxetine
  - —Escitalopram
  - —Citalopram
  - —Venlafaxine
  - —Desvenlafaxine

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Choice

Depends on

- Coexistence of mood disorder
- VMS more bothersome day or night
- Medication sensitivity
- Pharmacogenetic testing
- Patient preference

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SSRI Caution With Tamoxifen

Paroxetine and other CYP2D6 inhibitors (e.g., fluoxetine, duloxetine) should be used with caution in women on tamoxifen due to **potential reduction in effectiveness of tamoxifen**

Gabapentin, Pregabalin

- Moderate reduction of VMS
- Frequent side effects
- Variability of effects dictate individualized approach
- Many of the studies are on breast cancer patients

(Villaseca, 2012)
(Nelson et al., 2006)
(Montasser et al., 2015)
(Manson et al., 2015)
(NAMS 2015)

Clonidine

- If not responsive to SSRIs/SNRIs, gabapentin, pregabalin
- If no contraindications
- Less effective
- More side effects
- Transdermal patches are preferred over tablets-- more stable blood levels.

(Stuenkel et al., 2015)
(Manson et al., 2015)
(NAMS 2015)

Prescription therapies: Considerations

- Start lowest dose first; titrate up to effect, tolerance
- When stopping, taper therapy over 1-2 wk
- Re-evaluate carefully and regularly (eg, every 6-12 mo)

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Lifestyle Changes

- Triggers:
  - Hot drinks, hot or spicy foods
  - Cigarettes
  - Alcohol
  - Caffeine?
- Cool room temperature
- Dress in light breathable layers
  - remove outer layers quickly at onset

(Stuenkel et al., 2015)
(Kronenberg & Fugh-Berman, 2002)
(Huntley & Ernst, 2003)

Non Pharmacologic Recommended Therapies

- Cognitive behavioral therapy (CBT)
- Clinical hypnosis: Elkins protocol

North American Menopause Society. *Menopause*. 2015;22(11).

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May be beneficial

- Weight loss
- Mindfulness-based stress reduction
- S-equol derivative of soy
- Stellate ganglion block

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Weight Loss

- Decreases VMS
- Motivates women to engage in this health-promoting behavior!

(Thurston et al., 2015)

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May have other health benefits Unlikely to alleviate VMS

- Exercise
- Yoga
- Paced respiration
- Acupuncture

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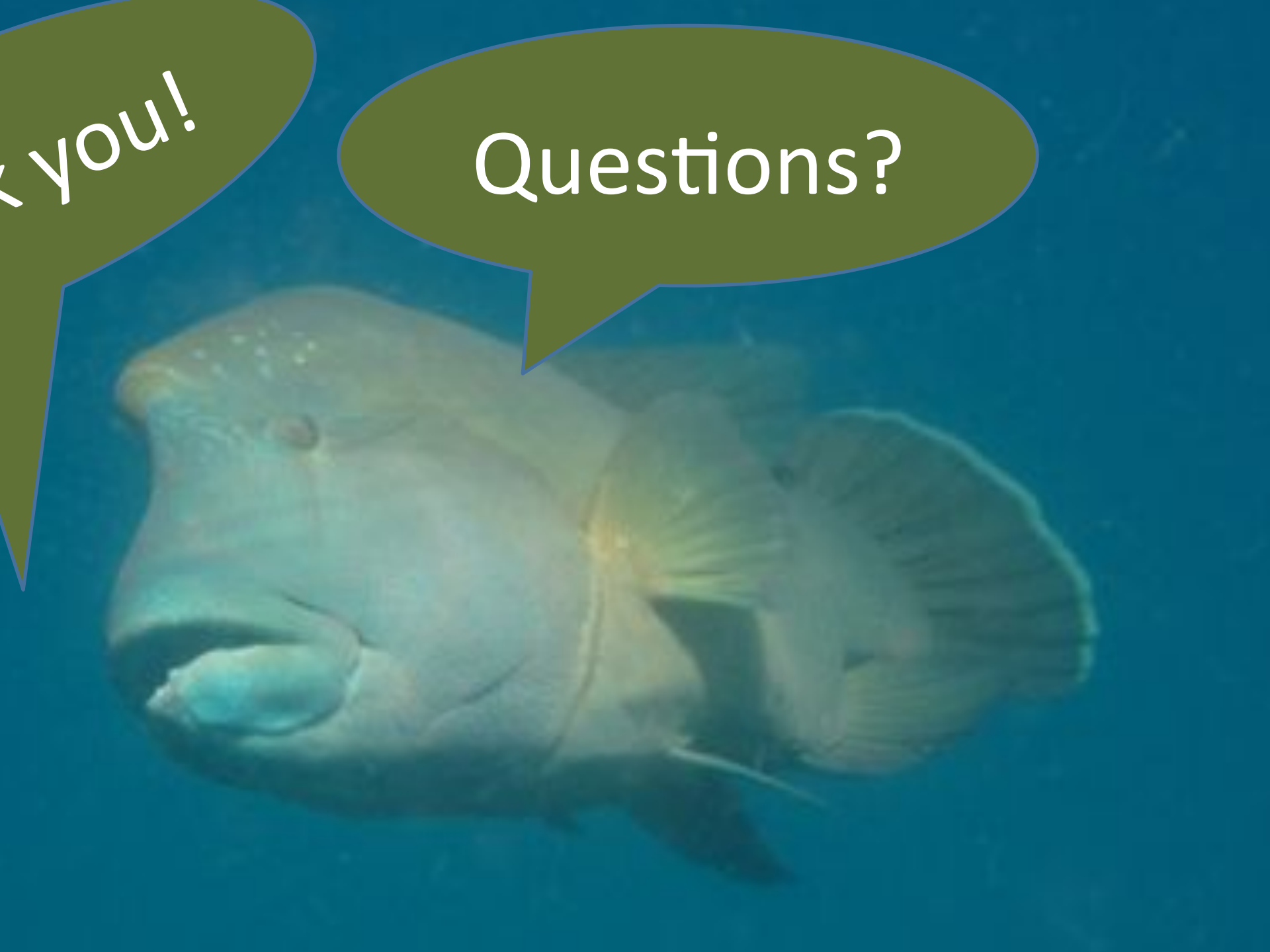
Exercise

- Not helpful for VMS
- Helpful for bone density
- Cardiovascular benefit
- Decreased risk of memory problems

(Aiello EJ. 2004)


k you!
Questions?

For your reference

SUPPLEMENTAL SLIDES

A decade after the Women's Health Initiative—the experts do agree

Cynthia A. Stuenkel, M.D., N.C.M.P.,[a] Margery L.S. Gass, M.D., N.C.M.P.,[b] JoAnn E. Manson, M.D., Dr.P.H., N.C.M.P.,[c] Rogerio A. Lobo, M.D.,[d] Lubna Pal, M.B.B.S., M.R.C.O.G., M.Sc., N.C.M.P.,[e] Robert W. Rebar, M.D.,[f]

The statement was endorsed by 15 medical associations

Published in:

The North American Menopause Society (*Menopause*),

The American Society for Reproductive Medicine (*Fertility and Sterility)*

The Endocrine Society (*Journal of Clinical Endocrinology and Metabolism*)

Aug 2012

Global Consensus Statement on Menopausal Hormone Therapy (MHT)

- MHT is the most effective treatment for menopause VMS at any age
- Benefits are more likely to outweigh risks
  - If bothered by moderate to severe symptoms
  - For healthy women ≤ age 60
  - <10 years of menopause

Osteoporosis-related Fractures

MHT is effective and appropriate to use for prevention in:

- **At-risk** women
- < age 60 years
- Or < 10 years after menopause.

And finally…


A decade after the Women's Health Initiative—the experts do agree

Cynthia A. Stuenkel, M.D., N.C.M.P.,[a] Margery L. S. Gass, M.D., N.C.M.P.,[b] JoAnn E. Manson, M.D., Dr.P.H., N.C.M.P.,[c] Rogerio A. Lobo, M.D.,[d] Lubna Pal, M.B.B.S., M.R.C.O.G., M.Sc., N.C.M.P.,[e] Robert W. Rebar, M.D.,[f]

- Lower risk with transdermal therapy
- The use of custom-compounded hormone therapy is not recommended
- Current safety data do not support the use of MHT in breast cancer survivors

Menopausal Symptoms: Comparative Effectiveness of Therapies

- Comprehensive literature review
- For Agency for Healthcare Research and Quality (AHRQ)

www.effectivehealthcare.ahrq.gov/reports/final.cfm

(Grant et al., 2015)

NAMS Algorithm and App

- moderate to severe VMS
- genitourinary symptoms
- links to treatment options
- The app calculates an atherosclerotic cardiovascular disease (CVD) risk score for each patient.

Botanicals

- Not better than placebo:
  - Soy isoflavones
  - Red clover isoflavones
  - Evening primrose oil
  - Dong quai
  - Ginseng
  - Vitamin E
- No studies: Chasteberry (Vitex)

(Pitkin J. 2012.)
(Rada G. *Cochrane Database Syst Rev.* 2010.)
(Krebs EE. 2004.)
(Alekel DL. 2015)

Cimicifuga Racemosa
Black Cohosh

- Not a phytoestrogen
- Has partial serotonin agonist action
- May have a modest effect on VMS
- Most trials on Remifemin®40 mg per day (20 mg BID)
- Effect on quality of life, sexuality, bone health, night sweats and cost-effectiveness warrants further investigation.

ach MJ. *Cochrane Database of Systematic Reviews*:2012)
aser B. 2011)
rma N D. 2011)

Non-pharmacological Therapies

Not shown to reduce VMS:

- Homeopathy
- Magnetic therapy

(Rada G. *Cochrane Database Syst Rev.* 2010)

Do not recommend at this time

- Over-the-counter supplements
- Herbal therapies
- Vitamins
- Relaxation
- Calibration of neural oscillations
- Chiropractic intervention

North American Menopause Society. *Menopause*. 2015;22(11).

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

Acupuncture: Data Conflicting

- Improves VMS
- Not greater than sham for frequency
- Possibly greater than sham for severity
- "Light touch of the skin might induce a limbic touch response, resulting in emotional and hormonal reactions such as release of β-endorphin"

(Chiu, HY et al. 2015)
(Rada G. Cochrane Database Syst Rev. 2010)

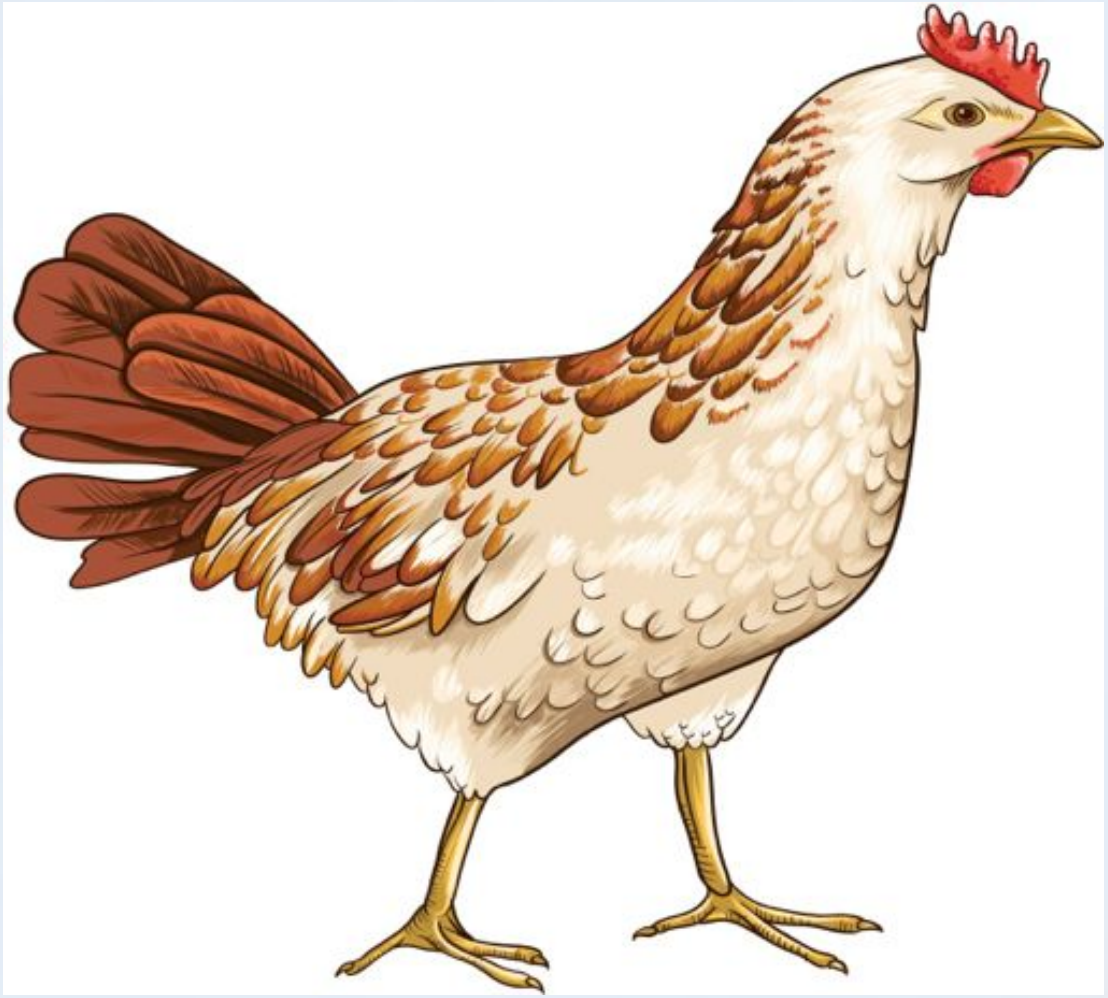
Sleep

Difficulty Falling Asleep

Early or Easy Awakening

Less deep sleep due to VMS

Which Comes First?



Question:

Are sleep problems in middle-aged women a primary disorder?

Or a consequence of VMS
….or underlying depression?

Rule Out:

- Primary sleep disorders:
  - Obstructive sleep apnea
  - Restless legs syndrome
- Psychiatric disorders:
  - Depression
  - Anxiety

VMS
Depression Symptoms

- Associated with different patterns of sleep disturbance
- Depression is associated with difficulty falling asleep and waking up earlier than desired
- VMS are related to frequent awakenings during sleep

Androgen?

- Moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogens alone.
- Not strong correlations between endogenous androgen levels & overall well-being or mood
- Not recommended to check androgen levels

Guerrieri GM. *Menopause.* 2014
Flores-Ramos M. *Gynecol Endocrinol.* 2014

Anxiety

VMS strongly associated with anxiety

History vs. New Onset Anxiety

- A history of anxiety disorder strongly predicts recurrence.
- Among those **without high anxiety at baseline** there may be vulnerability to onset of new anxiety during perimenopause & menopause

Bromberger JT. *Psychol Med* 2011.
Soares CN. *Menopause*. 2014.

Treatment

Antidepressants may have a positive effect on alleviating anxiety symptoms among perimenopausal and postmenopausal women.

Cognition

Memory

Verbal Fluency

Cognition- Verbal

- Age-independent menopause effects on verbal function
- Verbal fluency mechanisms are vulnerable during the menopausal transition.

Berent-Spillson A. *J Clin Endocrinol Metab*. 2012.

Soy Isoflavin Supplementation

Some data showing a positive effect:

- improving summary cognitive function
- visual memory

Cheng PF et al.. Menopause 2015

Cognition- Grandparenting

- Minding grandchildren for ≥5 days/wk predicts lower working memory performance and processing speed.
- Highly frequent grandparenting predicts lower cognitive performance.
- The highest cognitive performance is demonstrated by postmenopausal women who spend 1 day/week minding grandchildren

Burn KF et al. Menopause. 2014

HT
Cognitive Aging/Dementia

- Evidence is mixed on effect of HT
- HT not recommended at any age for preventing or treating cognitive aging or dementia

NAMS position statement. *Menopause* 2012.

NAMS
The North American Menopause Society

Caffeine

- Thought to increase VMS
- Studies show conflicting results regarding benefit to cognition
- Not adequate data

Faubion SS Menopause 2015

Body Pain

Arthralgia

Myalgia

Body Aches

CEE and Musculoskeletal Symptoms

- There may be incremental benefit from HT for joint or musculoskeletal symptoms
- Greater benefit in perimenopausal or recently postmenopausal women

Chlebowski RT. *Menopause.* 2013.

Headache

Migraine with Aura

Migraine Without Aura

Menstrual Headache

Migraine **Without** Aura in Perimenopause

- Fluctuating estrogen levels and estrogen "withdrawal" trigger menstrual migraine without aura
- Maintain a stable estrogen environment
  - Continuous CHC
  - Continuous transdermal E_2

MacGregor EA. *Maturitas.* 2012

Migraine **With** Aura

- Migraine with aura associated with a high estrogen environment
- Treatment with E_2 *not indicated*

MacGregor EA. *Maturitas.* 2012

Migraine
Non-hormonal Treatment Options

- Evidence of efficacy for fluoxetine and venflaxine
- Less evidence for gabapentin

MacGregor EA. *Maturitas.* 2012

Cognition- Grandparenting

- Minding grandchildren for ≥5 days/wk predicts lower working memory performance and processing speed.
- Highly frequent grandparenting predicts lower cognitive performance.
- The highest cognitive performance is demonstrated by postmenopausal women who spend 1 day/week minding grandchildren

(Burn et al., 2014)

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