Hormone therapy

Drug	Receptors & MOA	Indications	Administration	contraindications
1-Estrogens Interactions: *If given with:* *SERMs➔ additive side effects for both drugs *Aromatase inhibitors ➔↓ efficacy *Corticosteroids ↑ side effects (they have the same ADRs)	Types of Estrogen Receptors [ER]: ER α➔ mediates female hormonal functions (in female sexual organ): Endometrium, breast, ovaries, and hypothalamus. ER β➔mediates other hormonal functions: brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, and endothelial cells.	In menopause: • Improves hot flushes&night sweats • Controls sleep disturbance&mood swings. • Improves urethral & urinary symptoms • Improves vaginal dryness • Increases bone density • Protects CVS: enhance vasodilatation via ↑ NO production, & cholesterol clearance via ↑ HDL &↓ LDL hepatic expression thus ↓ atherosclerosis & ischemic insults • Improves insulin resistance & glycemic control in diabetics • Improves cognitive function , preventing Alzehimer 's. • Delays parkinsonism	1. Oral 2. Transdermal (estradiol) 3. Subcutaneous implant (estradiol) ➔ 4. Vaginal cream as such or as rings pessaries	Absolute (very dangerous): • Undiagnosed vaginal bleeding (Risk of cancer) • Severe liver disease (Because estrogens are metabolized in the liver) • Thromboembolic manifestations (because it increase the clotting factor) • Cancer: endometrial, breast (hormone sensitive), ovarian Relative (shoukd be more carful IN USING IT): • Headaches; specially migraine • History of uterine fibroid or atypical ductal hyperplasia of breast • Active gallbladder disease; cholangitis, cholecystitis
2-Progestins Naturally: Synthesis is induced by LH Produced by: Adrenal glands, Gonads, Brain, and Placenta Are precursor to estrogens, androgens, and adrenocortical steroids. Theraputically: • Progesterone is natural form destructed 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 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		*As HRT, usually given in combination with estrogen. Some use it alone with paitents in risk of cancer, but progesterone does not alleviate all menopausal symptoms (eg; hot flushing , we use it more as contraceptive mini pill) *Protects against possibility of estrogen induced endometrial cancer: 1-Estrogen causes cell growth and proliferation of the endometrium, and If unopposed ➔endometrial cell lining can show (atypical hyperplasia) 2-Progesterone beneficially➔ matures endometrial cell lining (become differentiated) &↑ apoptosis of atypical cells by activation of p53. *Natural progesterone protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, BUT WITH SYNTHETIC PROGESTINS protection not confirmed➔ so mamographyevery 6ms. *Confers neuroprotection, ↑ cognition &↓ incidence of Alzheimer's *Controls insomnia & depression ➔ precursor of melatonin & release 5HT *Contributes to CV protection ➔↑ NO & has anti-atherogenic actions *Counteract osteoporosis, directly +ve osteoblasts & indirectly blocking GC induced bone resorption	• Oral • IUS • Vaginal - naturalprogesterone gel / pessary. • Transdermal -sequential / continuous patch. Other indications: 1. Contraception 2. Dysmenorrhea 3. Infertility due to inadequate luteal phase	

3-SERMS: (Selective estrogen-receptor modulators)

SERMS are Classified according to how they bind to ER

- Raloxifeneis Antiestrogens that exhibits partial agonistic action;acting as an agonist in bone & an antagonist in breast.
- Tamoxifen competes with estrogen for binding to the estrogen receptor in breast tissue. It stabilizes ER in a conformation allowing transcription to occur on only certain ER-responsive genes(post receptor effect).
- An ideal SERM for use as HRT should be agonistic in brain, bone, CV system, vagina & urinary system but antagonistic in breast & uterus
- Tamoxifen→ ↑risk of venous thrombosis & tends to precipitate vaginal atrophy & hot flushes

Raloxifene→ has no effect on hot flushes.

4-Tibilone

Tibilone is a synthetic steroid that is metabolized to many metabolites that have estrogenic, androgenic &progestagenic properties .

Tibolone is close to being ideal HRT, because:

*It induces amenorrhoea
*Improves urogenital symptoms
*Enhances mood & libido.
*Protective on CVS system
*Prevents bone loss
*Protective on endometrium
*Least tendency of breast cancer

- With history of endometriosis, fibroids, or treated breast cancer.
- In diabetics, hypertriglyceridemics
- In thromboembolic tendency
- In lack of sexual arousal

N.B. Tibolone, can be effective in some women → has some androgen agonistic properties.

5-PHYTOESTROGENS:

Are supplements from plants; containing isoflavones (soya beans) or lignans (whole grains).

- They mimic action of estrogen on ER-b→ alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions.
- They block actions mediated by ER-a 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.

Summery:

- Menopausal Hormone Therapy Guidelines:
- Not given unless presence of symptoms and when is given never exceed 5 years administration
- Estrogen is given Alone only after hysterectomy and With progestin as HRT in the rest of conditions
- Types of Estrogen Receptors [ER]:
- ER α→ mediates female hormonal functions (in female sexual organ): eg:Endometrium, breast and ovaries.
- ER β→mediates other hormonal functions

- We use estrogen In menopause to :
- Improves hot flushes&night sweats ,Controls sleep disturbance&mood swings ,Improves urethral & urinary symptoms, Improves vaginal dryness ,Increases bone density
- Protects CVS, Improves insulin resistance & glycemic control in diabetics
- Improves cognitive function so preventing Alzehimer 's and Delays parkinsonism
- Estrogen is Contraindicated with:
- Undiagnosed vaginal bleeding , Severe liver disease
- Thromboembolic manifestations
- Cancer: endometrial, breast (hormone sensitive), ovarian
- We should be careful when using it with:
- Headaches; specially migraine
- History of uterine fibroid or atypical ductal hyperplasia of breast
- Active gallbladder disease; cholangitis, cholecystitis
- Drugs AS : SERMs , Aromatase inhibitors , Corticosteroids
- Progestins are synthetic HRT and Progesterone is natural form usually given in combination with estrogen. Some use it alone with patients in risk of cancer, but progesterone does not alleviate all menopausal symptoms we use it more as contraceptive mini pill
- An ideal SERM for use as HRT should be agonistic in brain, bone, CV system, vagina & urinary system but antagonistic in breast & uterus
- Raloxifeneis is Antiestrogens that exhibits partial agonistic action ;acting as an agonist in bone & an antagonist in breast.
- Tamoxifen competes with estrogen for binding to the estrogen receptor in breast tissue.
- Tamoxifen→↑risk of venous thrombosis & tends to precipitate vaginal atrophy & hot flushes
- Raloxifene→ has no effect on hot flushes
- Tibilone has estrogenic, androgenic &progestagenic properties and it close to being ideal HRT
- Tibilone is treatment of choice With patient :
- history of endometriosis, fibroids, or treated breast cancer.
- In diabetics, hypertriglyceridemics
- In thromboembolic tendency and In lack of sexual arousal
- PHYTOESTROGENS Are supplements from plants; They mimic action of estrogen on ER-b and They block actions mediated by ER-a
- ANDROGENS:Testosterone is responsible for sexual arousal in females but Tibolone is better