MANAGEMENT OF MENOPAUSAL BLUES

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MENOPAUSAL BLUES CASE BASED APPROACH

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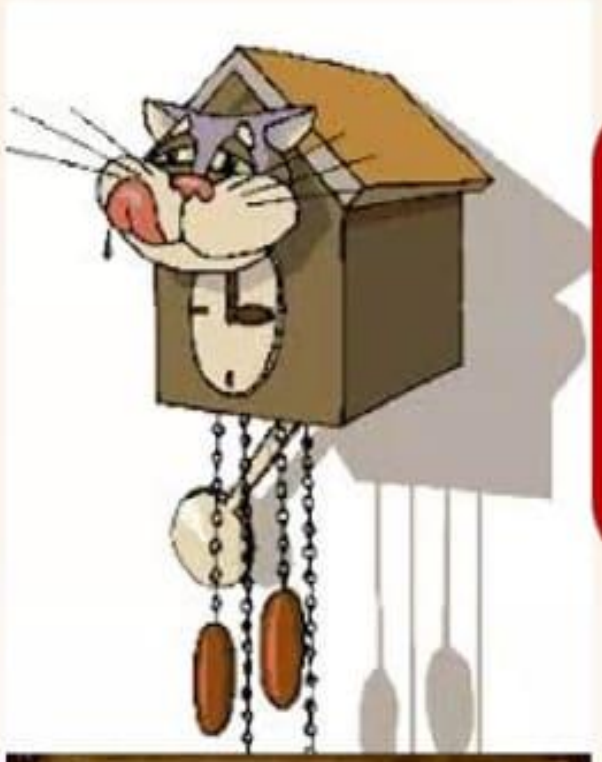
1965 HRT becomes available in the UK

1993 - starts in the USA – the Women's Health Initiative

1996 : Million Women Study starts in UK

2002 : WHI study stopped the combined (oestrogen and progestogen) HRT arm of the study prematurely



2003 Both doctors and HRT users are confused regarding safety issues. Many doctors advise their patients to come off HRT. Some women stop taking HRT immediately

2003-07
Amongst continuing health safety fears, **HRT users fall from 2 million to less than 1 million in the UK**

MHT – Scenario today

- The pendulum has swung so widely, from "hormone therapy is good for all women" to "it's bad for all women" to now somewhere in between.
- **This really does seem to be the appropriate place for the pendulum to come to rest**. But it's been a long saga getting there.

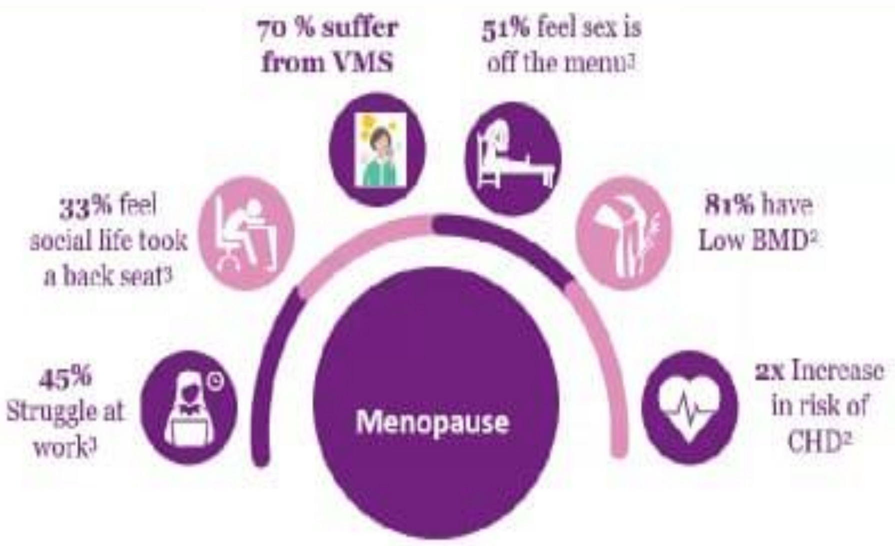
Dr. JoAnn Manson, lead investigator of the Women's Health Initiative and a professor of medicine at the Harvard School of Public Health

Femoston®

Menopause Strikes Early in Indian Woman at an Average Age of 46.2 Years*[1]

About 25 Years of Her Life She Silently Suffers in Estrogen Deficiency and Menopausal Distress#.

Consequence of estrogen deficiency is far reaching



1. Ahuja M. Age of menopause and determinants of menopause age: A PAN India survey by IMS. J Midlife Health. 2016;7(3):126-131.
2. Midlife health. 2018 jul-sep; 9(3):117-122
3. British menopause society fact sheet

*Average age of menopause in Western World is 51 Years

#Average life expectancy of Indian Women is 70.3 Years

CASE 1

Priya, married woman of 46 years , having periods in every 3 to 4 months for last 1 year.

She is not so bothered by this but by the fact that she is **unable to sleep at night** , **is having hot flashes** and is getting easily irritated at work and is **depressed.**

She has been to several gynaecologists and all have just reassured her and asked her to wait for periods to stop.

She is a non smoker with no medical problems and her BMI is 26.

- **Is she in Menopause? How do I confirm it?**
- **What do I advice her to relieve her symptoms ?**
- **Options: COC/MHT/ SSRI**

CONFIRMATION

- FSH is not essential to make a diagnosis.
- SWAN study – changes in menstrual patterns is a better predictor of menopausal stages than serum FSH
- In patients who want reassurance … FSH > 25 can be reassuring.

Perimenopausal -- MT

- Sequential MHT 1/10
- Low-dose oral contraceptive is often used to control bleeding and provide contraception and relieve her VMS
- Other Options – SSRI

MHT OR COC

- HRT was better than COCP for lumbar spine bone density
- No significant differences between HRT and COCP at total hip/femoral neck/bone markers

MHT	COCP
more 'physiological'	'peer friendly'
does not interfere with ovulation	contraception
negative connotations	reminder of subfertility

Cartwright,Robinson,Seed,Fogelman,Rymer J Clinical Endocrinol Metabol 2016

Case Contd…

Priya , is taking low dose OC and is quite comfortable.

She is now 48 years of age and wants to know if she has to continue it or stop it.

SWITCH OVER REGIMES

1. **Stop OCP** – FSH after 2 – 4 weeks.

2. From OCPs to HT
- Age of 48-50 years
- Serum FSH:LH ratio of > 1
- FSH > 30 IU/L

Would you consider SSRI in this case as she has depression , VMS and sleep disturbances ?

Use of SSRI or SNRI

Patient Selection:

- Whom estrogen is contraindicated,
- Not well tolerated,
- For women who have stopped estrogen and are experiencing recurrent symptoms but wish to avoid or cannot resume estrogen
- **VMS with depression**

Recommendations for SSRI

- **Paroxetine, citalopram, or escitalopram as our first-line drugs** (**Grade 2B**).

Low-dose paroxetine (10 -12.5 mg/day) as the first choice since this is the only agent that has received approval by the US Food and Drug Administration (FDA) for the treatment of hot flashes

- Sertraline and fluoxetine not recommended because neither has a clinically important effect on hot flashes.

- **For women with predominantly night time symptoms: Gabapentin (Grade 2C).**

A single bedtime dose of gabapentin (300 mg, or as low as 100 mg if needed, titrating up to 900 mg until symptom relief or side effects), which takes advantage of the sedating effect of gabapentin while minimizing daytime sedation

- For women on tamoxifen for any indication : Citalopram, escitalopram, or **venlafaxine** to treat hot flashes, as they have minimal effects to block *CYP2D6* (NO PARAXOTINE)

Venlafaxine: sustained release preparation starting with 37.5 mg/day for one week, increasing to 75 mg/day after the first week to reduce the incidence of initial nausea

Case 2

Anju, a 48-year-old female , presents to your clinic for evaluation of hot flashes. For the last year she has been experiencing 6-7 hot flashes per day and often wakes up at night drenched in sweat. She feels fatigued and irritable most of the time. **She has not had her menses for the last 2 years.**

Anju thinks that she might be going through "the change" and **wonders how long she will feel this way.**

VASOMOTOR SYMPTOMS

"Hot flashes"

The most common complaint during MT, occurring in up to 80 percent of women.

Only about 20 to 30 percent of women seek medical attention for treatment

DURATION:

- **SWAN STUDY** : the median total VMS **duration was 7.4 years**, with symptoms persisting for a median of 4.5 years after the FMP
- **Penn Ovarian Aging Study**, the mean duration of moderate/severe hot flashes was 4.9 years, **but one-third of women continued to experience moderate/severe hot flashes for 10 years after the final menstrual period**

Case Contd…

Anju says that she is desperate for some relief from hot flashes now.

She is a lawyer, and experiencing hot flashes during court has become very embarrassing. She has tried dressing in layers, avoiding hot beverages, and keeping the room cool, but nothing seems to work.

Her best friend was recently started on "hormone therapy" by her doctor. And she too wants it.

What would you consider and evaluate before starting MHT?

- **INDICATIONS**
- **WINDOW OF OPPORTUNITY**
- **CONTRAINDICATIONS**

INDICATIONS

- Bothersome VMS
- Genito urinary symptoms of Menopause
- Premature Ovarian Insufficiency
- Prevention of Osteoporosis in high risk patients

No longer recommended

- for **prevention** of chronic disease (CHD or osteoporosis)
- Use for cognitive function or prevention of dementia

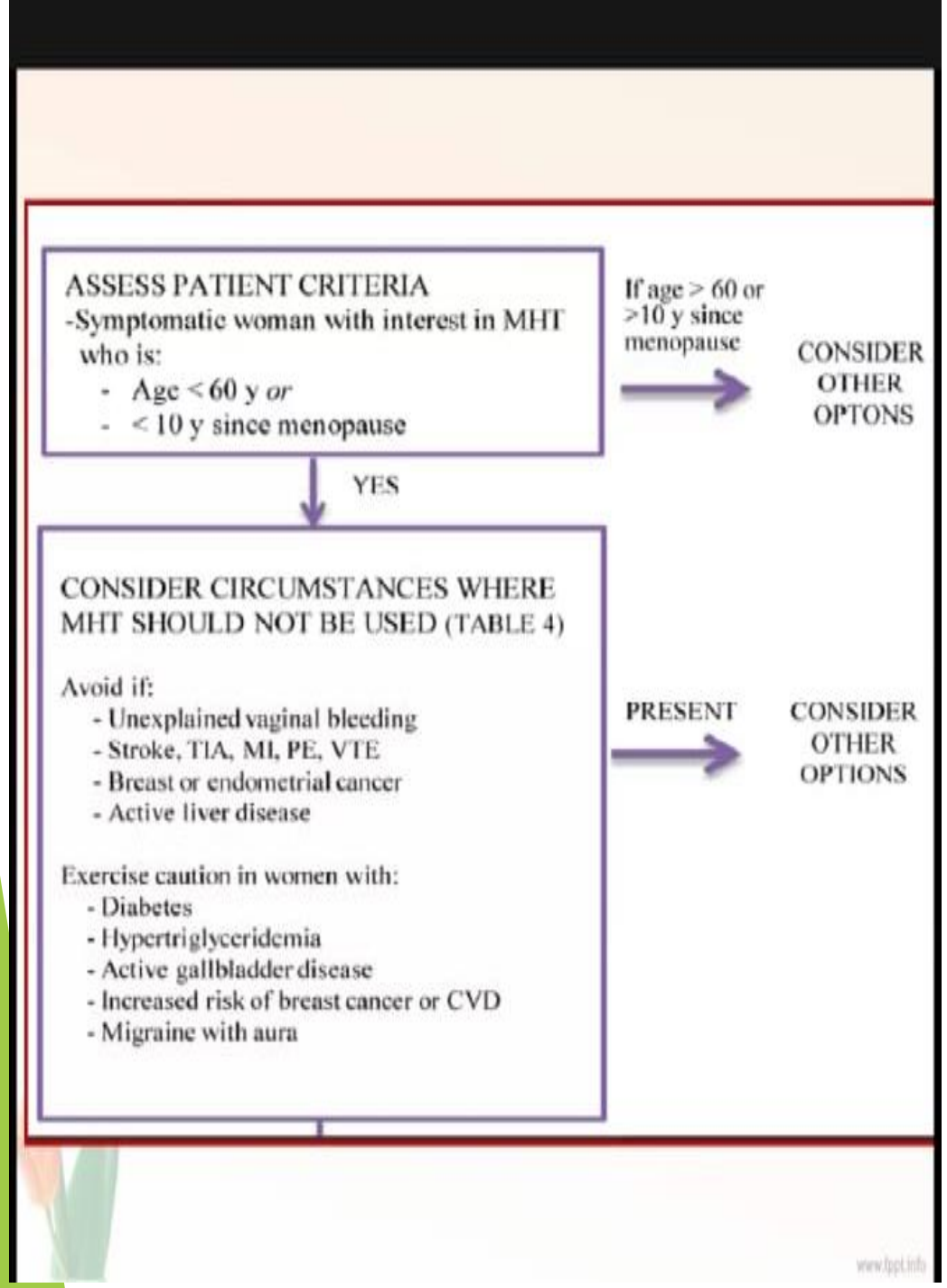
Choosing an Ideal Woman for MHT

- Healthy, symptomatic women
- Who are within 10 years of menopause or younger than age
- **(WINDOW OF OPPORTUNITY)**

- Who do not have contraindications

Individualizing MHT is the Key Recommendation from all guidelines

<40 Years	Premature Ovarian Insufficiency (POI) **MHT is Mandatory*** till Natural Age of Menopause
40-50 Years	**Benefits Exceed Risk**
50-60 Years	**Benefits Exceed Risk** (if <10 Years of Menopause)
>60 Years	**Risk can be More** (Need to evaluate)



Case Contd…

Anju is a non-smoker BMI 25 and her only medical problem is hypertension, which is well-controlled .

She has never had any abnormal mammograms, breast biopsies, or gynecologic surgeries.

Her **mother had a heart attack at the age of 65**, and Anju is worried about having one herself.

Her **third degree** relative had breast cancer.

She wonders if it will significantly increase her risk of MI and Breast Cancer if she starts HRT now.

Are there any risk calculators available?

Guidelines: CV Risk

Indian Menopause Society

	Indian Menopause Society, 2013	International Menopause Society, 2016	North American Menopause Society, 2012/ The Endocrine Society 2015
CVD	• No/lower risk in healthy women <60 years of age or within 10 years of menopause		

aring.

MHT and CVD risk - "timing hypothesis"

MHT started in the Perimenopausal or Early Postmenopausal period (<10 Years)

MHT begun Late after menopause (>10 Years)

Table 6. Evaluating CVD Risk in Women Contemplating MHT

	Years Since Menopause Onset	
10-y CVD Risk	**<5 y**	**6 to 10 y**
Low (<5%)	MHT ok	MHT ok
Moderate (5–10%)	MHT ok (choose transdermal)	MHT ok (choose transdermal)
High (>10%)[a]	Avoid MHT	Avoid MHT

CVD risk calculated by ACC/AHA Cardiovascular Risk Calculator (144). Methods to calculate risk and risk stratification vary among countries. Derived from J. E. Manson: Current recommendations: what is the clinician to do? *Fertil Steril.* 2014;101:916–921 (63), with permission. © Elsevier Inc.

[a] High risk includes known MI, stroke, peripheral artery disease, etc.

Endocrine Society guidelines on Menopause 2015

South-East Asia Region SEAR D

10 yr risk prediction chart for CVD event for India

Four sets each for male and female

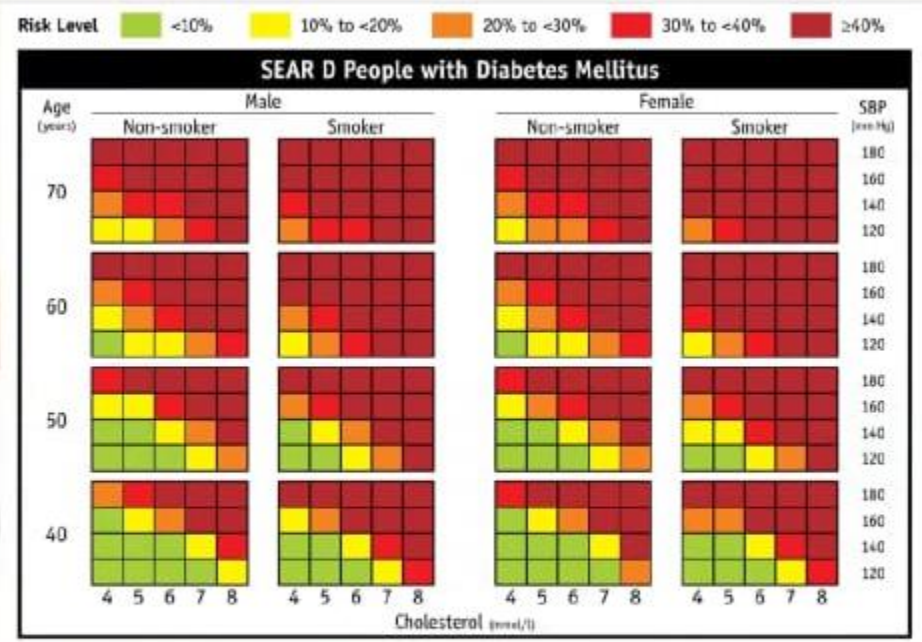
Two—Presence or absence of diabetes mellitus

Two-With and without the cholesterol readings

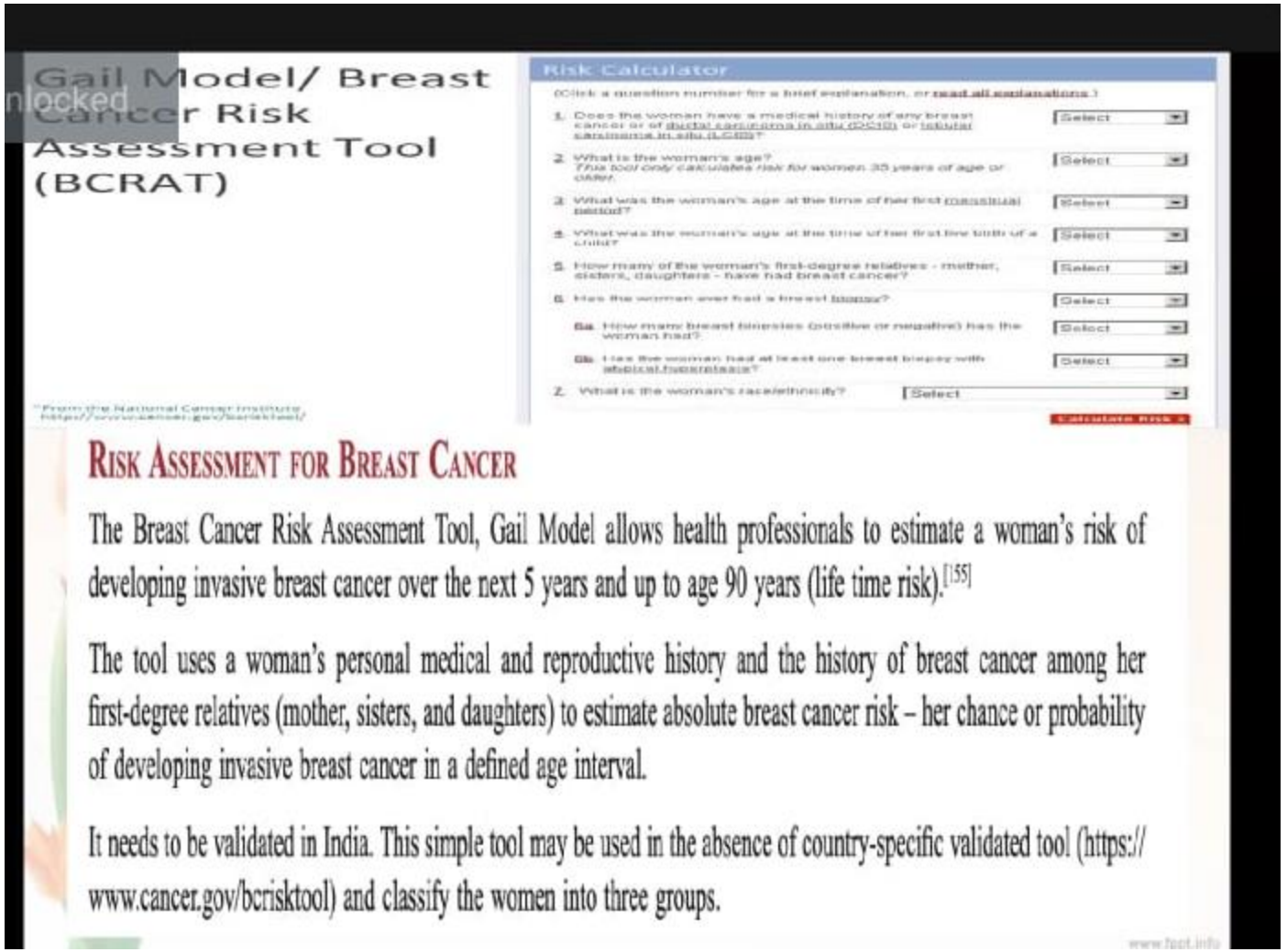
VARIABLES ON THE CHART

Gender,age, systolic blood pressure, smoking status,

Risk Level <10% 10% to <20% 20% to <30% 30% to <40% ≥40%



World Health Organization/ISH risk prediction charts for India Ten-year risk prediction chart for cardiovascular disease event by gender, age, systolic blood pressure, smoking status, cholesterol, and presence or absence of diabetes mellitus


Gail Model/ Breast Cancer Risk Assessment Tool (BCRAT)
Risk Calculator
RISK ASSESSMENT FOR BREAST CANCER
The Breast Cancer Risk Assessment Tool, Gail Model allows health professionals to estimate a woman's risk of developing invasive breast cancer over the next 5 years and up to age 90 years (life time risk).[55]
The tool uses a woman's personal medical and reproductive history and the history of breast cancer among her first-degree relatives (mother, sisters, and daughters) to estimate absolute breast cancer risk – her chance or probability of developing invasive breast cancer in a defined age interval.
It needs to be validated in India. This simple tool may be used in the absence of country-specific validated tool (https://www.cancer.gov/bcrisktool) and classify the women into three groups.

Menopause-Risk Assessment Models

Indian Menopause Soci

OFFLINE HARD COPY MODELS

VASOMOTOR SYMPTOMS-MENOPAUSE RATING SCALE

BMI CHART—OBESITY: WAIST CIRCUMFERENCE -VISCERAL OBESITY

CVD -RISK ASSESSMENT-WHO SEAR D

OSTEOPOROSIS -RISK ASSESSMENT-OSTA
WHO FRACTURE RISK ASSESSMENT TOOL (FRAX)

Muscle health is assessed by the SARC-F, a 5-item questionnaire

ONLINE MODELS

BREAST -RISK ASSESSMENT-Gail
WHO FRACTURE RISK ASSESSMENT TOOL (FRAX)

Case Contd…

After discussing her risks of HRT and assuring that her risk is low, Anju is very eager to start it.

What Pre HT investigations would we do?

What MHT would you recommend for her?

Assessment – Clinical Examination

Indian Menopause Society

Full assessment required irrespective of presenting reason of midlife woman

Examination

Height & Weight Blood Pressure & CVS Pelvic examination (+/- Pap Smear) Breast examination Thyroid Examination	Waist Circumference Physical fitness Assessment of mood and cognition Eye check-up—intraocular pressures, refractive index, and retina Dental check up

Assessment – Investigations

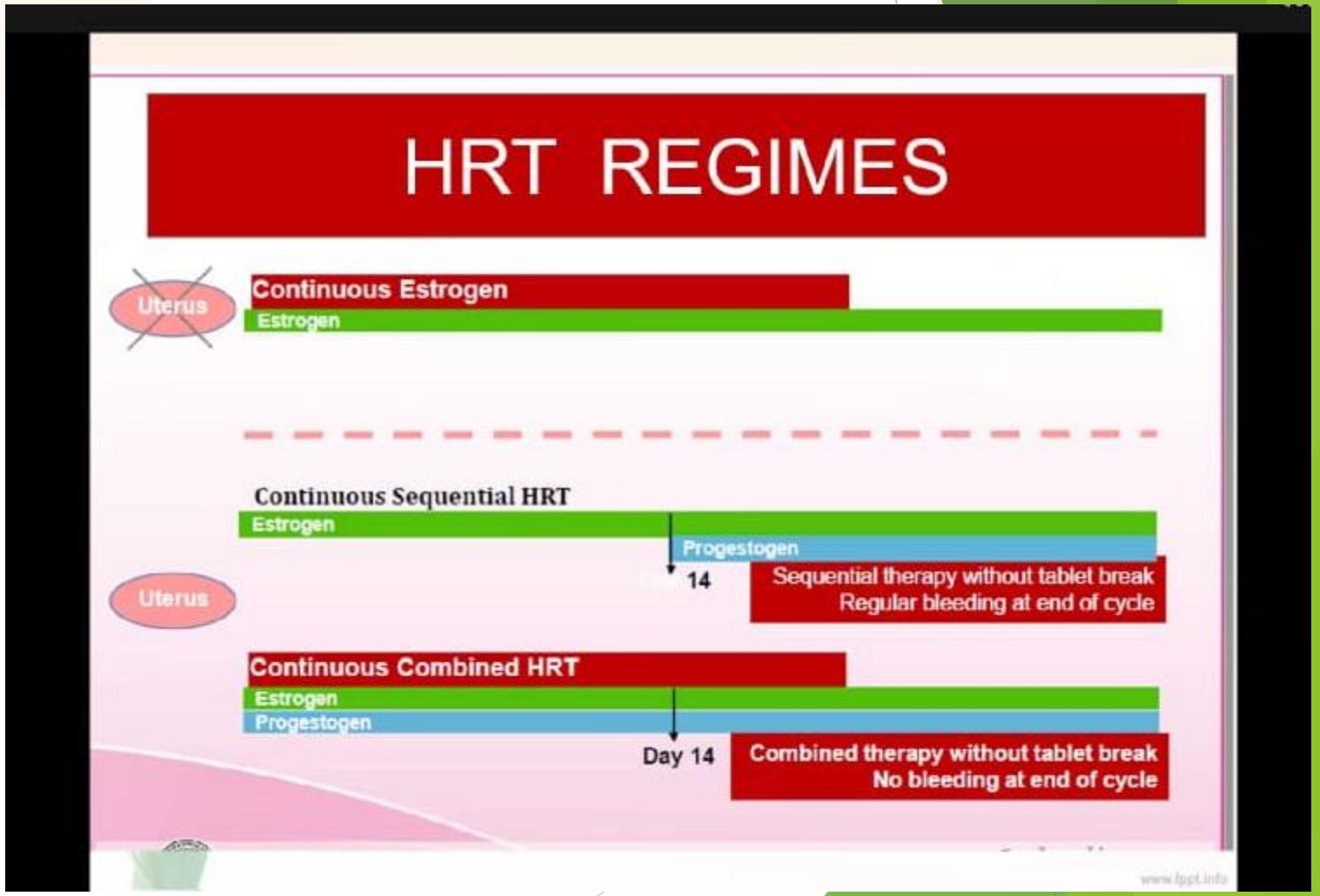
Indian Menopause Society

Full assessment required irrespective of presenting reason of midlife woman

Laboratory Tests	
Ideal	Complete blood picture
	Urine test routine
	Fasting blood glucose level
	Lipid profile
	Serum thyroid stimulating hormone
	Papanicolaou (PAP) smear
	Transvaginal ultrasound
	Mammogram

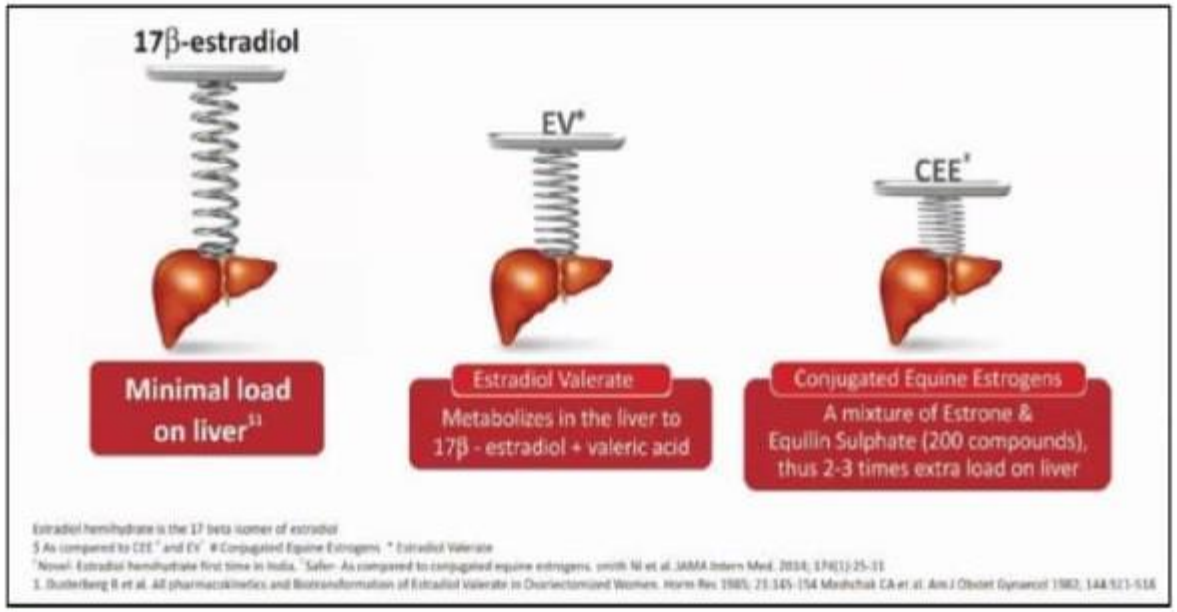
Further targeted investigations are done depending on the risks of a disease suspected on history and clinical examination

What MHT would you recommend for her?



Natural Estrogens Used For Menopausal HT

Indian Menopause Society



Estradiol hemihydrate is the 17 beta isomer of estradiol
$ As compared to CEE* and EV* # Conjugated Equine Estrogens * Estradiol Valerate
*Novel- Estradiol hemihydrate first time in India. *Safer- As compared to conjugated equine estrogens. smith NI et al. JAMA Intern Med. 2014; 174(1):25-31
1. Oosterberg R et al. All pharmacokinetics and Biotransformation of Estradiol Valerate in Ovariectomized Women. Horm Res 1985; 23:145-154 Mashchak CA et al. Am J Obstet Gynaecol 1982; 144:511-518

haring.

DOSE OF MHT

"One-size-fits-all" approach

- oral conjugated estrogen (0.625 mg/day)
- its equivalent oral 17-beta estradiol (1 mg/day)
- transdermal 17-beta estradiol (0.05 mg [50 mcg])

Trans dermal route -- preference

- Women with Hyperlipidaemia
- High Risk for VTE or Stroke
- Women on anticonvulsants
- Migraine

the baseline risk of both VTE and stroke is very low in otherwise healthy, young postmenopausal women : Hence patient preference and availability shall determine the route

Type of progesterone you would prefer to use for MHT?

Adding a Progesterone

- **Oral micronized Progesterone**
- **Dydrogesterone**
- Only to women with intact uterus

Reason: (although data is limited)

- it is effective for endometrial hyperplasia
- is metabolically neutral
- **does not appear to increase the risk of either breast cancer or CHD**

DOSE

MICRONISED PROGESTERONE

- 200 mg/day for 12 days/month for cyclic
- 100 mg daily for continuous regime

Perimenopausal or newly menopausal -- cyclic administration of oral micronized progesterone (200 mg/day for 12 days of each calendar month).

Women who are ≥2 to 3 years postmenopause: Continuous regimen (micronized progesterone 100 mg/day)

DYDROGESTERONE:

- 5 mg daily in continuous regime
- 10mg x 12days for sequential

Array of MHT in Indian Market Today

Oral Estrogen preparations available in India

Generic Name	Brand Name	Dosage
CEE	Premarin tablet (Wyeth Pfizer)	0.625 mg × 28s 0.3 mg × 28s
Estradiol Valerate	Progynova tablet (Zydus-German remedies)	1 mg × 28s 2 mg × 28s
Tibolone	Livial tablet (Organon) Tibofem tablet (Cipla)	2.5 mg × 28s 2.5 mg × 14s
Estriol	Evalon tablet (Sandoz)	1 mg × 10s 2 mg × 10s
Estradiol Hemihydrate	Estrabet Abbott	2mg

Oral progesterone formulations (for Menopausal-related symptoms)

Generic Name	Brand Name	Dosage
Medroxyprogesterone	Deviry (Elder) Modus (GSK)	2.5 mg × 10s 2.5 mg × 10s
Norethindrone	Crina NCR (Alembic) Sysron N (Systopic)	10 mg × 10s 5 mg
Micronized progesterone	Evagest tablet (Evacare) Neogest (VHB Genblotech)	100 mg × 10s 100 mg × 10s
Dydrogesterone	Duphaston (Abbott)	10 mg × 10s

Only Available Combined MHT in India

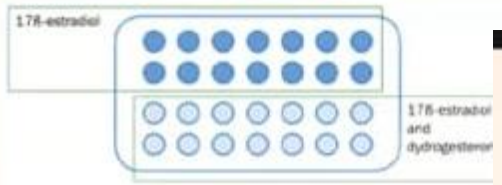
17ß-Estradiol + Dydrogesterone

Sequential MHT (sMHT)

Peri-menopause

POI

1 mg E2 + 10 mg Dydro



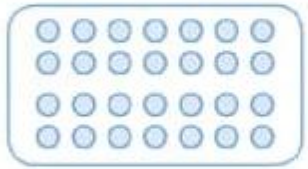
POI – Need at least 1mg E2 (2mg is Ideal

Duration of Rx – Till Natural Age of Menopause

Continuous combined MHT (ccMHT)

Post-Menopause

1 mg E2 + 5 mg Dydro



Case Contd…

- Anju starts using a combined continuous estrogen + progestin (EV + Dydro) oral treatment and experiences tremendous relief in her symptoms. However, she returns to your office three months later, with complains of marked breast tenderness and spotting.
- **How would we manage her?**
- **What is the follow up plan for her?**

Breast Tenderness

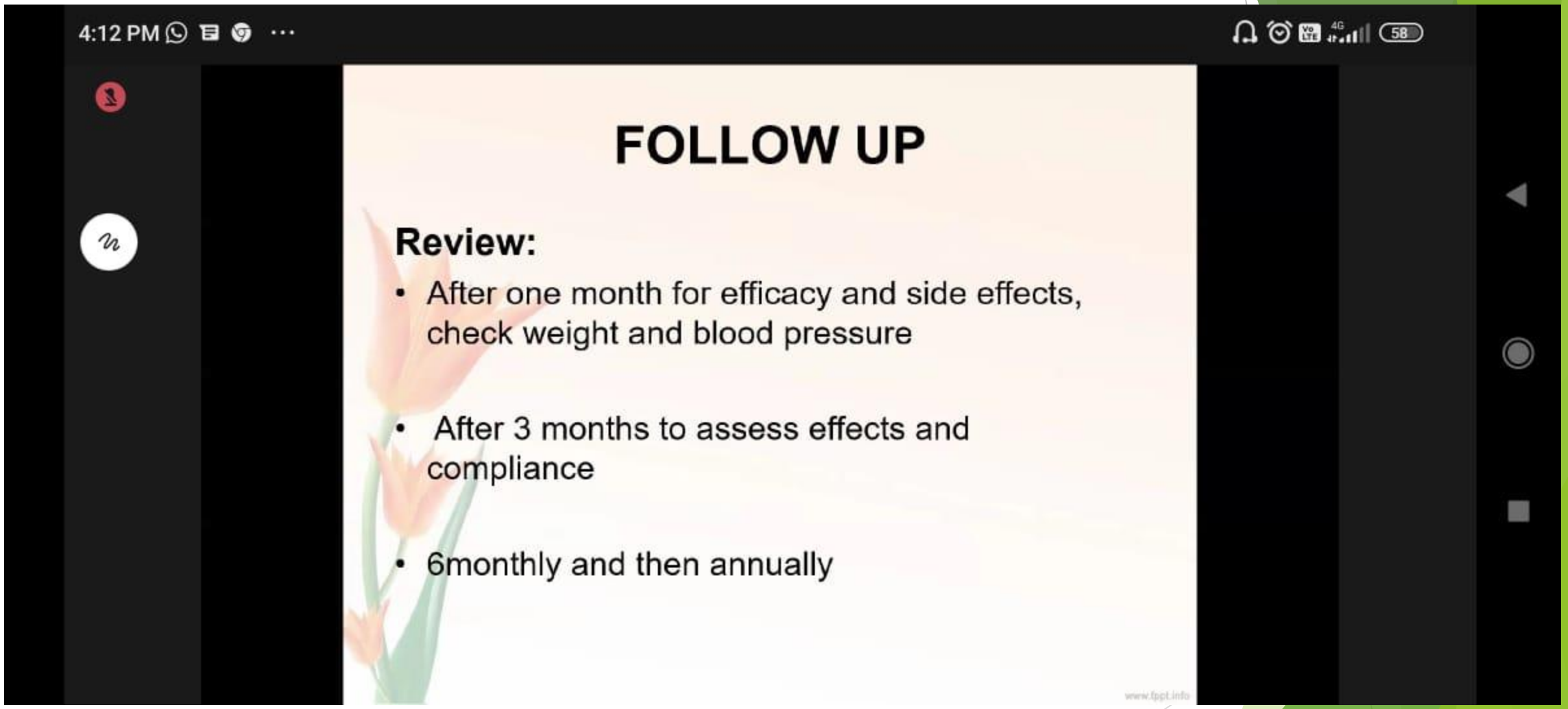
- Usually responds to a reduction in estrogen dose or change. Switch to another progestogen preparation.
- Restrict salt intake; cut down on caffeine and chocolate
- **Changing to tibolone** may be helpful in women who develop mastalgia on conventional MHT
- CEE/BZA may improve symptoms.

Transient bleeding is common in women taking continuous combined regimens

- Vaginal bleeding **can be followed for the first six months after beginning continuous combined therapy.**
- Endometrial biopsy is necessary if the bleeding persists beyond this point.
- Women who have uterine bleeding after a period of amenorrhea should have endometrial biopsy, due to the relatively increased incidence of intrauterine pathology

Monitoring:

1. **TVUS – in early cycle**
2. **Endometrial Biopsy : considered Gold Standard**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FOLLOW UP
Review:
• After one month for efficacy and side effects, check weight and blood pressure
• After 3 months to assess effects and compliance
• 6monthly and then annually
www.fppt.info

sharing.

Case Contd…

Her breast pain and spotting has been relieved.

She is scared about developing breast cancer and wants to stop the medication. She has heard about serious risks.

How would you counsel her?

If she insists on stopping it ,how would you stop it?

Risk Of Breast Cancer Is Not The Same With All MHTs

Concern	IMS-2016	NAMS-2017	NICE-2015	AACE-2017
Do MHT Cause "Significant" Risk of CA Breast?	**Small** (< 0.1% per Annum)	**Rare** risk of breast cancer with combined EPT in <60 Yr women and <10 Yr postmenopausal	HRT with oestrogen alone is associated with **little or no change** in the risk	Estrogen alone **does not initiate or promote** breast cancer
Does Progesterone Matters?	Risk primarily associated with the **synthetic progestogen** (CEE + MPA)	**More potent progestogens** such as MPA may have a **more adverse effect**	Yes, EPT can be associated with an increase in the risk	
Which Progesterone is safer?	Risk may be **lower with Dydrogesterone** or micronized progesterone	Micronized progesterone may be safer		Micronized progesterone is considered the safer alternative

The risk may be lower with Dydrogesterone or micronized progesterone than with a synthetic progestogen.

Benefits with MHT

- Reduces VMS & GUS
- Reduces Osteoporosis & Fracture Risk
- Improves in Osteoarthritis
- Reduces CVD Risk (<60 years)
- Reduces Risk of T2DM
- Reduces Abdominal Obesity
- Prevents Cognitive Impairment
- Reduces Neovascular Macular Lesions
- Reduces Risk of Colorectal CA
- Reduces Risk of Endometrial CA (E+P)
- Improve QOL

Risk with MHT

- Stroke
- VTE
- CA Breast
- CVD In >60 Years

Rare with Dydrogesterone & Micronized Progesterone

Women FIRST

Early Initiation of MHT Reduces the Risk of CHD, Fracture and All cause Mortality[1,2]

Reduces Osteoporosis & Fracture Risk[1]

48% Reduction in CHD Risk[2]

30% reduction in All Cause mortality[2]

MHT, started **<10 years postmenopause** in **<60 years of age, reduced the risk of all-cause mortality and CHD** compared with placebo or no treatment[2]

And safe for 5 years of the use.

1. [illegible]
2. Boardman HD-P, et al. Hormone therapy for preventing cardiovascular disease in postmenopausal women. Cochrane Database Syst Rev. 2015; Issue 3.
3. IQVIA MAT 2020
4. Baber RJ, Panay N, Fenton A, the IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric 2016;19(2):109-150.

*In terms of Breast Cancer *International Menopause Society

DURATION OF THERAPY

Short-term use is suggested

- **generally not more than five years**
- **or not beyond age 60 years**

VMS:

If symptoms are distressing , can be continued after explaining the risks

aring.

STOP THE THERAPY

- 40 to 50 percent of women who start MHT stop within one year and 65 to 75 percent stop within two years ON THEIR OWN.
- 55 percent will have some recurrent vasomotor symptoms if MHT is stopped abruptly (WHI)
- When tapering, one approach is to decrease the estrogen by one pill per week every few weeks (ie, six pills per week for two to four weeks, then five pills per week for two to four weeks, etc) until the taper is completed

TIBILONE

Patient Characteristics That May Be Favorable For Estrogen/Androgen Combination

Indian Menopause Society

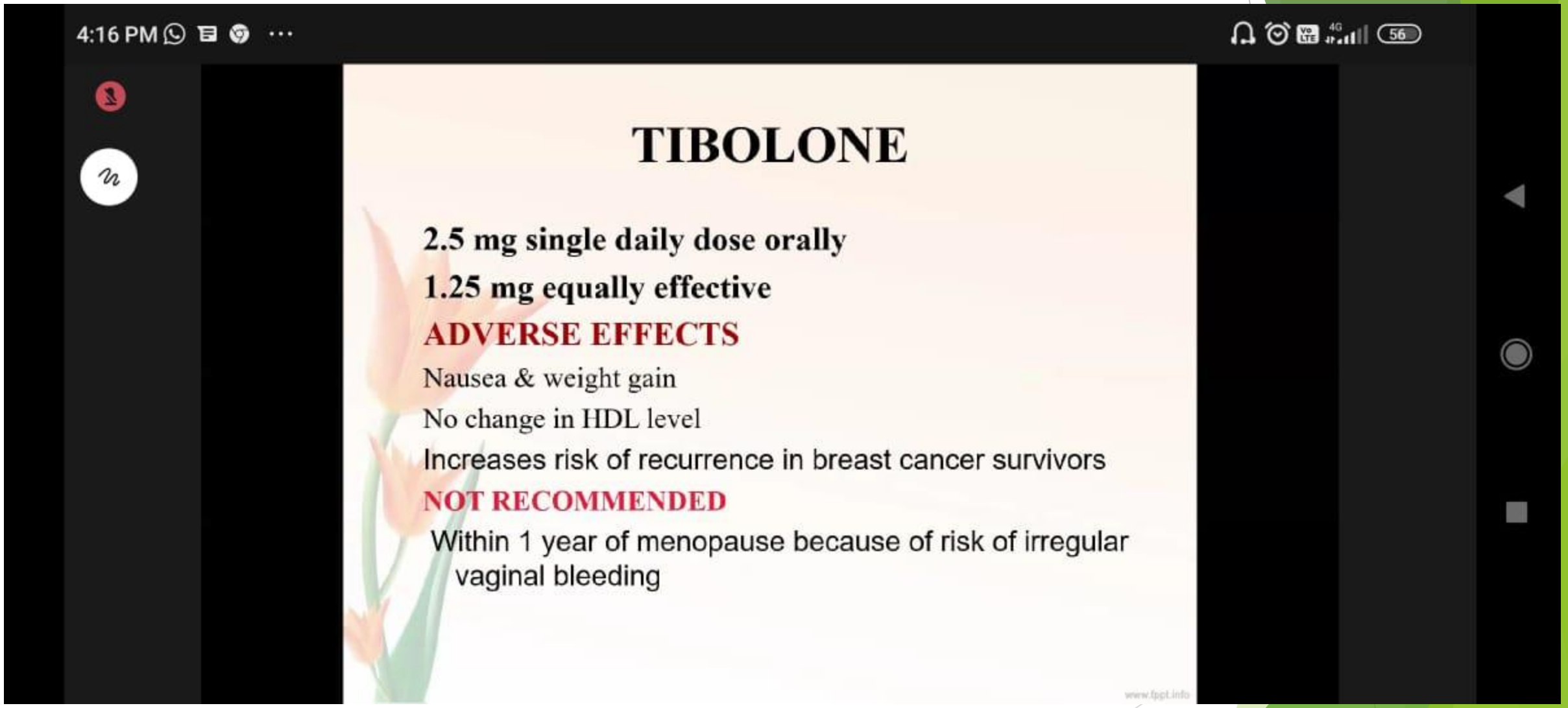
- Surgical menopause
- Continued VMS despite estrogen replacement
- Decreased well-being despite estrogen replacement
- Acquired sexual desire dysfunction
- In India, androgen formulations for use at menopause are unavailable

  Tibolone is a good alternative

TIBOLONE

Specific Indications:

- Mood & libido
- Adverse effects with conventional HRT
- Older women
- Family history of breast cancer
- History of endometriosis, fibroids
- Add back therapy with GnRH analogues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TIBOLONE
2.5 mg single daily dose orally
1.25 mg equally effective
ADVERSE EFFECTS
Nausea & weight gain
No change in HDL level
Increases risk of recurrence in breast cancer survivors
NOT RECOMMENDED
Within 1 year of menopause because of risk of irregular vaginal bleeding
www.fppt.info

TSEC

Tissue Selective Estrogen Complex

BZA 20 mg/CE 0.625 mg

- Combination of a SERM with Estrogen
- To provide efficacy of both components
- Fewer adverse effects
- Rationale is that tissue selective activity
- Treat menopausal symptoms and postmenopausal bone loss without stimulating the endometrium

SMART 1-5 TRIAL