SELECTIVE ESTROGEN RECEPTOR MODULATERS

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Endocrine & Reproduction-II Module
4th Year MBBS
Theme-6: Breast lump

Objectives

- By end of this presentation you will be able to
- Enlist Selective Estrogen Receptor Modulators (SERMs)
- Describe the mechanism of action and clinical uses of Tamoxifen

WHAT IS SERM ?

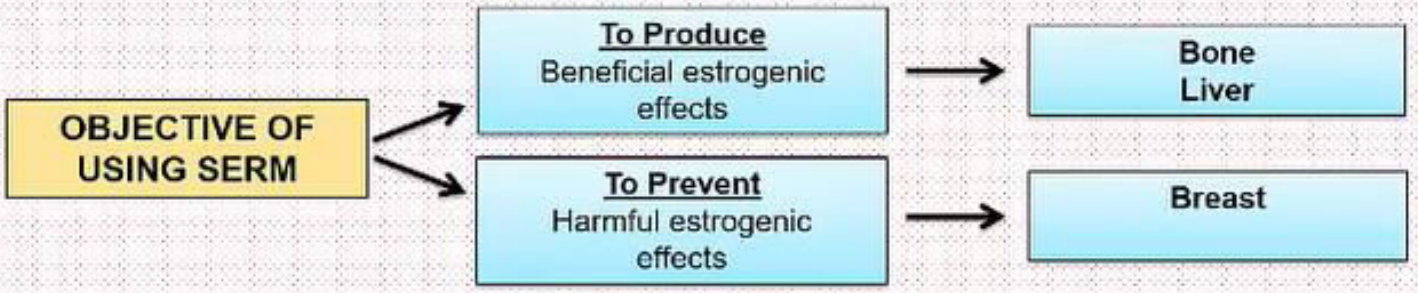
- Selective Estrogen Receptor Modulator (SERM) are non steroidal synthetic agents whose agonist or antagonist activities on estrogen receptor (ER) are tissue selective.

Enlist SERMS

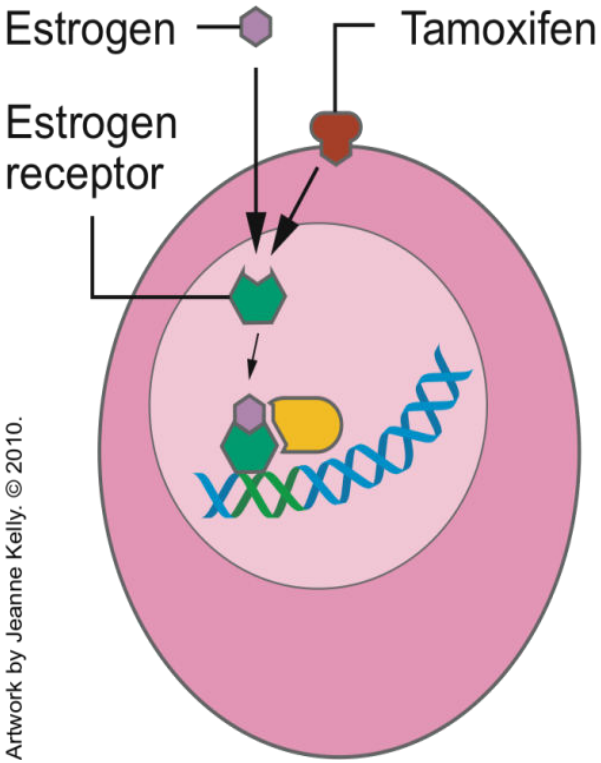
- SERMs are a class of estrogen-related compounds
- display selective agonism or antagonism for estrogen receptors **Depending On The Tissue Type.**
- Tamoxifen.(prototype drug)
- Raloxifen
- Ormeloxifen
- Toremifene
- Clomiphene & Ospemifene

WHAT ARE SERMs?
SELECTIVE ESTROGEN RECEPTOR MODULATORS

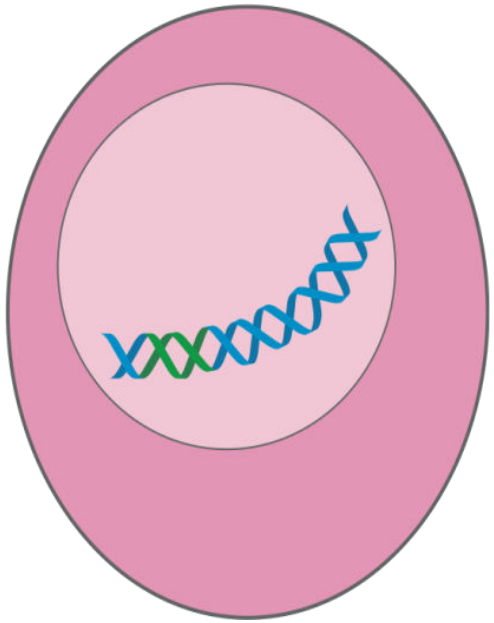
- Drugs with tissue selective actions
- Estrogenic action in some tissues
- Antiestrogenic action in some other tissues



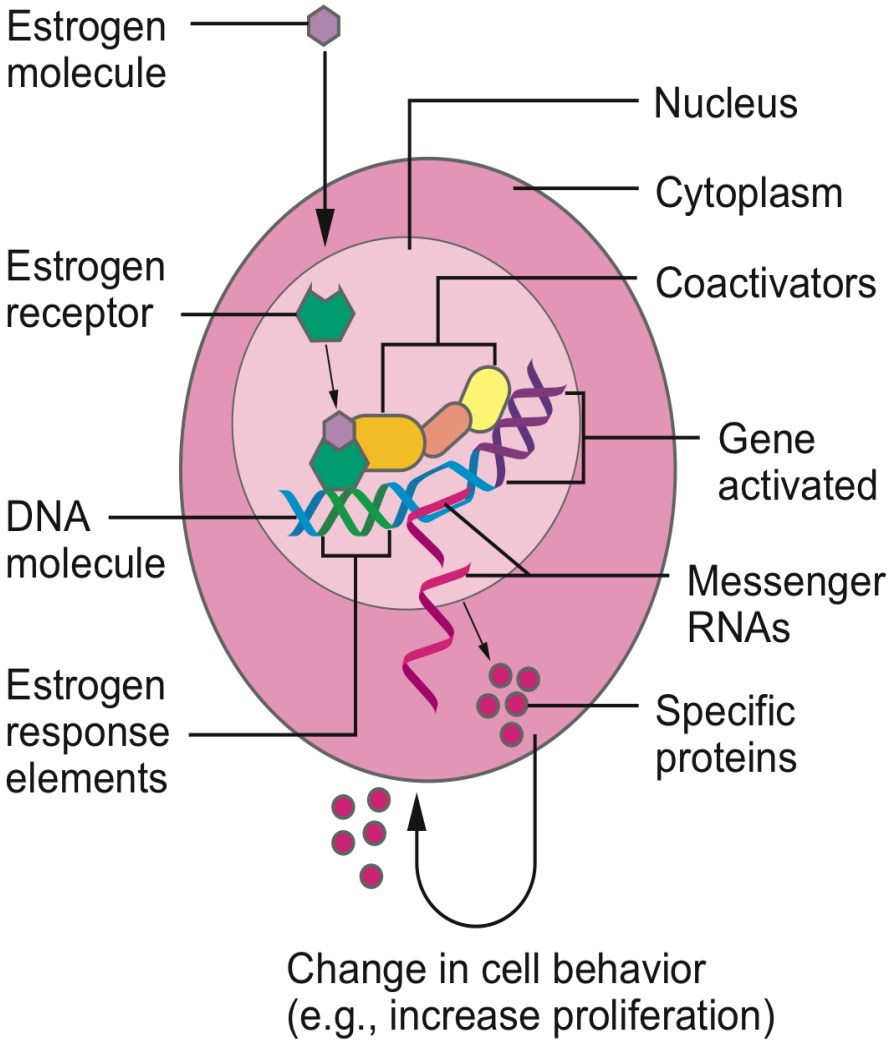
Estrogen target cell
(e.g., breast, uterine lining, liver, etc.)

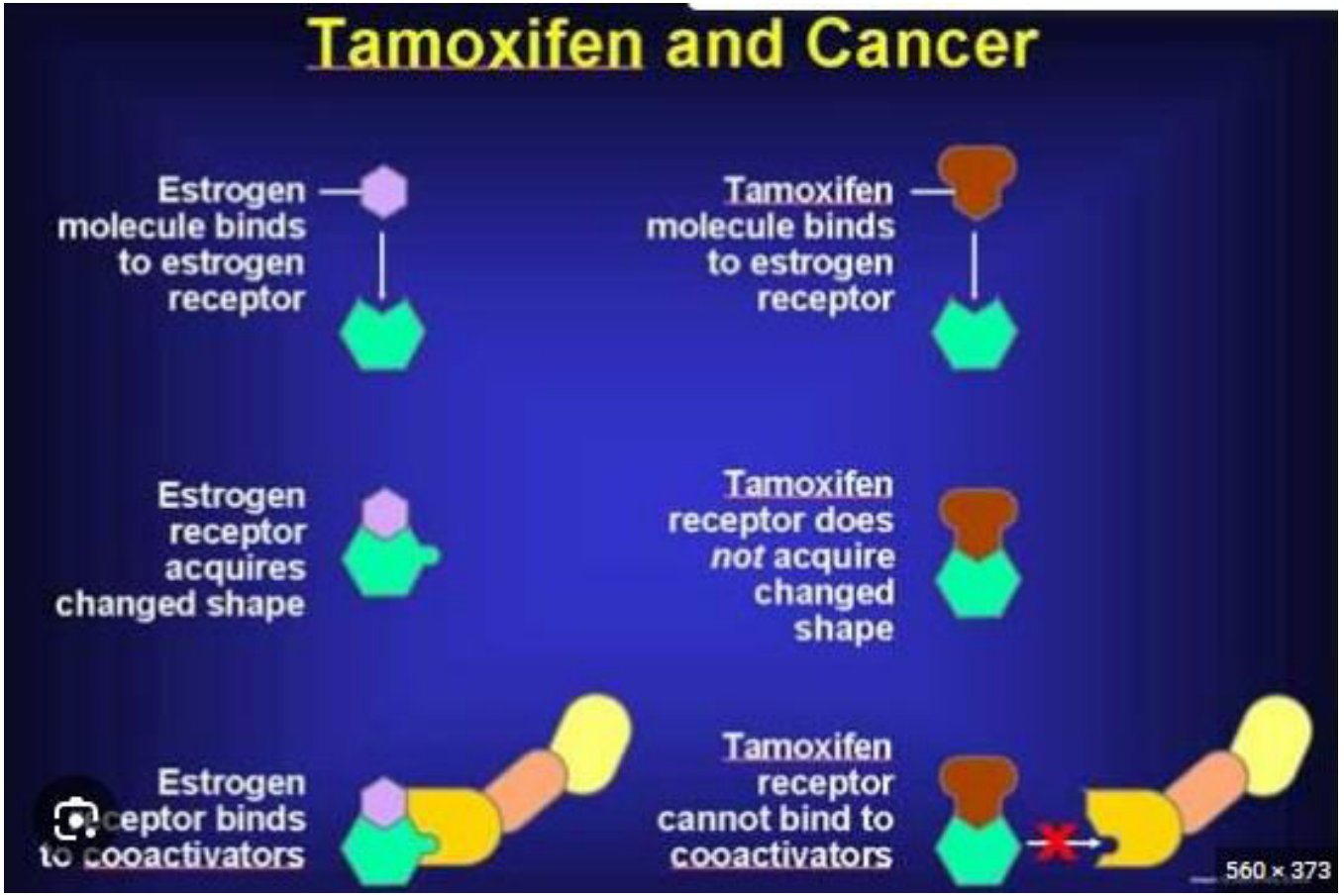


Non-target cell
(contains no estrogen receptor)



Estrogen Receptors Trigger Gene Activation




Tamoxifen and Cancer
Estrogen molecule binds to estrogen receptor
Tamoxifen molecule binds to estrogen receptor
Estrogen receptor acquires changed shape
Tamoxifen receptor does *not* acquire changed shape
Estrogen receptor binds to cooactivators
Tamoxifen receptor cannot bind to cooactivators
560 × 373

SERMs ACTION

- Tamoxifen, Toremifene, Raloxifene compete with estrogen for binding to the estrogen receptor in breast tissue.
- So breast tumors regress following treatment with these agents.
- Raloxifene acts as an estrogen agonist in bone,
  - leading to decreased bone resorption,
  - increased bone density,
  - decreased vertebral fractures

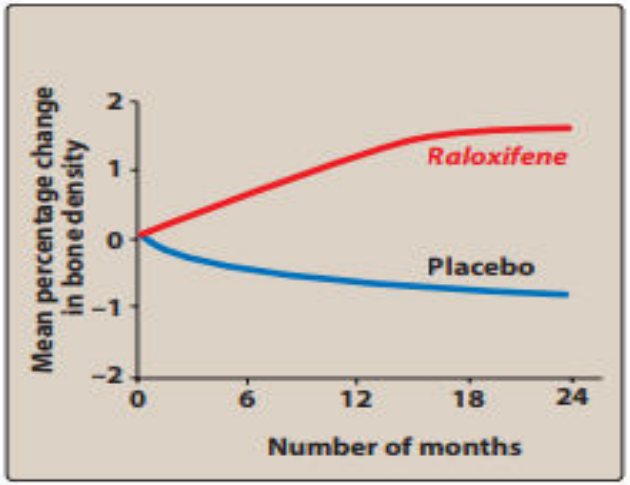
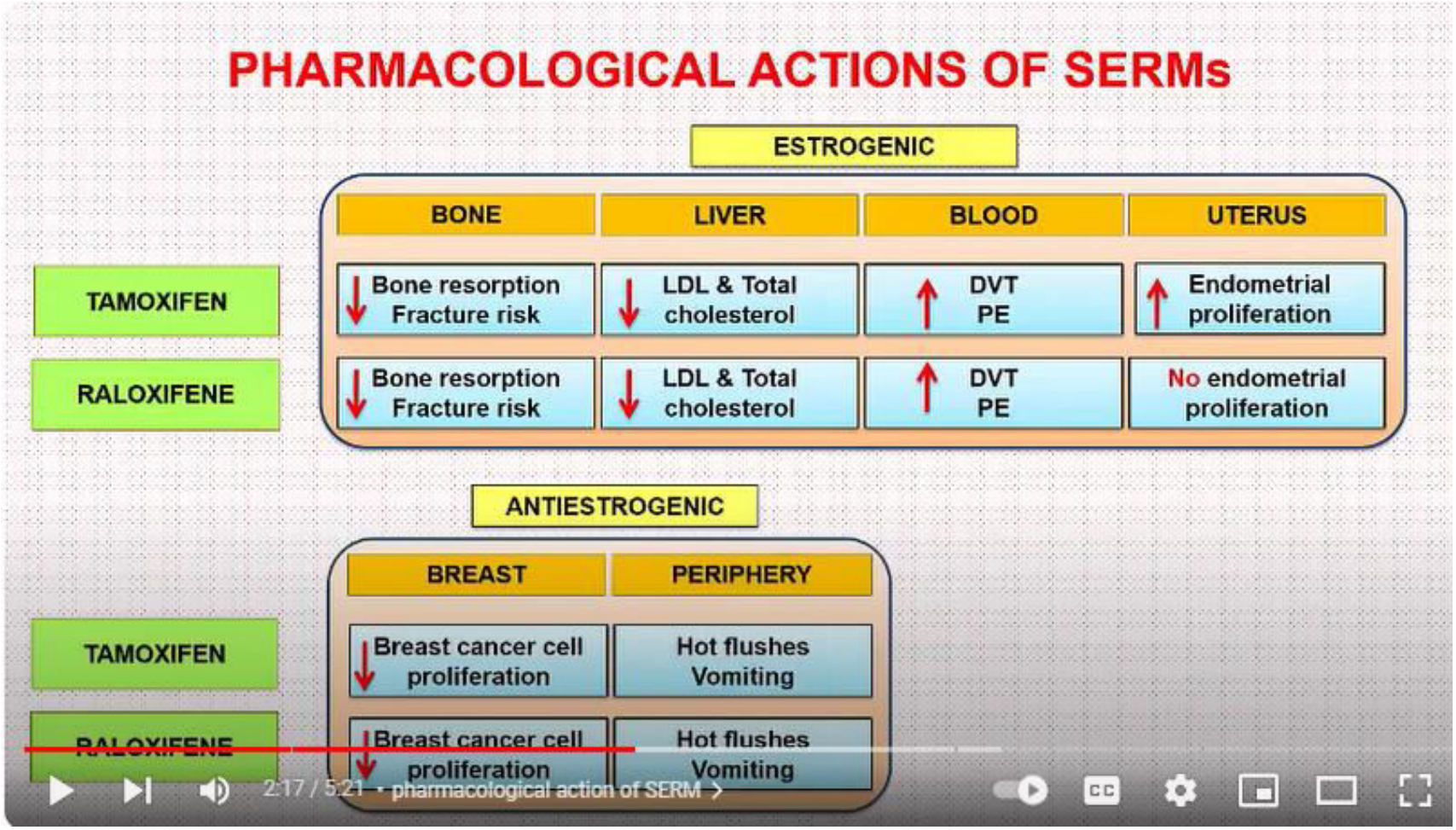


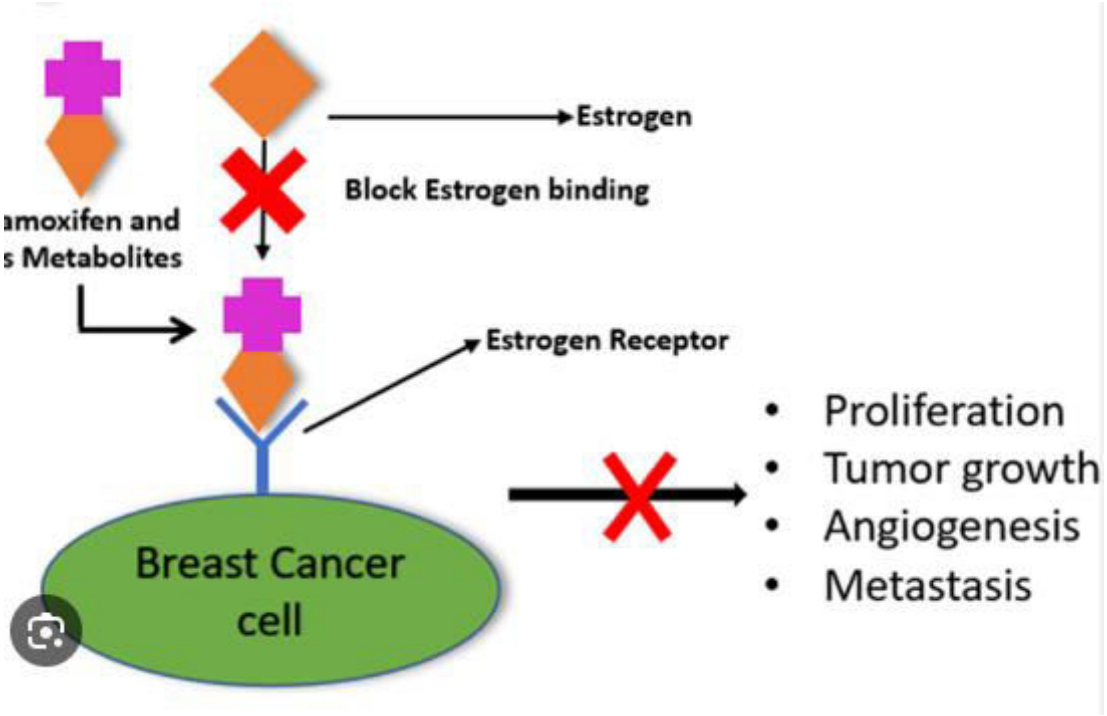
Figure 26.5
Hip bone density increases with *raloxifene* in postmenopausal women.


PHARMACOLOGICAL ACTIONS OF SERMs
ESTROGENIC
BONE
LIVER
BLOOD
UTERUS
TAMOXIFEN
Bone resorption
Fracture risk
LDL & Total
cholesterol
DVT
PE
Endometrial
proliferation
RALOXIFENE
Bone resorption
Fracture risk
LDL & Total
cholesterol
DVT
PE
No endometrial
proliferation
ANTIESTROGENIC
BREAST
PERIPHERY
TAMOXIFEN
Breast cancer cell
proliferation
Hot flushes
Vomiting
RALOXIFENE
Breast cancer cell
proliferation
Hot flushes
Vomiting
2:17 / 5:21 • pharmacological action of SERM
CC

- Raloxifene does not have estrogen agonist activity in the endometrium so does not predispose to endometrial cancer.
- Clomiphene a partial estrogen agonist & interferes with the negative feedback of estrogens on the hypothalamus.
  - stimulation of ovulation

Therapeutic uses

- Tamoxifen
  - Treatment of metastatic breast cancer,
  - Or as adjuvant therapy following mastectomy or radiation for breast cancer.



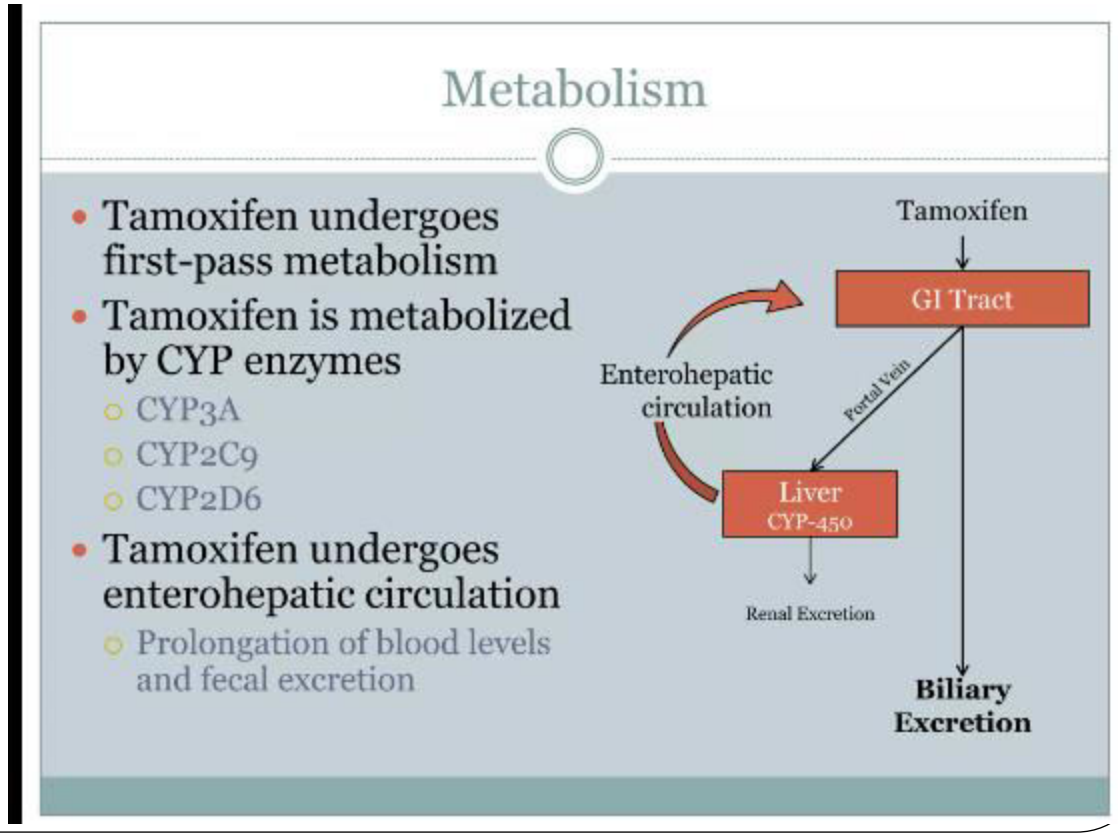
- Tamoxifen and Raloxifene as **prophylactic therapy** to reduce the risk of breast cancer in high-risk patients.
- Raloxifene is also approved for the prevention and treatment of osteoporosis in postmenopausal women.
- Clomiphene is useful for the treatment of infertility associated with anovulatory cycles.
- Ospemifene is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause

INDICATIONS OF SERMs

CLOMIPHENE	TAMOXIFEN	RALOXIFENE
• Female infertility (due to anovulation) • Male infertility • Invitro fertilization	• Treatment of breast cancer (both pre- & postmenopausal) • Prevention of breast cancer	• Treatment & prevention of osteoporosis (postmenopausal women)

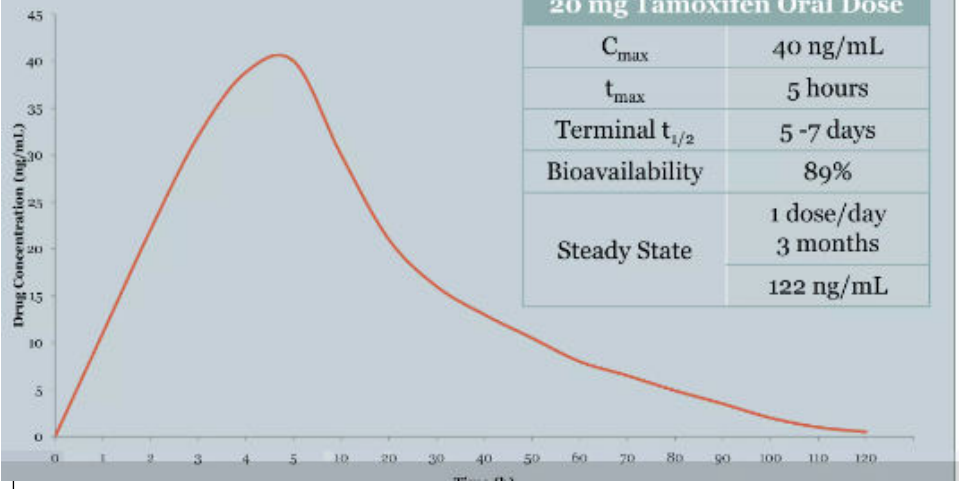
pharmacokinetics

- The SERMs are rapidly absorbed after oral administration.
- Raloxifene is rapidly converted to glucuronide conjugates through first-pass metabolism.



Tamoxifen

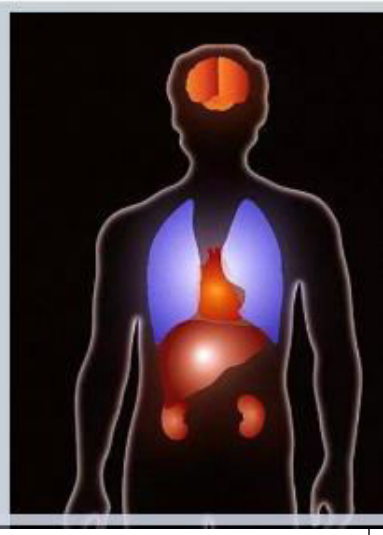
Absorption



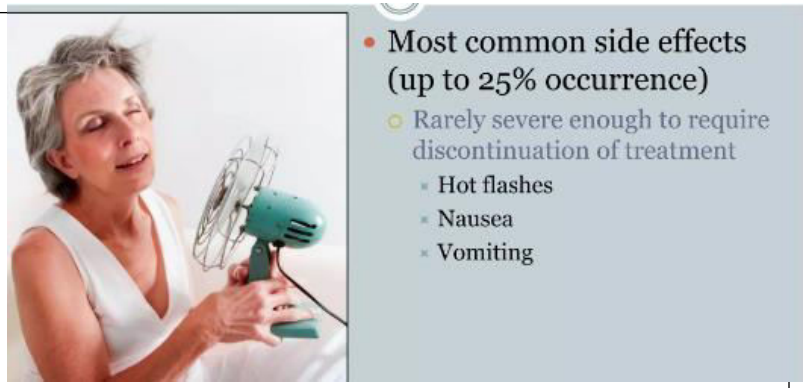
20 mg Tamoxifen Oral Dose	
C_{max}	40 ng/mL
t_{max}	5 hours
Terminal $t_{1/2}$	5 -7 days
Bioavailability	89%
Steady State	1 dose/day 3 months
	122 ng/mL

Distribution

- Tamoxifen is 99% albumin-bound in serum
- Volume of Distribution
  - 50 – 60 L/Kg
- This represents an extensive distribution to the peripheral tissues
- Areas of high concentration
  - Breast
  - Lung
  - Liver
  - Brain
  - Bone
  - Uterus



Adverse effects



- hot flashes and nausea.
- Endometrial hyperplasia and malignancies with tamoxifen therapy. So recommendations are use drug for short intervals

- Tamoxifen have drug interactions.
- Hot flashes and leg cramps

are common with raloxifene.

- Increased risk of DVT, pulmonary embolism, and retinal vein thrombosis.
- C/I in Patient with history of venous thromboembolic events

tamoxifen

Adverse Drug Reactions

- Increased risk of uterine cancer
  - Agonist in uterine ER
  - Increased cell proliferation
- Increased risk of blood clot formation
  - Increase in clotting factors
- Increased risk of cataract
  - Ophthalmic toxicities

Benefits of Drug

- Reduced risk of breast cancer
  - ER Antagonist
- Strengthens bones
  - ER Agonist
- Lower risk of heart disease
  - Increase HDL cholesterol
  - Reduce LDL cholesterol

ADVERSE EFFECTS OF SERMs

CLOMIPHENE	TAMOXIFEN	RALOXIFENE
• Ovarian hyperstimulation syndrome	• Increased risk of endometrial cancer	• DO NOT INCREASE endometrial cancer risk
• Polycystic ovaries	• Increased risk of deep vein thrombosis & pulmonary embolism	• Increased risk of deep vein thrombosis & pulmonary embolism
• Multiple pregnancies	• Nausea/vomiting	• Hot flushes
• Nausea/vomiting	• Hot flushes	• Leg cramps
• Hot flushes		

Thank you