



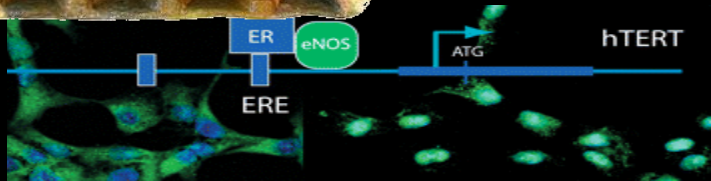
HORMONE REPLACEMENT THERAPY

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ILOs

By the end of this lecture you will be able to:

- ✳ Recognize menopausal symptoms & consequences
- ✳ Classify drugs used to alleviate such symptoms that are used as Hormonal Replacement Therapy [HRT]
- ✳ Expand on the mechanism of action, indications, preparations, side effects & contraindications of such agents.





HRT

Is a system of medical treatment that is designed to artificially boost female hormones, in hope to alleviate symptoms caused by ↓ in their circulating levels

1/3rd of total female population

PERI & POSTMENOPAUSE
 Natural, Pathological, Induced

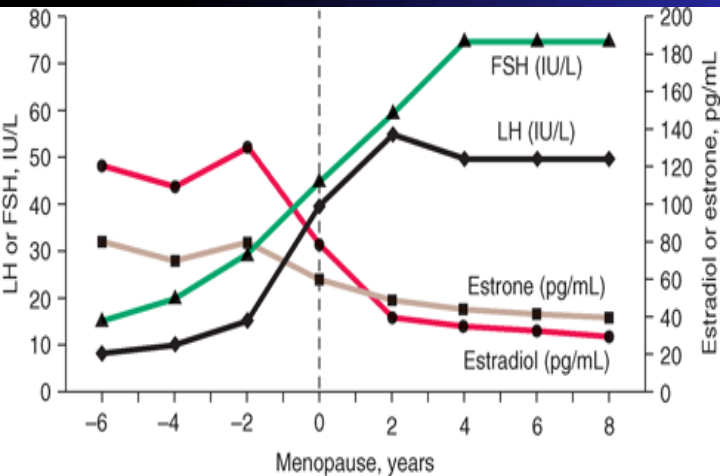
MENOPAUSE

A complex physiological change that occurs at the time when the last period ends generally as women age and loss fertility (age late 40s)

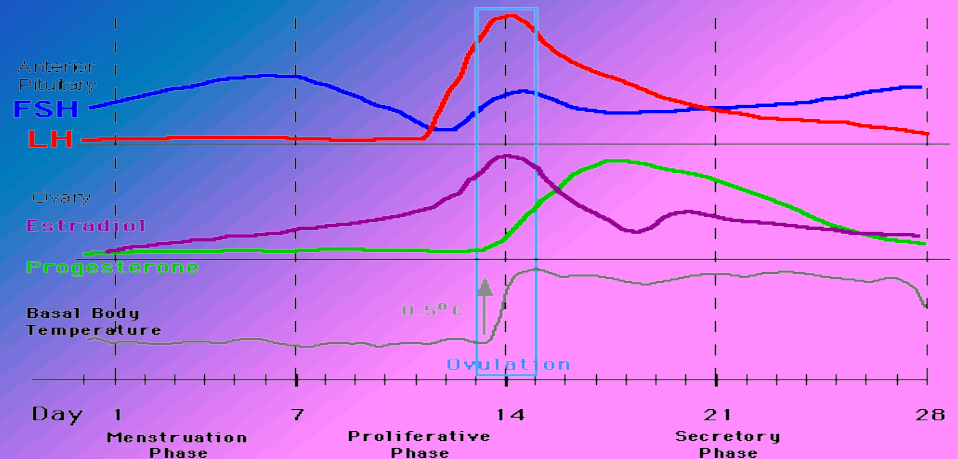
- ↓ Estrogen & Progesterone
- ↓ Androgens
- ↑ FSH & LH
- ↑ Insulin Resistance

'*menos*' (month)
'*pausis*' (cessation)

Normal menstruation



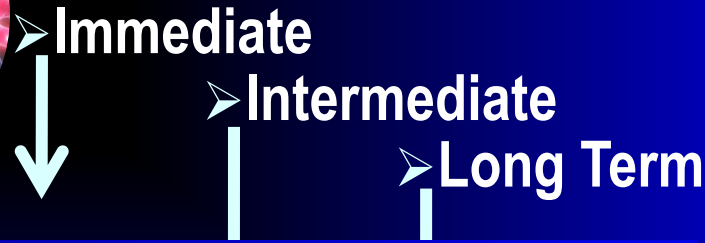
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com
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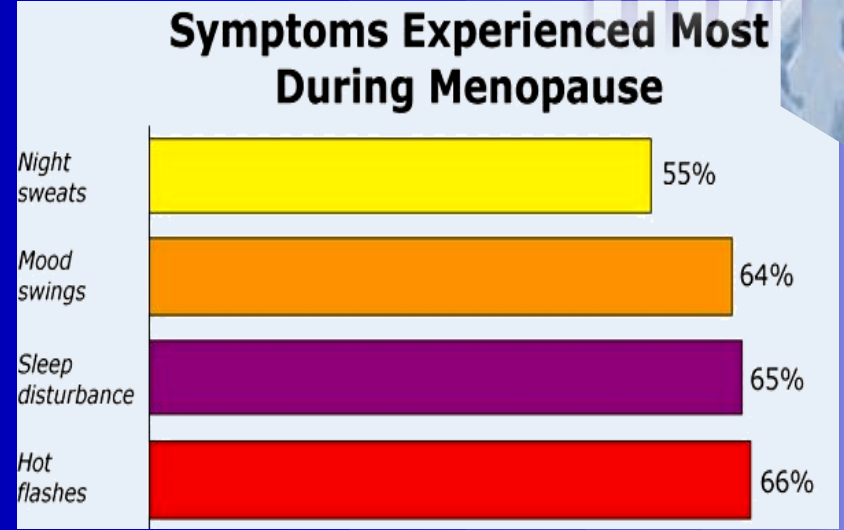


SYMPTOMS & CONSEQUENCES of MENOPAUSE

HRT



- Hot Flashes / Night Sweats (vasomotor symptoms)
- Insomnia, Anxiety, Irritability
- Mood Disturbances
- Reduction In Sexuality & Libido
- Poor Concentration / Memory Loss



20% no symptoms, 60% some symptoms, 20% severe symptoms

- Dyspareunia & vaginal dryness
- Urethral syndrome
(dysuria, urgency & frequency)
- Incontinence, difficulty in voiding
- Increased bruising
- Generalized aches and pains

- Osteoporosis
- CVS Risks; ↑ LDL/HDL ratio, CHD, stroke,..
- C N S deficits; Alzheimer's, dementia



Menopausal Symptoms

→ ↓ Estrogen



Replace the Estrogen ← Alleviate



⚠ Estrogen → Some undesirable side effects



add Progestins; *but not if there is hysterectomy*

⚠ Selective ER-Modulators [SERMs]

⚠ Phytoestrogens

⚠ Androgens → *responsible for sexual arousal* → *given only if there is loss of libido & orgasm*

HRT

Given for short term; never exceed 5 years → to control menopausal symptoms without allowing ample time for malignant transition that might be induced by estrogen

No more preferred

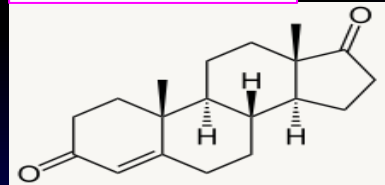
~~Long-term~~ administration was only indicated in osteoporosis & CVS protection but now better drugs are available

HRT



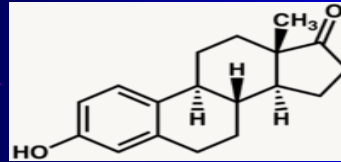
1. ESTROGEN

In NATURE



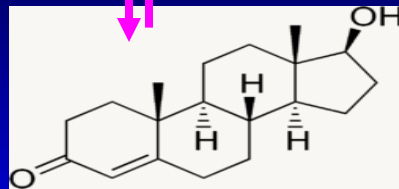
Androstenedione

Aromatase



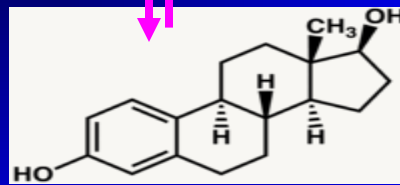
Estrone

Ovaries & adrenals pre-menopausal
Adrenals in menopause



Testosterone

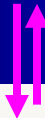
Aromatase



Estradiol

Ovaries in pre-menopause

Dehydrogenase



As Therapy

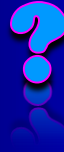
Estradiol; Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, intradermal implant,

Conjugated estrogens → mixture of Na salts of sulfate esters of estrone & equilin.

Esterified estrogens



What does estrogen do
It binds to its receptors



ESTROGEN



Types of Estrogen Receptors [ER]

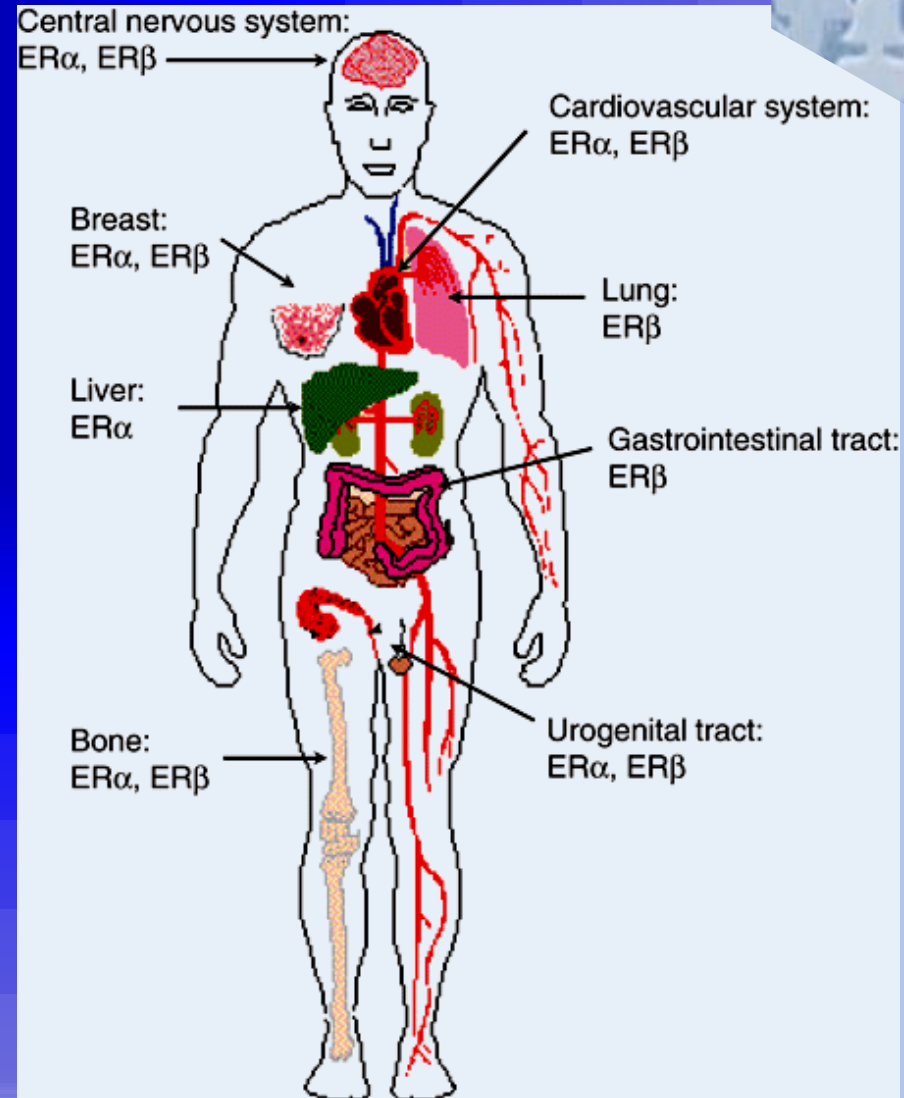
ER α \rightarrow

> mediates female hormonal functions
Endometrium, breast, ovaries, hypothalamus,...

ER β \rightarrow

> mediates other hormonal functions
brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells,....

Distribution of ER

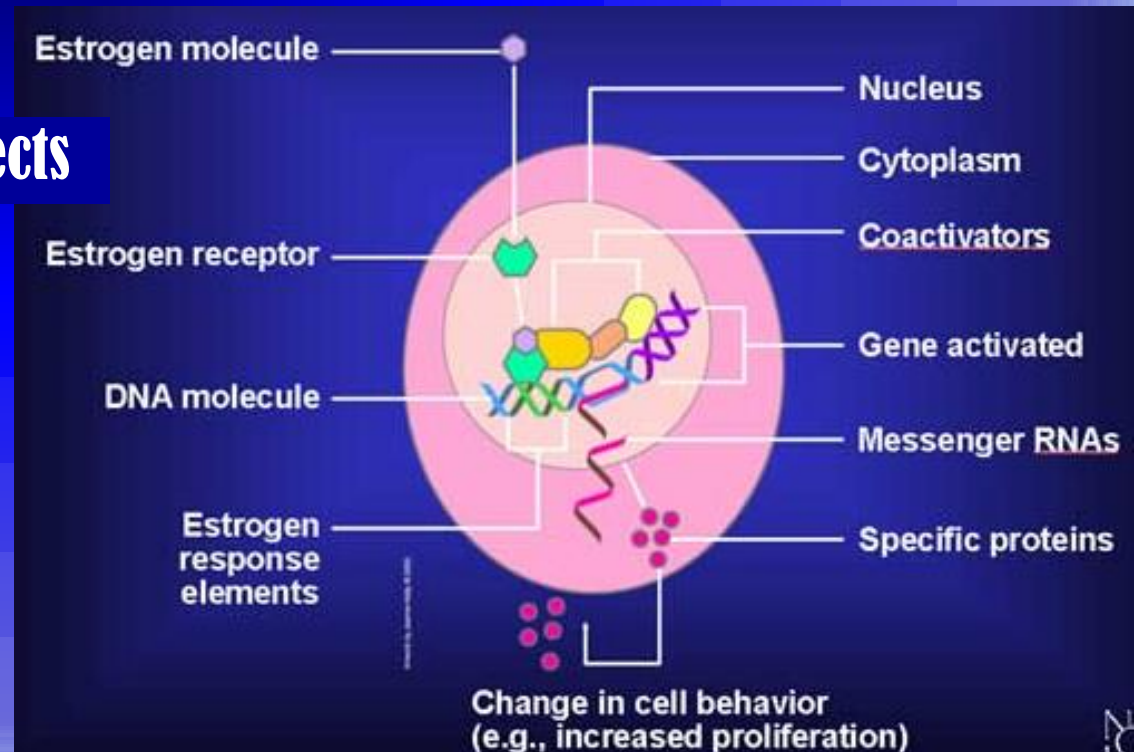


Estrogens bind to ER (α or β) that exist either;

■ **Cytoplasmic:** mediates its **genomic actions** → hrs– dys time scale
 → development, neuro- endocrines, metabolism

■ **Membranous:** GPER → 2nd messenger → ↑ Ca or cAMP or ↑ MAP Kinase
 > mediates its **non-genomic actions** → sec – min. time scale → on NO, neuro-
 transmitters, endometrium,

Genomic effects



GPER; G protein ER
 MAP Kinase; mitogen activated
 protein kinase that activate
 transcription factors to promote
 mitogenesis



INDICATIONS

ESTROGEN★

- A. In Menopause** Not given unless presence of symptoms; alone only after hysterectomy or with progestin as HRT (never exceed 5 yrs administration)
- Improves hot flushes & night sweats
 - Controls sleep disturbance & mood swings by acting on NE, DA & 5HT at reticular formation
 - Improves urethral & urinary symptoms by ↑ epithelial thickness & vascularity, collagen content at urethra & NE transmission that contract sphincters & relax detrusal muscles
 - Improves vaginal dryness by ↑ epithelial thickness & vascularity, collagen content (topical and systemic estrogens prep are effective)
 - Increases bone density by ↑ calcitonin release from thyroid to ↓ osteoclastic activity.
 - Progestins act synergistic by blocking cortico-steroid induced bone resorption. (Decrease incidence of hip fracture)



- Protects CVS; enhance vasodilatation via ↑ NO production, & ↑ HDL & ↓ LDL thus ↓ atherosclerosis & ischemic insults (HRT started at the beginning of menopause will prevent CVS problems) **HRT increases CVs problems (long term)**
- Improves insulin resistance & glycaemic control in diabetics
- Improves cognitive function via ↑ expression of ER in brain & by ↓ amyloid deposition thus preventing Alzheimer 's.
- Delays parkinsonism by acting on DA system in midbrain

B. Other Uses

- Contraception
- Primary ovarian failure
- Amenorrhea & Hirsutism caused by excess androgens





Administration

Oral: -
Conjugated equine

Estradiol valerate

Estril succinate

- Ⓢ Transdermal (estradiol);
Patches → 24 hour twice weekly.
Gel → 24 hours daily.
- Ⓢ Subcutaneous implant (estradiol) → 6 monthly.
- Ⓢ Vaginal cream as such or as rings pessaries

ADRs

- Irregular vaginal bleeding (**patients discontinue HRT**).
- Nausea.
- Vaginal discharge.
- Fluid retention. Weight gain.
- Breast tenderness (**patients discontinue HRT**)..
- Spotting or darkening of skin (on face)





Contraindications

Absolute:

- Undiagnosed vaginal bleeding
- Severe liver disease
- Thromboembolic manifestations
- Cancer; endometrial, breast (hormone sensitive), ovarian

Interactions

- ⚠ See contraception
- ⚠ NB. If given with
 - Ⓜ SERMs → additive side effects for both drugs
 - Ⓜ Aromatase inhibitors → ↓ efficacy
 - Ⓜ Corticosteroids ↑ side effects

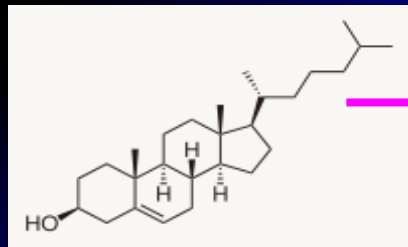


2. PROGESTINS

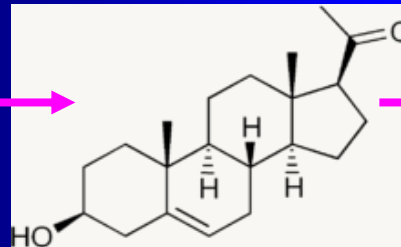
In NATURE

Produced by; Adrenal glands, Gonads, Brain, Placenta

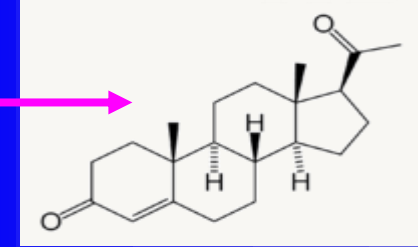
Synthesis;
Induced by LH



Cholesterol



Pregnenolone



Progesterone

As Therapy

- ✚ Progesterone is destroyed in GIT, so can be given only parentally
- ✚ Progestins are synthetic progestogens that have progestinic effects similar to progesterone but are not degraded by GIT.

Progestin preparations; as in contraceptive pills

Binds to its receptors

What does progesterone do?

↓ Two types of progesterone receptors [PR] → PR-A & PR-B
They could exist cytoplasmic → mediating genomic long term effects
or membranous → mediating non-genomic rapid effects



INDICATIONS

PROGESTIN 

A. In Menopause As HRT, usually given in combination with estrogen
Some use it alone in risk of cancer but does not ↓
all menopausal symptoms

- Protects against possibility of estrogen induced endometrial cancer
Estrogen → ↑ cell growth. If unopposed → endometrial cell lining can show (atypical hyperplasia)
Progesterone beneficially → matures endometrial cell lining (become differentiated) & ↑ apoptosis of atypical cells by activation of p53.
- Progesterone (natural) protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, but this effect is not as clear with synthetic progestins. Mamography recommended every 6ms.
- Confers neuroprotection, mild effect
- Controls insomnia & depression → little effect
- Counteract osteoporosis, directly +ve osteoblasts

B. Other Uses

1. Contraception (Estradiol + Progestins)
2. Dysmenorrhea
2. Menopausal symptoms (Estradiol + Progestins, given together)

Administration

- ⊗ Oral; Micronized progesterone or progestins → see contraception
- ⊗ IU; as Levonorgestrel or Progestasert
- ⊗ Vaginal - natural progesterone gel / pessary.
- ⊗ Transdermal - sequential / continuous patch.

ADRs

- Mood changes, as anxiety, irritability
- Headache, dizziness or drowsiness
- Nausea, vomiting, abdominal pain or bloating (distention).



Benefits and Risks of HRT

- **Definite benefits**
- Symptoms of menopause (vasomotor, genitourinary)
- Osteoporosis (Definite increase in bone mineral density; probable decrease in risk of fractures)
- **Definite risks**
- Endometrial cancer (estrogen only)
- Venous thromboembolism (long term)
- Breast cancer (long term 5 yrs)
- **Uncertain benefits**
- Cognitive functions
- **Note: the risk of CVS problems and breast cancer with HRT is more than their benefits)**

3. SERMs Tamoxifen, Raloxifene (oral and non-hormonal)

- **Raloxifen** antagonist in breast and uterus and agonist in bone
- **Tamoxifen** Antagonist in breast and partial agonist in bone and endometrium.

An ideal SERM for use as HRT should be agonistic in brain, bone, CV system (not necessarily the liver), vagina & urinary system but antagonistic in breast & uterus

		Brain	Uterus	Vagina	Breast	Bone	CVS
+ = agonist	Estradiol	++	++	++	++	++	++
- = antagonist	<u>Ideal SERM</u>	++	—	++	—	++	++
Not Ideal	Tamoxifen	—	+	—	—	+	+
	Raloxifene	—	—	—	—	++	+

Tamoxifen → ↑ risk of venous thrombosis & tends to precipitate vaginal atrophy & **hot flushes**

Raloxifene → has no effect on hot flushes or **increases hot flushes**

(very effective preventing vertebral bone fracture and CVs problems less compared to Estrogen) for osteoprosis use of bisphosphonate is better than

SERMs

5. PHYTOESTROGENS

supplements from plants; containing isoflavones (soya beans, flaxseeds) or lignans (whole grains). Avoid in estrogen dependent breast cancer

■ They mimic action of estrogen on ER- β → alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions. (data limited on their efficacy)

■ They block actions mediated by ER- α in some target tissues → lower risks of developing endometrial & breast cancer.

6. ANDROGENS

■ **Testosterone** is responsible for sexual arousal in females. It is given as the sole therapy to menopausal women in whom their menopausal symptoms are focused on **lack of sexual arousal**. It is given as adjuvant to combined estrogen & progestin if all other menopausal symptom exist.

N.B. Tibolone, can be effective in some women → has some androgen agonistic properties. (androgens use is not approved by FDA in women)

The Women's Health Initiative (WHI) and HRT

- **Menopausal Hormone Therapy**
- For decades, hormone therapy widely used in menopausal symptoms.
- **Estrogen** has been used alone in menopausal women who **have had their uterus removed**.
- **Progestin**, the synthetic form of an estrogen-related hormone called progesterone, is combined with estrogen in menopausal women **who still have their uterus**.
- The Women's Health Initiative (WHI), **a 15-year research program launched in 1991**, addressed the most common causes of death, disability, and poor quality of life in postmenopausal women.
- **The research program examined the effectiveness of hormone replacement therapy in women**. In 2002, findings from two WHI clinical trials examined:
 - **The use of estrogen plus progestin in women with a uterus**
 - **The use of estrogen only in women without a uterus**.
- In both studies, women were randomly assigned to receive either the hormone medication or placebo.
- **In both studies, when compared with placebo, the hormone medication (whether estrogen plus progestin or estrogen only) resulted in an increased risk of stroke and blood clots**. In addition, the estrogen plus progestin medication resulted in an increased risk **of heart attack and breast cancer**.
- **These concerns are one reason that many women are turning to mind and body practices and natural products to help with menopausal symptoms.**

Non-hormonal agents used in management of menopausal symptoms

- Fluoxetine (SSRI)
- Clonidine (centrally acting antihypertensive)
- Gabapentin (anti-convulsant)
- Physical activity: exercise, smoking cessation and relaxation of mind will improve symptoms of menopause (e.g hot flushes) and fall preventing strategies prevents chances of fracture.

HRT



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