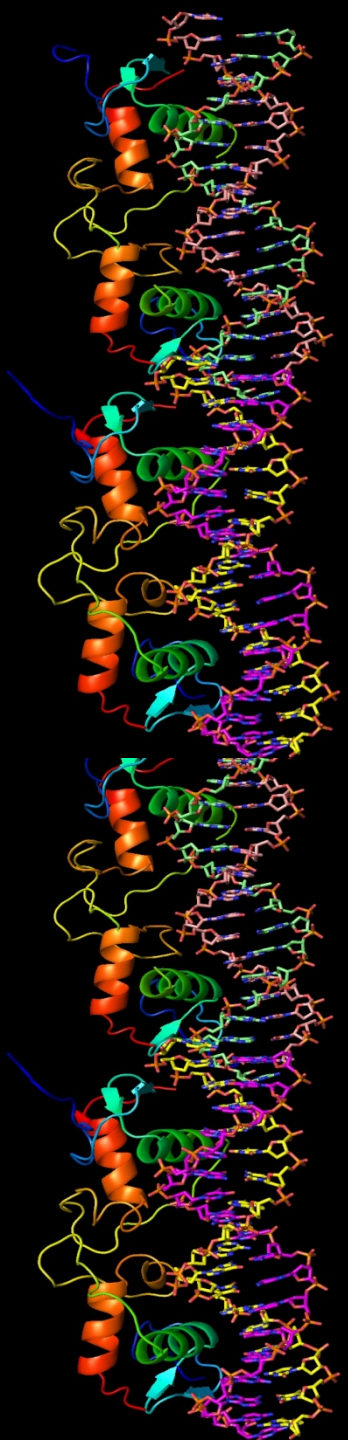
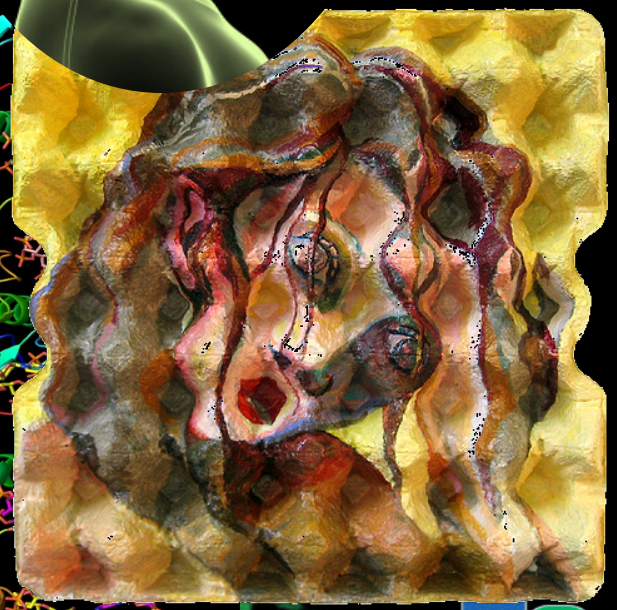


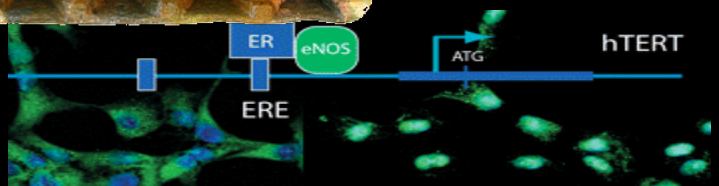
HORMONE REPLACEMENT THERAPY

ILOs

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

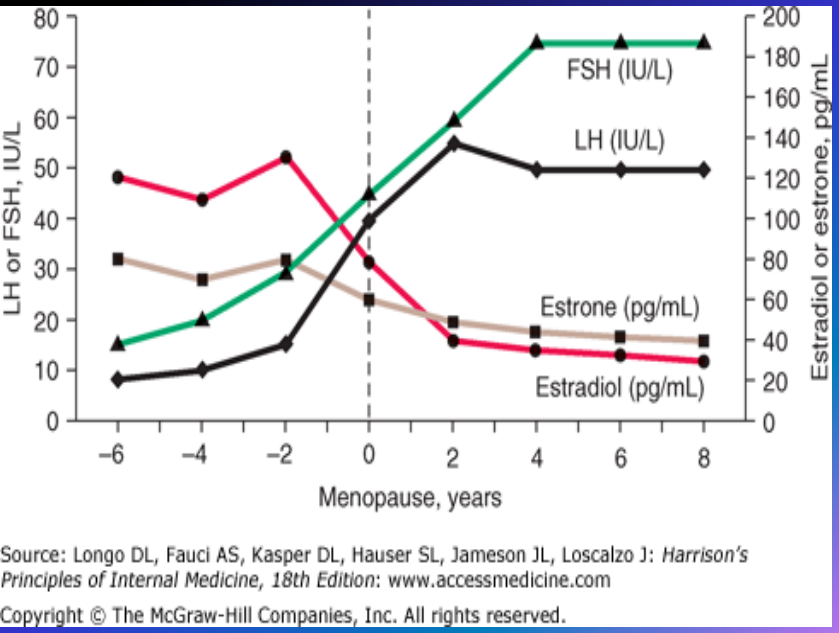
- Recognize menopausal symptoms & consequences
- Classify drugs used to alleviate such symptoms that are used as Hormonal Replacement Therapy [HRT]
- Expand on the mechanism of action, indications, preparations, side effects & contraindications of such agents.





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

The physiological changes that occur at the time when the last period ends generally as women get older and lose fertility (age late 40s)



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

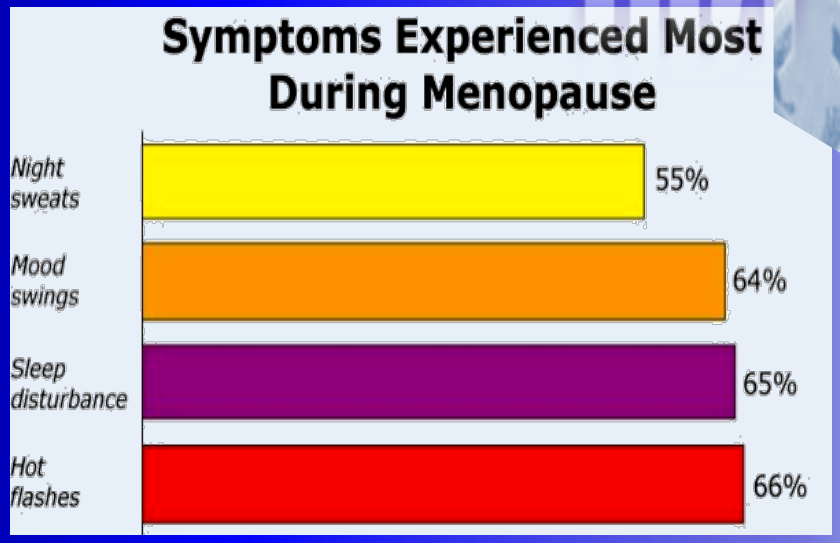
' menos'(month)
'pausis'(cessation)

SYMPTOMS & CONSEQUENCES of MENOPAUSE

HRT

- Immediate
- Intermediate
- Long Term

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



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,..
- CNS deficits; Alzheimer's, dementia

Menopausal Symptoms → ↓Estrogen

HRT

Replace the Estrogen ← Alleviate

- Estrogen → Some undesirable side effects

  ↑

  add Progestins; *but not if there is hystrectomy*
- Selective ER-Modulators [SERMs]
- Phytoestrogens
- Androgens → *responsible for sexual arousal* → *given only if there is loss of libido & orgasm*

HRT

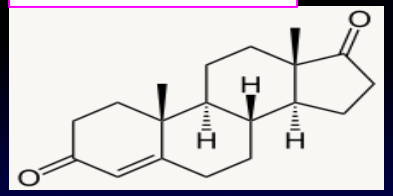
Given for short term; never exceed 5 years →to control meno-pausal symptoms without allowing ample time for malignant transition that might be induced by estrogen

No more preferred

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

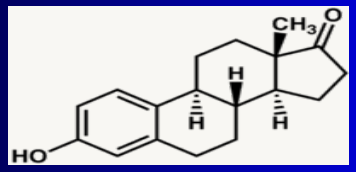
1. ESTROGEN

In NATURE



Androstenedione

Aromatase

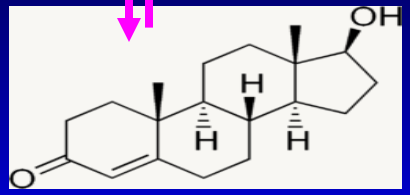


Estrone

Ovaries & adrenals pre-menopausal

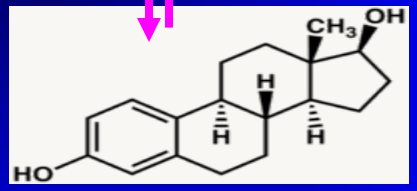
Adrenals in menopause

Dehydrogenase



Testosterone

Aromatase



Estradiol

Ovaries in pre-menopause

As Therapy

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

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

Esterified estrogens

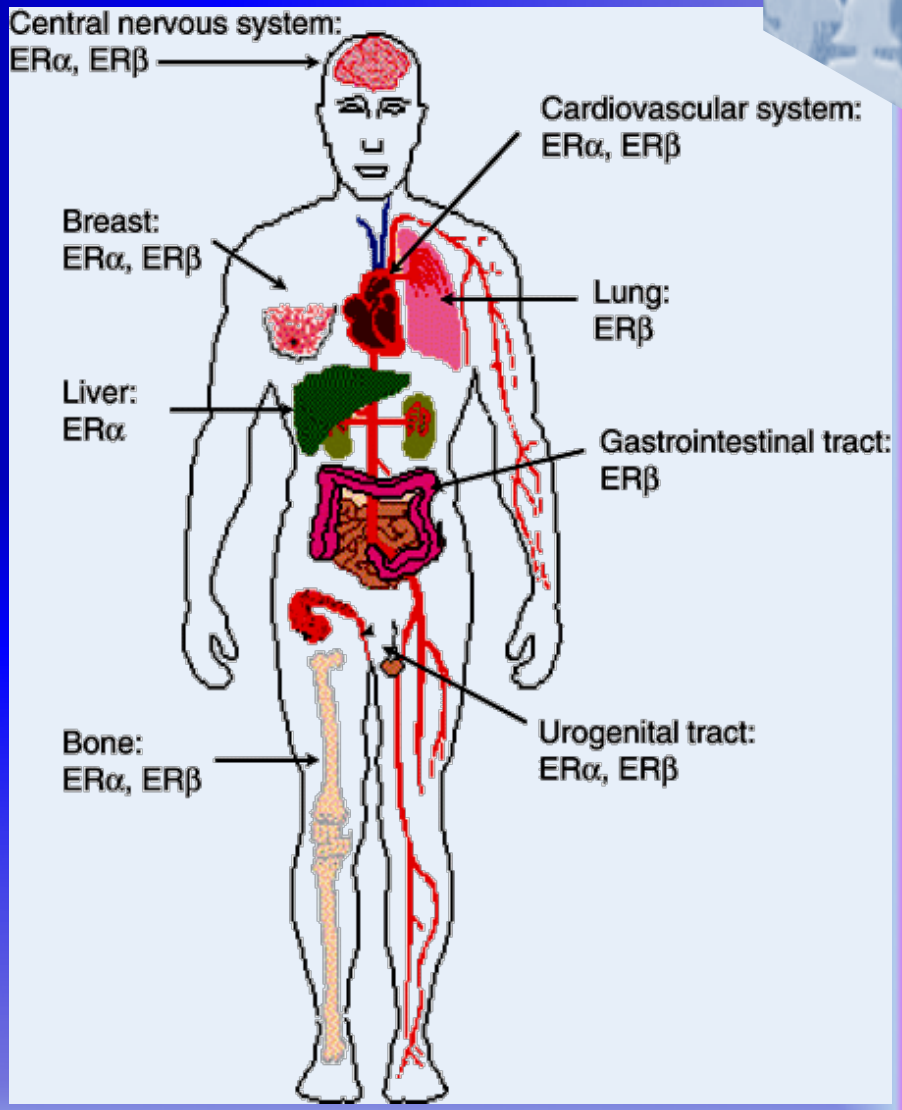
ESTROGEN

What does estrogen do
It binds to its receptors

Types of Estrogen Receptors [ER]

- ER α →
  > mediates female hormonal functions
  Endometrium, breast, ovaries, hypothalamus,…
- ER β →
  > mediates other hormonal functions
  brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells,….

Distribution of ER



INDICATIONS

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 synergestic by blocking cortico- steroid induced bone resorption. (Decrease incidence of hip fracture)

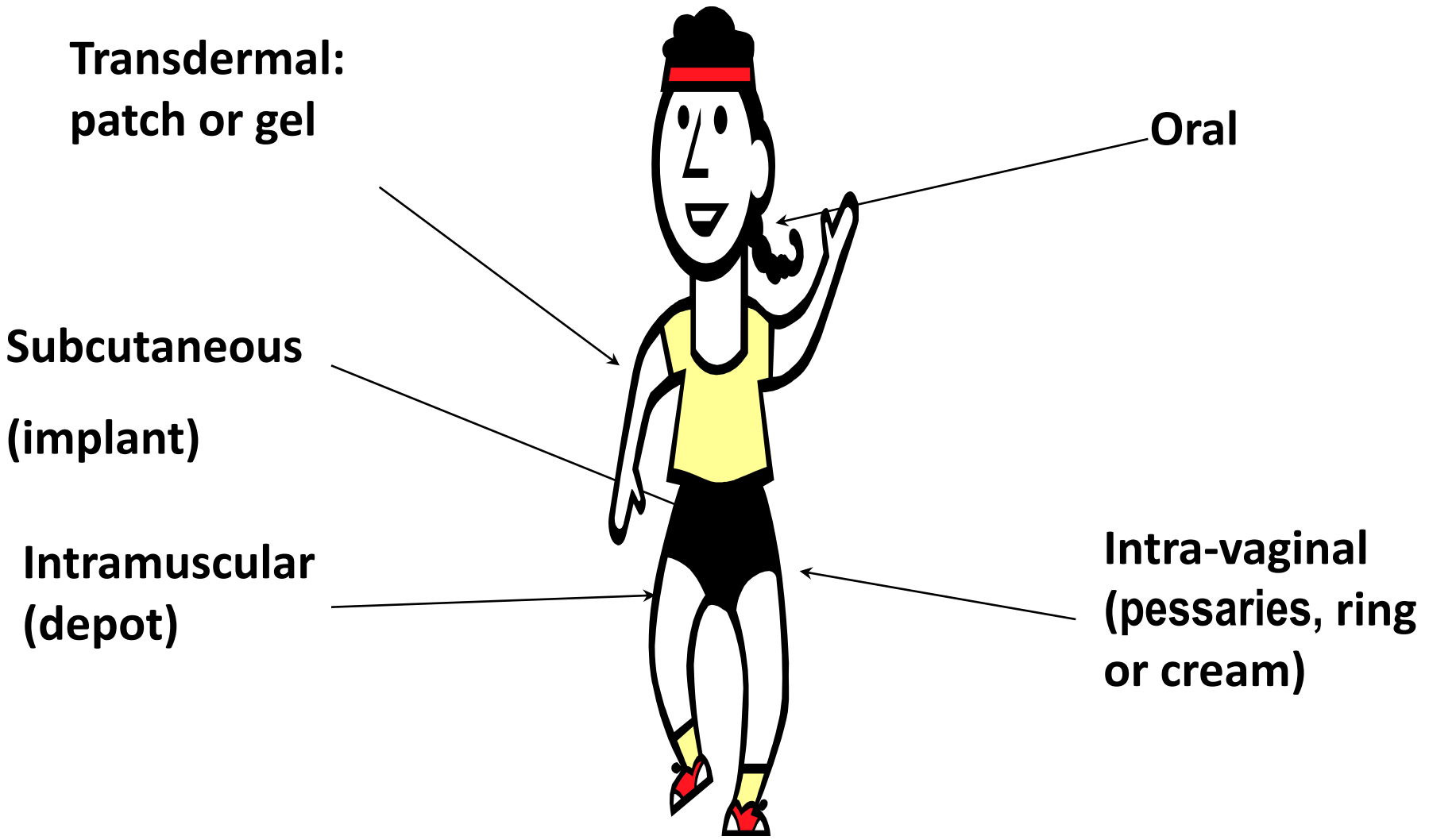
ESTROGEN

- 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 Alzehimer ‘s.
- Delays parkinsonism by acting on DA system in midbrain

B. Other Uses

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

Prescription of HRT: ROUTES



ESTROGEN

Administration

- Oral: -
  - Conjugated equine
  - Estradiol valerate
  - Estrial 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)

ESTROGEN

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

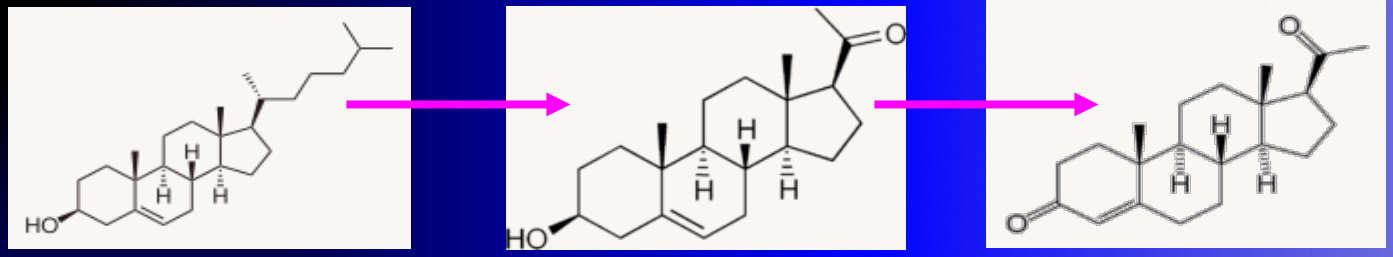
2. PROGESTINs

In NATURE

Produced by; Adrenal glands, Gonads, Brain, Placenta

Synthesis;

Induced by LH



Cholesterol → Pregnenolone → Progesterone

Are precursor to estrogens, androgens, and adrenocortical steroids.

As Therapy

- **Progesterone** is degraded in GIT, so can be given only <u>parentally</u>
- **Progestins** are synthetic progestogens that have effects similar to progesterone but are **not degraded by GIT.**

Progestin preparations; as in contraceptive pills

What does progesterone do?

Binds to its receptors

↓ 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.
- Progesterone (natural) protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, but this effect is not as clear with synthetic progestins. Mammography recommended every 6ms.

- Confers neuroprotection, mild effect
- Controls insomnia & depression → little effect
- Counteract osteoporosis, directly +ve osteoblasts

PROGESTIN

B. Other Uses

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

Administration

- Oral; Micronized progesterone or progestins
- 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).
- Hirsutism , masculinization (Not with new preparations)

Benefits and Risks of HRT

Definite benefits

- Alleviates 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

+ = agonist
- = antagonist

		Brain	Uterus	Vagina	Breast	Bone	CVS
	Estradiol	++	++	++	++	++	++
	Ideal SERM	++	—	++	—	++	++
Not Ideal	Tamoxifen	—	+	—	—	+	+
Not Ideal	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 esterogen 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.

HRT

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,* is a synthetic steroid drug with estrogenic, progestogenic, and weak androgenic actions . *(androgens use is not approved by FDA in women)*

The Women's Health Initiative (WHI) and HRT

- 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) reduces vasomotor symptoms
- **Clonidine** (centrally acting antihypertensive, alpha 2 agonist) helps with vasomotor symptoms.
- **Gabapentin** (anticonvulsant) reduces severity and frequency of hot flushes
- **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.