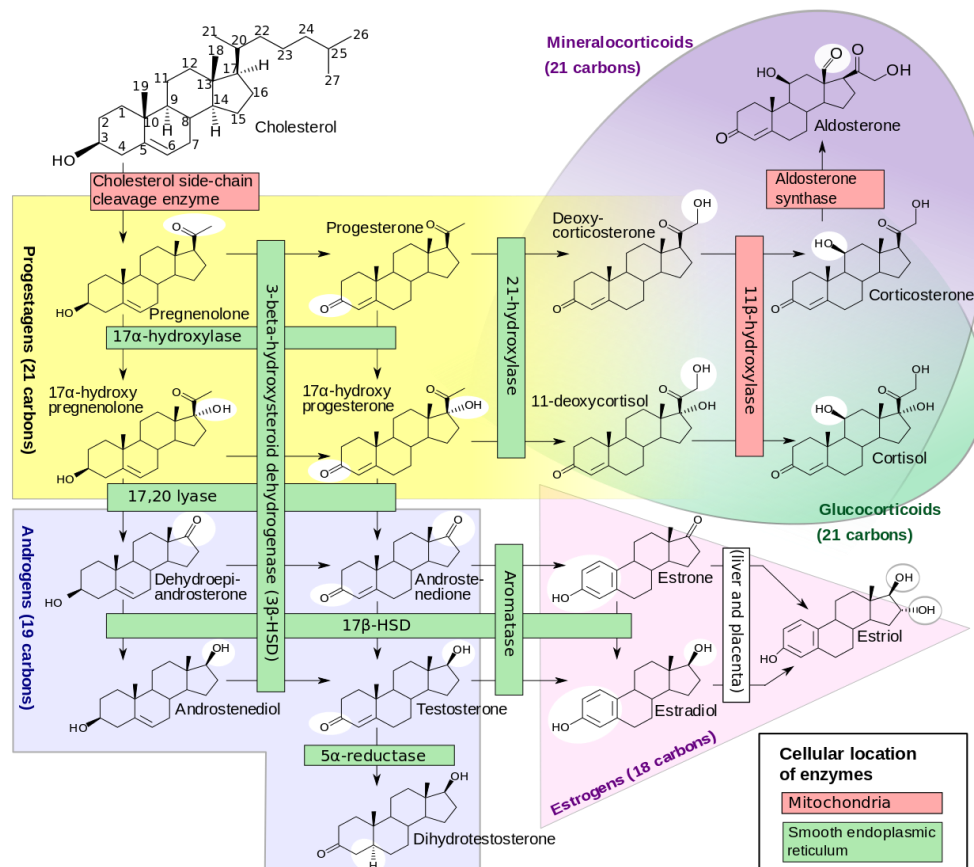


Lecture 16: Hormonal agents

The survival and proliferation (growth) of some cancer cells is dependent on the action of steroid hormones. Early stage breast cancer and early stage prostate cancer are the two best examples of this. Early breast cancer requires estrogenic hormones, and early prostate cancer requires androgenic hormones. Hence, decreasing estrogen or androgen production can be useful for slowing the growth and treating these diseases. More discussion on this approach appears later in this lecture.

The biosynthesis of all steroid hormones starts from cholesterol (see Figure 1). The initial steroids formed from cholesterol are the pregnenolones and progesterones (progestins, shown in yellow area below). These steroids can be further converted to glucocorticoids and mineralocorticoids (shown in dark purple and green areas below). Alternatively, the progestins can be converted to the androgens (light purple area). The most potent androgens are testosterone and dihydrotestosterone. Finally, the androgens can be further metabolized into estrogens (pink area). The most potent estrogen is estradiol. The actions of all steroid hormones are mediated through steroid receptors. After the steroids enter target cells, they bind to the steroid receptors in the cytosol. This binding triggers translocation of the receptor-hormone complex into the nucleus. Once in the nucleus, the complex binds to DNA at specific response elements that initiate transcription of specific genes. These genes are transcribed into specific messenger RNA (mRNA), which exits the nucleus back into the cytosol. In the cytosol, the mRNA strands are translated into specific proteins giving rise to the appropriate signals for that hormone.

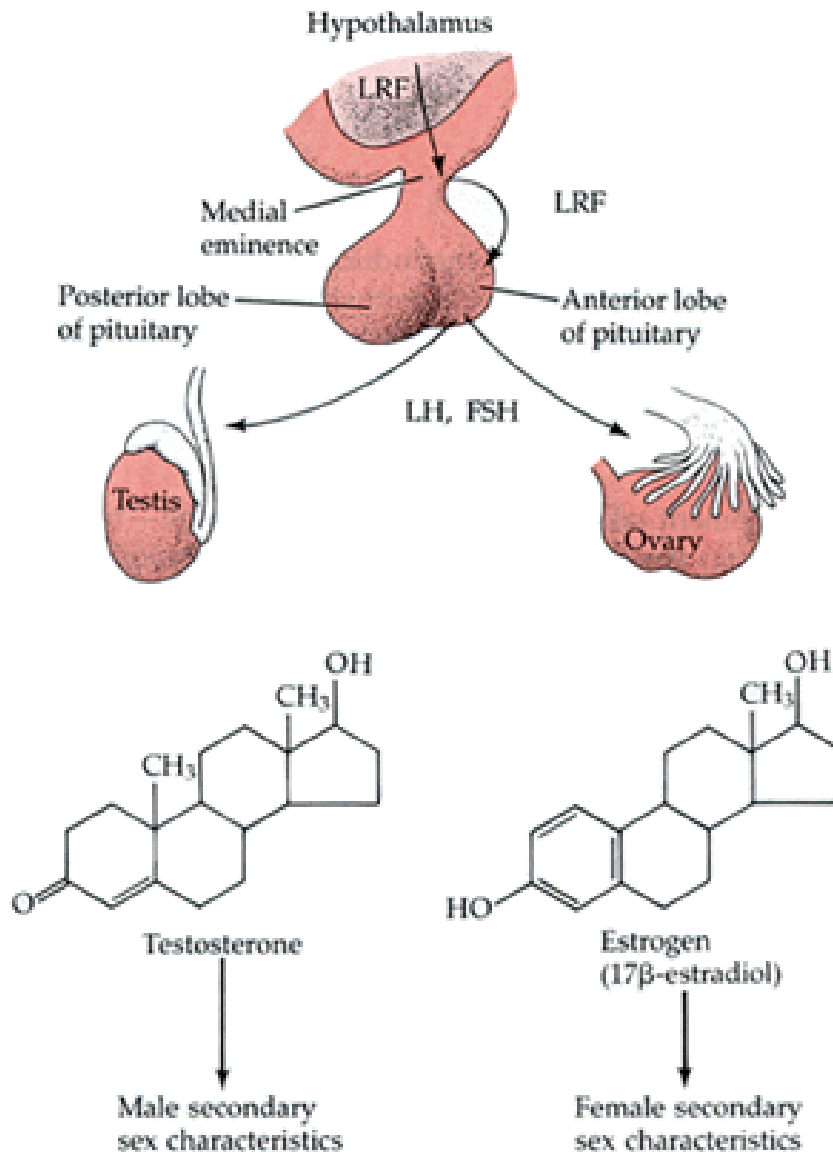
Figure 1. Major pathways of steroid biosynthesis



Hypothalamus-pituitary-gonadal axis:

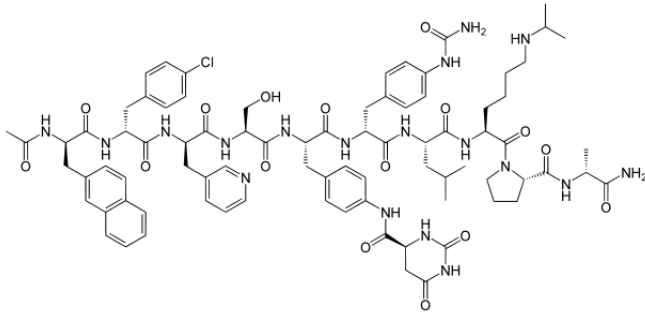
The hypothalamus secretes gonadotropin releasing hormone (GnRH) in a pulsatile manner and it acts on the pituitary to release luteinizing hormone (LH) or follicle stimulating hormone (FSH). LH and FSH stimulate specific cells in the testes and ovaries to cause several effects, including the production of androgens and estrogens (Figure 2).

Figure 2. Schematic of the hypothalamus-pituitary-gonadal axis



1. Gonadotropin antagonists

Degarelix (Firmagon):



Uses: Prostate cancer to cause immediate lowering of testosterone levels. This approach is used less often these days because more specific drugs exist.

Mechanism: A gonadotropin receptor antagonist and blocks release of luteinizing hormone (LH)* and follicle stimulating hormone (FSH) from the pituitary. A form of chemical castration.

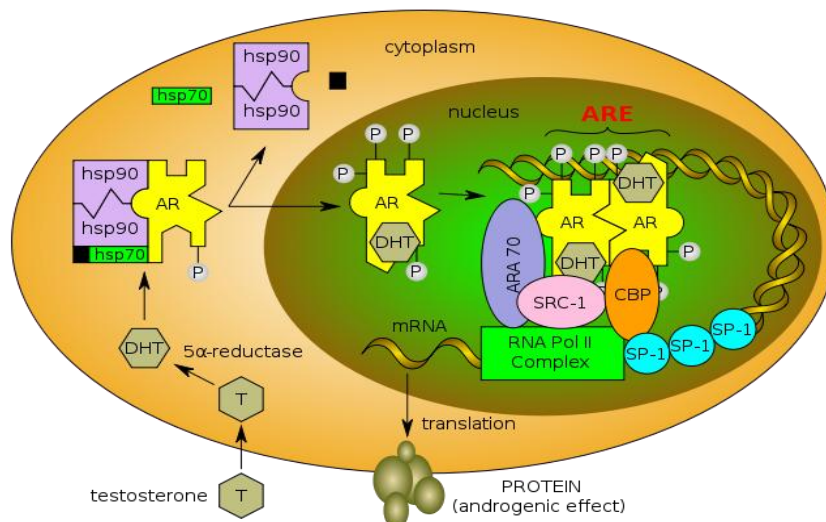
Toxicities: Hot flushes, headache, nausea, weight gain.

ADME: Because the agent is a peptide (synthetic) it is metabolized by amino acid peptidases.

Note(s): In males, *LH acts upon the Leydig cells of the testis, which are responsible for production of testosterone.

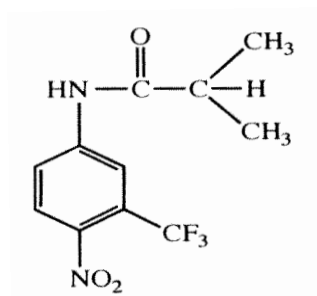
2a. Antiandrogens (Androgen receptor antagonists)

Figure 3. Androgen signaling is mediated through the androgen receptor (AR)



Testosterone is often further activated to dihydrotestosterone by 5 α -reductase in cells. This enzymatic step is targeted for treating hair loss but not cancer. Why is this?

Flutamide (Eulexin):



Uses: Hormone dependent prostate cancer (early stage); some rare cases of androgen dependent breast cancer. Administered PO.

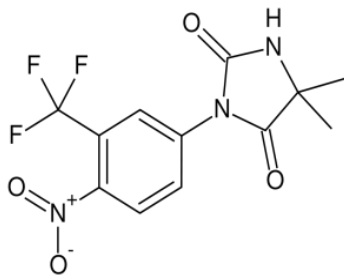
Mechanism: Binds directly to the androgen receptor and prevents the binding of endogenous androgens (testosterone and dihydrotestosterone); also, when it binds to the AR it binds in an “antagonist” way so there is reduced translocation to the nucleus. The α -hydroxyl metabolite of flutamide contributes significantly to activity.

Toxicities: Gynecomastia; liver toxicity* that can be severe – has led to death.

ADME: Good absorption and major metabolite (α -hydroxy) which is active is formed mainly by CYP1A2; potential interaction by CYP1A2 inhibitor (ketoconazole) or inducers; because of the short t_{1/2} of flutamide (~ 9 hrs) it must be dosed q.i.d. (3 x 250 mg); the t_{1/2} of the α -hydroxy metabolite is about 8 hrs.

Note(s): Use of this agent is largely replaced by bicalutamide, because of its superior properties. Data indicate that liver toxicity of flutamide might be consequence of N-deacetylation, followed by 2-hydroxylation of aromatic ring.

Nilutamide (Nilandron):



Uses: As for flutamide, hormone dependent prostate cancer (early stage); some rare cases of androgen dependent breast cancer. Administered PO.

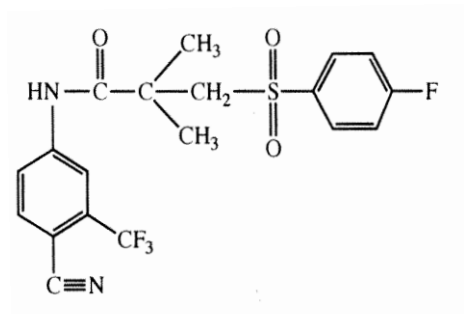
Mechanism: Like flutamide, it binds directly to the androgen receptor and prevents the binding of endogenous androgens (testosterone and dihydrotestosterone); also, when it binds to the AR it binds in an “antagonist” way so there is reduced translocation to the nucleus.

Toxicities: Interstitial pneumonitis*, some liver toxicity but less than flutamide.

ADME: Extensively metabolized by the liver by several P450 enzymes; overall hepatic impairment can lead to high levels and toxicity of nilutamide; t_{1/2} of 50-60 hrs; dosed daily (250 mg).

Note(s): More potent than flutamide. *Data indicate that lung toxicity likely caused by the formation of radical intermediates generated by reduction of nilutamide in lung tissue by P450 reductase.

Bicalutamide (Casodex):



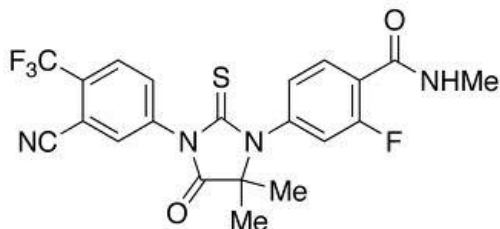
Uses: As for flutamide and nilutamide, hormone dependent prostate cancer (early stage); some rare cases of androgen dependent breast cancer. Administered PO once daily (50 mg).

Mechanism: Binds directly to the androgen receptor and prevents the binding of endogenous androgens (testosterone and dihydrotestosterone); also, when it binds to the AR it binds in an “antagonist” way so there is reduced translocation to the nucleus. Also some data suggest bicalutamide can cause some decrease in levels of the AR (mechanism unknown).

Toxicities: Liver and lung toxicity less severe than flutamide and nilutamide; believed to be a consequence of replacement of the nitro group with cyano.

Note(s): More potent than flutamide and nilutamide.

MDV3100 (Enzalutamide, Xtandi): Approved by FDA in 2012



Uses: Metastatic, castrate resistant prostate cancer*.

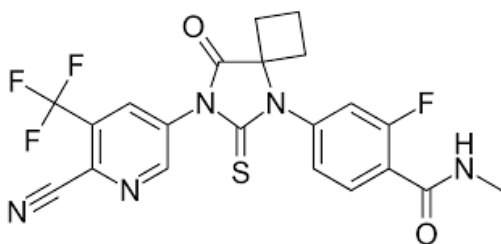
Mechanism: Binds directly to the androgen receptor but in an “antagonist” manner so that it does not cause efficient translocation of the AR into the nucleus. However, the AR complex that does get translocated does not interact correctly with the response elements of DNA for proper transcription of mRNA. Finally, it also causes a decrease in levels of the AR.

Toxicities: Generally well tolerated: asthenia (weakness), arthralgia, diarrhea, hypertension, seizures (but rare).

ADME: Good absorption and CYP2C8 and CYP3A4 primarily responsible for its metabolism; active metabolite (N-desmethyl) formed by CYP2C8. Has a long t_{1/2} of about 6 days and about 8 days for the active metabolite.

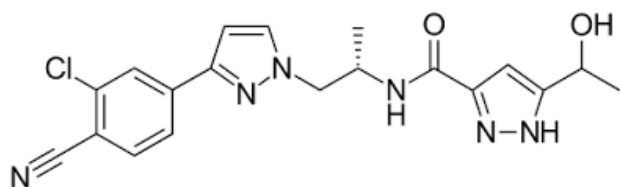
*Note(s): The term “castrate resistant prostate cancer” is used to describe patients who have low “castrate levels” of endogenous androgens, yet their tumors continue to grow by support of the low levels of androgens. The explanation for this phenomenon is that the tumors themselves produce the androgens. Thus, generation of androgens by the testes is no longer necessary.

Apalutamide (Erleada): Approved by FDA in May, 2018



Uses: Non-metastatic, castrate resistant prostate cancer. Note that this is for non-metastatic cancer. The company is now in the process of running new clinical trials to get approval for use in metastatic cancer. They will need to enroll the patients with metastatic disease to obtain the appropriate data.

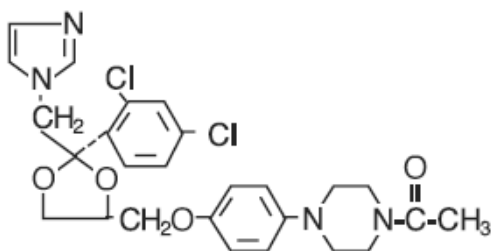
Darolutamide (Nubeqa): Approved by FDA in July, 2019.



Uses: Like apalutamide, for non-metastatic, castrate resistant prostate cancer but is used in conjunction with surgical or medical castration. Administered b.i.d. with food. It has been referred to as a second- or third-generation non-steroidal anti-androgen (NSAA).

2b. Antiandrogens (Androgen synthesis inhibitors)

Ketoconazole (Nizoral): Actually an important antifungal agent, not an important anticancer agent. But understanding its mechanism of action has led to new anticancer agents.



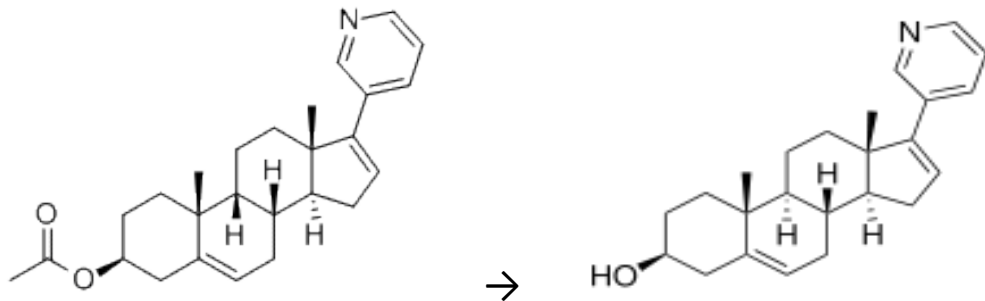
Uses: Early exploratory agent for hormone dependent prostate cancer and castrate resistant prostate cancer. Administered PO.

Mechanism: Actually developed as an anti-fungal agent because it inhibits fungal cytochrome P450 enzymes. Later found to be an inhibitor of cytochrome P450 C17-hydroxylase/17,20-lyase, also called CYP17A1 (see figure 1 above).

Toxicities: Liver toxicity with chronic use.

Note(s): Old drug and not a specific inhibitor of CYP17A; also not very potent.

Abiraterone acetate (Zytiga): Approved by FDA in 2011.



Abiraterone acetate (prodrug)

Abiraterone (active form)

Uses: Metastatic, castrate resistant prostate cancer. Administered PO daily (fasted state).*

Mechanism: An acetate prodrug; hydrolysis to abiraterone can occur in the plasma and liver. Abiraterone (not the prodrug form) binds to CYP17A1 and irreversibly inactivates the enzyme. The enzyme cannot be reactivated; new enzyme must be biosynthesized for continued androgen biosynthesis. New enzyme synthesis takes weeks but the drug is dosed daily to maintain inhibition.

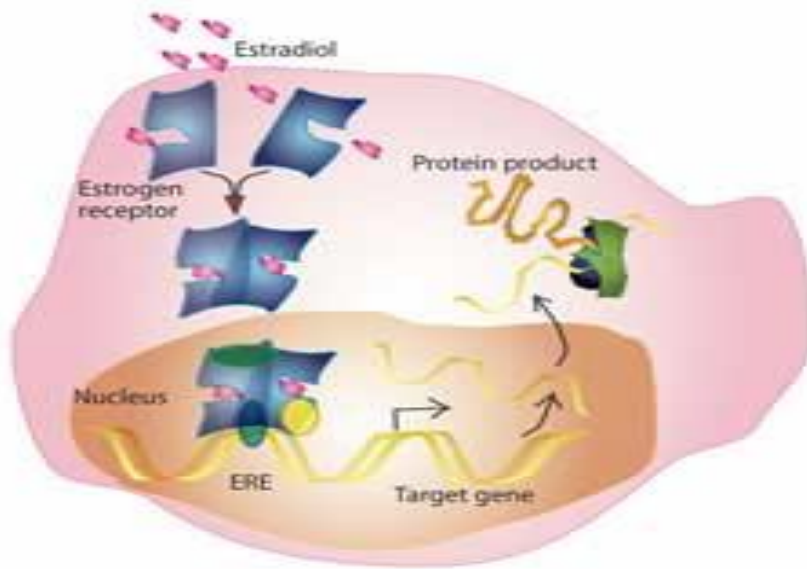
Toxicities: Hypertension. The blockade of CYP17A1 causes the progestins (pregnenolone and progesterone) to be pushed through the mineralocorticoid pathway, to aldosterone (see Figure 1 above).

ADME: *Although dosed PO, the bioavailability of this drug is actually very low (<10%) and it has a positive “food effect”. When taken with a meal, the C_{max} and AUC can increase more than 10-fold. This issue can be serious if a patient ignores the dosing directions repetitively. Hypertension can lead to heart failure, especially in elderly men with compromised heart function. The two main circulating metabolites of abiraterone in human plasma are inactive. They are abiraterone sulphate, and N-oxide abiraterone sulphate. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate, respectively.

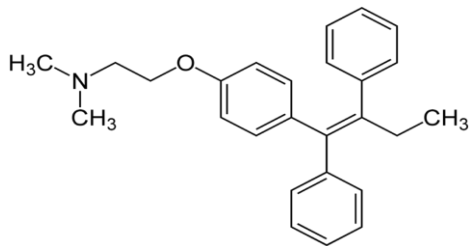
3a. Antiestrogens (Estrogen receptor antagonists)

Just like androgens, estrogen (e.g. estradiol) causes translocation of its receptor into the nucleus which triggers estrogen dependent transcription (see Figure 4). Antiestrogens work by interfering with the function of the estrogen receptor (ER). Interestingly, the ER actually dimerizes with itself prior to entry into the nucleus. Perhaps interfering with the binding of estrogens to the ER has a bigger impact than the binding of androgens to the AR. In any event, antiestrogens were developed as drugs before antiandrogens were developed.

Figure 4. Estrogen signaling is mediated through the estrogen receptor (ER)



Tamoxifen (Nolvadex):



Uses: ER positive breast cancer (early stage); some later stage cancers but tumors must remain ER+.

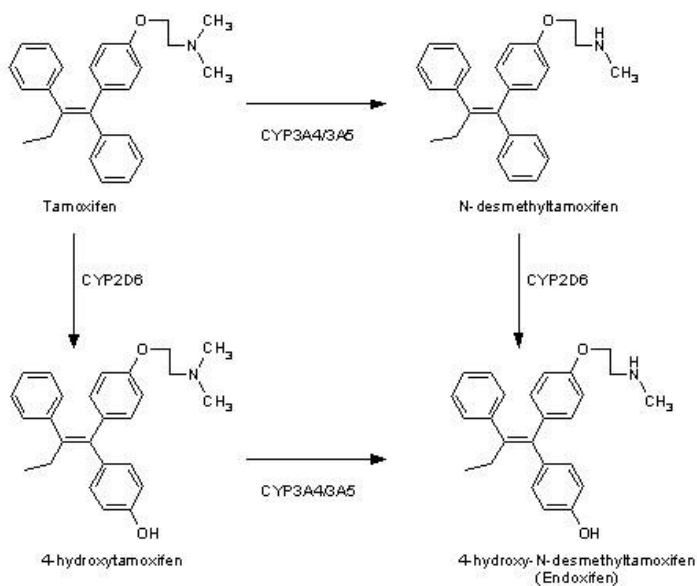
Mechanism: Binds directly to the ER and prevents the binding of endogenous estrogens (mainly estradiol); binds to the ER in an “antagonist” way, so there is reduced translocation to the nucleus. The ER-tamoxifen complex that does enter the nucleus does not lead to proper transcription of genes in DNA.

Toxicities: Thromboembolism, steatosis type hepatitis (fatty liver). Also, tamoxifen is a partial estrogen agonist in the endometrium so it can promote endometrial cancer which can appear years later. Some QT prolongation can occur (mainly with CYP3A4 inhibitors present).

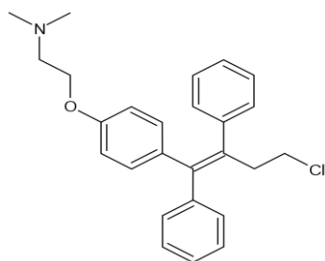
ADME: Tamoxifen is metabolized extensively to an active metabolite (Figure 5). 4-Hydroxy-N-desmethyltamoxifen (endoxifen) is a very active metabolite generated by CYP3A4/5 and CYP2D6; therefore it is susceptible to the CYP2D6 polymorphism and drug-drug interaction issues (e.g. with antidepressants that are also metabolized by CYP2D6).

Note(s): Clues to the discovery of the polymorphic role of CYP2D6 in tamoxifen metabolism and its activity was discovered accidentally when women with breast cancer were taking antidepressants. Rapid metabolizers of CYP2D6 make more endoxifen but also clear their antidepressants faster.

Figure 5. Conversion of tamoxifen into endoxifen by CYP3A4 and CYP2D6



Toremifene (Fareston):



Uses: ER positive in metastatic breast cancer.

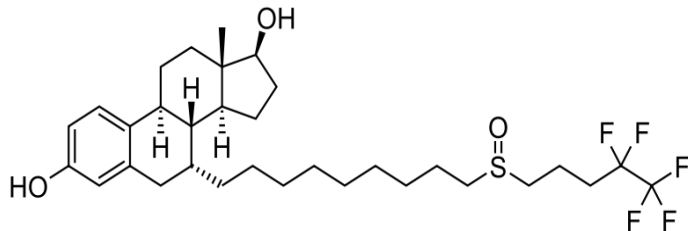
Mechanism: Binds directly to the estrogen receptor and prevents the binding of endogenous estrogens (mainly estradiol); it binds to the ER in “antagonist” and “agonist” ways so its pharmacology is complex. The ER-toremifene complex that enters the nucleus does not lead to proper transcription of DNA.

Toxicities: QT prolongation, cardiac failure, hot flashes, arthralgia, cataracts after chronic use.

ADME: Elimination $t_{1/2}$ of about 5 days and partly due to enterohepatic recycling; extensively metabolized by CYP3A4 to less active N-desmethyl metabolite; use of agents that are strong CYP3A4 inhibitors should be avoided. Not as much 4-hydroxy metabolite formed as for tamoxifen.

Note(s): Grapefruit juice (P450 inhibitor) may also increase plasma concentrations of toremifene and should be avoided. Finally, toremifene has some auto-induction activity for CYP3A4.

Fulvestrant (Faslodex):



Uses: ER positive metastatic breast cancer; also for patients with disease progression following prior antiestrogen therapy.

Mechanism: ER antagonist as above but also causes down-regulation of the ER, along with some destruction of the ER. The precise mechanism(s) for these effects is an area of active research. Has given rise to SERM (selective estrogen receptor modulator) research.

Toxicities: Generally well tolerated but nausea and asthenia; lower rate of arthralgias than preceding antiestrogens; some hepatotoxicity with chronic use.

ADME: Fulvestrant is metabolized in the liver by CYP3A4 but not extensively. No drug interactions appear to exist with fulvestrant.

3b. Antiestrogens (Estrogen synthesis inhibitors)

All endogenous estrogens are synthesized directly from androgens. The enzyme responsible is cytochrome P450 19A1, also called CYP19A1 or aromatase (Figure 6). Because the mechanism of aromatase is so unusual, it has been the subject of much research. The enzymatic process is believed to occur in several steps (see Figure 7). Note the removal of the 19-methyl group and aromatization of the A ring.

Figure 6. Estrogen synthesis is accomplished by the action of CYP19A1 (aromatase)

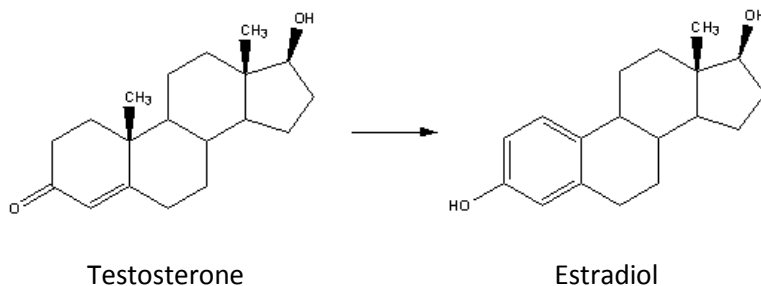
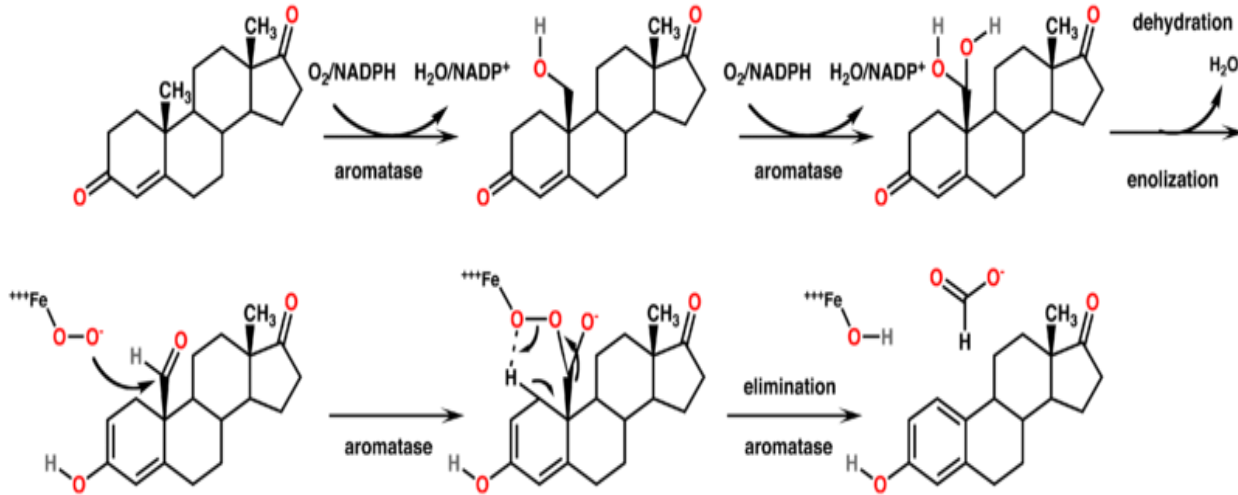
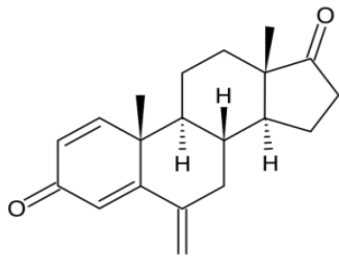


Figure 7. Proposed steps performed by aromatase in the production of estrogens (e.g. estrone)



Exemestane (Aromasin):



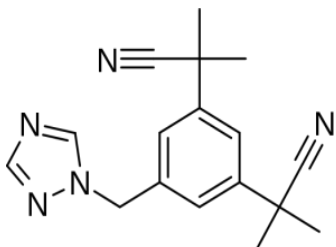
Uses: ER positive breast cancer (both adjuvant setting and later stage); also most commonly used post tamoxifen; for postmenopausal women only. * Administered PO.

Mechanism: Steroidal inhibitor of CYP19A1 (aromatase) and irreversibly inhibits (kills) the enzyme. Such an inhibitor is also called a suicide inhibitor because the enzyme attempts to convert it to an estrogen but the enzyme is killed in the process. *Exemestane mainly inhibits non-ovarian aromatase (adrenals, adipose tissue, cancer tissues) therefore not to be used for premenopausal women.

Toxicities: Hot flushes, fatigue, arthralgia, insomnia. Because the agent lowers estrogen levels dramatically, bone density can decrease and lead to osteoporosis over extended use.

ADME: Exemestane is metabolized mainly by CYP3A4. The dose of the agent should be doubled if administered with an inducer of CYP3A4 (e.g. rifampin, phenytoin).

Anastrozole (Arimidex):



Uses: ER positive breast cancer (both adjuvant setting and later stage); for postmenopausal women only.* Again, optimized for inhibition of non-ovarian aromatase. Administered PO.

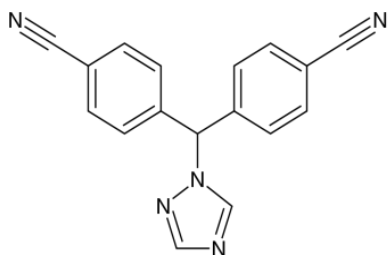
Mechanism: Non-steroidal inhibitor of CYP19A1 (aromatase) and reversibly inhibits the enzyme. Anastrozole outcompetes with endogenous androgens for the aromatase enzyme. Anastrozole preferentially inhibits non-ovarian aromatase (adrenals, adipose tissue, cancer tissues) therefore not to be used for premenopausal women.* More potent than exemestane.

Toxicities: Bone density loss appears more extreme than for tamoxifen. Generally well tolerated but hot flashes, fatigue, arthralgia, insomnia. Anastrozole lowers estrogen levels quite effectively, so bone density can decrease and lead to osteoporosis over extended use. Estradiol inhibits osteoclasts which resorb bone; less estradiol allows for more bone resorption by the osteoclasts.

ADME: Absorption is rapid and good; metabolism of anastrozole occurs by several P450 enzymes to N-dealkyl and hydroxyl metabolites. Glucuronidation also occurs and excretion is mainly fecal.

Note(s): Because it is non-steroidal, it avoids some off target effects of exemestane.

Letrozole (Femara):



Uses: ER positive breast cancer (both adjuvant setting and later stage); also commonly used post tamoxifen; for postmenopausal women only*. Administered PO.

Mechanism: Another non-steroidal inhibitor of CYP19A1 (aromatase) and reversibly inhibits the enzyme. Selective for aromatase and very potent. Non-steroidal inhibitor of CYP19A1 (aromatase) and

reversibly inhibits the enzyme. *Letrozole can inhibit ovarian and non-ovarian aromatase (adrenals, adipose tissue, cancer tissues).

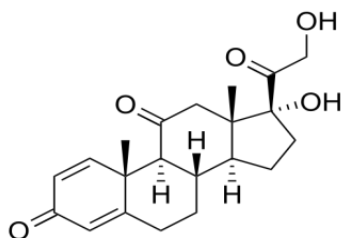
Toxicities: Because the agent lowers estrogen levels dramatically, bone density can decrease and lead to osteoporosis over extended use; arthralgia, and cases of myocardial infarction, but rare (non-QT).

ADME: Absorbed well; metabolized mainly by the liver especially CYP3A4. The dose of this agent should be reduced to 50% if severe cirrhosis or liver dysfunction is present.

4. Glucocorticoids – old agents, multiple effects; not true anti-cancer drugs

Prednisone (Deltasone):

Don't get confused that prednisone sounds like the progestins (pregnenelone or progesterone).



Uses: Many types of cancer; has minor if any real anti-cancer properties. Used in combination with many other agents agent in some leukemias and multiple myeloma; also aids in comfort, and anti-emetic; seldom used alone. Administered PO. Dosage levels are variable and depend on the disease being treated as well as the condition of the patient.

Mechanism: Binds to glucocorticoid receptor. Has many effects but in oncology mainly used for its anti-inflammatory and immunosuppressant effects.

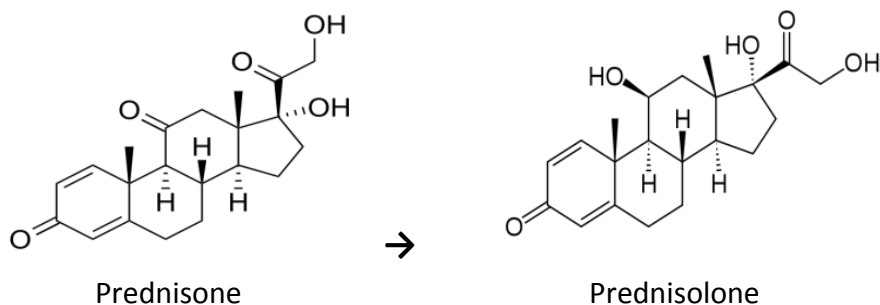
Toxicities: Fluid retention, congestive heart failure, hypertension; cataracts with long term use.

Note(s): Also used in many other diseases (e.g. RA, MS). Because of immunosuppressant properties, care must be taken if patient has ongoing infection; also new infections may appear when using prednisone; or diseases like measles or chickenpox can be worse.

Prednisolone (Omnipred):

Actually a metabolite of prednisone generated by reduction of the carbonyl at carbon 11 into the alcohol (Figure 8). But prednisolone can be made synthetically and used as a drug as it is slightly more potent than prednisone.

Figure 8. Reduction of prednisone into prednisolone.



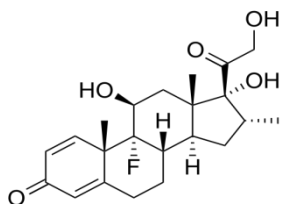
Uses: Same as for prednisone. Administered PO. Dosage levels are variable and depend on the disease being treated as well as the condition of the patient.

Mechanism: Actually a metabolite of prednisone but somewhat more potent; prednisone is metabolized in the liver to form prednisolone; formed by carbonyl reduction at the 11 position. Binds to glucocorticoid receptor. Has many effects but in oncology mainly used for its anti-inflammatory and immunosuppressant effects.

Toxicities: Fluid retention, congestive heart failure, hypertension; cataracts with long term use.

Note(s): Also used in many other diseases (e.g. RA, MS). Because of immunosuppressant properties, care must be taken if patient has ongoing infection; also new infections may appear when using prednisone; or diseases like measles or chickenpox can be worse.

Dexamethasone (Decadron):



Uses: Same as for prednisone and prednisolone but more potent than both of them. Administered PO.

Mechanism: A synthetic analog of prednisone; note same change as for prednisolone but fluorine added at C-9 and additional methyl group at C-16; both changes increase binding of the molecule to the glucocorticoid receptor.

Toxicities: Fluid retention, congestive heart failure, hypertension; cataracts with long term use.

Note(s): Also used in many other diseases (e.g. RA, MS). Because of immunosuppressant properties, care must be taken if patient has ongoing infection; also new infections may appear when using dexamethasone; or diseases like measles or chickenpox can be worse.

The choice of which of these agents depends on the institution or physician's experience. Dosage levels are variable and depend on the disease being treated as well as the condition of the patient. And because of potency differences, the following are approximate adjustments compared to a 5 mg dose of prednisone:

Prednisone (5 mg), Prednisolone (4 mg), Dexamethasone (0.75 mg)

Always check institution policies for proper dosage adjustments.