King Saud University

College of Medicine

2nd Year,

Reproduction Block

PHARMACOLOGY 433

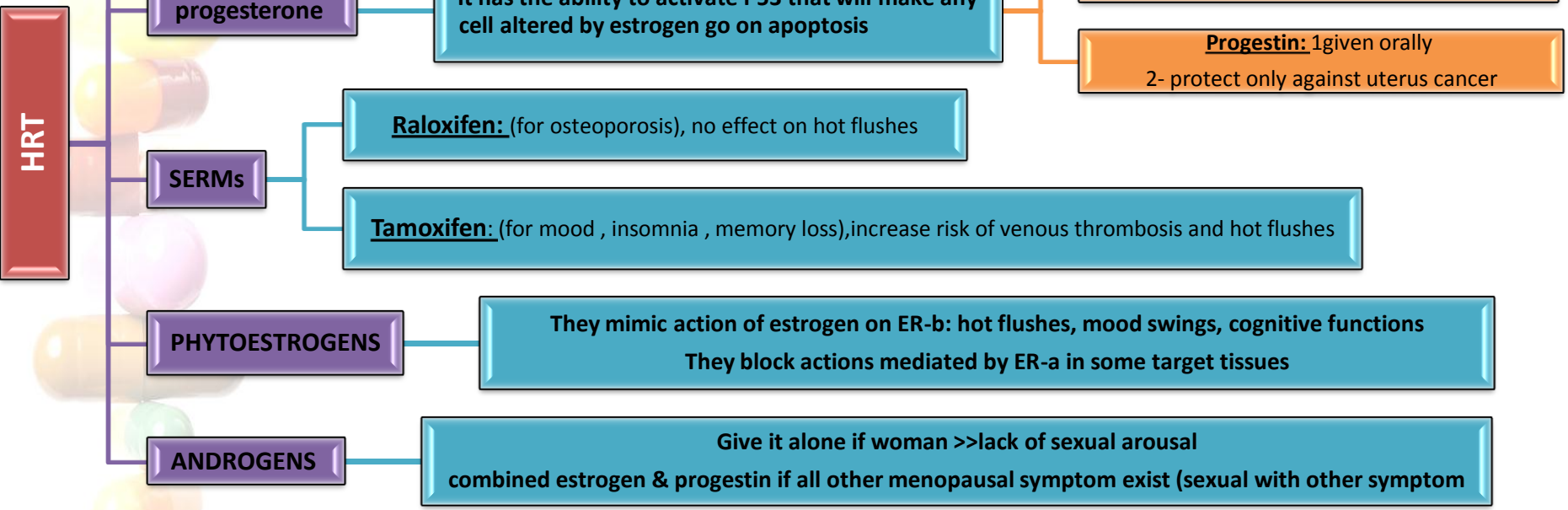
MED 433 Teams

L7-Hormone Replacement Therapy

Objectives

- 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.

Mind Map


HRT
Estrogen
-Not given unless presence of symptoms
-Alone only after hysterectomy
-With progestin as HRT in the rest of conditions
-When given never exceed 5 years administration
-Conjugated estrogens (Conjugated equine estrogen)
-Esterified
Esterified estrogens (Estradiol valerate Estrial succinate)
progesterone
-It has the ability to activate P53 that will make any cell altered by estrogen go on apoptosis
Progestrone : 1-not given orally, 2-protect against, breast and uterus cancer
Progestin: 1given orally 2- protect only against uterus cancer
SERMs
Raloxifen: (for osteoporosis), no effect on hot flushes
Tamoxifen: (for mood , insomnia , memory loss),increase risk of venous thrombosis and hot flushes
PHYTOESTROGENS
They mimic action of estrogen on ER-b: hot flushes, mood swings, cognitive functions
They block actions mediated by ER-a in some target tissues
ANDROGENS
Give it alone if woman >>lack of sexual arousal
combined estrogen & progestin if all other menopausal symptom exist (sexual with other symptom

Introduction

Menopause:

A complex physiological change that occurs at the time when the last period ends generally as women age and loss fertility, and may be:

- ✓ Physiological
- ✓ Pathological
- ✓ Induced by drugs

What happens in Menopause?

- ✓ ↓Estrogen & Progesterone
- ✓ ↓ Androgens (from ovarian source)
- ✓ ↑ FSH & LH
- ✓ ↑ Insulin Resistance

And we treat it by:

*Obese women have milder menopausal manifestations because fat can store estrogen.

Hormonal replacement therapy:

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

Menopausal symptoms	Immediate	Intermediate	Long Term
	✓ Hot Flushes / Night Sweats	✓ Rapid loss of collagen	✓ Osteoporosis
	✓ Insomnia, Anxiety, Irritability	✓ Dyspareunia & vaginal dryness	✓ CVS Risks
	✓ Mood Disturbances	✓ Urethral syndrome (dysuria, urgency & frequency)	✓ CNS deficits
	✓ Reduction In Sexuality & Libido	✓ Incontinence, difficulty in voiding	
	✓ Poor Concentration / Memory Loss	✓ Increased bruising	
	*Our target in HRT	✓ Generalized aches and pains	

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Introduction

Estrogen:

- **With progesterone:** in case of existing uterus
- **Without progesterone:** in case of Hysterectomy

progesterone

Selective ER-Modulators [SERMs]

Phytoestrogens

*More important in prevention than in treatment

Androgens:

- responsible for promotion of sexual desires
- given only if there is loss of libido & orgasm

❖ **HRT:**

- **Given for short term; never exceed 5 years (WHY?)** ➔ to control meno-pausal symptoms without allowing ample time for malignant transition that might be induced by estrogen
- **Long term use NOT more preferred in indicated in osteoporosis & CVS protection because now better drugs are available**

We use estrogen + progestrone to reduce the risk of endometrial cancer but it won't prevent breast cancer.

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1- Estrogen

Estrogen

In NATURE

1-Androstenedione with Aromatase + Estrone work on Ovaries & adrenals pre-menopausal Adrenals in menopause

2-Testosterone with Aromatase =Estradiol Work Ovaries in pre-menopause

As Therapy

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

2-Conjugated estrogens

3-Esterified estrogens

Types of Estrogen receptors [ER]

1-ER alpha ➔

mediates **female hormonal functions**

Endometrium, breast, ovaries, hypothalamus,…

2-ER beta ➔

mediates **other hormonal functions**

brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells

Estrogens bind to ER (a or b) that exist either

1-Cytoplasmic; activate, translocate, dimerize on ERE of DNA ➔ Transcription & Translation to regulatory proteins mediates its genomic actions ➔ hrs– dys time scale ➔development, neuro- endocrines, metabolism

2-Membranous; G protein ER➔2nd messenger ➔ ↑ Ca or cAMP …etc ➔ mediates its non-genomic actions➔ sec – min. time scale ➔as on NO, neuro- transmitters,

1- Estrogen

INDICATIONS

In Menopause*

- Improves hot flushes & night sweats by acting on opiate, NE & 5HT regulating heat dissipation at hypothalamus.
- Controls sleep disturbance & mood swings by acting on NE, DA & 5HT at reticular formation, perioptic areas & hypothalamus
- 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
- Increases bone density by ↑ calcitonin release from thyroid
- ↑ osteoclast apoptosis & growth factors from osteoblasts + ↓No. & depth of resorption cavities & release of cytokines
- Protects CVS; enhance vasodilatation via ↑ NO production, & cholesterol clearance via ↑ HDL & ↓ LDL hepatic expression thus ↓ atherosclerosis & ischemic insults
- 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

Other Uses

- Contraception
- Primary ovarian failure
- Amenorrhea & Hirsutism caused by excess androgens
- Prostatic carcinoma in males ; but cause feminizing characters so other drugs better given

***Not given unless presence of symptoms;**
1-Alone only after hysterectomy
2-With progestin as HRT in the rest of conditions
3-When given never exceed 5 years administration

1- Estrogen

Administration

- Oral: - Conjugated equine estrogen *(CEE); (Estrone Sulphate + equilin sulphate +17 d dihydro equilin) from female horse

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

**In contraception we use patches every day and upon detachment we give emergency hormonal contraception to prevent pregnancy.

*In HRT we can give estradiol or estrone .

ADRs

1.Nausea and breast tenderness.
2.Headache.
3.↑ Skin Pigmentation.
4.Impair glucose tolerance.
5.↑ incidence of breast, vaginal & cervical cancer?
6.Cardiovascular - major problem
•Thromboembolism
•Hypertension
7.↑ frequency of gall bladder disease.

1- Estrogen

Interactions

- SERMs → additive side effects for both drugs (can lead to toxcity)
- Aromatase inhibitors → ↓ efficacy
- Corticosteroids ↑ side effects

Contraindications

Absolute;	Relative;
▪ Undiagnosed vaginal bleeding (it could be cancer) ▪ Severe liver disease ▪ Thromboembolic manifestations ▪ Cancer; endometrial, breast (hormone sensitive), ovarian	▪ Headaches; specially migraine ▪ History of uterine fibroid or atypical ductal hyperplasia of breast ▪ Active gallbladder disease; cholangitis, cholecystitis

2- Progestins

progesterone

In NATURE

1-Produced by; Adrenal glands, Gonads, Brain, Placenta

2-Are precursor to estrogens, androgens, and adrenocortical steroids.

As Therapy

Progesterone is 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

types of progesterone receptors [PR]

1-PR-A

2-PR-B

They could exist cytoplasmic ➔mediating genomic long term effects or membranous ➔mediating non-genomic rapid effects *like estrogen*

Administration

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

2- Progestins

Indications

In Menopause

- **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.

- **Natural progesterone protects against breast cancer** development by anti-inflammatory & apoptotic mechanisms, **BUT WITH SYNTHETIC PROGESTINS protection not confirmed → so mamography every 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

Other Uses

1. Contraception
2. **Dysmenorrhea**
3. **Infertility** due to inadequate luteal phase**

*Estrogen is more effective in cvs and bone protection

**We give more progestins in pregnancy to stabilize the embryo.

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2- Progestins

ADRs	
1.Nausea, vomiting. 2.Headache. 3.Fatigue, depression of mood.	4.Menstrual irregularities. 5.Weight gain. 6.Hirsutism , masculinization. 7.Ectopic pregnancy.

3- Androgens*

Testosterone	
Indications	1-promotion of sexual desire in females. 2-It is given as the sole therapy to menopausal women in whom their menopausal symptoms are focused on lack of sexual desire. It is given as adjuvant to combined estrogen & progestin if all other menopausal symptom exist.

*in small dose to avoid acne and hair growth

4- Phytoestrogens**

Are supplements from plants; containing isoflavones (soya beans) or lignans (whole grains)	
Indications	1-They mimic action of estrogen on ER-b➔ alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions. 2-They block actions mediated by ER-a in some target tissues ➔ lower risks of developing endometrial & breast cancer.

**In prevention or in mild symptoms but not as treatment.

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5- SERMs

Classified according to how they bind to ER

1- Raloxifene*

Antiestrogens that exhibits partial agonistic action ; acting as an agonist in bone & an antagonist in breast

Raloxifene → has no effect on hot flushes.

2- Tamoxifen

Antiestrogens that stabilizes ER in a conformation allowing trans- cription to occur on only certain ER-responsive genes

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

An ideal SERM for use as HRT should be agonistic in brain, bone, CV system, vagina & urinary system but antagonistic in breast & uterus.

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

We use:
Raloxifene in osteoprosis.
Tamoxifen as anti-cancer in breast& HRT (can be given in insomnia)
Chlonophine in ovulation induction.
We don't use : Raloxifene \ Tamoxifen in hot flushes

We prefer to use:
1-in ovulation induction Chlonophine then Tamoxifen
2- in male infertility Tamoxifen then Chlonophine
3- menopause Raloxifene then Tamoxifen

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SUMMARY

Estrogen -Estradiol (Not orally) -Conjugated Estrogens -Esterified Estrogens #Given with progesterone if uterus is exist.	**Uses:** **- Menopause:** to decrease: hot flushes & night sweat, mood swings, urethral & urinary symptoms, vaginal dryness, osteoporosis, Protect CVS, improve insulin resistant and cognitive function. - **Other uses: Contraceptive, Primary ovarian syndrome, Amenorrhea & hirsutism caused by excessive androgens**. **ADRs:** -CVS : Thromboembolism & Hypertension (Contraindication in thromboembolic manifestation & undignosed vaginal bleeding) - ↑ breast & uterine cancer (Contraindication) - ↑ liver diseases (Contraindication in severe liver diseases)
Progesterone -Progesterone (Parentally) -Progestins (Synthetic & Orally)	**Used** in menopause with estrogen to protects against possibility of estrogen induced endometrial cancer, and protects against breast cancer. **ADRs:** Hirsutism and musculization.
SERMs	**Raloxifen:** For osteoporosis (No effect on hot flushes) **Tamoxifene:** For mood, insomnia, memory loss (Increase risk of venous thrombosis and hot flushes)
Phyroestrogens	Supplements from plants, mimic action of estrogen on ER-β , and block actions mediated by ER-α.
Androgens	- Given alone when female lack sexual arousal. - Given with estrogen and progestin when other menopausal symptoms exist.

Quiz yourself

Q1: Menopausal woman came to you complain of loss the desire for sexual intercourse with her husband and when you ask her about other menopausal symptom, her answer was no other symptom. What is the drug of choice?
A) androgen alone
B) Estrogen alone
C) Both androgen with estrogen or SERMs

Q2: Menopausal woman came to you complain of loss the desire for sexual intercourse with her husband and when you ask her about other menopausal symptom, her answer was yes, she has hot flushes, insomnia, mood disturbances. What is the drug of choice ?
A) androgen alone
B) Estrogen alone
C) Both androgen with estrogen or SERMs

Q3: Menopausal woman has hot flushes, insomnia, mood disturbances without sexual problems. What is the drug of choice?
A) SERMs
B) Estrogen alone
C) we can use both

Q4: HRT is not associated with which of the following :
A) Thromboembolic disease
B) increase incidence of breast,ovarian, vaginal &cervical cancer
C) Alzheimer's disease
D) increase frequency of gall bladder Disease

Q5: In which one of the following conditions is estrogen absolutely contraindicated?
A) Undiagnosed vaginal bleeding
B) Amenorrhea
C) Poly cystic ovaries

Q6: Which one of the following is used for dysmenorrhea?
A)Tamoxifen
B) Estrogen
C) Progesterone

Q7: which one of the following protect against both uter us and breast cancer ?
A) progestin
B) progesterone
C) Estrogen

Q8: The duration of HRT should never exceed ..... to control meno-pausal symptoms without allowing ample time for malignant transition that might be induced by estrogen
A) 10 years
B) 5 years
C) 10 month

Q9: This type of HRT is usually recommended for women who have had their uterus and ovaries removed by hysterectomy.
A) progesterone only
B) Estrogen only
C) combined of both

Q10: Estrogen if given with which one of the following could cause additiveside effects ?
A) SERMs
B) Aromatase inhibitors
C) Corticosteroids

Answers: 1-A 2-C 3-C 4-C 5-A 6-C 7-B 8-B 9-B 10-A

Done by

PHARMACOLOGY 433

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