Estrogen and the Selective Estrogen-Receptor Modulators (SERMs)

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Reference: NEJM, Riggs & Hartman 2003; 348: 618-29

Uses of Estrogens

- Oral contraception
- Treatment of symptoms of menopause (HRT)
- Prevention of osteoporosis
- Treatment of vaginal atrophy
- Treatment of hypo-estrogenism
- Treatment of primary amenorrhoea
- Treatment of dysmenorrhoea

Uses of Estrogens (contd)

- Treatment of oligomenorrhoea
- Treatment of certain neoplastic diseases
- Treatment of hereditary haemorrhagic telangiectasia
- Palliative treatment of prostate cancer

Contraindications to Hormone Therapy:

- Current , past or suspected breast cancer.
- Known or suspected estrogen-sensitive malignant tumors
- Undiagnosed genital bleeding.
- Untreated endometrial hyperplasia.
- Pregnancy.
- Current venous thrombo-embolism(VTE) or previous idiopathic VTE.
- Known CHD.
- Untreated hypertension.
- Active liver disease.
- Porphyria cutanea tarda.
- Systemic lupus erythematosus.

In Hormone Replacement Therapy: The Women's Health Initiative (WHI)

- The WHI focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women

Conclusion

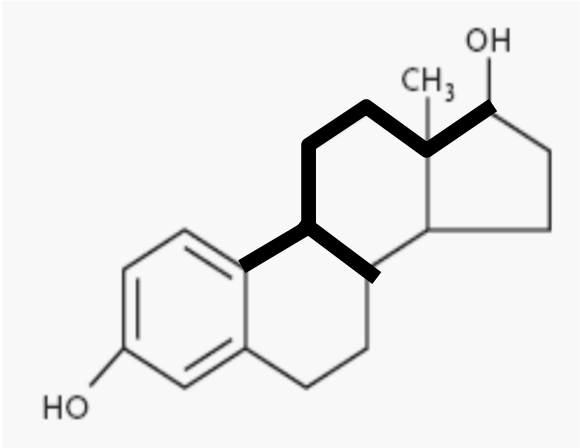
- Overall health risks exceed benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women

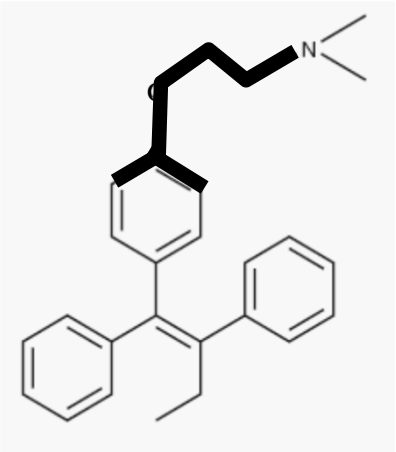
- JAMA. 2002; (3): 321-333

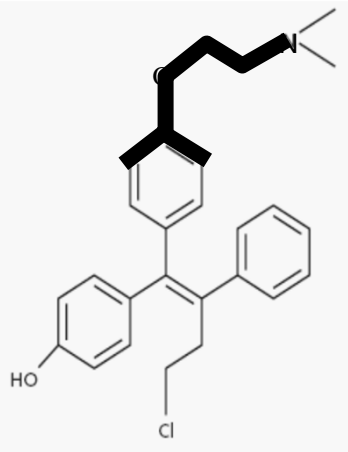
What now? – how do we treat post-menopausal symptoms?

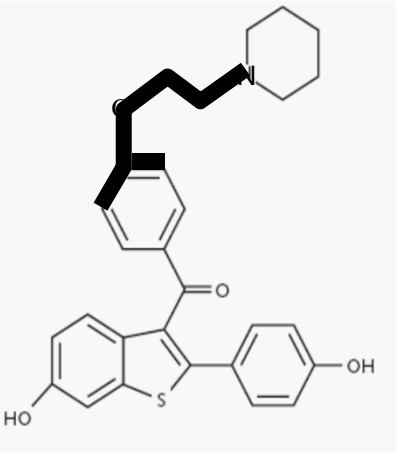
- How can we affect the Estrogen Receptors?
- Do other drugs act on the ER's?
- What would anti-estrogens do?
- Should we only suppress progesterone?
- Are there pure estrogen antagonists?
- Should we prevent estrogen production – Aromatase Inhibitors?
- Are there other ways of modulating the ER's?

- The SERMs exert selective agonist or antagonist effects on various estrogen target tissues
  - Chemically diverse - ?
  - Lack the steroid structure of estrogens

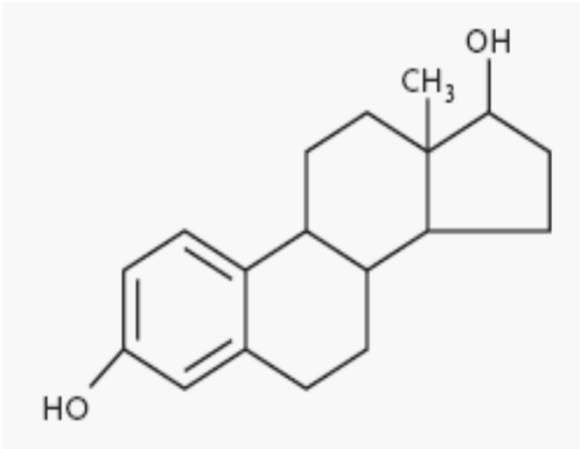


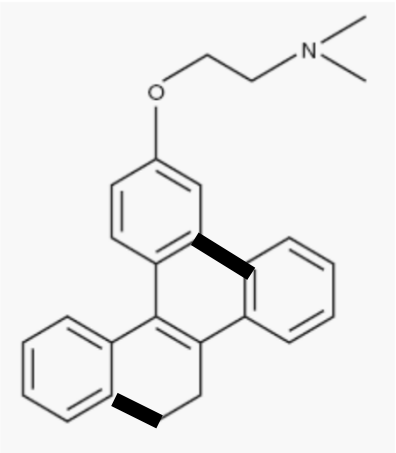


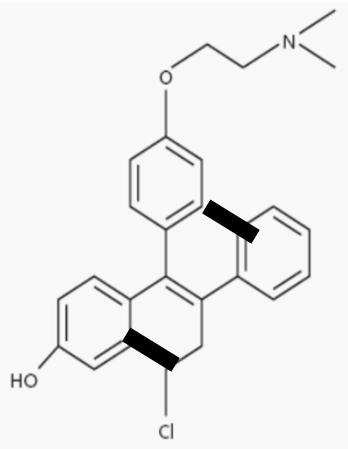


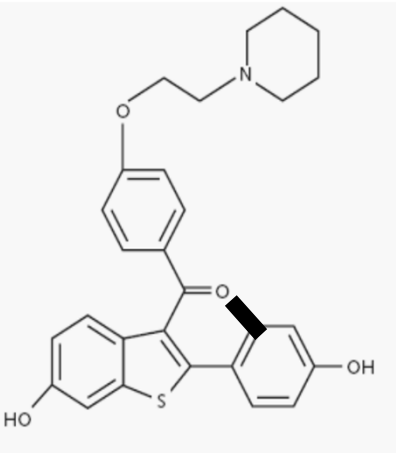


17β-Estradiol **Tamoxifen** **Toremifene** **Raloxifene**









17β-Estradiol **Tamoxifen** **Toremifene** **Raloxifene**

- Unique Pharmacology – differential estrogen-receptor-
  - Expression in a given target tissue
  - Conformation on ligand binding
  - Binding & expression of coregulator proteins

- TARGET CELLS FOR ESTROGEN - varying concentrations of homodimers estrogen receptor α and β + ERα and β heterodimers
  - ERα = an activator
  - ERβ = an inhibitor- can inhibit the action of ERα by forming a heterodimer with it.

- TAMOXIFEN & RALOXIFENE bind to both iso forms → affect cellular responsiveness

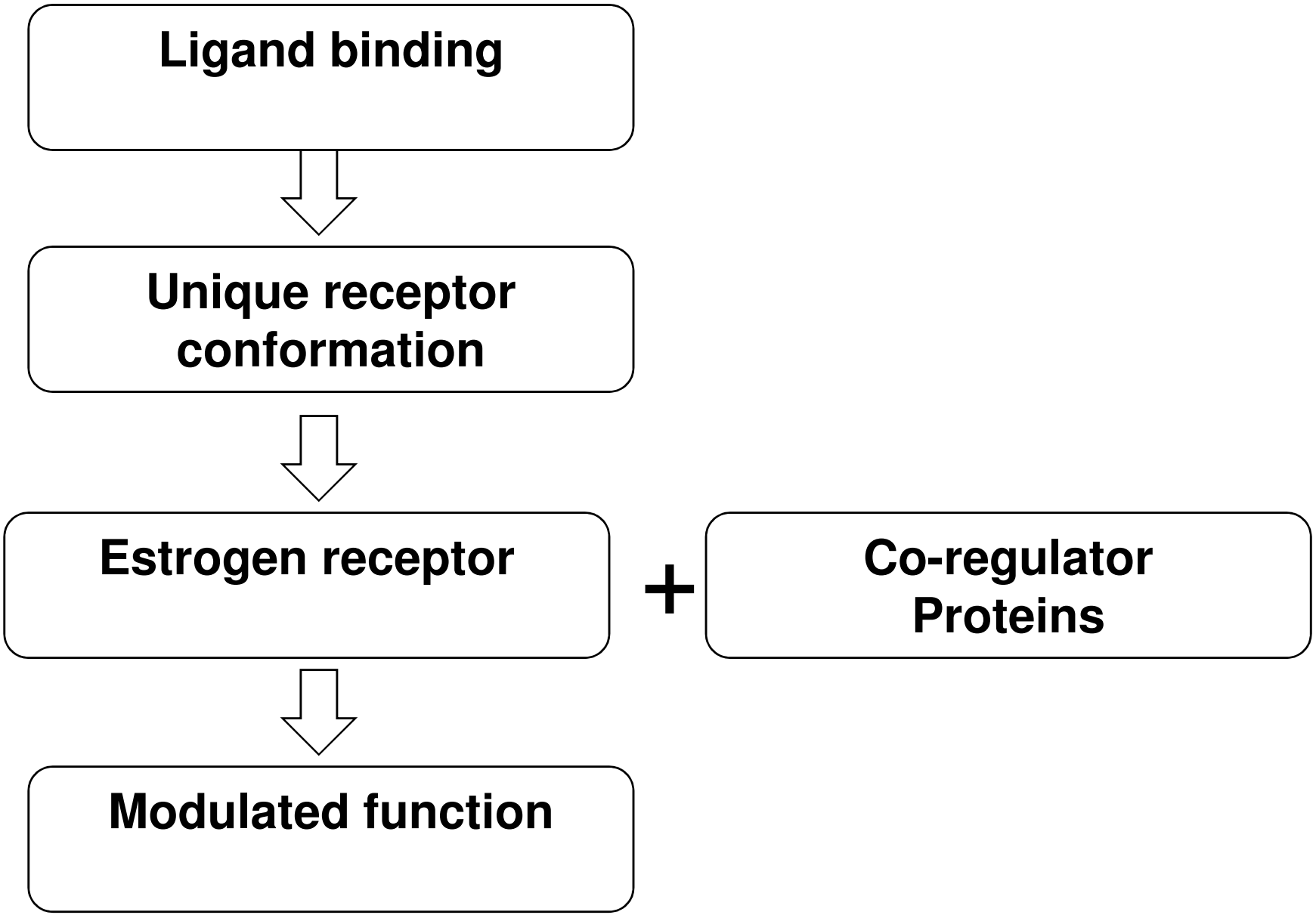
  ◦◦ They function as pure antagonists when acting through ERβ on genes containing estrogen response elements , but function as partial agonists when acting on them through ER α

- BINDING BY ESTRADIOL, TAMOXIFEN, RALOXIFENE OR ICI/64.384, the pure estrogen antagonist , results in a …..
  - Unique estrogen-receptor conformation for each ligand with a estrogen-receptor conformation spectrum ranging from estrogen → anti-estrogen
- SERMs → assume a continuum of intermediate shapes

- More than 20 coregulator proteins have been discovered that bind to estrogen receptors

→ modulation of ER function

→ + or – transcriptional regulator


Ligand binding
Unique receptor conformation
Estrogen receptor
+
Co-regulator Proteins
Modulated function

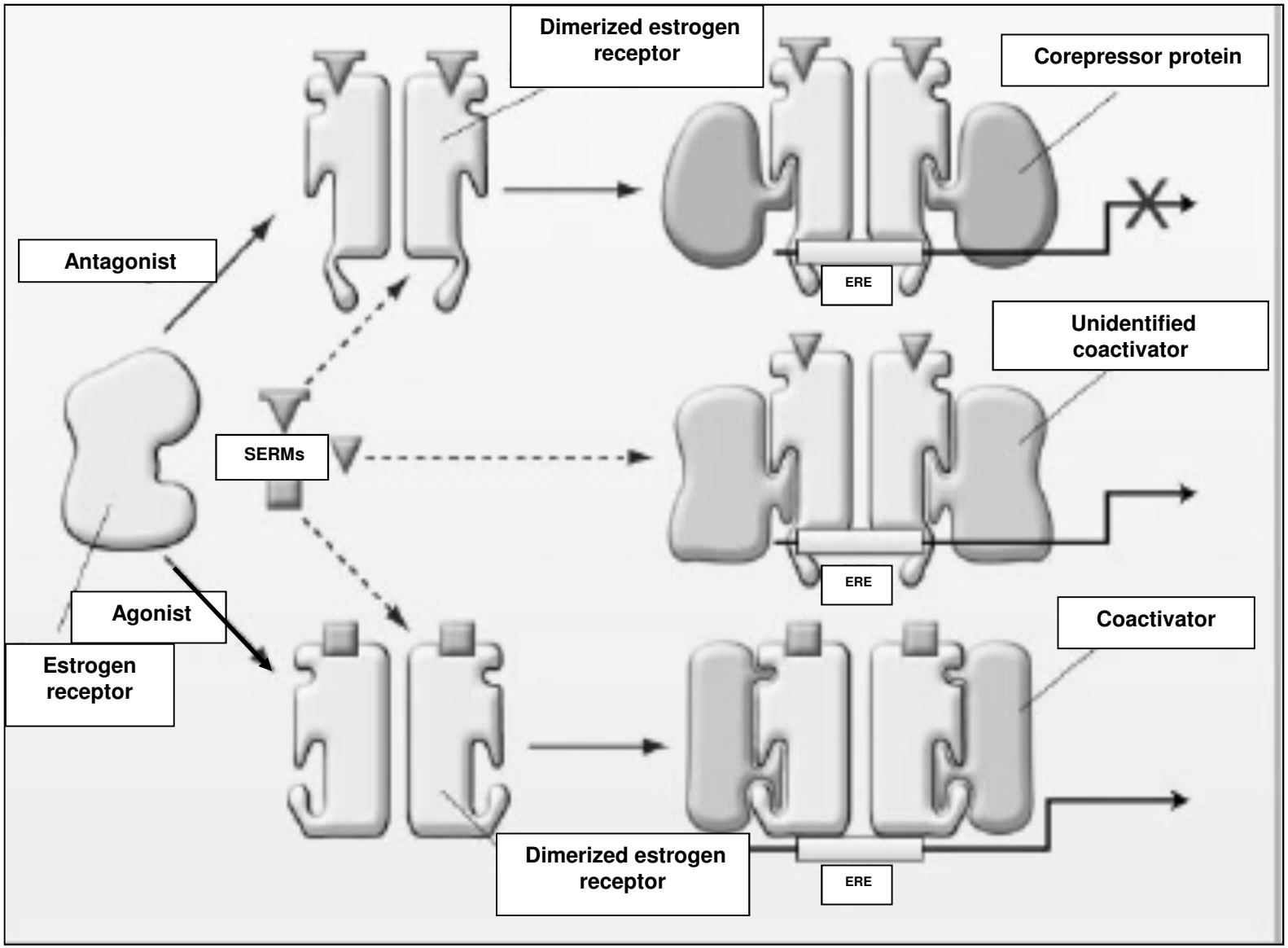

Dimerized estrogen receptor
Corepressor protein
Antagonist
ERE
Unidentified coactivator
SERMs
ERE
Agonist
Coactivator
Estrogen receptor
Dimerized estrogen receptor
ERE

Table 1. Comparison of Selected Actions and Side Effects of Estrogen and Clinically Available SERMs.*

Side Effect	Estrogen	Tamoxifen	Toremifene	Raloxifene
Hot flashes	↓↓↓	↑†	↑†	↑†
Uterine bleeding	↑↑↑	↑	↑	↔
Risk of endometrial cancer	↑↑‡	↑	?	↔
Prevention of postmenopausal bone loss	↑↑↑	↑	↔	↑↑
Risk of breast cancer	↑↑	↓↓	↓↓§	↓↓
Favorable pattern of serum lipids	↑↑↑¶	↑	↑↑	↑
Venous thrombosis	↑↑	↑↑	?	↑↑

Table 2. Results of Major Randomized Clinical Trials of SERMs with Regard to Bone Mineral Density.

Trial	Study Subjects	Duration	Change in Bone Mineral Density as Compared with Placebo Group		
			Total-Body Bone Mineral	Lumbar Spine	Proximal Femur
		months	*percent*		
Tamoxifen (20–30 mg/day)					
Love et al.[27]	140 postmenopausal women with breast cancer	24	—	1.6*	—
Grey et al.[28]	57 normal late-postmenopausal women	24	0.5†	2.1†	0.6
Powles et al.[29]	179 healthy women in chemoprevention trial for breast cancer				
	54 postmenopausal women	36	—	4.7*	3.6†
	125 premenopausal women	36	—	−2.6*	−4.3†
Raloxifene (60 mg/day)					
Delmas et al.[30]	302 normal postmenopausal women	24	2.0*	2.4*	2.4*
Lufkin et al.[31]	143 postmenopausal women with osteoporosis and vertebral fractures	12	−0.1	1.8†	1.0†
Ettinger et al.[32]	5140 postmenopausal women with osteoporosis	36	—	2.6*	2.1*
Johnston et al.[33]	576 healthy early-postmenopausal women	36	1.7*	2.6*	2.5*

* $P<0.05$ for the comparison with placebo.
† $P<0.005$ for the comparison with placebo.

Table 3. Results of Major Trials of SERMs for the Primary Prevention of Breast Cancer.*

Variable	NSABP P-1 Study[36]	Royal Marsden Hospital Trial[52]	Italian Trial[53]	IBIS-I[54]
Primary outcome	Breast cancer	Breast cancer	Breast cancer	Breast cancer
Secondary outcome	Bone, cardiovascular	—	Cardiovascular, psychometrics	Thromboembolic, cardiovascular, endometrial cancer
Eligibility	Age ≥60 yr, or 35–59 yr with a 5-yr predicted risk of ≥1.66%, lobular carcinoma in situ	Age 30–70 yr with a family history	Age 35–70 yr after hysterectomy	Age 35–70 yr with a family history, lobular carcinoma in situ or atypia
No. of women	13,388	2471	5408	7152
Study drugs	Tamoxifen vs. placebo	Tamoxifen vs. placebo	Tamoxifen vs. placebo	Tamoxifen vs. placebo
Age distribution (%)				
<50 yr	39	61	38	—†
50–60 yr	31	39	50	
>60 yr	30		12	
Family history of breast cancer (%)	77	96	18	97
Mean follow-up (mo)	55	70	46	50
Effect on invasive breast cancer				
No. taking placebo in whom breast cancer developed	175 89	64 54	Not reported —	85 64
No. taking tamoxifen in whom breast cancer developed	–49‡	—§	—§	–25¶
Relative difference (%)				

* IBIS-I denotes International Breast Cancer Intervention Study I, and NSABP National Surgical Adjuvant Breast and Bowel Project.
† The median age in the trial was 51 years.
‡ $P<0.001$.
§ The difference was not significant.
¶ The confidence interval was 54 to 104.

Table 4. Major Large-Scale Trials Involving SERMs.

ATLAS (Adjuvant Tamoxifen Longer against Shorter) trial[61]*
- Assessment of optimal duration of tamoxifen adjuvant therapy
- Accrual goal is 20,000 pre- and postmenopausal patients with breast cancer who are receiving adjuvant tamoxifen
- Therapy: tamoxifen for 5 yr vs. 10 yr (or longer)

ATTOM (Adjuvant Tamoxifen Treatment Offers More) trial[62]*
- Assessment of optimal duration of tamoxifen adjuvant therapy
- Accrual goal is 8000–20,000 pre- and postmenopausal patients with breast cancer who are receiving adjuvant tamoxifen
- Therapy: tamoxifen for 2 yr (group 1) vs. 7 yr (group 2)

$IBIS_2$ (International Breast Cancer Intervention $Study_2$)[63]*
- Primary prevention of breast cancer
- Accrual goal is 16,000 women at high risk for breast cancer (age, 35–70 yr)
- Therapy: anastrozole vs. placebo

STAR (Study of Tamoxifen and Raloxifene)[60]
- Primary prevention of breast cancer
- Accrual goal is 22,000 postmenopausal women at high risk for breast cancer
- Therapy: 20 mg tamoxifen per day vs. 60 mg of raloxifene per day for 5 yr

CORE (Continuing Outcomes Relevant to Evista)
- 4000 postmenopausal women who were previous participants in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial
- Receiving raloxifene or placebo for an additional 4 yr, completion by 2003
- Primary end point is breast-cancer prevention; secondary end points are non-vertebral fractures and uterine safety

RUTH (Raloxifene Use in the Heart)[64]†
- Effect of raloxifene vs. that of placebo in prevention of coronary events and death from coronary causes
- 10,000 postmenopausal women at risk for coronary disease
- Duration of 7.5 yr, completion by 2005

* The trial is not open in the United States.
† The trial has been completed, and the data are under analysis.

Table 5. Comparative Effects of Oral Hormone-Replacement Therapy and SERMs on Serum Lipids, Indexes of Inflammation, and Blood Coagulation.*

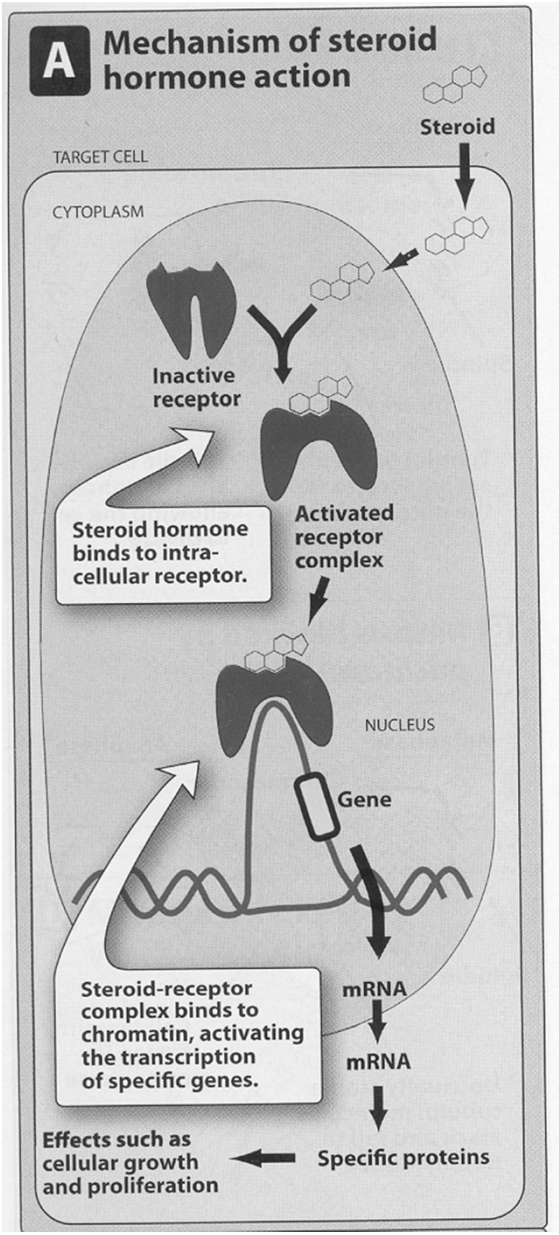
Variable	Hormone-Replacement Therapy	Tamoxifene	Toremifene	Raloxifene
	percent difference from change with placebo			
Low-density lipoprotein cholesterol	−12†	−19†	−21†	−12†
High-density lipoprotein cholesterol	7†	−2	14†	0
Triglycerides	18†	31†	−4	−4
Apolipoprotein A-I	13†	5	13†	3
Apolipoprotein B	−4	−9†	−10†	−9†
Lp(a) lipoprotein	−19†	−14†	−53†	−7†
Fibrinogen	−1	—	—	−10†
Plasminogen activator inhibitor type 1	−19†	—	—	8
Homocysteine	−7†	—	—	−8†
C-reactive protein	84†	—	—	−7
Tumor necrosis factor α	−11†	—	—	−5†
Interleukin-6	11	—	—	1

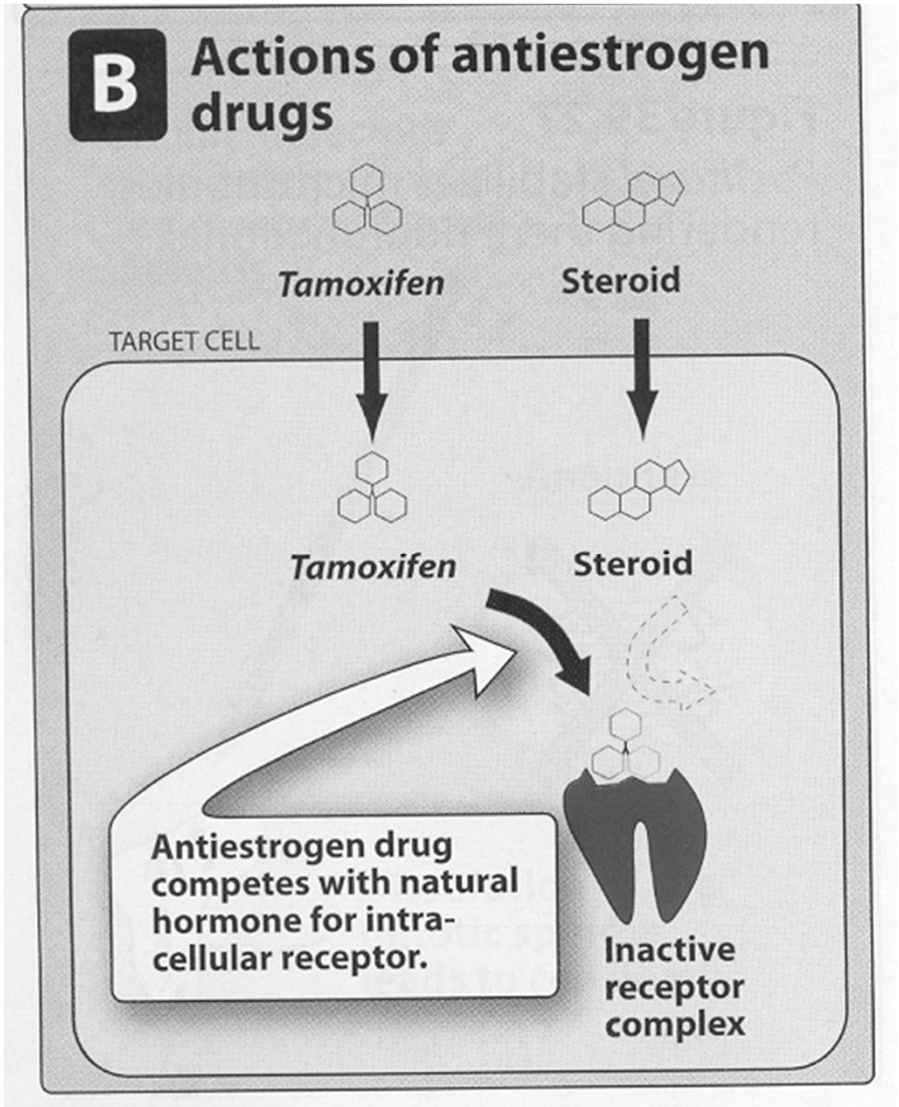
* Data are from the Postmenopausal Estrogen/Progestin Interventions Trial Writing Group,[20] Love et al.,[69] Walsh et al.,[70] Saarto et al.,[71] Walsh et al.,[72] and Cox et al.[73]

† $P<0.05$ for the comparison with placebo.

TAMOXIFEN

- Indications:
  - Palliative treatment of metastatic breast cancer in post-menopausal women
  - Adjuvant treatment following mastectomy or radiation
  - To decrease the risk of breast cancer in high risk patients
  - Anovulatory infertility
- Side effects:
  - Hot flushes
  - Nausea
  - Menstrual irregularities
  - Endometrial hyperplasia and malignancies


A Mechanism of steroid hormone action
Steroid
TARGET CELL
CYTOPLASM
Inactive receptor
Steroid hormone binds to intra-cellular receptor.
Activated receptor complex
NUCLEUS
Gene
Steroid-receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Effects such as cellular growth and proliferation


B
Actions of antiestrogen drugs
Tamoxifen
Steroid
TARGET CELL
Tamoxifen
Steroid
Antiestrogen drug competes with natural hormone for intra-cellular receptor.
Inactive receptor complex

RALOXIFENE

- 2nd generation SERM
- Indications:
  - Prevention of osteoporosis
  - Reduction in the incidence of non-traumatic vertebral fractures – post menopausal women
  - Breast cancer in high risk post-menopausal women
- Side effects:
  - Hot flushes
  - Leg cramps
  - DVT
  - Pulmonary embolism

TOREMIFENE

- Indications:
  - Treatment of hormone-dependent metastatic breast cancer in post-menopausal women

  Data on risk of endometrial hyperplasia & malignancy

  Is lacking

CLOMIPHENE

- Acting as a partial estrogen agonist and interferes with the negative feedback of estrogen on the hypothalamus
  → Increased secretion of GRH & gonadotropins
  → OVULATION
- Side effects:
  – Headache
  – Nausea
  – Flushes
  – Visual disturbances
  – Ovarian enlargement

THIRD GENERATION SERMs

- Idoxifene, droloxifene
- Lasofoxifene
  - > 100 Fold selectivity for ER over all other steroid receptors
  - Affinity same as estradiol

SERDs (downregulators!)

- FULVESTRANT (Faslodex) is a novel ER antagonist
  - Blocks the agonist activity of E
  - ↑ ER – degradation
  - Disrupts ER shuttling from the membrane → nucleus

❖ Not associated with tamoxifen-like agonist effects

❖ Not cross-resistant to tamoxifene & the aromatase inhibitors

❖ Treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in post-menopausal women

FUTURE INDICATIONS?

- Prevention of prostate cancer

  20mg toremifene: 21.8% reduction in cumulative risk of prostate cancer in men with High Grade Prostatic Intra-epithelial Neoplasia (HGPIN) and no cancer

CLINICAL STUDY

- **Ellis *et al*.: JAMA, August 19 2009:**

  "Lower-dose vs. high-dose estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer"

RESULTS:

Oestradiol treatment not only stopped disease progression in about a third of patients, but in some patients metastatic tumors became resensitized and again responded to anti-oestrogen treatments.

"Sustained clinical benefit can be achieved by alternating between inhibitory and stimulatory oestrogen receptor modulation"

Munster & Carpenter (Editors)

“Study is intriguing because clinical benefits were observed at low doses, with reduced toxicity”

6mg

ULTIMATE SERM RESEARCH GOAL:

- “The discovery of a tissue-selective drug that has all the beneficial effects of oestrogen, has none of its adverse effects and offers protection against breast cancer”
- Development of a SERM with super-agonist protective actions on the CVS and skeletal system
- New drugs that will selectively express the desirable actions and selectively suppress the undesirable actions of the various steroid hormones.

Riggs & Hartman

THANK YOU!