DRUG NAME: Tamoxifen

SYNONYM(S): Tam, Tamoxifene

COMMON TRADE NAME(S): NOLVADEX-D®, TAMOFEN®

CLASSIFICATION: endocrine anti-hormone

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Tamoxifen and several of its metabolites are thought to act as estrogen antagonists, by competitively binding to estrogen receptors on tumour and other tissue targets, producing a nuclear complex that decreases DNA synthesis.[1,2] This mechanism appears to have cytostatic effects, causing cells to accumulate in G0 and G1 phases.[1] Tamoxifen may also have cytotoxic activity; tamoxifen may induce apoptosis independent of estrogen receptor expression.[3,4] It is also recognized that tamoxifen acts as an estrogen agonist on endometrium, bone and lipids.[2]

PHARMACOKINETICS:

Interpatient variability	considerable variation in serum concentrations after single doses and at steady state;[5,6] genetic polymorphism may influence the efficacy and toxicity of tamoxifen and its metabolites[7-9]	
Oral Absorption	well absorbed[1]	
	time to peak plasma concentration	3-7h
Distribution	high concentrations found in uterus and breast tissue[1]	
	cross blood brain barrier?	yes[10]
	volume of distribution[11]	20 L/kg
	plasma protein binding[1]	99%
Metabolism	metabolized by hepatic cytochrome[1] P450; major CYP3A4, 2C8/9, 2D6; minor 2A6, 2B6, 2E1	
	active metabolite(s)	N-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-N-desmethyltamoxifen (endoxifen)[7]
	inactive metabolite(s)	yes
Excretion	extensive enterohepatic circulation[2,5]	
	urine[1]	9-13%
	feces[1,2,5]	26-65%, excreted into bile[12]
	terminal half life	5-7 days, range 3-21 days; major metabolite 9-14 days[5]
	clearance	no information found

Adapted from standard reference[2] unless specified otherwise.

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USES:

Primary uses:
*Breast cancer
Brain tumours[14-16]
Melanoma[1,19]
Soft tissue sarcoma[1,20]

Other uses:
Carcinoid tumour[5,13]
Endometrial cancer[13,17,18]
Pancreatic cancer[1]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- the incidence of ***ischemic cerebrovascular and thromboembolic events*** is increased with tamoxifen therapy; patients with a history of stroke, deep venous thrombosis, or pulmonary embolism OR are receiving tamoxifen in combination with cytotoxic drugs may be at increased risk[21]
- ***microvascular thrombosis*** has been reported in women treated with tamoxifen; the risk of complications after microvascular breast reconstruction may be increased[21]
- tamoxifen may increase the risk of ***wound healing*** complications (e.g., fat necrosis, infection, delayed wound healing); temporary discontinuation may limit complications[22]
- tamoxifen increases the risk of uterine fibroids and ***endometrial*** or ***uterine cancer***[21]
- tamoxifen may induce ***porphyria cutanea tarda*** due to its partial estrogenic activity; onset may be delayed[23,24]

Carcinogenicity: Tamoxifen is carcinogenic in humans and animals.[25] An increased incidence of uterine malignancies has been reported in association with treatment with tamoxifen citrate. Most uterine malignancies are adenocarcinomas of the endometrium; however, rare uterine sarcomas have also been reported. The underlying mechanism is unknown, but it may be related to the estrogen-like effect of tamoxifen. Although no causal link has been established, a number of second primary tumours occuring at sites other than the endometrium and the opposite breast have been reported following treatment of breast cancer with tamoxifen citrate. In animal studies, hepatocellular carcinomas and gonadal tumours were reported.[21]

Mutagenicity: Tamoxifen is not mutagenic in Ames test and in the mammalian *in vivo* mutation test.[26] It is not known if tamoxifen is clastogenic.[27]

Fertility: Tamoxifen may cause disturbances of menstrual cycle, including infrequent/irregular/heavy menstruation and amenorrhea, although a proportion of those women will return to normal cyclical bleeding on cessation of therapy.[21] Conversely, tamoxifen has also been used to treat infertility in women by stimulating ovulation.[28-33] In men, tamoxifen has caused impotence and decreased libido.[25] In animal studies, severe atrophic changes of the reproductive organs was reported and the weight of the ovaries, testes, seminal vesicles, and ventral prostate was reduced relative to body weight. With low doses, male test subjects had atrophic tubules and reduced numbers of spermatocytes. With high doses, male test subjects showed scattered necrotic cells in the seminiferous epithelium and cessation of maturation of the spermatozoa. In females, the uterotrophic effects of estrogen and vaginal cornification were inhibited. Uterine size and the number of corpora lutea and follicular cysts was reduced in female test subjects. The endometrium showed a complete absence of glands, areas of flattening, and squamous metaplasia with severe endometritis. Tamoxifen has also been shown in animals to have an inhibitory effect on ovulation through interference with the feedback action of estrogen at the hypothalamic and/or pituitary level and terminates early pregnancy by preventing implantation of the blastocysts. The possibility that tamoxifen may also inhibit the endogenous production of estrogen in some species cannot be excluded.[21]

Pregnancy: Although no causal relationship has been established, a small number of spontaneous abortions, birth defects, and fetal deaths have been reported when women have taken tamoxifen during pregnancy. Tamoxifen has been shown in animals to terminate early pregnancy by preventing implantation of the blastocysts. Therefore, tamoxifen should not be given during pregnancy. For women of childbearing potential, non-hormonal contraception is recommended during treatment and for nine months following the cessation of therapy.[21]

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Breastfeeding is not recommended due to the potential secretion into breast milk and the possibility of serious adverse reactions in the nursing infant.[25] Tamoxifen may inhibit lactation in humans.[34]

Special populations: The risk of serious adverse events is higher in patients older than ***50 years of age***.[25]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[35] When placebo-controlled trials are available, adverse events are included if the incidence is ≧5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	hypersensitivity reactions (≤3%)[1,26,36]
	vasculitis[5,37]
blood/bone marrow/ febrile neutropenia	myelosuppression; anemia,[2,36] leukopenia,[36,38] neutropenia,[26] thrombocytopenia[26]; transient[5] (≤10%)[1,36,39,40]
cardiovascular (arrhythmia)	QT prolongation[41]
cardiovascular (general)	cardiovascular events (4%, severe 1%)[42]
	hypertension (7-11%)[39,40,43]
	ischemic heart disease (1-3%, severe <1%)[40,42,44]
	thromboembolic events (2-5%, severe 1-2%)[40,42-46]
constitutional symptoms	fatigue (4-24%, severe 2%)[1,43-45]
	sweating (6-18%, severe 3%)[39,45,46]
	weight gain (8-9%)[39,43]
	weight loss (23%)[1]
dermatology/skin	alopecia (<5%)[1,46]
	cutaneous lupus erythematosus[47]
	nail changes (3%)[40]
	porphyria cutanea tarda[48]; has occurred after years on treatment[48]
	radiation recall[49-51]
	rash (<13%)[1,26,39,43]
	skin changes (6-19%)[1]
	Stevens-Johnson syndrome, erythema multiforme, bullous pemphigoid (<1%)[1]
endocrine	***hot flashes*** (25-81%, severe 4%)[1,2,5,42,44,45]
gastrointestinal	anorexia (1-3%)[1,46]
	constipation (1-8%)[1,39,43,46]
	diarrhea (2-7%, severe <1%)[39,40,43,45]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dyspepsia (6%)[39]
	dry mouth (2%)[40]
	nausea (5-26%, severe 1%)[1,2,39,43-46]
	vomiting (2%)[46]
hemorrhage	hemorrhage[5]
	vaginal bleeding (2-23%, severe <1%)[1,39,42-45]
hepatobiliary/pancreas	cholestasis (≤0.1%)[36]
	gallstones; generally occurs after 2-3 years of treatment[52]
	pancreatitis (<1%)[1,5,36]
	liver dysfunction, hepatitis (<1%)[1,36,40]
infection	urinary tract infection (10%)[39,40]
	vulvovaginal candidiasis[53] (4%)[40]
lymphatics	peripheral edema (8-11%)[39,43]
metabolic/laboratory	elevated creatinine[5]
	hypercalcemia (<1%)[1]; with metastatic disease; generally occurs shortly after starting treatment[2,5]
	altered lipid profile; decreased total and LDL cholesterol, decreased HDL cholesterol,[5] hypercholestremia (3%)[40], increased triglycerides (≤1%)[5,36,54,55]; onset may be delayed months or years[5,54,55]
	elevated liver function tests[5,26] (≤1%)[36]
musculoskeletal	arthritis (14%)[39]
	arthrosis (4%)[43]
	favorable effect on bone mass[56-58]
	fractures (4-8%)[39,40,42,44]
	osteoporosis (6-7%)[39,40,45]
neurology	anxiety (6%)[39]
	depression (4-12%, severe <1%)[39,45]
	dizziness (8-12%, severe <1%)[39,45]
	ischemic cerebrovascular events (1-3%, severe 1%)[42-44]
	insomnia (6-17%, severe 1%)[39,43,45]
	paresthesia (5%)[39,40]
ocular/visual	***cataracts*** (<7%)[1,26,36,39,43-45]
	corneal changes (≤0.1%)[36]
	retinopathy (≤1%)[1,26,36]; can occur within weeks-years[59]
	vision changes (6%, severe 0.4%)[45]
pain	abdominal pain (7-9%)[39]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	arthralgia/myalgia (4-29%, severe <1%)[42,44,45]
	back pain (10%)[39]
	bone pain (6%)[44]; generally occurs shortly after starting treatment[2,5]
	breast pain (6%)[39]
	chest pain (5%)[39]
	cramps (4%, severe <1%)[45]
	headache (2-16, severe <1%)[39,43,45,46]
	pain not specified (16%)[39]
	tumour pain; generally occurs shortly after starting treatment[2]
pulmonary	cough (4-10%)[1,5,39,43]
	pharyngitis (≤14%)[39,43]
	pneumonitis (<1%)[1]
renal/genitourinary	endometrial polyps, hyperplasia, endometriosis (≤1%)[1,36]
	ovarian cysts (<3%)[1,5,36,60,61]
	pruritus vulvae (<1%)[1], vulvovaginitis (5%)[39]
	urinary incontinence (4%)[40]
	uterine fibroids (≤1%)[1,26,36]
	non-infectious vaginal discharge, leukorrhea (9-13%)[39,44,45]
	vaginal dryness (<3%)[1,43]
secondary malignancy	***endometrial cancer*** (1%)[40,44]; uterine sarcoma
sexual/reproductive function	impotence (<1%)[1]
	menstrual dysfunction
	priapism[5]
syndromes	flu syndrome (6%)[39]
	tumour flare (<10%)[36]; generally occurs shortly after starting treatment[2]

Adapted from standard reference[2] unless specified otherwise.

Tamoxifen generally has a favorable effect on ***bone mass***. Tamoxifen reduces bone resorption and decreases bone turnover as manifested by reductions in bone turnover markers and increases in bone density. Tamoxifen acts mainly on trabecular bone, such as lumbar spine, and has little effect on cortical bone. The effect of tamoxifen on bone density may depend on menopausal status, as premenopausal women have demonstrated a loss of bone mineral density of the lumbar spine and hip. Further information is needed to evaluate the long-term effects of tamoxifen on the risk of osteoporosis and fracture.[5]

Tamoxifen has a stimulant effect on the ***endometrium***, possibly by acting as a partial estrogenic agonist. Tamoxifen use has been associated with an increased incidence of endometrial changes, including hyperplasia, polyps, uterine fibroids, and endometriosis.[5]

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A ***flare response*** (e.g., transient increase in bone pain, local disease flare with an increase in size of preexisting lesions, swelling and redness, and/or hypercalcemia) may occur at the initiation of therapy in patients with metastatic disease.[2] Serum calcium should be evaluated in any patient with extensive bony metastases on tamoxifen who have symptoms suggestive of hypercalcemia.[35] The so-called tamoxifen flare response may be a favourable sign,[2] although hypercalcemia may require treatment.

Hepatotoxicity usually consists of transient asymptomatic elevation of hepatic enzymes. However, more serious liver abnormalities, including fatty liver, cholestasis, and hepatitis, have occurred infrequently.[2] Rarely fatalities have been reported.[59]

Hot flashes are one of the most common adverse events reported in women taking tamoxifen, but are rarely severe.[5] If severe, they may be controlled in some patients by a decreased or divided dose. Patients who have their sleep interrupted by drenching night sweats may benefit by taking their tamoxifen in the morning.[35] Several medications have been shown to decrease the frequency and severity of hot flashes.[62,63] Occasionally tamoxifen must be discontinued due to severe hot flashes which significantly decrease quality of life.[35] (See *Hormone Replacement Therapy after a Diagnosis of Breast Cancer* at ***Breast Cancer Management Guidelines: Survivorship Care - Other post-treatment issues.***)

Tamoxifen favorably affects ***lipid profiles*** by decreasing total and low-density lipoprotein cholesterol concentrations[5]; this effect does not translate to a reduced risk of ischemic heart disease.[5,64,65] Less favorably, tamoxifen appears to moderately decrease high-density lipoprotein cholesterol concentrations and increase triglyceride levels.[2,5] Rarely, cases of pancreatitis have occurred.[2] Periodic monitoring of plasma cholesterol and triglyceride concentrations is advised for patients taking tamoxifen who have preexisting hyperlipidemias or other clinical indications.[5,66,67]

Myelosuppression has been reported with tamoxifen. Temporary decreases in platelet and leukocyte counts may occurr. Hemorrhagic tendencies are uncommon, and platelet counts have returned to normal without treatment interruption.[2] If myelosuppression is suspected, monitor complete blood counts.[2,66,67] Use tamoxifen with caution in patients with thrombocytopenia or leukopenia.[2]

Ocular changes (retinopathy, corneal opacities, decreased visual acuity) have been reported in patients receiving tamoxifen.[2,68] A modest increase in the risk of developing cataracts has been associated with tamoxifen treatment.[64,69] The relationship between tamoxifen dose and cataract formation is not known.[69] Cataract formation may be due to inhibition of chloride channels in the lens by tamoxifen.[70] Macular degeneration does not appear to predispose patients to tamoxifen-related ocular toxicity, nor does tamoxifen accelerate progression of macular degeneration.[68] Patients receiving or who have received tamoxifen should be questioned about symptoms of ocular toxicity during follow-up and should seek prompt medical attention for changes in vision.[5,68]

Thromboembolic events, including deep vein thrombosis, stroke, and pulmonary embolism are increased with tamoxifen.[2] Use tamoxifen with caution in individuals with a history of thromboembolic events,[1] particularly those not receiving systemic anticoagulation therapy.

Uterine malignancies associated with tamoxifen are typically adenocarcinomas of the endometrium; however, uterine sarcomas, an endometrial cancer with poor prognosis, have also been rarely reported.[5,71] The relative risk of endometrial cancer increases with duration of tamoxifen therapy. This relative risk is small, and must be weighed against the potential benefits of tamoxifen.[7] Women receiving or who have received tamoxifen should have routine gynecological care and should be advised to immediately report any abnormal gynecologic symptoms, such as menstrual irregularities, abnormal vaginal bleeding or discharge, or pelvic pain and pressure.[5] Imaging, including endovaginal ultrasound and/or endometrial biopsy may be necessary to rule out malignancy.[35]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aldesleukin[72]	increased risk of hypersensitivity reactions	unknown	monitor for signs and symptoms of hypersensitivity reactions
aminoglutethimide[73,74]	decreased concentration of tamoxifen and its active metabolites	increased metabolism of tamoxifen	avoid concurrent use
anastrozole	tamoxifen decreases plasma anastrozole level by 27%, but has no significant effect on estrogen suppression by anastrozole[75]; anastrozole has no significant effects on the pharmacokinetics of tamoxifen[75,76]		
bexarotene[77-79]	35% decrease in tamoxifen plasma concentrations	unknown; likely be due to induction of CYP 3A4 by bexarotene	clinical significance unclear; consider alternate agent(s)
bromocriptine[5]	increased tamoxifen concentrations	decreased metabolism of tamoxifen	caution
cyclophosphamide[80]	decreased cytotoxic effects of cyclophosphamide	unknown	avoid concurrent use; start adjuvant tamoxifen after chemotherapy is completed
cytotoxic agents[2]	increased risk of thromboembolic events	unknown	caution
doxorubicin[80]	decreased cytotoxic effects of doxorubicin	unknown	avoid concurrent use; start adjuvant tamoxifen after chemotherapy is completed
estrogens[59]	may interfere with therapeutic effect of tamoxifen	may counter the estrogen suppression effect of tamoxifen	*see below
exemestane[81]	no significant effects on tamoxifen or exemestane pharmacokinetics		
fluorouracil[80]	decreased cytotoxic effects of fluorouracil	unknown	avoid concurrent use; start adjuvant tamoxifen after chemotherapy is completed
grapefruit juice[82]	may affect bioavailability of tamoxifen and its active metabolites[83,84]	may inhibit CYP 3A4 metabolism of tamoxifen in the intestinal wall	monitor for tamoxifen toxicity †see below

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AGENT	EFFECT	MECHANISM	MANAGEMENT
letrozole	tamoxifen decreases plasma letrozole level by 38%, but has no significant effect on estrogen suppression by letrozole[85]; letrozole has no effects on the pharmacokinetics of tamoxifen and its major metabolites[86]		
mitomycin[74]	increased risk of hemolytic uremic syndrome	unknown	avoid concurrent use
paroxetine[9,87,88] and other selective serotonin inhibitors that inhibit CYP 2D6	reduced tamoxifen active metabolite concentrations	inhibits CYP 2D6 metabolism of tamoxifen	‡see below
rifamycins (e.g., rifabutin, rifampin, rifapentine)[36,89-91]	reduced tamoxifen concentrations; potentially increased levels of NDM-TAM metabolite, and subsequently endoxifen	induces CYP 3A4 metabolism of tamoxifen	no alteration of efficacy expected; clinical impact is unknown
thyroid function tests[5,92,93]	elevated thyroid hormone levels (T_4 and T_3)	increased thyroxine-binding globulin	none, thyroid function does not appear to be affected
warfarin[2,89]	possible increased anticoagulant effect (delayed, major effect)	unknown	monitor prothrombin time, adjust warfarin dose accordingly

Tamoxifen, N-desmethyltamoxifen, and 4-hydroxytamoxifen are inhibitors of cytochrome P450 mixed function oxidases, (isoenzymes 2B6, 2C8/9 and 3A4).[1,5] The effect of tamoxifen on medications that require mixed function oxidases for activation is unknown.[5]

CYP3A4, CYP2D6 and, CYP 2C8/9 inhibitors may decrease metabolism and increase tamoxifen plasma concentrations.[1,94] Tamoxifen active metabolite concentrations may be affected.[90] The clinical impact of this interaction is not known.

CYP3A4, CYP2D6, and CYP 2C8/9 inducers may increase metabolism and decrease tamoxifen plasma concentrations.[1,94]Tamoxifen active metabolite concentrations may be affected.[90] The clinical impact of this interaction is not known.

Estrogen use with tamoxifen: While hormone replacement therapy is not recommended following estrogen receptor positive breast cancer or while on tamoxifen, postmenopausal symptoms can cause considerable distress to patients. Replacement therapy may be considered if other treatment options fail. If estrogen is used, prescribe the lowest dose to relieve symptoms, monitor patient carefully and consider short term use. For vaginal complaints such as dyspareunia, dryness and sexual dysfunction, REPLENS®, a long-lasting vaginal moisturizer can be tried. If ineffective, low dose topical estrogen may then be considered. ESTRING® produces a local effect with systemic levels measurable only for the first 24 hours of the three month ring. PREMARIN® cream can be used but may have variable systemic levels related to the absorption through the vaginal tissues. The potential risks and benefits should be discussed, the lowest dose to relieve symptoms should be used, and treatment should be assessed regularly.[35,62] (See *Hormone Replacement Therapy after a Diagnosis of Breast Cancer* at ***Breast Cancer Management Guidelines: Survivorship Care - Other post-treatment issues.***)

†***Grapefruit juice and tamoxifen:*** Grapefruit juice inhibits the CYP 3A4 metabolism of tamoxifen in the intestine and may increase tamoxifen plasma levels.[82] The clinical significance of a low rate of intestinal metabolism to active metabolites is unknown. Monitor for tamoxifen toxicity.

‡***Antidepressant use with tamoxifen:*** The metabolism of tamoxifen to active 4-hydroxy-N-desmethyl-tamoxifen (endoxifen) metabolites is inhibited by paroxetine, a potent inhibitor of CYP2D6.[88] Other selective serotonin reuptake

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inhibitors (SSRI's) that inhibit CYP2D6 also inhibit the metabolism of tamoxifen.[88] The magnitude of reduction in endoxifen plasma concentration associated with CYP 2D6 inhibitors also depends on variations in CYP 2D6 genotypes.[8,9,88] The minimally active levels of tamoxifen and its active metabolites are not known.[95] The clinical significance of a low rate of hydroxylation to endoxifen is not known. The potential benefit of antidepressant use must be weighed against the potential risk.[8,9,12,96] Antidepressants that are weak inhibitors or do not inhibit CYP 2D6 may be considered.[88] **(More information under "List of Antidepressants and Tamoxifen Interactions" after References)**

SUPPLY AND STORAGE:

Oral:
Apotex Inc. supplies tamoxifen as 10 mg and 20 mg tablets. Tablets contain lactose. Store at room temperature. Protect from light.[21]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:	***20 mg PO once daily***[5,66,67] ***20 mg (range 20-120 mg) PO twice daily***[5,14-16,19,20] Doses greater than 20 mg should be administered in two divided doses 5 mg PO once daily or ***10 mg PO once every other day***[98,99]
Concurrent chemotherapy:	tamoxifen should be started after completing chemotherapy in most circumstances[80]
Concurrent radiation:	tamoxifen may be started before commencing or after completing radiation treatment; initiating treatment during radiation therapy should be avoided[100]
Dosage in renal failure:	no adjustment required[11,101]
Dosage in hepatic failure:	adjustment required, no details found[102]; dosing may be based on serum levels of tamoxifen and its active metabolites[103]
Dosage in dialysis	no adjustment required[102]

Children: safety and effectiveness not established in children[74]

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REFERENCES:

1. Rose BD editor. Tamoxifen: Drug Information. UpToDate 2006 ed. Waltham, Massachusetts: UpToDate; 2006
2. GenPharm Inc. Tamoxifen Product Monograph. Etobicoke, Ontario; 18 August 2003
3. Lens MB, Reiman T, Husain AF. Use of tamoxifen in the treatment of malignant melanoma: Systematic review and metaanalysis of randomized controlled trials. Cancer 2003;98(7):1355-1361
4. Hui A, Zhang W, Chen W, et al. Agents with selective estrogen receptor (ER) modulator activity induce apoptosis in vitro and in vivo in ER-negative glioma cells. Cancer Res 2004;64(24):9115-9123
5. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2006. p. 1185-1192
6. Peyrade F, Frenay M, Etienne MC, et al. Age-related difference in tamoxifen disposition. Clin Pharmacol Ther 1996;59(4):401-10
7. MARTINDALE - The Complete Drug Reference (database on the Internet). Tamoxifen Citrate. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 16 June, 2006
8. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. Journal of the National Cancer Institute 2005;97(1):30-39
9. Stearns V, Johnson MD, Rae J, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. Journal of the National Cancer Institute 2003;95(23):1758-1764
10. Lien EA, Wester K, Lonning PE, et al. Distribution of tamoxifen and metabolites into brain tissue and brain metastases in breast cancer patients. Br J Cancer 1991;63(4):641-5
11. Aronoff GR, Brier ME, Berns JS, et al. The Renal Drug Book, Tamoxifen. Available at: http://www.kdp-baptist.louisville.edu/renalbook/. Accessed June 26, 2006
12. Chabner, B.A., Longo,D.L., editor. Cancer Chemotherapy and Biotherapy: Principles and Practice. Philadelphia, PA: Lippincott Williams and Wilkins; 2001. p. 101-110
13. Perry MC, editor. The Chemotherapy Source Book. Baltimore, Maryland: Williams and Wilkins; 1992. p. 420-1041
14. Couldwell WT, Hinton DR, Surnock AA, et al. Treatment of recurrent malignant gliomas with chronic oral high-dose tamoxifen. Clin Cancer Res 1996;2(4):619-622
15. BC Cancer Agency CNS Tumour Group. (CNTAM) BCCA Standard Protocol-Tamoxifen for Patients with Recurrent Brain Tumors Which are Resistant to First Line Chemotherapy. Vancouver: BC Cancer Agency; 1 August 2006
16. BC Cancer Agency CNS Tumour Group. (CNTAMCAR) BCCA Protocol Summary for the Second and Third Line Treatment of Recurrent Gliomas with Carboplatin and High Dose Tamoxifen. Vancouver: BC Cancer Agency; 1 August 2006
17. Swenerton KD. Treatment of advanced endometrial adenocarcinoma with tamoxifen. Cancer Treat Rep 1980;64(6/7):805-11
18. Swenerton KD, White GW, DA. B. Treatment of advanced endometrial carcinoma with tamoxifen (Letter). N Engl J Med 1979;301(2):105
19. BC Cancer Agency Melanoma Tumour Group. (SMTAM) BCCA Protocol Summary for Palliative Therapy for Malignant Melanoma Using Tamoxifen. Vancouver: BC Cancer Agency; 1 June 2003
20. BC Cancer Agency Sarcoma Tumour Group. (SATAM) BCCA Protocol Summary For Tamoxifen For Patients With Recurrent Desmoid Tumors/Aggressive Fibromatosis. Vancouver: BC Cancer Agency; 26 September 1996
21. Apotex Inc. Apo-Tamox product monograph. Toronto, Ontario; January 21 2022
22. Billon R, Bosc R, Belkacemi Y, et al. Impact of adjuvant anti-estrogen therapies (tamoxifen and aromatase inhibitors) on perioperative outcomes of breast reconstruction. Journal of Plastic, Reconstructive & Aesthetic Surgery 2017;70(11):1495-1504
23. Cruz MJ, Alves S, Baudrier T, et al. Porphyria cutanea tarda induced by tamoxifen. Dermatology Online Journal 2010;16(9:2)
24. Palmieri C, Vigushin DM, Peters TJ. Managing malignant disease in patients with porphyria. Q J Med: An International Journal of Medicine 2004;97(3):115-126
25. AHFS Drug Information® (database on the Internet). Tamoxifen Citrate. Lexi-Comp Inc., 2024. Available at: http://online.lexi.com. Accessed March 27, 2024
26. AstraZeneca. Nolvadex-D® product monograph. Mississauga, Ontario; 23 November 2004
27. Feiona Jaffer BScPhm. Medical Information Specialist AstraZeneca Canada Inc. Personal Communication. 12 July2006
28. Ruiz-Velasco V, Rosas-Arceo J, Matute MM. Chemical inducers of ovulation: comparative results. Int J Fertil 1979;24(1):61-4
29. Wu CH. Less miscarriage in pregnancy following tamoxifen treatment of infertile patients with luteal phase dysfunction as compared to clomiphene treatment. Early Pregnancy 1997;3(4):301-5
30. Oktay K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol 2005;23(16):3858-9
31. Steiner AZ, Terplan M, Paulson RJ. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. Hum Reprod 2005;20(6):1511-5
32. Annapurna V, Dhaliwal LK, Gopalan S. Effect of two anti-estrogens, clomiphene citrate and tamoxifen, on cervical mucus and sperm-cervical mucus interaction. Int J Fertil Womens Med 1997;42(3):215-8
33. Dhaliwal LK, Suri V, Gupta KR, et al. Tamoxifen: An alternative to clomiphene in women with polycystic ovary syndrome. Journal of Human Reproductive Sciences 2011;4(2):76-79
34. Masala A, Delitala G, Lo Dico G, et al. Inhibition of lactation and inhibition of prolactin release after mechanical breast stimulation in puerperal women given tamoxifen or placebo. Br J Obstet Gynaecol 1978;85(2):134-7
35. Caroline Lohrisch MD. BC Cancer Agency Breast Tumour Group. Personal Communication. 16 August2006
36. Repchinsky C, editor. Compendium of Pharmaceuticals and Specialties Nolvadex-D. Ottawa: Canadian Pharmacists Association; 2006. p. 1455-1456

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37. Baptista MZ, Prieto VG, Chon S, et al. Tamoxifen-related vasculitis. J Clin Oncol 2006;24(21):3504-3505
38. Mike V, Currie VE, Gee TS. Fatal neutropenia associated with long-term tamoxifen therapy. Lancet 1994;344(8921):541-2
39. AstraZeneca. Arimidex-adjuvant product monograph. Mississauga, Ontario; 16 June 2004
40. The ATAC Trialists Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncology 2006;7(8):633-643
41. De Ponti F, Poluzzi E, Cavalli A, et al. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: An overview. Drug Safety 2002;25(4):263-286
42. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353(26):2747-2757
43. AstraZeneca. ARIMIDEX® product monograph. Mississauga, Ontario; 16 June 2004
44. ATAC Trialists Group. Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. The Lancet 2005;365(9453):60-62
45. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350(11):1081-92
46. Novartis Pharmaceuticals. Letrozole product monograph. Dorval, Quebec; 22 March 2004
47. Fumal I, Danchin A, Cosserat F, et al. Subacute cutaneous lupus erythematosus associated with tamoxifen therapy: Two cases [8]. Dermatology 2005;210(3):251-252
48. Agarwal R, Peters TJ, Coombes RC, et al. Tamoxifen-related porphyria cutanea tarda. Medical Oncology 2002;19(2):121-123
49. Parry BR. Radiation recall induced by tamoxifen. Lancet 1992;340(8810):49
50. Bostrom A, Sjolin-Forsberg G, Wilking N, et al. Radiation recall - Another call with tamoxifen. Acta Oncologica 1999;38(7):955-959
51. Extermann M, Vogt N, Forni M, et al. Radiation recall in a patient with breast cancer treated for tuberculosis. Eur J Clin Pharmacol 1995;48(1):77-8
52. Akin ML, Uluutku H, Erenoglu C, et al. Tamoxifen and gallstone formation in postmenopausal breast cancer patients: retrospective cohort study. World J Surg 2003;27(4):395-9
53. Sobel JD, Chaim W, Leaman D. Recurrent vulvovaginal candidiasis associated with long-term tamoxifen treatment in postmenopausal women. Obstetrics & Gynecology 1996;88(4 II SUPPL.):704-706
54. Colls BM, George PM. Severe hypertriglyceridaemia and hypercholesterolaemia associated with tamoxifen use. Clin Oncol (R Coll Radiol) 1998;10(4):270-1
55. Kanel KT, Wolmark N, Thompson PD. Delayed severe hypertriglyceridemia from tamoxifen. N Engl J Med 1997;337(4):281
56. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992;326(13):852-6
57. Love RR, Barden HS, Mazess RB, et al. Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. Arch Intern Med 1994;154(22):2585-8
58. Grey AB, Stapleton JP, Evans MC, et al. The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. Am J Med 1995;99(6):636-41
59. USPDI® Drug Information for the Health Care Professional (database on the Internet). Tamoxifen (Systemic). Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 9 June, 2006
60. Shushan A, Peretz T, Uziely B, et al. Ovarian cysts in premenopausal and postmenopausal tamoxifen-treated women with breast cancer. American Journal of Obstetrics & Gynecology 1996;174(1):141-144
61. Mourits MJ, de Vries EG, Willemse PH, et al. Ovarian cysts in women receiving tamoxifen for breast cancer. Br J Cancer 1999;79(11-12):1761-4
62. BC Cancer Agency Breast Tumour Group. Cancer Management Guidelines: Breast Follow-up - Hormone Replacement Therapy After a Diagnosis of Breast Cancer. Vancouver, British Columbia: BC Cancer Agency; March 1, 2006
63. Mom CH, Buijs C, Willemse PHB, et al. Hot flushes in breast cancer patients. Critical Reviews in Oncology-Hematology 2006;57(1):63-77
64. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute. 1998;90(18):1371-88
65. Reis SE, Costantino JP, Wickerham DL, et al. Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. J Natl Cancer Inst 2001;93(1):16-21
66. BC Cancer Agency Breast Tumour Group. (BRAJTAM) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Tamoxifen. Vancouver: BC Cancer Agency; 1 July 2005
67. BC Cancer Agency Breast Tumour Group. (BRAVTAM) BCCA Protocol Summary for Palliative Therapy for Breast Cancer Using Tamoxifen. Vancouver: BC Cancer Agency; 1 July 2002
68. Nayfield SG, Gorin MB. Tamoxifen-associated eye disease. A review. J Clin Oncol 1996;14(3):1018-1026
69. Bradbury BD, Lash TL, Kaye JA, et al. Tamoxifen and cataracts: a null association. Breast Cancer Res Treat 2004;87(2):189-96
70. Zhang JJ, Jacob TJ, Valverde MA, et al. Tamoxifen blocks chloride channels. A possible mechanism for cataract formation. J Clin Invest 1994;94(4):1690-7
71. Arenas M, Rovirosa A, Hernandez V, et al. Uterine sarcomas in breast cancer patients treated with tamoxifen. International Journal of Gynecological Cancer 2006;16(2):861-865
72. Wolters Kluwer Health I. Tamoxifen. Drug Interaction Facts. St. Louis, MO: Drug Facts and Comparisons 4.0 [online]; May 4, 2006

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Revised: 1 May 2024

73. Lien EA, Anker G, Lonning PE, et al. Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. Cancer Res 1990;50(18):5851-7
74. DRUGDEX® Evaluations (database on the Internet). Tamoxifen. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 29 June, 2006
75. Dowsett M, Cuzick J, Howell A, et al. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. Br J Cancer 2001;85(3):317-24
76. Dowsett M, Tobias JS, Howell A, et al. The effect of anastrozole on the pharmacokinetics of tamoxifen in post-menopausal women with early breast cancer. British Journal of Cancer 1999;79(2):311-5
77. Eisai Inc. TARGRETIN® Capsules Package Insert. Woodcliff Lake, New Jersey; May 2007
78. Rose BD editor. Bexarotene. UpToDate 15.3 ed. Waltham, Massachusetts: UpToDate®; 2008
79. Esteva FJ, Glaspy J, Baidas S, et al. Multicenter Phase II Study of Oral Bexarotene for Patients With Metastatic Breast Cancer. J Clin Oncol 2003;21(6):999-1006
80. Albain KS, Green SJ, Ravdin PM, et al. Adjuvant chemohormonal therapy for primary breast cancer should be sequential instead of concurrent: initial results from intergroup trial 0100 (SWOG-8814). Proceedings of the American Society of Clinical Oncology 2002;21 (Part 1 of 2):37a (Abstract 143)
81. Hutson PR, Love RR, Havighurst TC, et al. Effect of exemestane on tamoxifen pharmacokinetics in postmenopausal women treated for breast cancer. Clinical Cancer Research 2005;11(24):8722-8727
82. Patel P. Cytochrome P450 Drug Interactions. Compendium of Pharamceuticals and Specialties. Ottawa, Ontario, Canada: Canadian Pharmacists Association; 2006. p. L76-L78
83. Crewe HK., Ellis SW., Lennard MS.,Tucker GT. Variable contribution of cytochromes P450 2D6 and 3A4 to the 4-hydroxylation of tamoxifen by human liver microsomes. Biochemical Pharmacology 1997;53(2)(Jan):171-8
84. Crewe HK., Notley LM., Wunsch RM., Lennard MS.,Gillam EM. Metabolism of tamoxifen by recombinant human cytochrome P450 enzymes. Drug Metabolism and Disposition: The Biological Fate of Chemicals 2002;30(8)(Aug):869-74
85. Dowsett M, Pfister C, Johnston SR, et al. Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. Clinical Cancer Research 1999;5(9):2338-43
86. Ingle JN, Suman VJ, Johnson PA, et al. Evaluation of tamoxifen plus letrozole with assessment of pharmacokinetic interaction in postmenopausal women with metastatic breast cancer. Clinical Cancer Research 1999;5(7):1642-9
87. Goetz MP LC. A hot flash on tamoxifen metabolism. Journal of the National Cancer Institute 2003;95(No. 23):1734-1735
88. Borges S, Desta Z, Li L, et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther 2006;80(1):61-74
89. Wolters Kluwer Health I. Tamoxifen. Drug Facts and Comparisons. St. Louis, MO: Drug Facts and Comparisons 4.0 [online]; May 4, 2006
90. Kivisto KT, Villikka K, Nyman L, et al. Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. Clinical Pharmacology & Therapeutics 1998;64(6):648-654
91. Drug Interaction Facts (database on the Internet). Tamoxifen. Facts and Comparisons 4.0, 2010. Available at: http://online.factsandcomparisons.com. Accessed 31 March, 2010
92. Anker GB, Lonning PE, Aakvaag A, et al. Thyroid function in postmenopausal breast cancer patients treated with tamoxifen. Scandinavian Journal of Clinical & Laboratory Investigation 1998;58(2):103-107
93. Zidan J, Rubenstein W. Effect of adjuvant tamoxifen therapy on thyroid function in postmenopausal women with breast cancer. Oncology 1999;56(1):43-45
94. Rose BD. Lexi-Interact™ Online Tamoxifen. UpToDate, 2006. Available at: www.uptodate.com. Accessed 16 June, 2006
95. Ratliff B, Dietze EC, Bean GR, et al. Re: Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine (multiple letters) [1]. Journal of the National Cancer Institute 2004;96(11):883-885
96. Lehmann D, Nelsen J, Ramanath V, et al. Lack of attenuation in the antitumor effect of tamoxifen by chronic CYP isoform inhibition. Journal of Clinical Pharmacology 2004;44(8):861-865
97. Teva Canada Limited. Teva-Tamoxifen product monograph. Toronto, Ontario; June 7 2022
98. BC Cancer Breast Tumour Group. (BRAJLDTAM) BC Cancer Protocol Summary for the Adjuvant Treatment of Resected Ductal Carcinoma in Situ using Tamoxifen. Vancouver, British Columbia: BC Cancer; 1 May 2024
99. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. J Clin Oncol 2019;37(19):1629-1637
100. Karen Gelmon MD. BC Cancer Agency Breast Tumour Group. Personal Communication. 2005
101. Sutherland CM, Sternson LA, Muchmore JH, et al. Effect of impaired renal function on tamoxifen. J Surg Oncol 1984;27(4):222-223
102. Susan Halasi MScPhm. Genpharm Drug Information Pharmacist. Personal Communication. 27 June2006
103. Floren LC, Hebert MF, Venook AP, et al. Tamoxifen in liver disease: Potential exacerbation of hepatic dysfunction. Annals of Oncology 1998;9(10):1123-1126

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List of Antidepressants and Tamoxifen Interactions

(Developed by BC Cancer Provincial Drug Information Service, in collaboration with the Breast Tumour Group and Vancouver Cancer Centre psychiatrists).
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Tamoxifen is converted into its active metabolites 4-hydroxy-tamoxifen, endoxifen and other active metabolites by the CYP2D6 liver enzyme. The efficacy of tamoxifen may vary between individuals due to heterogeneous genetic variation in CYP2D6 activity, and by co-administration of a number of drugs that may modulate the activity of the enzyme.

Selective Serotonin Reuptake Inhibitors (SSRIs) are a commonly used class of antidepressants which inhibit CYP2D6 to varying degrees. Concurrent administration of some SSRIs and tamoxifen has been shown to lower levels of endoxifen, but not of 4-hydroxy-tamoxifen. The clinical implications of this decline in endoxifen levels are unclear because tamoxifen concentrations do not appear to change substantially. However, retrospective evidence presented at ASCO 2009 reported that concomitant use of tamoxifen and moderate/potent CYP2D6 inhibitors significantly increased the risk of breast cancer recurrence. In the SSRI subanalysis, moderate or potent, CYP2D6 inhibitors were associated with 25-92% greater relative risk of breast cancer recurrence, depending on duration of co-exposure, compared with taking no SSRIs with tamoxifen. Weak CYP2D6 inhibitors were not associated with an increased breast cancer recurrence in this study. A recent retrospective study from Ontario also suggests that the greater risk of breast cancer recurrence with paroxetine may be associated with increased cancer death.

Drugs that could potentially cause reduction in efficacy and thus should be used with caution include any strong CYP2D6 inhibitors such as: fluoxetine, paroxetine, chlorpromazine, miconazole, quinidine, and bupropion. Moderate inhibitors include: ketoconazole, trazodone and amiodarone. The safest course of action is to avoid co-administration of tamoxifen and any of these medications. However, each individual's particular need and circumstances should be evaluated to determine what is best for them.

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) like venlaflaxine and desvenlafaxine are weak CYP2D6 inhibitors and do not lower the concentration of endoxifen. These are better choices for women taking tamoxifen who also require medication for depression or relief of hot flashes.

The following table lists examples of commonly used antidepressants and their association with CYP2D6 and tamoxifen. NOTE: The following table is not an all-inclusive list and the contents are subject to change over time. Therefore, this table is not intended to be used as the sole source of information regarding antidepressant-tamoxifen interactions and should always be used in conjunction with standard drug interaction resources.

User Guide for table (Definitions for Probability of Interaction):
Drug interactions assigned documentation levels as outlined by Facts & Comparisons 4.0:
- Certain: proven to occur in studies or recommended by reputable guidelines
- Probable: very likely, but not proven in controlled studies
- Possible: could occur, but data are very limited
- Not likely: no good evidence of an altered clinical effect

Class of drugs	*Drug*	*CYP2D6 activity*	*Tamoxifen Interaction*
SSRIs	Fluoxetine	Strong inhibitor	Probable
	Paroxetine	Strong inhibitor	Probable
	Sertraline	Moderate inhibitor	Possible
	Fluvoxamine	Weak inhibitor	Not likely
	Citalopram	Weak inhibitor	Not likely
	Escitalopram	Weak inhibitor	Not likely
SNRIs	Duloxetine	Moderate inhibitor	Possible
	Venlafaxine	Weak inhibitor	Not likely
	Desvenlafaxine	Weak inhibitor	Not likely
MAOIs	Tranylcypromine	Moderate inhibitor	Possible
	Selegiline	Weak inhibitor	Not likely
Tricyclics	Clomipramine	Moderate inhibitor	Possible
	Amitriptyline	Weak inhibitor	Not likely
	Desipramine	Moderate inhibitor	Possible
	Nortryptyline	Weak inhibitor	Not likely
	Imipramine	Moderate inhibitor	Possible
	Doxepin	Major substrate	Not likely
	Trimipramine	Major substrate	Not likely
Others	Buspirone	Minor substrate	Not likely
	Trazodone	Major substrate	Not likely
	Mirtazapine	Weak inhibitor	Not likely
	Bupropion	Strong inhibitor	Probable

Bibliography:

1. Aubert RE, Stanek EJ, Yao, JR, et al. Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors. J Clin Oncol 2009;27 (suppl):18s (abstr CRA508).
2. Juurlink D. Clin Info: Cytochrome P450 drug interactions. In: Repchinsky C, editor. In: Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association. 2009. p. L28-L35.
3. Dezentje V, Van Blijderveen NJ, Gelderblom H. Concomitant CYP2D6 inhibitor use and tamoxifen adherence in early-stage breast cancer: a pharmacoepidemiologic study. J Clin Oncol 2009;27 (suppl):18s (abstr CRA509).
4. Facts and Comparisons. How to use Drug Interactions Facts™. www.factsandcomparisons.com . Accessed Sept 23, 2009
5. Henry NL, Stearns V, Flockhart DA, et al. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. Am J Psychiatry 2008;165:1251-5.
6. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97(1):30-9.
7. Stearns V, Hayes DF, Jin Y, et al. The effect of CYP 2D6 genotype and CYP2D6 inhibitors on tamoxifen. J Clin Oncol 2004;22(suppl):14s (abstr 508).
8. UpToDate. www.uptodate.com. Accessed Sept 12, 2014
9. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 2003;95(23):1758-64.
10. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ 2010;340:c693 (published online: 8 February 2009 as doi:10.1136/bmj.c693).
11. AHFS. www.medicinescomplete.com. Accessed Sept 17, 2014
12. Lexicomp. www.lexi.com. Accessed Sept 17, 2014

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