Pharmacology 439

MED439

pharmacology Team 438

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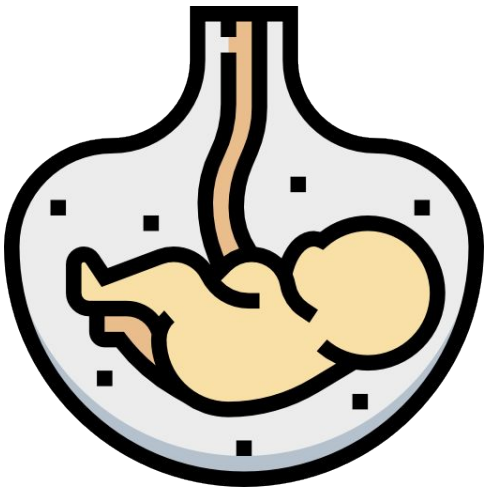


Editing File

Reproduction Block

Pharmacology team 439

Hormonal Replacement Therapy

Objectives:

By the end of the lecture , you should know:

- 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 agent

Color index:

Black : Main content
Red : Important
Blue: Males' slides only

Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)

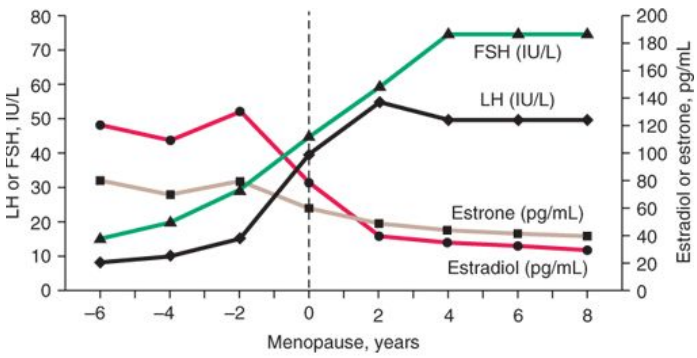
Green: Dr. notes (438)

Menopause

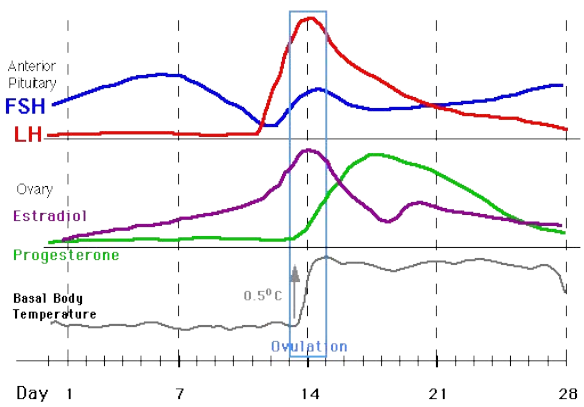
Definition: menos (month) pausis (cessation), so menopause means a complex physiological changes that occur at the time when the last period ends generally as women get older and lose fertility, usually in late 40s of age.

Characteristics of Menopause: low estrogen and progesterone, low androgen, High FSH & LH, high insulin resistance.

Menopause



Normal Menstruation



Symptoms & Consequences of Menopause

Immediate

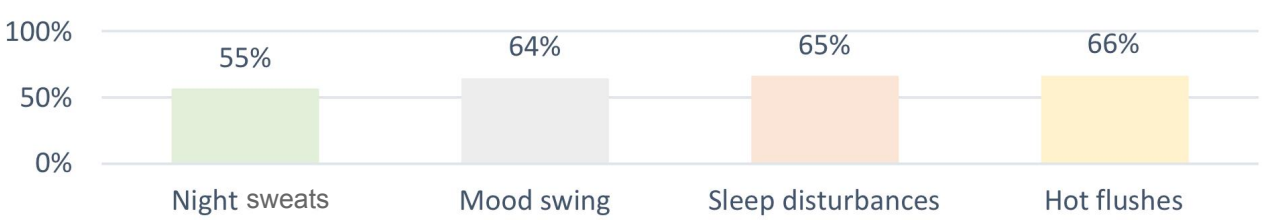
- Hot flushes / Night sweats (vasomotor symptoms).
- Insomnia, Anxiety, irritability.
- Mood disturbances.
- Reduction in Sexuality & lipido.
- Poor concentration / Memory loss.

Intermediate

- Dyspareunia[1] & vaginal dryness.
- Urethral syndrome (Dysuria, urgency & frequency).
- Incontinence, difficulty in voiding.[2]
- Increased bruising. Generalized aches and pains.

Long term

- Osteoporosis
- CVS Risks; ↑ LDL/ HDL ratio, coronary heart disease, storke.
- CNS deficits; Alzheimer's, dementia



Symptoms Experienced Most During Menopause:
20% no symptoms,
60% some symptoms,
20% severe symptoms

1:difficult or painful sexual intercourse.
2: Due to weakness of sphincters and abdominal muscles

Hormonal Replacement Therapy (HPT)

Definition:

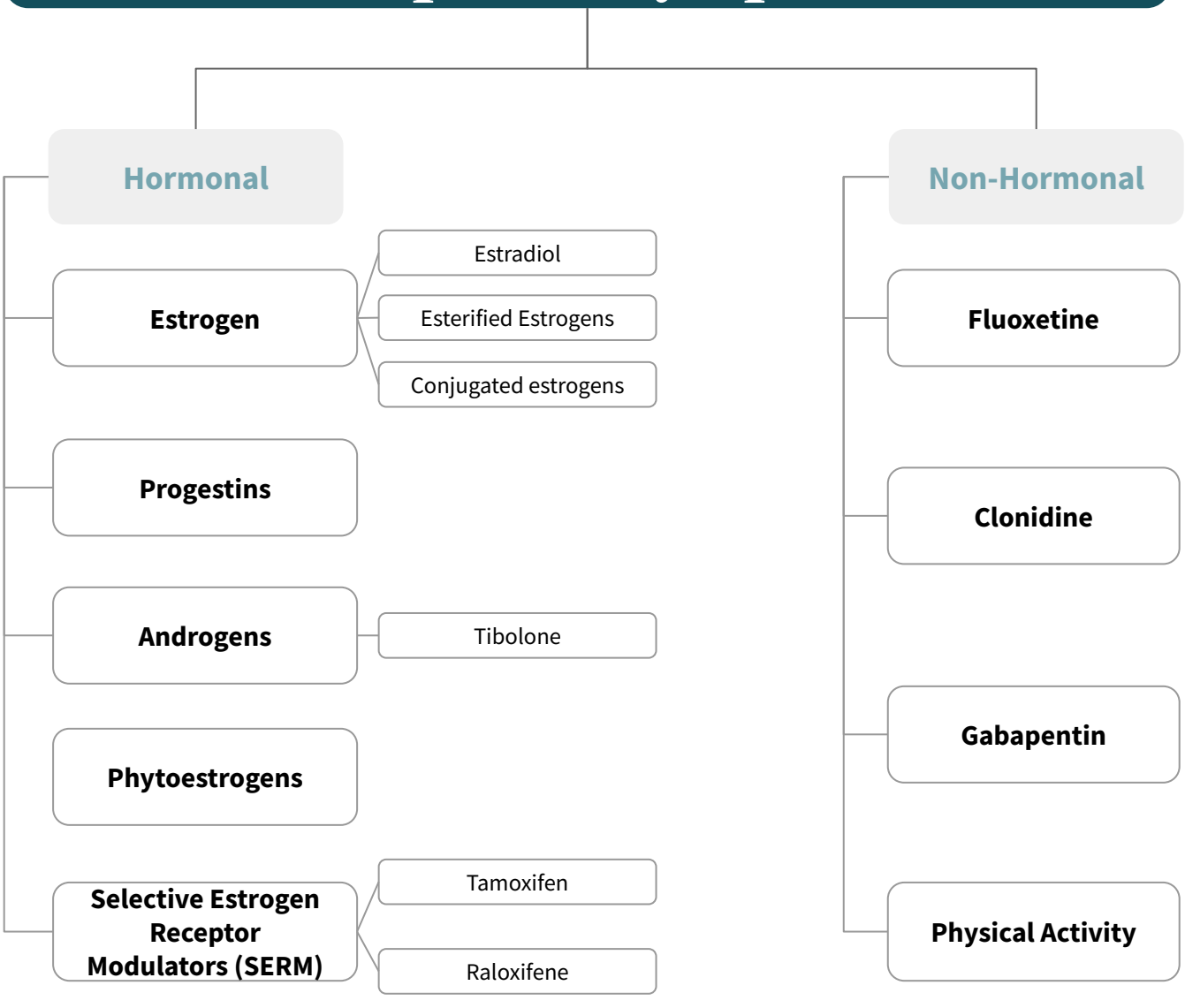
- Is a system of medical treatment that is designed to artificially boost female hormones, in hope to alleviate symptoms caused by decrease in their circulating levels.
- This decrease in female hormones could be natural, pathological or induced.
- HRT is used in 1/3rd of total female population (Perimenopause & Postmenopause).

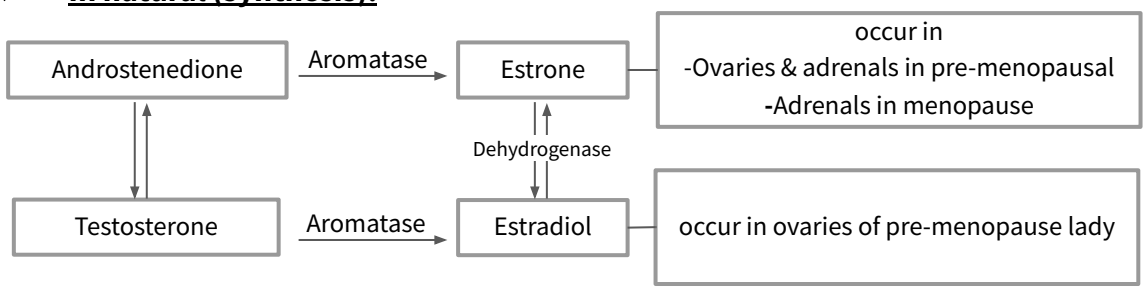
Administration:

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 (**CANCER**).

Long-term administration (No more preferred): Was only indicated in osteoporosis & CVS protection but now better drugs are available.

Agents used in management of Menopausal Symptoms



Drug	Estrogen
General Info	❖ **In natural (synthesis):**  ❖ **As therapy:** • **Estradiol** (Not stable)**:** Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, intradermal implant and subcutaneous implant. • **Conjugated estrogens** (Stable) **:** mixture of Na salts of sulfate esters of estrone & equilin. • **Esterified estrogens** High estrogen is one of the major risk factors for endometrial cancer, this risk can be inhibited by adding progestin with estrogen. For patient with hysterectomy, estrogen alone is enough.
MOA	**What does estrogen do?** It binds with its receptors. • **Types of estrogen receptors (ER):** 1. **ER α :** mediates female hormonal functions. They are located in (Endometrium, breast, ovaries, hypothalamus). 2. **ER β:** mediates other hormonal functions. They are located in (brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells). • **Estrogens bind to ER (α or β) that exist either:** 1. **Cytoplasmic:** mediates its genomic actions (hours to days time scale) and this kinds of receptors important for development, neuroendocrine, metabolism. 2. **Membranous:** G protein estrogen receptors(GPER) ⟶ 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. (GPER activate transcription factors to promote mitogenesis) This mechanism is general for all steroidal drugs, you just need to remember that genomic takes longer time than non genomic, because it goes inside the membrane into the DNA
Admin. No need to remember	• **Oral:** Conjugated equine, Estradiol valerate, Estrial succinate. • **Transdermal (estradiol):** 1. Patches (24 hour twice weekly). 2. Gel (24 hours daily). • **Subcutaneous implant (estradiol):** 6 monthly. • **Intravaginal "topical" :**Vaginal cream as such or as rings pessaries These natural estrogen prep have less risk of adverse CVS effects associated with synthetic estrogen used in oral contraceptive e.g ethinylestradiol.
Uses	★ **in menopause:** Not given unless presence of symptoms 1. Alone only **after hysterectomy** 2. In the presence of uterus, combined with progestin as HRT to **avoid** cancer (never exceed 5 years administration) ❖ **Other uses:** 1. Contraception. Depends on dose 2. Primary ovarian failure. 3. Amenorrhea & Hirsutism caused by excess androgens. These result from hormone imbalance, for example in patients with PCOS."

Drug	Estrogen
Advantages	Advantages of estrogen when used for menopausal women: 1. **Improves vaginal dryness by ↑ epithelial thickness , vascularity & collagen content** (topical[1] and systemic estrogens preparation are effective). 2. **Increases bone density by ↑ calcitonin release from thyroid to ↓ osteoclastic activity**. Progestins act synergistic by blocking corticosteroid induced bone resorption (decrease incidence of hip fracture). 3. **Protects CVS** by enhance vasodilatation via ↑ nitric oxide production & ↑ HDL & ↓ LDL thus ↓ atherosclerosis & ischemic insults (HRT started at the beginning of menopause will prevent CVS problems) ★ However HRT increases cardiovascular problems and thromboembolism **in long term**[2] IMP 4. Improves hot flushes & night sweats. 5. Controls sleep disturbance & mood swings by acting on norepinephrine, dopamine & serotonin at reticular formation. 6. Improves urethral & urinary symptoms by ↑ epithelial thickness, vascularity & collagen content at urethra & norepinephrine transmission that contract sphincters & relax detrusor muscles of the urinary bladder. 7. Improves insulin resistance & glycemic control in diabetics. 8. Improves cognitive function via ↑ expression of estrogen receptor in brain & by ↓ amyloid deposition thus preventing Alzheimer's. 9. Delays parkinsonism by acting on dopamine system in midbrain.
ADRs	★ Irregular vaginal bleeding (patients should discontinue the therapy). ○ Bleeding can be prevented if progesterone is given with estrogen through out ★ Breast tenderness (patients should discontinue the therapy). ● Nausea. ● Vaginal discharge. ● Fluid retention, Weight gain. Edema ● Spotting or darkening of skin (on face). Freckles is a normal reversible side effect in HRT
C.I	❖ **<u>Absolute:</u>** ● Undiagnosed vaginal bleeding. ● Cancer in: endometrial, breast (hormone sensitive), ovarian. ● Severe liver disease. ● Thromboembolic manifestations (deep vein thrombosis and pulmonary embolism) because they increase clotting factors
Inter-action	● as **contraception:** 1. Impairing absorption e.g Antibiotics 2. CYT P450 Inducers e.g. Phenytoin, Phenobarbitone, Rifampin. 3. CYT P450 Inhibitors e.g. Acetaminophen, Erythromycin. 4. Altered in clearance↑ in their toxicity. e.g. Warfarin, Cyclosporins, Theophylline. ● With **selective estrogen receptors modulators (SERM):** additive side effects for both drugs. ● With **Aromatase inhibitors:** ↓ efficacy. Interfere with natural estradiol synthesis ● With **Corticosteroids:** ↑ side effects. Skin pigmentation, edema, weight gain .etc

1: Topical estrogen is a very effective treatment for <u>premenopausal</u> women who suffer from vaginal dryness only
2: Estrogen increases the blood coagulability so the incidence of thrombosis and coronary heart diseases will be increased too. Remember; NEVER EXCEED 5 YEARS 📢

Drug	Progestins
General Info	❖ **<u>In nature (synthesis):</u>** ● Produced by Adrenal glands, Gonads, Brain, Placenta ● The synthesis is induced by LH ● Are precursor to estrogens, androgens, and adrenocortical steroids. Cholesterol → Pregnenolone → Progesterone ❖ **As therapy:** ● Progesterone (Not stable) is degraded in GIT, so can be given only parentally ● Progestins (Stable) are synthetic progestogens that have effects similar to progesterone but are not degraded by GIT ● Progestin preparations as in contraceptive pills: ○ Old preparations = Norethindrone, Levonorgestrel & Medroxyprogesterone acetate (have systemic androgenic effects) ○ New preparations = Norgestimate, Desogestrel & Drospirenone (lack androgenic effects)
MOA Same as Estrogen	**What does progesterone do?** Binds to its receptors. ● There are two types of progesterone receptors [PR]: PR-**α** & PR-**β** ● They could exist cytoplasmic to mediate genomic long term effects or exist membranous to mediate non-genomic rapid effects
Admin. No need to remember	● **Oral**: Micronized progesterone or progestins ● **IntraUterine (IU):** as Levonorgestrel or Progestasert ● **Vaginal**: natural progesterone gel, pessary. ● **Transdermal**: sequential (replaced daily), continuous patch
Uses	❖ **In menopause:** 1. As HRT, usually given in combination with estrogen 2. Some use it alone in risk of cancer **but does not ↓ all menopausal symptoms as estrogen** . ❖ **Other uses:** ● Contraception (Estradiol + Progestins) ● Dysmenorrhea
Advantages	Advantages of Progestins when used for menopausal women: 1. **Protects against possibility of estrogen induced endometrial cancer** a. Estrogen ↑ cell growth. If unopposed → endometrial cell lining can show atypical hyperplasia (seen if not given additive progesterone) b. Progesterone beneficially matures endometrial cell lining. Become differentiated & ↑ apoptosis of atypical cells by activation p53 2. Progesterone (natural) protects against breast cancer development by antiinflammatory & apoptotic mechanisms, **but this effect is not as clear with synthetic progestin.** Although it's effective when given with estrogen, the natural form is more efficient a. Mammography recommended every 6 months. 3. Confers neuroprotection (mild effect) 4. Controls insomnia & depression (little effect) 5. Counteract osteoporosis by a direct activation of osteoblast. (Natural form)
ADRs No serious ADR, not like estrogen	● Mood changes e.g. 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:**

1. Alleviates symptoms of menopause (vasomotor, genitourinary).
2. Improve osteoporosis (Definite increase in bone mineral density → probable decrease risk of fractures)

❖ **Uncertain benefits:**

1. Improve cognitive functions.

❖ **Definite risks:**

1. Endometrial cancer (estrogen only).
2. **Venous thromboembolism (long term)** IMP
3. Breast cancer (Long term 5 years[1])

★ The risk of CVS problems and breast cancer with HRT is more than their benefits

"That's why we don't recommend using it for minor symptoms"

Selective Estrogen Receptor Modulators

Drugs	Raloxifene	Tamoxifen[2]
MOA	• **Antagonist in the breast and uterus.** No chances of cancer • **Agonist in bone**	• **Antagonist in the breast.** • **Partial agonist in bone and endometrium.** Risk for endometrial cancer
Effects	• Very effective preventing vertebral bone fracture. • Has no effect on hot flushes or increase hot flush. • Cardiovascular problems are less compared to Estrogen. • For osteoporosis use of bisphosphonate is better than SERMs.	• Increase the risk of venous thrombosis. • Tends to precipitate vaginal atrophy & hot flushes.

Selectivity

Against = + Antagonist = -	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERM	++	-	++	-	++	++
Tamoxifen	-	+	-	-	+	+
Raloxifene	-	-	-	-	++	+

(Tamoxifen and Raloxifene: Not ideal)

- 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[3]

1: A nice reminder to NOT EXCEED 5 YEARS of administration. Thank you :)
2: More toxic
3: There isn't an ideal SERM available yet, even Raloxifene and Tamoxifen they are not ideal

Other Types of HRT

Drug	Phytoestrogens "Can't rely on these for major symptoms"
Source	• Supplements from plants containing isoflavones (soya beans, flaxseeds) or lignans (whole grains).

Uses	• They mimic the action of estrogen on estrogen **receptor-β:**
	  ○ alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions. (data are limited on their efficacy)
	• They block actions mediated by estrogen **receptor-α** in some target tissues:
	  ○ lower risks of developing endometrial & breast cancer.

C.I	• **Avoid in estrogen dependent breast cancer.** Avoid combination with other HRT

Drug	Androgen | Tibolone
Source	• **Testosterone** is responsible for sexual arousal in females, given only if there is loss of libido & orgasm ★ **Tibolone** is a synthetic steroid drug with estrogenic, progestogenic and weak androgenic actions
Uses	• Testosterone is given alone to menopausal women in whom their menopausal symptoms are focused on **lack of sexual arousal** • Tibolone, can be effective in some women □has some androgen agonistic properties. (androgens use is not approved by FDA in women) • It is given as adjuvant to combined estrogen & progestin if all other menopausal symptom exist.

Non-hormonal Agents

Fluoxetine	• Selective Serotonin Reuptake Inhibitor (SSRI) • Reduces vasomotor symptoms.
Clonidine	• Centrally acting antihypertensive, α2 agonist • Helps with vasomotor symptoms.
Gabapentin	• Anticonvulsant (Mood stabilizer) • 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 prevention strategies prevents chances of fracture.

The Women's Health Initiative (WHI) and HRT

SELF READING, NOT FOR EXAM

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.

Quiz

MCQ

Q1: Which of the following has protective effect against breast cancer ?

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

Q2:A 35 years old female underwent hysterectomy for treatment of fibroids, she requires hormone replacement therapy because of her complaints of hot flushes, urinary incontinence and vaginal dryness. Which of the following would be appropriate for her condition?

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

Q3: A 65-year-old female who has been diagnosed with postmenopausal osteoporosis. She has no history of fractures and no other pertinent medical conditions such breast or ovary cancer. Which of the following would be most appropriate for management of her osteoporosis?

A. Clomiphene **B.** Progestin **C.** Tamoxifen **D.** Raloxifene

Q4: Which of the following should be combined with estrogen in hormone replacement therapy to reduce the incidence of endometrial cancer ?

A. Phytoestrogens **B.** Progestin **C.** Tamoxifen **D.** Testosterone

Q5: A 47 years old female who start to develop symptoms such as hot flushes, night sweating, mood Disturbances, vaginal dryness, difficulty in voiding and Loss of Sexual Arousal & Libido. Which of the following would be helpful in her case?

A. Estradiol + progestin + Raloxifene
B. Clomiphene + Estradiol + Progestin
C. Testosterone + Estradiol + progestin
D. Estradiol + Progestin

SAQ

- **A 55 years old female complaining about hot flushes, sleep disturbance, night sweats, past medical history of hysterectomy 4 years ago.**

  Q1) What is the management of her case?

  Q2) Enumerate 3 ADR

- **A 52 years female with menopausal symptoms: hot flushes, night sweats, urinary symptoms, sleep disturbance, with no history of cancer in the family or relatives.**

  Q1) What is the best management in her case?

  Q2) Give 1 non-hormonal agents that can be used in her case.

Answers:

MCQ

Q1	B
Q2	A
Q3	D
Q4	B
Q5	C

SAQ

Q1	Estrogen (ALONE)
Q2	1. Irregular vaginal bleeding 2. Breast tenderness 3. Nausea
Q3	Estrogen + Progestin
Q4	Physical activity

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

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