Supplementary Table S1. Pharmacokinetic studies involving tamoxifen and antidepressants.

Reference	Study Design/Subjects	Methods	Antidepressant	Results (in presence of CYP2D6 inhibitor)
Desmarais et al, 2009[12]	PubMed Literature Review on clinical and nonclinical studies published prior to September 2008: included 7 clinical trials.	Search Criteria: tamoxifen and SSRIs; tamoxifen and CYP2D6 inhibitors; and antidepressant and breast cancer recurrence. A fourth search with CYP2D6 inhibition and the generic names of individual antidepressant was carried out.	Paroxetine Fluoxetine Venlafaxine	Effect on Tamoxifen's Metabolism: ▪ Fluoxetine – inconsistent evidence ▪ Paroxetine – inconsistent evidence ▪ Venlafaxine – little to no effect ▪ Desvenlafaxine – little to no effect
Hemeryck et al, 2002[13]	Literature Review of *in vitro* and *in vivo* evidence with respect to CYP-mediated drug-drug interactions with SSRIs, as well as the evidence for clinical significance of interactions.	N/A	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Effect on CYP2D6: ▪ Citalopram – little interaction potential ▪ Fluoxetine – potent inhibitory effect, inhibitory effects can persist for several weeks given long half-life and active metabolite norfluoxetine ▪ Fluvoxamine – mild to moderate inhibitory effect ▪ Paroxetine – potent inhibitory effect ▪ Sertraline – modest inhibitory effect
Skinner et al, 2003 [25]	In-vivo pharmacokinetic study of duloxetine in healthy men and women between 21-63 years old with genotype of CYP2D6 EM.	**Study 1**: Desipramine 50mg QD administered in the presence of duloxetine 60mg BID. Desipramine was used as a probe substrate because of its nearly complete dependence on CYP2D6 for metabolic elimination. **Study 2**: Steady-state pharmacokinetics of duloxetine 40mg QD were determined with and without steady-state paroxetine 20mg QD.	Duloxetine Paroxetine Sertraline	Effect on CYP2D6: ▪ Duloxetine (60mg BID): moderately potent inhibitor (intermediate between paroxetine and sertraline). Conclusion on utilization: ▪ Caution should be used when CYP2D6 inhibitors or substrates are coadministered with duloxetine.
Jin et al, 2005 [14]	Prospective trial	Plasma levels of tamoxifen and	Paroxetine Sertraline	Effect on Endoxifen's Mean Plasma Concentration:

	N=78 with breast cancer on tamoxifen	metabolites measured at baseline and at 4 months	Venlafaxine	▪ Paroxetine – significant reduction vs. patients who were not taking concomitant inhibitor. ▪ Sertraline – intermediate reduction between paroxetine and venlafaxine's effect. ▪ Venlafaxine – minimal effect
Dean L, 2012 [26]	Review article on amitriptyline therapy.	N/A	Amitriptyline	▪ Amitriptyline – metabolized mainly via CYP2C19 and CYP2D6 pathways.
Szewczuk-Boguslawska et al, 2004 [27]	In-vivo pharmacokinetic study of doxepin. N=11	Patient's sparteine metabolic ratio (MR1) was assessed before and 2 weeks of doxepin treatment (MR2 estimated).	Doxepin	▪ Doxepin – statistically significant increase in sparteine metabolic ratio (MR) after doxepin treatment compared to before doxepin treatment.
English et al, 2012 [15]	Review article on clinically significant psychotropic drug interactions.	N/A	Fluoxetine Paroxetine Sertraline Duloxetine Citalopram Escitalopram	<u>Level of CYP2D6 Inhibition</u>: ▪ Fluoxetine - high ▪ Paroxetine – high ▪ Sertraline – negligible-low ▪ Duloxetine – moderate ▪ Citalopram – negligible-low ▪ Escitalopram – negligible-low
Jornil et al, 2010 [28]	In-vitro pharmacokinetic study of toremifene.	IC_{50} determinations for human liver CYP450 for toremifene.	Toremifene	<u>Metabolic Pathways</u>: ▪ Toremifene did not significantly inhibit CYP1A2 or CYP2D6. ▪ Toremifene is a competitive inhibitor of CYP3A4, noncompetitive inhibitor of CYP2A6, 2C8, 2C9, 2C19, and 2E1. ▪ Toremifene is unlikely to play a critical role in drug-drug interactions with substrate drugs of CYP1A2 and CYP2D6.
Sun et al, 2013 [29]	In vitro characterization of raloxifene metabolism.	N/A	Raloxifene	Raloxifene is extensively metabolized by glucuronidation to form raloxifene-6-glucuronide and raloxifene-4''-glucuronide.
Sideras et al, 2010 [30]	Review article on coprescription of tamoxifen and CYP2D6 inhibitors.	N/A	Paroxetine Fluoxetine Bupropion Duloxetine Sertraline Citalopram Fluvoxamine Venlafaxine Desvenlafaxine Escitalopram Mirtazapine Clomipramine Doxepin Desipramine Imipramine Amitriptyline Nortriptyline	Major drug classes divided by known CYP2D6 inhibitory activity. ▪ Moderate-to-Potent: Paroxetine, Fluoxetine, Bupropion, Duloxetine ▪ Weak-to-Moderate: Sertraline, Citalopram, Fluvoxamine, Clomipramine, Doxepin, Desipramine, Imipramine, Amitriptyline, Nortriptyline Little In Vivo Inhibition: Venlafaxine, Desvenlafaxine, Escitalopram, Mirtazapine

Goetz et al, 2008 [31]	Retrospective analysis of prospective adjuvant tamoxifen trial.			
Donneyong et al, 2016 [16]	Population-based cohort study: Cohort 1: n=6067 Cohort 2: n=8465	Reviewed 5 US databases covering individuals enrolled in private and public health insurance programs from 1995-2013. Cohort 1 consisted of women who started taking SSRI during tamoxifen treatment and Cohort 2 consisted of women already taking SSRI when they started tamoxifen treatment. Outcomes include all cause mortality in each cohort.	Paroxetine Fluoxetine Citalopram Escitalopram Fluvoxamine Sertraline	<u>All-cause Mortality</u>: ▪ Cohort 1: 991/6067 deaths ▪ Cohort 2: 1014/8465 deaths <u>Conclusion</u>: ▪ Concomitant use of tamoxifen and potent CYP2D6 inhibiting SSRIs vs other SSRIs was not associated with increased risk of death.
Haque et al, 2016 [32]	Retrospective cohort study: N=16887 breast cancer survivor diagnosed between 1996-2007 and treated with tamoxifen in 2 California health plans.	Reviewed comprehensive health records of insured patients. Outcomes include subsequent breast cancer during follow-up through 2009.	Paroxetine Fluoxetine Tricyclics Other SSRIs	<u>Incidence of subsequent breast cancer</u>: ▪ Absolute subsequent breast cancer rates were similar in women who used paroxetine concomitantly with tamoxifen vs tamoxifen-only users. ▪ For other antidepressants looked at, no association found as well. ▪ This study could not evaluate venlafaxine due to the small number of patients taking venlafaxine.
Kelly et al, 2010 [33]	Population-based retrospective cohort study of women living in Ontario aged 66 years or older treated with tamoxifen for breast cancer between 1993-2005 who had overlapping treatment with a single SSRI.	Analyzed prescription records of the Ontario Public Drug Benefit Program and identify women with breast cancer through the Ontario Cancer Registry.	Paroxetine	<u>Breast Cancer-related Mortality</u>: ▪ N=2430 ▪ Deaths: 374 (15.4%) ▪ Absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with paroxetine were associated with 24%, 54%, and 91% increases in risk of death from breast cancer, respectively.
Lash et al, 2010 [17]	Case-control study of breast cancer recurrence nested in the population of female residents of Denmark who were diagnosed with non-metastatic estrogen-	Ascertained complete prescription histories by linking civil registration numbers of cases and controls to Danish national prescription registry.	Citalopram	<u>Incidence of recurrence of breast cancer</u>: ▪ N=366 ▪ Recurrence: 37/366 ▪ Matched controls: 35/366 ▪ Same proportion of recurrent cases in recurrent group and matched control group with both groups receiving at least one prescription of

	receptor positive breast cancers between 1994-2001 and who took tamoxifen for at least one year.			citalopram or escitalopram while taking tamoxifen (Adjusted Odds Ration = 1.1). Conclusion: ▪ Citalopram and possibly other SSRI do not adversely affect the outcome of adjuvant therapy with tamoxifen.
Dezentie et al, 2010 [34]	Observational study: N=1962 breast cancer patients treated with adjuvant tamoxifen between 1994-2006 according to data from PHARMO, PALGA and Dutch Medical Register in the Netherlands were included.	Cox proportional hazards model with time-dependent definition for concomitant CYP2D6 inhibitor exposure was used. Adherence calculated over the first year after tamoxifen initiation.	Bupropion Paroxetine Fluoxetine	Conclusion: ▪ No detected effect of concomitant CYP2D6 inhibitor use on tamoxifen response in the largest patient population thus far.

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