

Tamoxifen, Endoxifen, and CYP2D6

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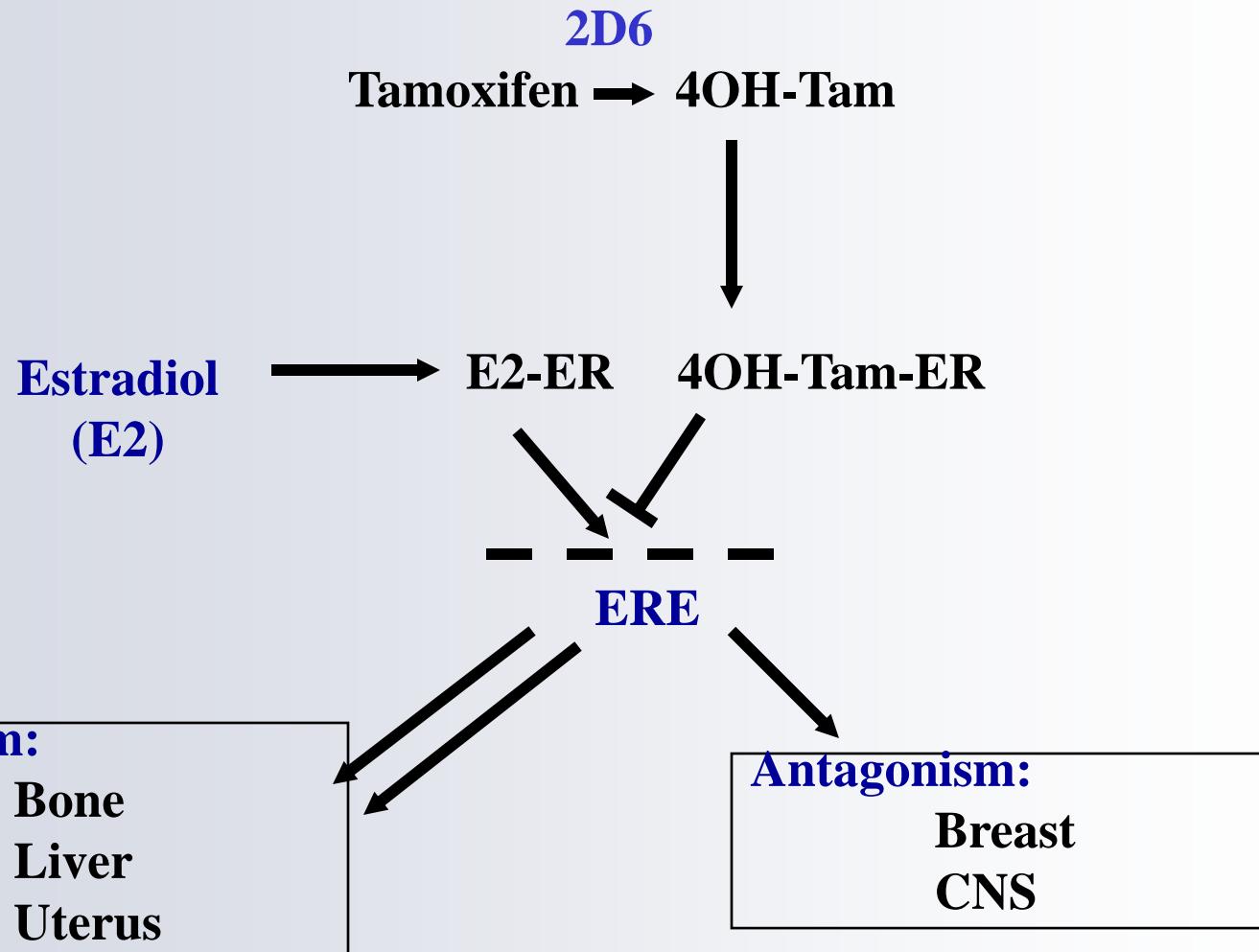
Outline

- Exposure to tamoxifen and metabolites after administration of tamoxifen
- Pharmacology of tamoxifen, endoxifen, and other metabolites
- CYP2D6-mediated metabolism of tamoxifen and formation of endoxifen *in vitro*
- Role of CYP2D6 in formation of endoxifen *in vivo*
 - CYP2D6 genotype
 - Strong Inhibitors of CYP2D6

Case Report

- 45 year-old woman presented with intense, intolerable hot flashes after being prescribed 20 mg of tamoxifen per day for a week.
- Placed on 10 mg per day of paroxetine for depression
- Resolution of hot flashes within a week
- Hot flashes resumed when taken off paroxetine

Classic Understanding of Tamoxifen Pharmacology



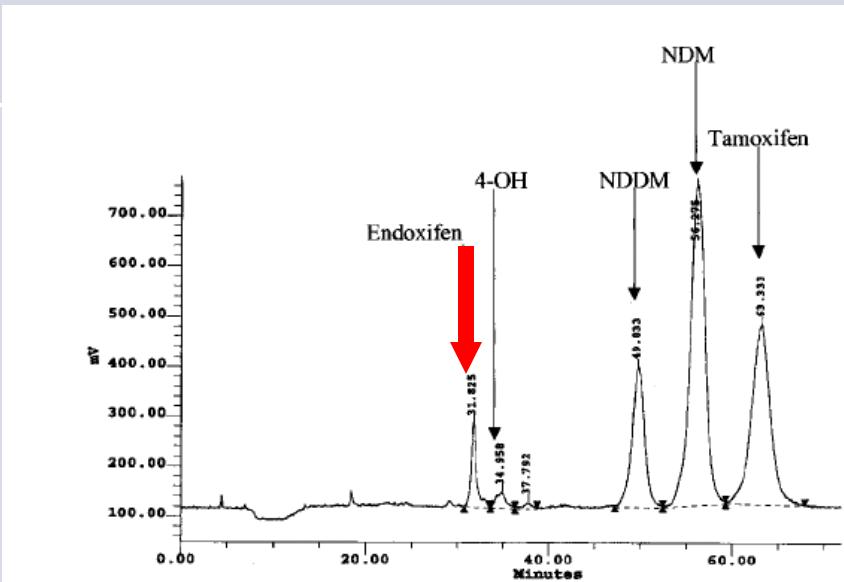
Hypothesis:

CYP2D6 inhibition interferes with formation of 4-OH-tamoxifen

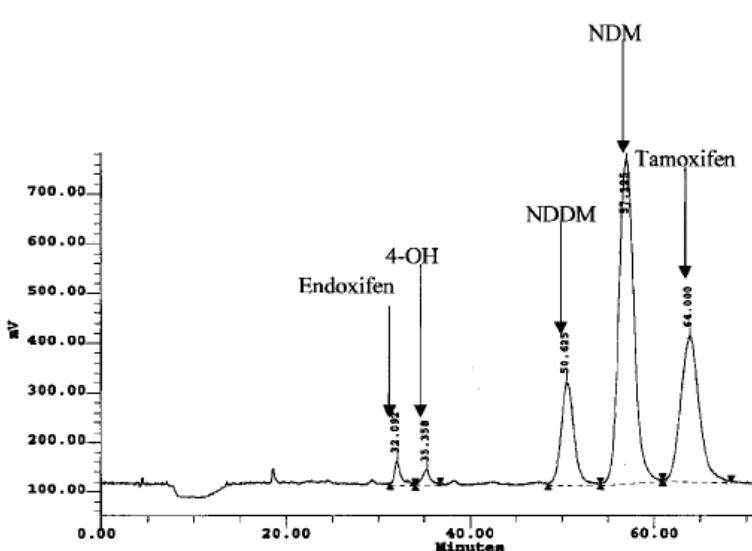
- 12 women with hx of breast cancer receiving tamoxifen (20 mg/day) as adjuvant treatment for at least 4 weeks before starting the study
 - History of troublesome hot flashes for which treatment with a non-hormonal agent was considered to be appropriate
- Blood samples collected before and after 4 weeks of co-administration of tamoxifen with 10 mg/day paroxetine

Paroxetine Administration Decreased the Concentration of One Metabolite

Before



After



Separated, purified,
identified
and synthesized
metabolite X:

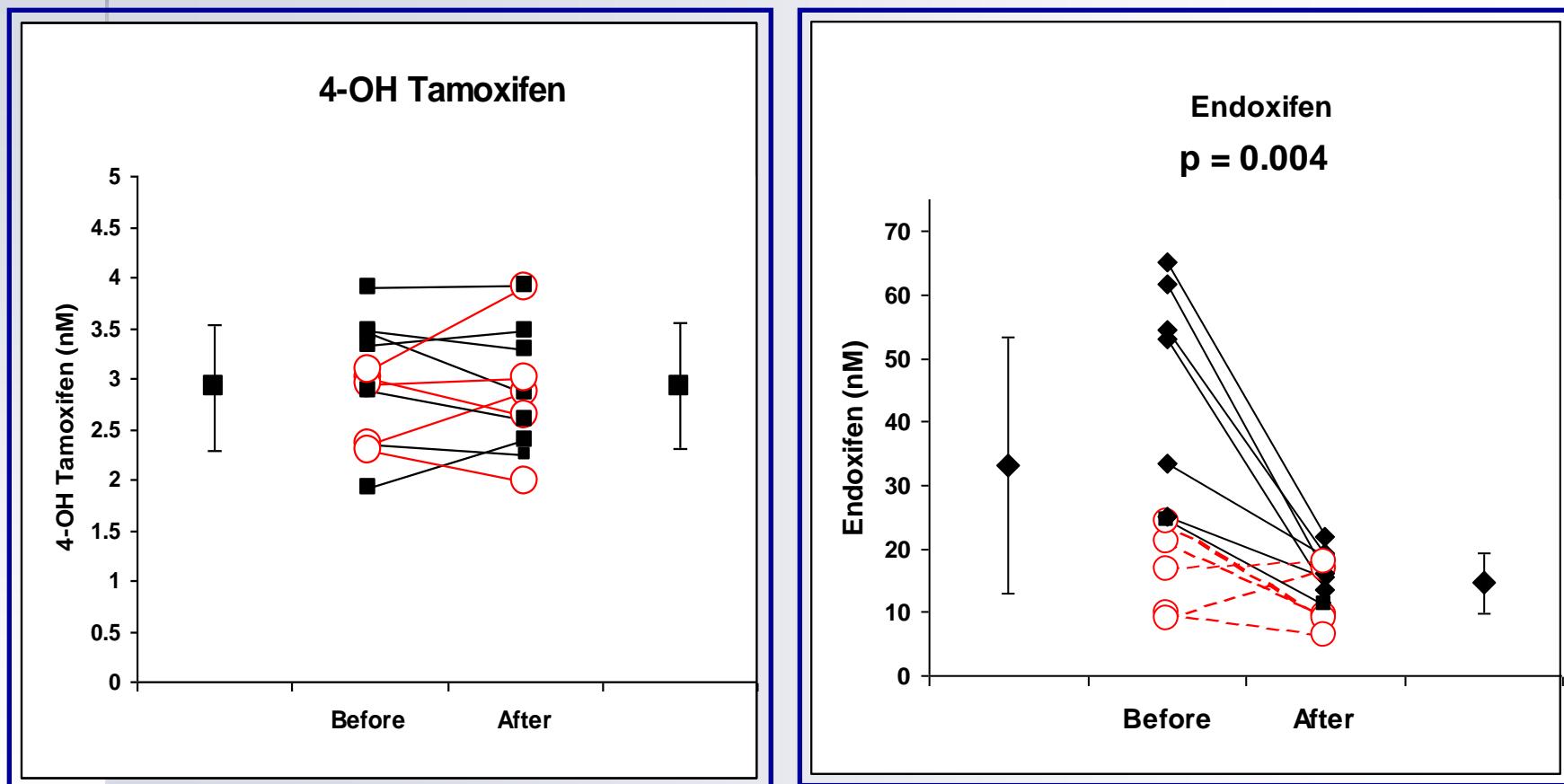
4-hydroxy-N-desmethyl
tamoxifen
(Endoxifen)

**Concentration of
endoxifen is ~
10x > 4-OH-tamoxifen**

As modified from Stearns et al.
JNCI 2003; 95:1758-1764.

Paroxetine and CYP2D6 genotype change the plasma concentrations of endoxifen

(but not of tamoxifen, N-desmethyl, or 4-hydroxy-tamoxifen)



from Stearns et al. JNCI 2003: 95:1758-1764, as communicated by D. Flockhart

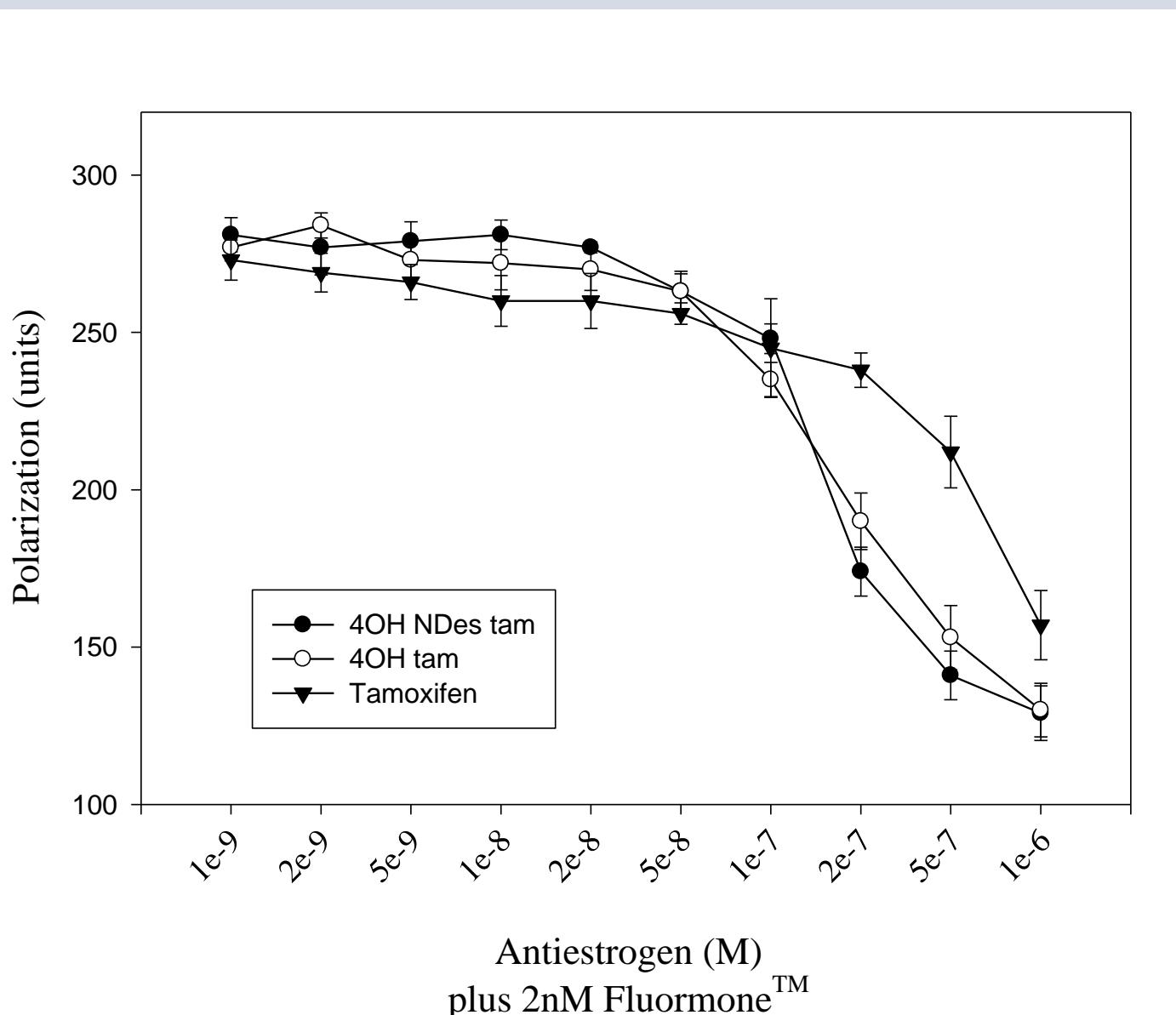
What is the relative pharmacological activity of tamoxifen and its metabolites?

- Tamoxifen and N-desmethyl-tamoxifen have similar pharmacologic activity¹
- 4-OH-tamoxifen is 30-100 times more potent as antiestrogen than tamoxifen²
- Endoxifen is equipotent to 4-OH-tamoxifen (and has 5-10x higher concentration)

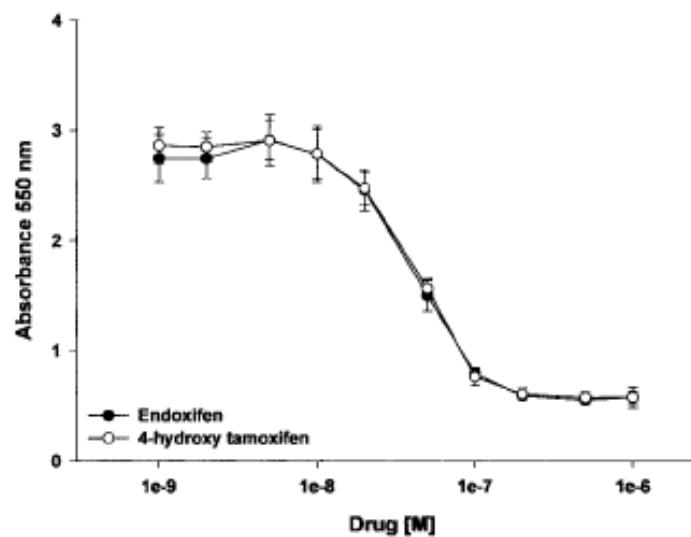
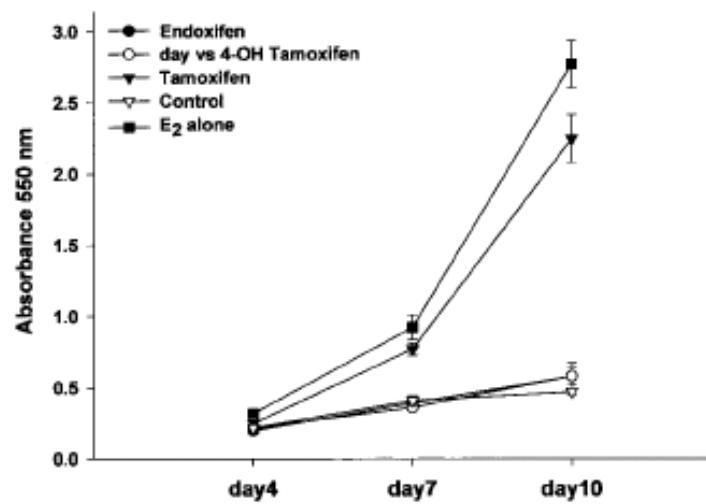
¹Nolvadex (Tamoxifen Citrate) label. 9-27-2005. Wilmington, Delaware, AstraZeneca Pharmaceuticals LP.

²Coezy E, Borgna JL, and Rochefort H. Cancer Res. 1982;4:317-23.

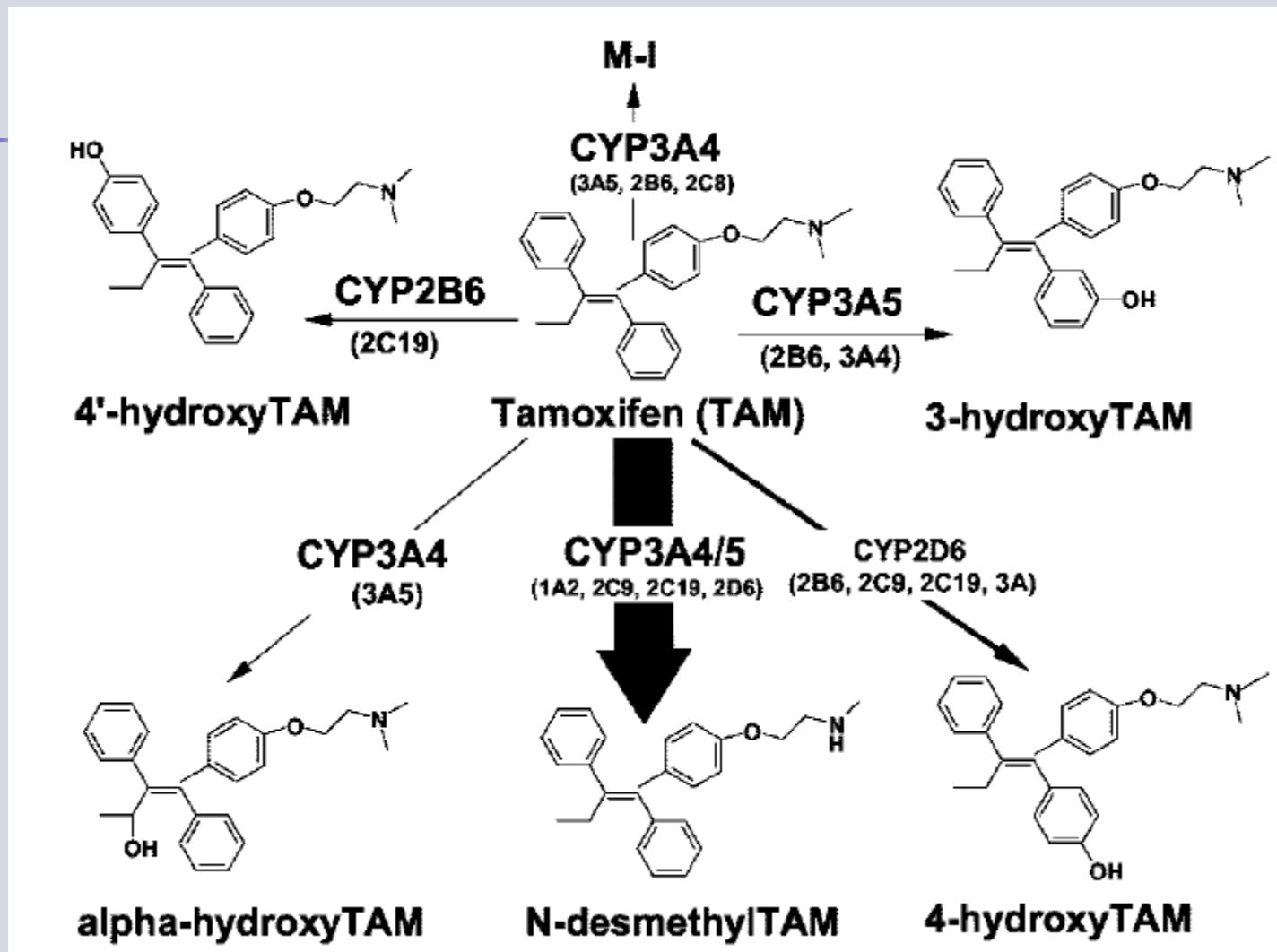
4-OH-Tamoxifen and 4-OH-N-Des-Tamoxifen have equal affinities for Estrogen Receptor α



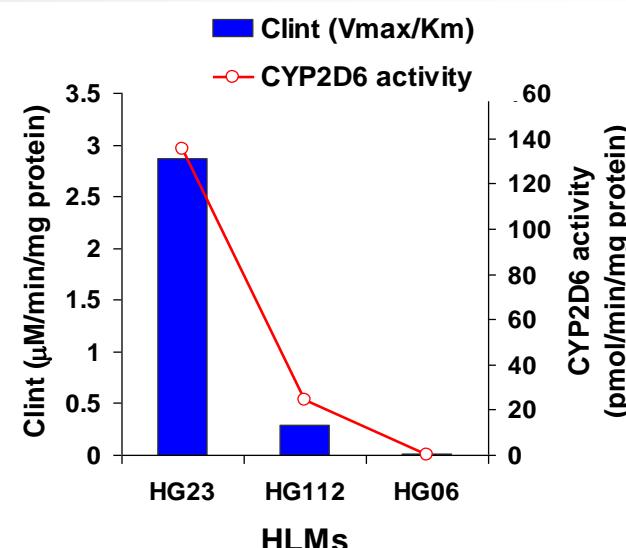
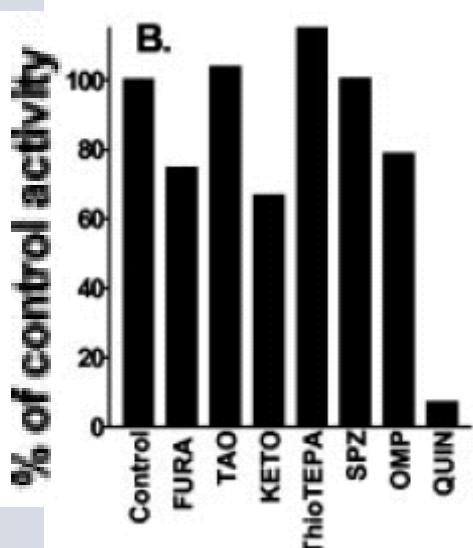
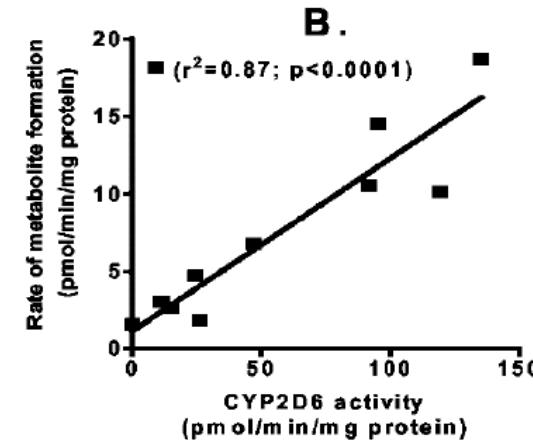
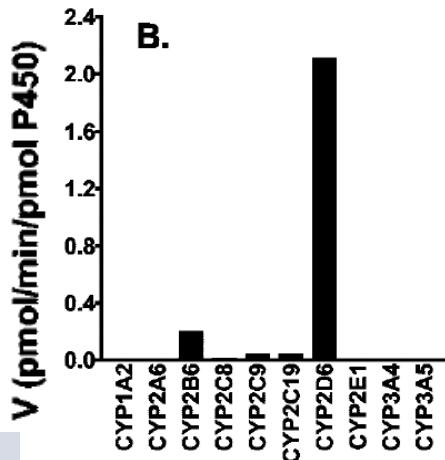
Endoxifen and 4-OH-Tamoxifen are Equipotent as Inhibitors of Estrogen Stimulated Cell Proliferation in MCF7 Cells



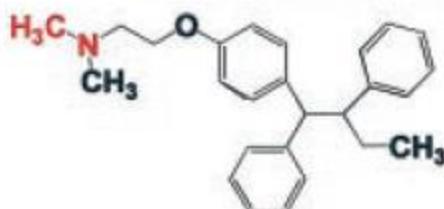
In vitro studies suggest N-desmethyl-TAM accounts for majority of primary TAM oxidation



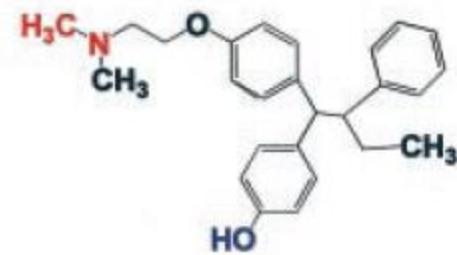
CYP2D6 is the principal route of metabolism to Endoxifen



Tamoxifen (TAM)



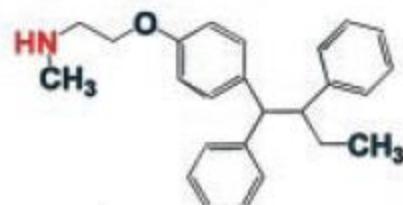
4-hydroxyTAM



CYP2C9
CYP2C19
CYP2D6
CYP3A4

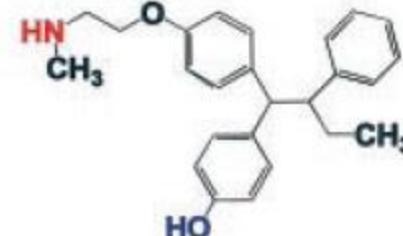
CYP3A
CYP2C9

N-desmethylTAM



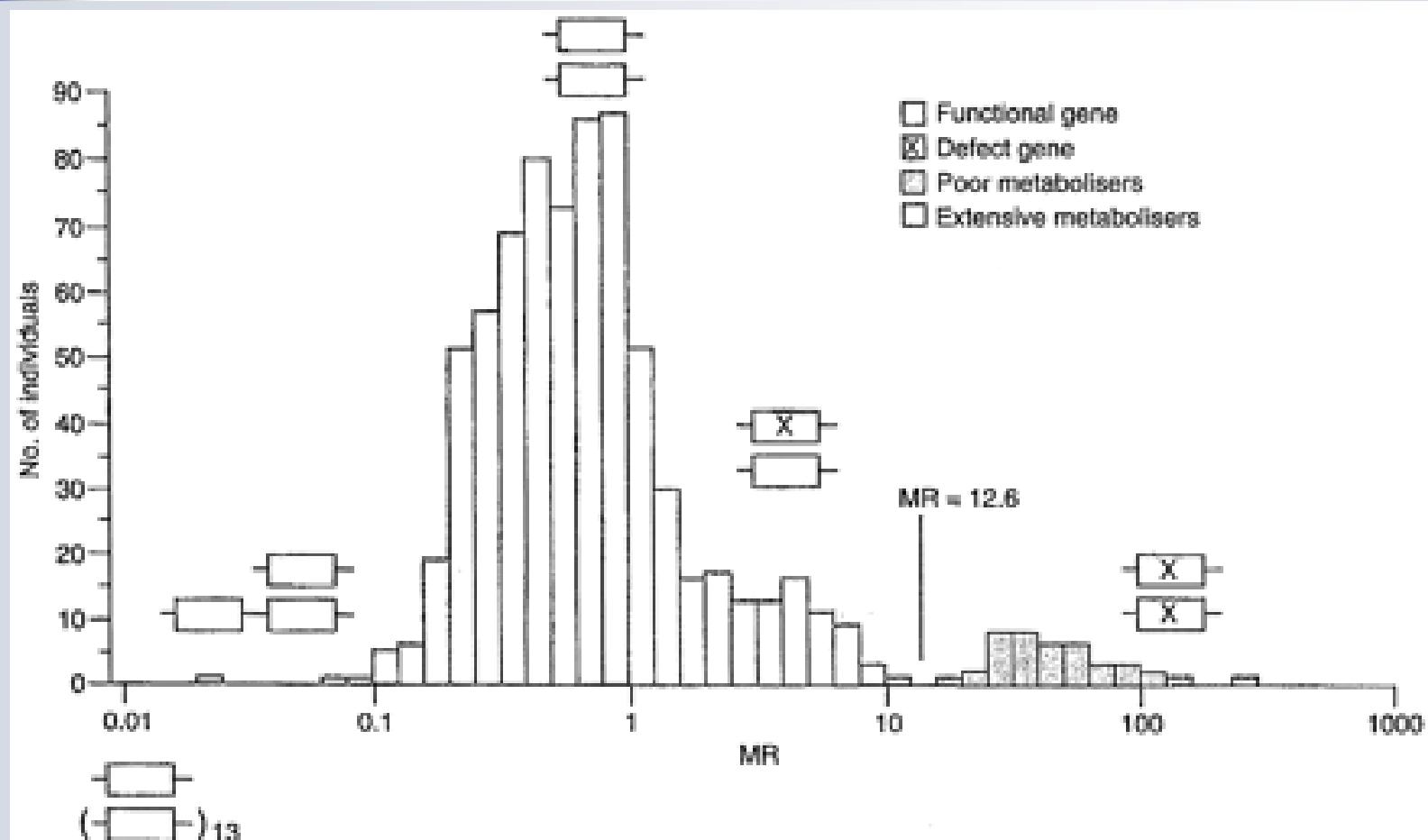
CYP2D6

Endoxifen



modified from Stearns et al. JNCI 2003: 95:1758-1764

Pharmacogenetics of CYP2D6 (debrirosquine metabolic ratio)

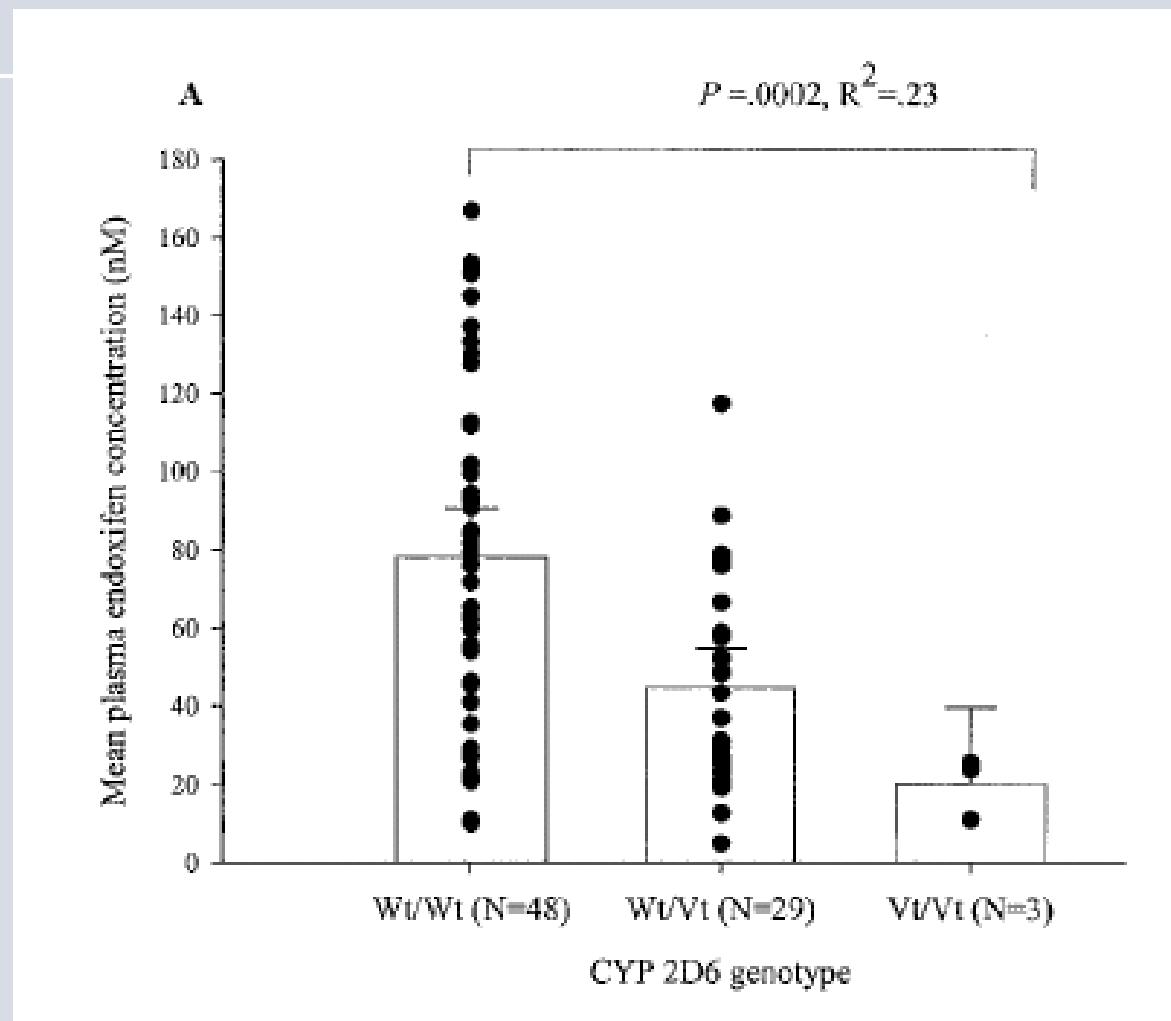


Alvan G, Bertilsson L, Dahl M.-L., Ingleman-Sundberg M, and Sjöqvist F.
Drug Metab Disp 2001; 29:580-585

CYP2D6 Genotype, CYP2D6 Inhibitors, and Tamoxifen Exposure

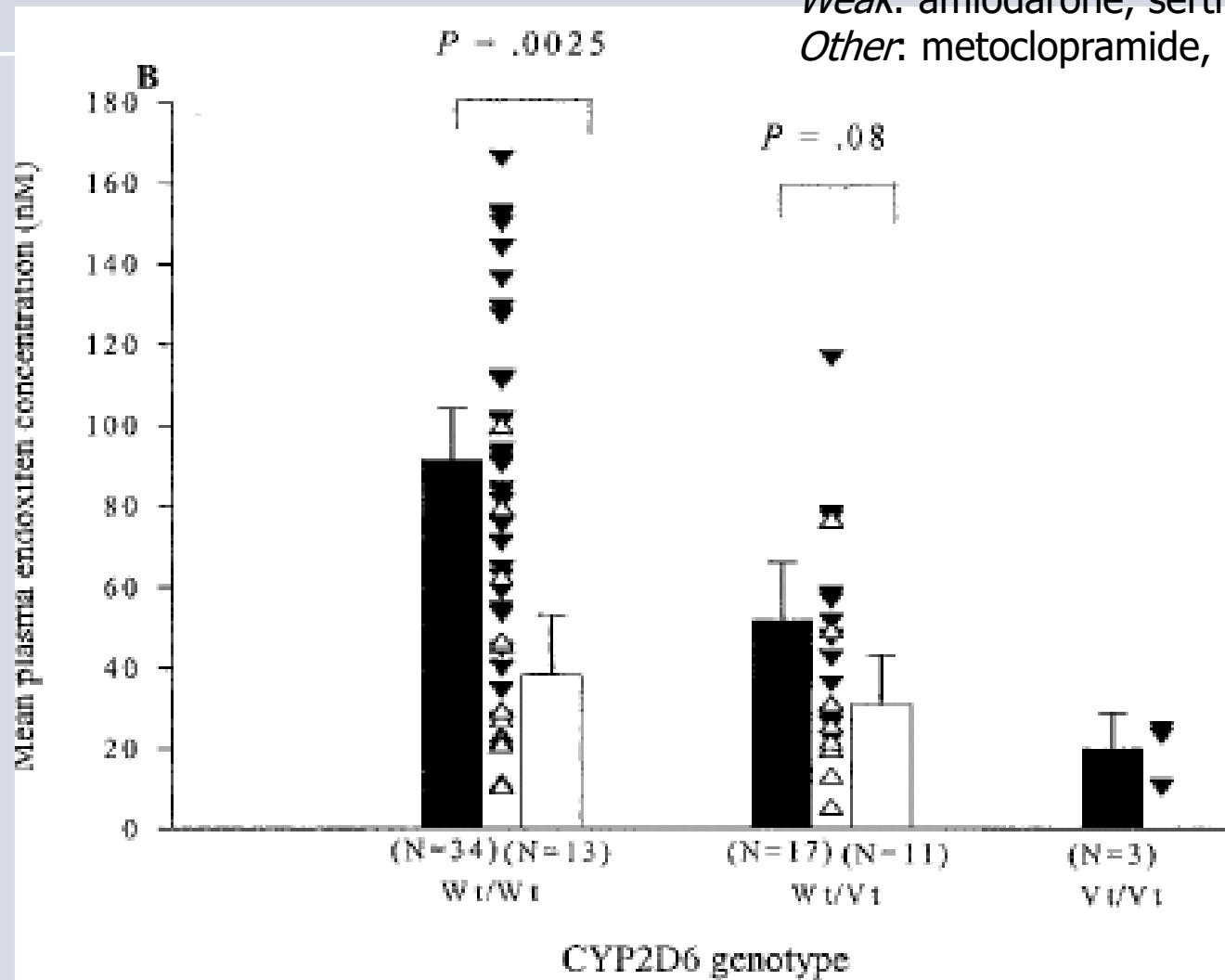
- 80 pre- and postmenopausal women with newly diagnosed breast cancer starting tamoxifen (20 mg/day) as adjuvant therapy
- Blood samples for determination of tamoxifen and metabolites in plasma
- Genotype functional and variant alleles of:
 - CYP3A5 (*1, *3)
 - CYP2D6 (*1, *3, *4, *5, *6)
 - CYP2C9 (*1, *2, *3)
 - SULT1A1 (*1,*2)
- No statistically significant associations of candidate genotypes with tamoxifen or metabolite exposure except for CYP2D6

CYP2D6 Vt/Vt genotype has decreased endoxifen exposure

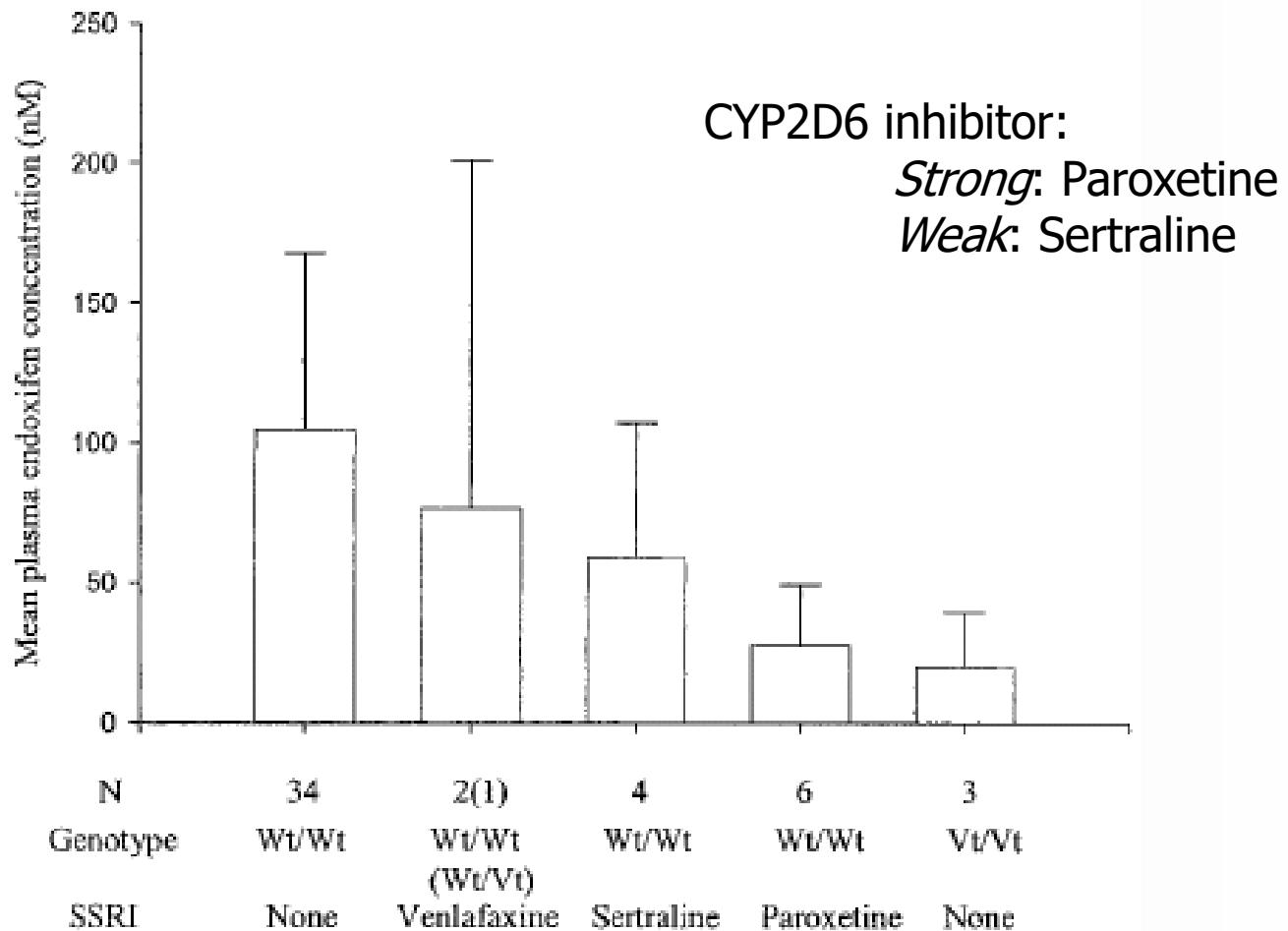


CYP2D6 inhibitors decrease endoxifen exposure

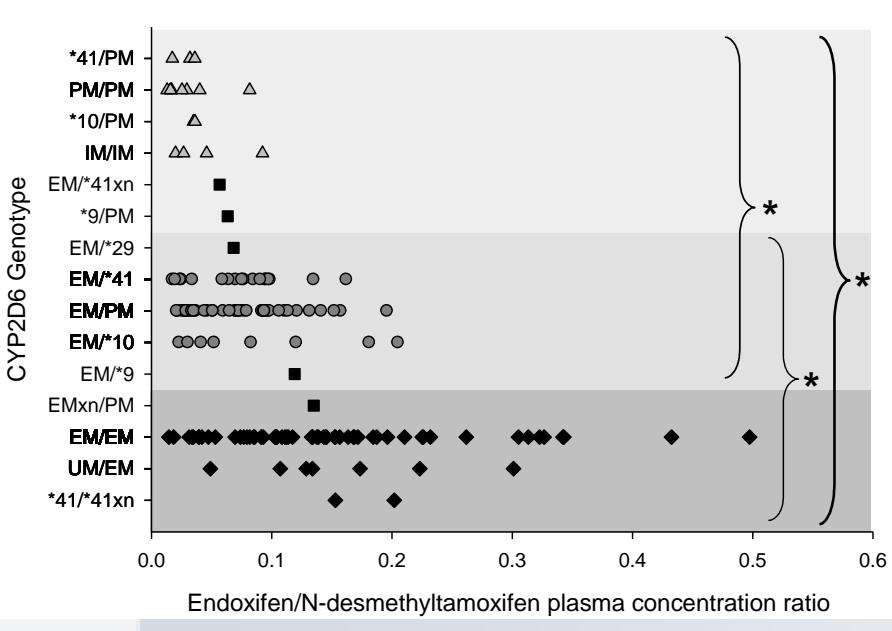
Strong: paroxetine, fluoxetine
Weak: amiodarone, sertraline
Other: metoclopramide, citalopram



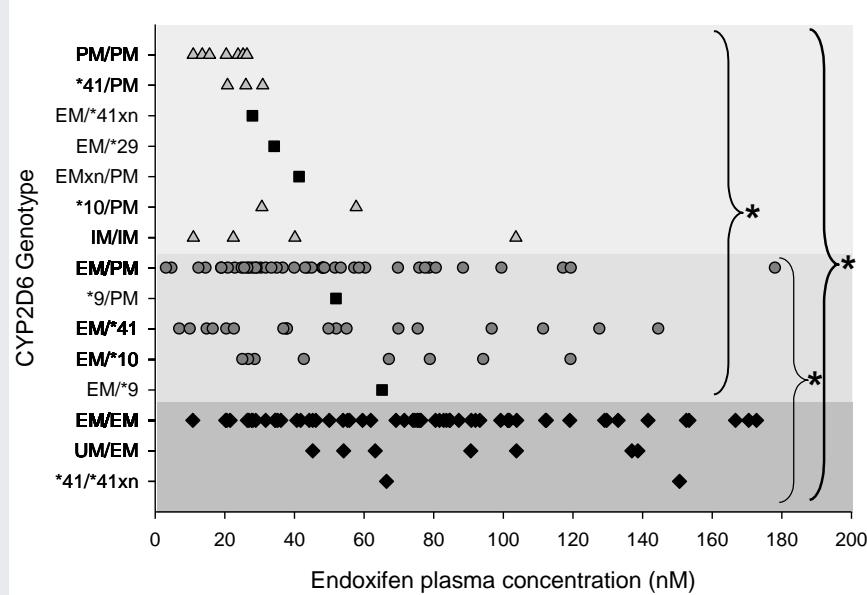
Commonly used antidepressants and endoxifen concentrations



Effect of CYP2D6 genotype on endoxifen/NDM ratio and endoxifen plasma concentration (n=158)



*, P < 0.001



*, P < 0.01

Conclusions

- Endoxifen is an active metabolite of tamoxifen, present in patients at 5-10 x greater concentration than 4-OH-tamoxifen
- *In vitro* studies demonstrate the primary role of CYP2D6 in the formation of endoxifen.
- Potent inhibitors of CYP2D6 reduce endoxifen concentrations in patients taking tamoxifen
- CYP2D6 genotype correlates with endoxifen concentrations in patients taking tamoxifen

Acknowledgements

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