Pharmacology
Team 437

Hormonal replacement therapy

Objectives:

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

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Color index:
Important Note Extra

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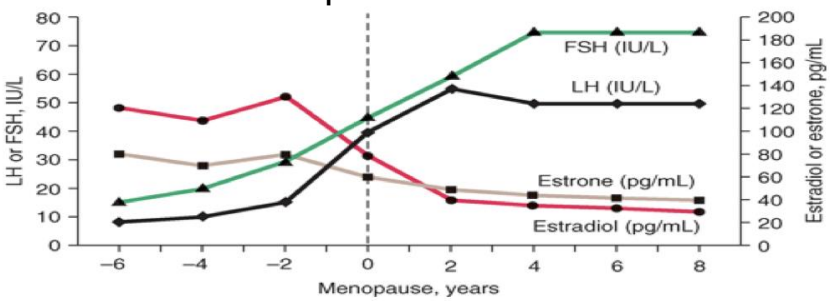
Introduction

Definition

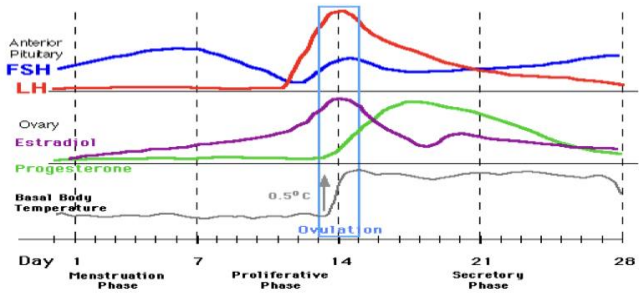
Menopause: menos'(month) 'pausis'(cessation),so menopause means a complex physiological changes that occur at the time when the last period ends generally as women get older and lose fertility (age late 40s).

Characteristics of menopause: low estrogen and progesterone, low androgen, high FSH & LH, high insulin resistance. (the aim of hormone replacement therapy is to boost these hormones)

Menopause



Normal menstruation



Symptoms & consequences of Menopause

Immediate

- Hot flushes/night sweat(vasomotor symptoms).
- Insomnia,anxiety & irritability.
- Mood disturbance.
- Reduction in sexuality & libido.
- Poor concentration.
- Memmory loss

Intermediate

- Dyspareunia & vaginal dryness. (caused by atrophic vaginitis due to thinning of vaginal mucosa)
- Urethral syndrome (dysuria, urgency & frequency)
- Incontinence, Difficulty in voiding.
- Increased bruising.
- Generalized ache & pain.

Long term

- Osteoporosis
- CVS Risks; ↑ LDL/HDL ratio, coronary heart disease, stroke, etc
- CNS deficits, Alzheimer's, Dementia

Symptoms Experienced Most During Menopause

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

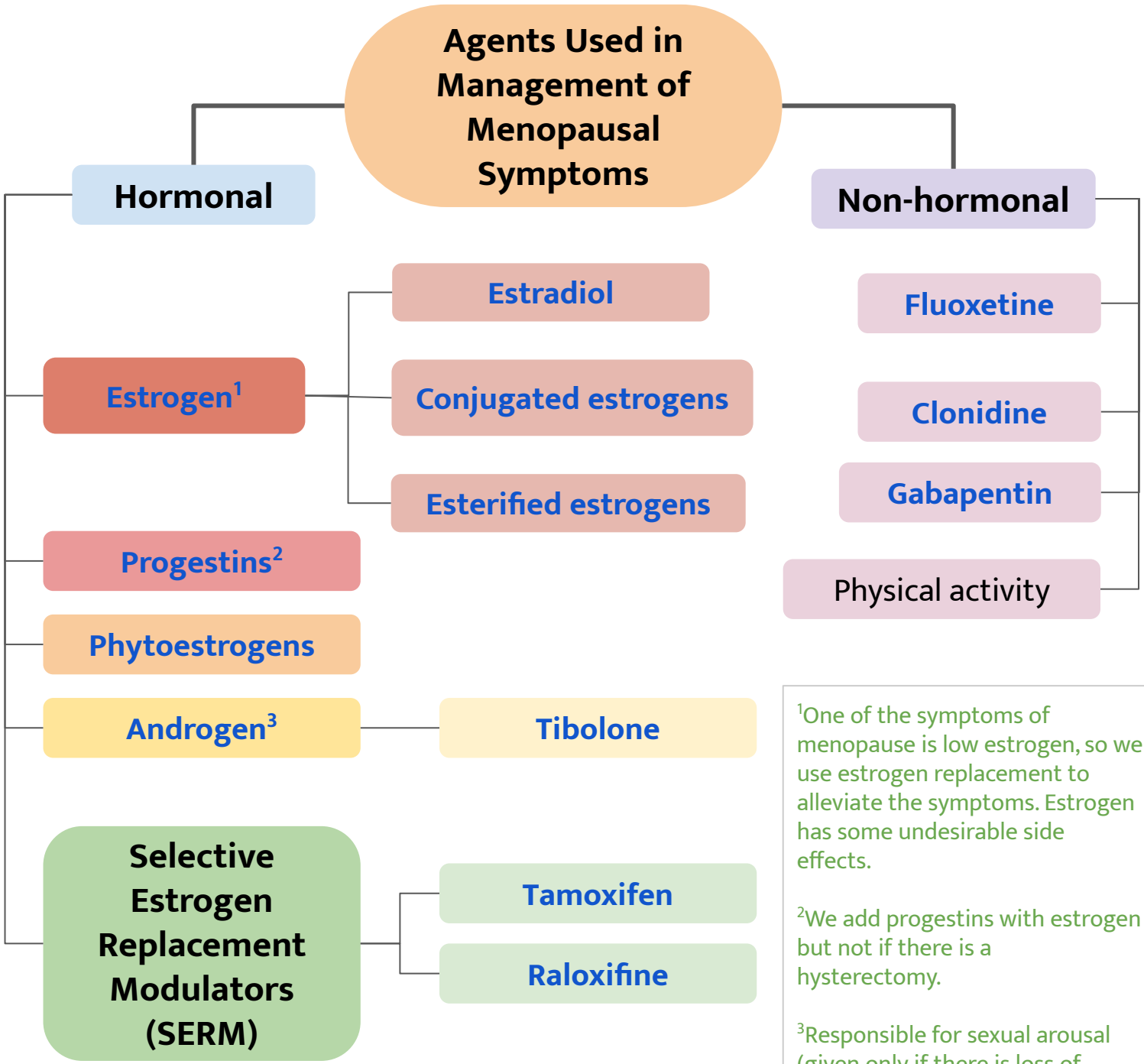
Hormonal replacement therapy

Definition

Hormonal Replacement Therapy (HRT): Is a system of medical treatment that is designed to artificially boost female hormones, in hope to alleviate symptoms caused by decrease in their circulating levels. The decrease in the hormonal level appears In ⅓ of total female population (Perimenopause & postmenopause). Maybe natural, pathological or induced.

Administration

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



[1]One of the symptoms of menopause is low estrogen, so we use estrogen replacement to alleviate the symptoms. Estrogen has some undesirable side effects.

[2]We add progestins with estrogen but not if there is a hysterectomy.

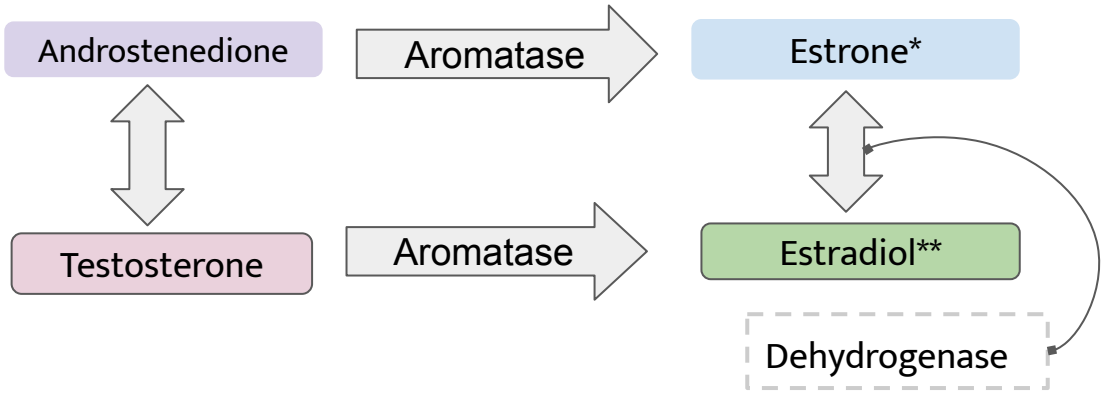
[3]Responsible for sexual arousal (given only if there is loss of libido & orgasm)

Estrogen

Estrogen

General information

In nature:



As therapy:

- **Estradiol** :Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, subcutaneous implant, etc
- **Conjugated estrogens:** mixture of Na salts of sulfate esters of estrone & equilin
- **Esterified estrogens.**

*ovaries & adrenal in **premenopausal**. **Adrenal in **menopause**. **ovaries in **premenopausal**

Receptors

What does estrogen do?

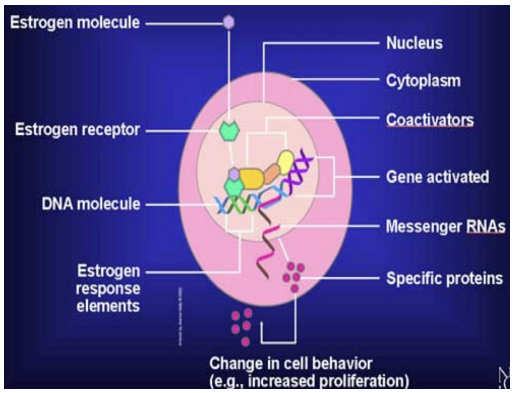
It binds with its receptors Types of estrogen receptors (ER):

- **ER α** : mediates female hormonal functions. They are located in (Endometrium, breast, ovaries, hypothalamus,...) in female genitalia (to produce the sexual effect)
- **ER β**: mediates other hormonal functions. They are located in (brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells,....).

Estrogens bind to ERm(α or β) that exist either:

1. **Cytoplasmic**: mediates its genomic actions (hours to days time scale) and this kind of receptors are important for development, neuroendocrine, metabolism.
2. **Membranous**: G protein estrogen receptors →2nd messenger → ↑ Ca or cAMP or↑ mitogen activated protein (MAP) Kinase* → mediates its non-genomic actions** → seconds to minutes time scale. E.g. receptors of: nitric oxide, neurotransmitters, endometrium, etc

Genomic effects: when the hormone enters the cell and binds with intracellular receptors → binds to hormone response element → gene activation → transcription → translation → protein → effects. e.g(increase cells proliferation).



*activate transcription factors to promote mitogenesis.
**There will be no activation of DNA, instead where will be enzyme phosphorylation.

CONT'D

Administration*	I. **Oral**: Conjugated equine (venous thromboembolism is a serious side effect), **Estradiol valerate , Estriol succinate.** II. **Transdermal** (estradiol): ✓ Patches (24 hour twice weekly) ✓ Gel (24 hours daily). III. **Subcutaneous implant** (estradiol): 6 monthly. IV. **Vaginal cream:** as such or as rings pessaries.
Indications	• **In menopause:** Not given unless presence of symptoms; alone only after hysterectomy or with progestin as HRT (never exceed 5 years administration) to avoid cancer. • Improves vaginal dryness by ↑ epithelial thickness & vascularity, collagen content (topical 'pessaries or rings' and systemic estrogens preparation 'oral, transdermal patches, or subcutaneous implant' are effective) • Increases bone density by ↑ calcitonin release from thyroid to ↓osteoclastic activity. Progestins act synergistically by blocking corticosteroid induced bone resorption. (Decrease incidence of hip fracture). • Protects CVS by enhance vasodilatation via ↑ neritic oxide production & ↑ HDL & ↓ LDL thus ↓ atherosclerosis & ischemic insults (HRT started at the beginning of menopause will prevent CVS problems, **however HRT increases CVs problems in long term;** since it may cause deep venous thrombosis → embolism to lung, brain, etc.... • Improves hot flushes & night sweats. • Controls sleep disturbance & mood swings by acting on norepinephrine, dopamine & serotonin at reticular formation. • Improves urethral & urinary symptoms by ↑ epithelial thickness & vascularity, collagen content at urethra & norepinephrine transmission that contract sphincters & relax detrusor muscles of the urinary bladder, and thus improves the urinary continence. • Improves insulin resistance & glycemic control in diabetics. • Improves cognitive function via ↑ expression of estrogen receptor in brain & by ↓ amyloid deposition thus preventing Alzheimer's. • Delays parkinsonism by acting on dopamine system in midbrain. • **Other uses:** ✓ Contraception. ✓ Primary ovarian failure. ✓ Amenorrhea & Hirsutism caused by excess androgens.
ADR	❖ Irregular vaginal bleeding (patients discontinue HRT5). ❖ Breast tenderness (patients discontinue HRT5). ❖ Nausea. ❖ Vaginal discharge. ❖ Fluid retention, Weight gain. ❖ Spotting or darkening of skin (on face) (chloasma/وحمة).
C.I	**Absolute** • Undiagnosed vaginal bleeding because we suspect cancer • Severe liver disease. • Thromboembolic manifestations. • Cancer in: endometrium ,breast (hormone sensitive), ovaries
Interaction	• With contraception • With (SERM): additive side effects for both drugs. • With Aromatase inhibitors: ↓ **efficacy**. • With Corticosteroids: ↑ **side effects.**

Progestins

Progestins

General Information

- **In nature:**
  - ➢ Produced by Adrenal glands, Gonads, Brain, Placenta
  - ➢ The synthesis is induced by LH
  - ➢ Are precursors to estrogens, androgens, and adrenocortical steroids.

Cholesterol → Pregnenolone → Progesterone

- **As therapy:**
  - ❑ Progesterone is degraded in GIT, so can be given only parenterally
  - ❑ Progestins are synthetic progestogens that have effects similar to progesterone (progestinic effects) but are not degraded by GIT, so we can give it orally
  - ❑ Progestin preparations as in contraceptive pills

M.O.A

- **What does progesterone do?** Binds to its receptors. There are two types of progesterone receptors [PR]: **PR-A & PR-B.**
- They could exist in the cytoplasm to mediate genomic long term effects
- They could exist in the membrane to mediate non-genomic rapid effects

Indications

- ❖ **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 on the other hand, Progesterone beneficially matures endometrial cell lining 'becomes 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 6 months. To make sure if there is breast cancer or not
- ❖ Confers neuroprotection (mild effect)
- ❖ Controls insomnia & depression (little effect)
- ❖ Counteract osteoporosis bc it is directly +ve (stimulate) osteoblasts
- ❖ **Other uses:**

✓Contraception (Estradiol + Progestins)

✓Dysmenorrhea

Menopausal symptoms (Estradiol + Progestins given together

Important note if we have menopause lady and here uterus is present we DON'T give estrogen alone, if there is no uterus we use estrogen ALONE

Cont'D	
ADRs	❏ Mood changes e.g. anxiety, irritability. ❏ Headache, dizziness, drowsiness ❏ Nausea, vomiting, abdominal pain or bloating (distention). ❏ Hirsutism, masculinization (Not with new preparations)
Administration	• **Oral**: Micronized progesterone or **progestins** • **IntraUterine(IU):** as **Levonorgestrel** or **Progestasert** • **Vaginal**: natural progesterone gel, pessary. • **Transdermal**: sequential (replaced daily), continuous patch.

Benefits and Risks of HRT

Benefits	Risks
• **Definite benefits:** ➢ Alleviates symptoms of menopause (vasomotor, genitourinary) ➢ Osteoporosis (Definite increase in bone mineral density and probable decrease in risk of fractures) • **Uncertain benefits:** ➢ Cognitive functions (Alzheimer's symptoms)	• **Definite risks:** ➢ Endometrial cancer (estrogen only) ➢ Venous thromboembolism (long term) because estrogen increase the coagulability ➢ Breast cancer (long term 5 yrs.) **Note:** the risk of CVS problems and breast cancer with HRT is more than their benefits

Selective Estrogen Receptors Modulators

Selective Estrogen Receptors Modulators

General Information	An ideal SERM for use as HRT should be agonistic in brain, bone, cardiovascular system (not necessarily the liver), vagina & urinary system but antagonistic in breast & uterus, so it will not cause breast or uterine cancer like estrogen	
	Raloxifene	Tamoxifen
	Antagonist in breast and uterus and agonist in bone	Antagonist in breast and partial agonist in bone and endometrium (may lead to endometrial cancer).
Effect	• Very effective preventing vertebral bone fracture • Has no effect on hot flushes or increases hot flushes • Cardiovascular problems less compared to Estrogen • Increase the risk of venous thrombosis • For osteoporosis use of bisphosphonate is better than SERMs	• Increase the risk of venous thrombosis • tends to precipitate vaginal atrophy & hot flushes

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERM	++	—	++	—	++	++
Tamoxifen	—	+	—	—	+	+
Raloxifene	—	—	—	—	++	+

Not Ideal

Has good effect in bone

Hormonal Replacement therapy

	Phytoestrogens	Androgen
General Information	• supplements from plants containing **isoflavones** (soya beans, flaxseeds) or lignans (whole grains). • Avoid in estrogen dependent breast cancer	Testosterone is responsible for sexual arousal in females
M.O.A	• They mimic action of estrogen on estrogen receptor-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 estrogen receptor-α in some target tissues: lower risks of developing endometrial & breast cancer.	
Indications		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[8], can be effective in some women bc it has some androgen agonistic properties[9] (androgens use is not approved by FDA in women)

Non-Hormonal agents

Fluoxetine	Selective Serotonin Reuptake Inhibitor (SSRI) reduces vasomotor symptoms
Clonidine	• (centrally acting antihypertensive, alpha 2 agonist) • helps with vasomotor symptoms. (female slides)
Gabapentin	• Anticonvulsant • reduces severity and frequency of hot flushes (only female slides)
Physical activity	exercise, smoking cessation and relaxation of mind will improve symptoms of menopause (e.g. hot flushes) and fall prevention strategies prevents chances of fracture.

The women's health initiative and HRT (not that important)

- Menopausal Hormone Therapy: For decades, hormone therapy widely used in menopausal symptoms. (only male slides)
- Estrogen has been used alone in menopausal women who have had their uterus removed. (Male slides)
- Progestin, the synthetic form of an estrogen-related hormone called progesterone, is combined with estrogen in menopausal women who still have their uterus. (only male slides)
- 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:

1. The use of estrogen plus progestin in women with a uterus
2. 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.

Summary

Estrogen

Admin.	• Orally (Conjugated equine, Estradiol valerate and estriol succinate). • Also available as: Transdermal patches (estradiol), Subcutaneous implant (estradiol) and Vaginal cream.
Indications	• Improves vaginal dryness by ↑ epithelial thickness & vascularity, collagen content • Increase bone density. • Improves insulin resistance., • Protects CVS in short use, however HRT increases CVs problems in long term. • Improves hot flushes & night sweats. • Improves urethral & urinary symptoms. • Contraception. • Primary ovarian failure • Amenorrhea and hirsutism. • Improves cognitive function • Controls sleep disturbance & mood swings
ADRs	Breast tenderness. Vaginal discharge. Spotting and darkening of the skin. Spotting or darkening of skin
Inter.	• Other contraceptives. • With Aromatase inhibitors. • With corticosteroids.

Progestin

Indications	• Protect against estrogen induced endometrial and breast cancer. • Confers neuroprotection. • Controls insomnia and depression • Dysmenorrhea. • Menopausal symptoms
Admin.	• Progesterone can be given onl parentally • Progestins are not degraded by GIT, so we can give it orally • Oral Micronized progesterone or progestins • IntraUterine (IU): Levonorgestrel or Progestasert • Vaginal: natural progesterone gel /pessary. • Transdermal: sequential (replaced daily) / continuous patch.

SERM

information	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.	
Effects	Raloxifen: Antagonist in breast and uterus and agonist in bone. 1-very effective preventing vertebral bone fracture 2-Has no effect on hot flushes or increases hot flushes 3-CVs problems less compared to Estrogen	Tamoxifen: Antagonist in breast and partial agonist in bone and endometrium. Increase the risk of venous thrombosis & tends to precipitate vaginal atrophy & hot flushes

	Phytoestrogens	Androgen
information	• Supplements from plants; containing isoflavones (soya beans, flaxseeds) or lignans (whole grains). • Avoid in estrogen dependent breast cancer	Testosterone is responsible for sexual arousal in females.
Interaction		N.B. **Tibolone**, is a synthetic steroid drug with estrogenic, progestogenic, and weak androgenic actions. (synthetic form of androgen, to given to menopausal women in whom their menopausal symptoms are focused on lack of sexual arousal)

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

Non-hormonal agents	
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

Quiz

Q1: 49 years old female is diagnosed with pelvic inflammatory disease and she has high risk to develop uterine cancer, so her doctor decide to do hysterectomy. Which one of the following drugs can be safe in her case to treat postmenopausal osteoporosis ?

A. Estrogen
B. Progesterone
C. Tamoxifen
D. Raloxifene

Q2: Generalized ache & pain is one of..... consequences of menopause?

A. Immediate.
B. Intermediate.
C. Late.

Q3: Breast tenderness is an ADR of?

A. Progestin.
B. Estrogen.
C. Raloxifene.
D. Tamoxifen.

Q4: mediate female hormonal function?

A. ER a
B. ER b
C. Both
D. None of the above

Q5: Which of the following used to protect against estrogen-induced endometrial cancer ?

A. Tamoxifen
B. Raloxifene
C. Progestin
D. Phytoestrogen

Q6: Which one of the following drugs is prescribed to reduce vertebral fracture in postmenopausal women ?

A. Androgens
B. Progesterone
C. Raloxifene
D. Tamoxifen

Q7:A 45 years old female came in for a routine checkup, the densitometry revealed that she has osteoporosis. Which one of the following is good for her to be used ?

A. Raloxifene
B. Tamoxifen
C. Clomiphene
D. Syntocinon

Q8:Which of the following is non-hormonal agent ?

A. Progestin
B. Raloxifene
C. Phytoestrogen
D. Fluoxetine

Answers :

1) A
2) B
3) B
4) A
5) C
6) C
7) A
8) D

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Thanks for those who worked on the lectures :

Mohammed Alomar
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Mohammed Nouri
Fahad Alfaiz

Notes by

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References:

- ✓ Team 436
- ✓ Doctors notes and slides

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