POPULAR ANTIDEPRESSANT BLOCKS THE LIFE-SAVING BENEFITS OF TAMOXIFEN IN BREAST CANCER PATIENTS

TORONTO, February 8, 2010 – In women with breast cancer, tamoxifen significantly reduces the likelihood of recurrence and death due to breast cancer. But a study performed at the **Institute for Clinical Evaluative Sciences (ICES)** has found using a popular antidepressant at the same time can stop the benefits of tamoxifen, leaving women at increased risk of death.

"Clinicians have suspected for years that some antidepressants, particularly paroxetine (Paxil and generics), might interfere with the beneficial effects of tamoxifen. But until now we've had no confirmation of the relevance of this drug interaction, and no sense of the risk it presents for patients", says the study's lead author and Breast Medical Oncologist, Dr. Catherine Kelly, who carried out this work while in the Breast Cancer Research Fellowship Program at Sunnybrook Odette Cancer Centre.

Tamoxifen is a 'prodrug', meaning it must be converted into an active metabolite (endoxifen) by the liver in order to work. However, some drugs can interfere with this process. Antidepressants are of particular importance because they are commonly used by women with breast cancer, often for long periods of time. Although many antidepressants have little or no impact on tamoxifen's metabolism, paroxetine, a member of the so-called SSRI class, is a potent inhibitor of the metabolic step that converts tamoxifen to endoxifen.

The study examined 2,430 women aged 66 years or older with breast cancer living in Ontario who were treated with tamoxifen between 1993 and 2005. These women also received a SSRI anti-depressant medication while taking tamoxifen. Among the study's findings were:

- Use of an antidepressant with tamoxifen was common about 30 per cent of women were prescribed an antidepressant during tamoxifen therapy, and paroxetine was the most commonly used SSRI in the study.

- Use of paroxetine, but NOT other SSRIs, in combination with tamoxifen, was associated with an increased long-term risk of breast cancer death, in a fashion that correlated with the extent of drug overlap.

- Treatment with paroxetine for 41 per cent of the total time on tamoxifen (the median in this study) will result in one additional breast cancer death

at 5 years for every 20 women so treated. The risk with more extensive overlap is greater.

"Our findings indicate that the choice of antidepressant can significantly influence survival in women receiving tamoxifen for breast cancer. This observation is consistent with what we know about tamoxifen's metabolism. These results highlight a drug interaction that is extremely common, widely underappreciated and potentially life-threatening, yet uniformly avoidable," says one of the study's authors and **ICES** Scientist Dr. David Juurlink.

The authors indicated that various treatment options exist for women receiving tamoxifen who require an antidepressant. However, they stressed the importance of not suddenly stopping paroxetine based upon these findings. "For women taking these two drugs together, I think there are better options for the treatment of depression. But it's important to realize that this is a marathon, not a sprint, and stopping paroxetine suddenly can cause its own set of problems." Juurlink suggests if treatment changes are made, they should be done gradually and only after consultation with a physician.

Juurlink also cautioned against potential misinterpretation of the findings. Specifically, the results should not lead patients to stop taking tamoxifen, and do not imply that paroxetine itself causes or influences the course of breast cancer. "This is simply a situation in which paroxetine impairs the effectiveness of tamoxifen" he said, adding "There is an important silver lining to this story. This research gives breast cancer patients and their doctors fresh new insights into how we can optimize the benefits of tamoxifen - an inexpensive but tremendously important medication - simply by avoiding the use of other drugs that can interfere with it.

The study "Selective Serotonin Reuptake Inhibitors and Breast Cancer Mortality in Women Receiving Tamoxifen: A Population-Based Cohort Study" by Kelly et al. is in the February 8, 2010 of the British Medical Journal (BMJ).

More detailed study findings on the ICES website: www.ices.on.ca

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FOR FURTHER INFORMATION PLEASE CONTACT:

Deborah Creatura

Acting Media Advisor, ICES
deborah.creatura@ices.on.ca
416-480-4780 or cell 647-406-5996

Selective Serotonin Reuptake Inhibitors and

Breast Cancer Mortality in Women Receiving Tamoxifen:

A Population-Based Retrospective Cohort Study

Catherine M. Kelly, *Medical Oncology Fellow* , David N. Juurlink, *Division Head, Clinical Pharmacology*, Tara Gomes, *Epidemiologist*, Minh Duong-Hua, *Analyst*, Kathleen I. Pritchard, *Professor*, Peter C. Austin, *Senior Statistician*, Lawrence F. Paszat, S*enior Scientist*

Affiliations: Department of Medicine, Sunnybrook Health Sciences Centre (CMK, DNJ, KIP, LFP); Departments of Medicine (DNJ, KIP, LFP), Pediatrics (DNJ), Health Policy, Management, and Evaluation (CMK, DNJ, KIP, PCA, LFP) at the University of Toronto; the Canadian Institute for Health Information (MD-H); The Institute for Clinical Evaluative Sciences (DNJ, TG, PCA, LFP)

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Correspondence   David Juurlink, MD, PhD
Sunnybrook Health Sciences Centre G-106
2075 Bayview Avenue, Toronto, Ontario
Canada M4N 3M5
dnj@ices.on.ca

What this paper adds

What is already known on this subject:

- Tamoxifen is globally the most important drug used for the endocrine treatment of breast cancer.
- Tamoxifen is a prodrug converted by cytochrome P450 2D6 (CYP2D6) to its active metabolite endoxifen.
- Selective serotonin inhibitor (SSRI) antidepressants are widely prescribed to women with breast cancer taking tamoxifen, but inhibit CYP2D6 to varying degrees and may influence tamoxifen's effectiveness.

What this study adds:

- Use of paroxetine (a potent, irreversible CYP2D6 inhibitor) during tamoxifen therapy increases the subsequent risk of death due to breast cancer, in a fashion that correlates with the duration of combined use.
- We estimate that treatment with paroxetine for 41% of tamoxifen therapy (the median in our study) will result in one additional breast cancer death at 5 years for every 20 women so treated.

This week in BMJ (123 words)

Tamoxifen significantly improves survival in patients with breast cancer. To be effective, however, it must first be metabolized in the liver by cytochrome P450 enzyme 2D6, a process that can be inhibited by other drugs. Kelly et al. examined the healthcare records of 2430 older women with breast cancer who received tamoxifen in combination with a selective serotonin reuptake inhibitor (SSRI) antidepressant. They found that use of paroxetine, but not other SSRIs, in combination with tamoxifen was associated with an increased risk of death breast cancer, in a fashion that correlated with the extent of drug overlap. These results are predicted by basic pharmacologic principles and suggest that paroxetine can reduce or abolish the beneficial effect of tamoxifen in women with breast cancer.

ABSTRACT

Objective: To characterize whether some selective serotonin reuptake inhibitor (SSRI) antidepressants reduce tamoxifen's effectiveness by inhibiting its bioactivation by cytochrome P450 2D6 (CYP2D6).

Design: Population-based cohort study

Participants: Women living in Ontario aged 66 years or older treated with tamoxifen for breast cancer between 1993 and 2005 and who had overlapping therapy with a single SSRI.

Main outcome measures: Risk of death from breast cancer after completion of tamoxifen therapy, as a function of the proportion of time on tamoxifen during which each SSRI had been co-prescribed.

Results: Among 2430 women treated with tamoxifen and a single SSRI, 374 (15.4%) died of breast cancer during follow-up After adjustment for age, duration of tamoxifen therapy and other potential confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine (an irreversible inhibitor of CYP2D6) were associated with 24%, 54% and 91% increases in the risk of death from breast cancer, respectively ($p < 0.05$ for each comparison). In contrast, no such risk was seen with other antidepressants. We estimate that use of paroxetine for 41% of tamoxifen

therapy (the median in our sample) would result in 1 additional breast cancer death within 5 years after cessation of tamoxifen for every 20 women so treated.

Conclusion

Paroxetine use during tamoxifen therapy is associated with an increased risk of death from breast cancer. This supports the hypothesis that paroxetine-mediated CYP2D6 inhibition can reduce or abolish the survival benefit of tamoxifen in women with breast cancer.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women worldwide, and it is estimated that 1.5 million new cases will be diagnosed in 2010.[1] Tamoxifen is a selective estrogen receptor modulator that has been used for the treatment of breast cancer for over three decades.[2] In women with early stage estrogen receptor (ER)-positive breast cancer, tamoxifen reduces the risk of recurrence by about half and the risk of breast cancer death by about one third. These benefits are largely independent of chemotherapy, age, progesterone receptor status or other tumor characteristics.[3]

Tamoxifen is a prodrug that is metabolized by the hepatic cytochrome P450 enzyme system to the active metabolites 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen).[4 5] Both metabolites have an affinity for the estrogen receptor 100-fold higher than the parent compound; however, endoxifen is considered the most important metabolite because its plasma concentrations are several-fold higher than those of 4-hydroxytamoxifen.[6 7] Conversion of tamoxifen to endoxifen is catalyzed predominantly by cytochrome P450 isoenzyme 2D6 (CYP2D6).[4 7] This enzyme is highly polymorphic,[8] and in some studies loss-of-function variants are associated with lower endoxifen concentrations,[5] an increased risk of breast cancer relapse and a shorter time to recurrence during tamoxifen therapy.[9-14] Consequently, therapy with drugs that inhibit CYP2D6 may reduce the clinical benefit of tamoxifen by interfering with its bioactivation, particularly when these drugs are used for an extended period.

Indeed, patients who receive tamoxifen in combination with a CYP2D6 inhibitor display endoxifen concentrations that vary inversely with the degree of CYP2D6 inhibition.[5 15 16]

Up to 25% of breast cancer patients experience a depressive disorder.[17] Newer antidepressants are widely used in women with breast cancer for treatment of depression, and are prescribed for tamoxifen-related hot flashes and various other indications.[18-21] This is particularly relevant in the context of tamoxifen therapy because selective serotonin reuptake inhibitor (SSRI) antidepressants inhibit CYP2D6 to varying degrees. For example, paroxetine is an exceptionally potent CYP2D6 inhibitor, and is the only SSRI that exhibits mechanism-based ("suicide") inhibition, resulting in irreversible loss of enzyme function until new CYP2D6 is synthesized.[22-24]

Whether antidepressant-related CYP2D6 inhibition is associated with adverse outcomes in patients receiving tamoxifen is unknown. To explore this possibility, we linked prescribing records with detailed clinical data from a large population-based cancer registry and other population-based healthcare datasets to explore the clinical consequences of the potential drug interaction between SSRI and tamoxifen.

METHODS

Setting and Design

We conducted a population-based retrospective cohort study among female residents of Ontario, Canada, who were 66 years of age or older and who commenced tamoxifen therapy between January 1, 1993 and December 31, 2005. These individuals have universal access to health care, including hospital care, physicians' services and prescription drug coverage. The study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Canada.

Data sources

We analyzed the computerized prescription records of the Ontario Public Drug Benefit Program, which contains comprehensive records of prescription medications dispensed to all Ontario residents 65 years of age or older. We identified women with breast cancer using the Ontario Cancer Registry, a population-based tumor registry that contains pathology reports, hospital discharge abstracts, and death certificates of patients with a diagnosis of cancer. Hospital admissions were identified using the Canadian Institute for Health Information Discharge Abstract Database, which contains information on hospital visits, including detailed clinical and demographic information on all hospitalizations. Physicians' services were identified using the Ontario Health Insurance Plan database, and we obtained basic demographic information, including date of death, from the Registered Persons Database. Finally, we

estimated socioeconomic status by linking residential postal codes with Statistics Canada population census data. These datasets were linked using an encrypted version of each patient's 10-digit health card number to ensure anonymity, and are regularly used to study drug safety, including the clinical consequences of drug interactions.[25-31]

Design and analysis

We identified a cohort of women initiating tamoxifen therapy, beginning with the first tamoxifen prescription following each patient's 66th birthday. All patients were newly treated with tamoxifen (defined as no tamoxifen prescription in the preceding year), and had a diagnosis of breast cancer in the Ontario Cancer Registry (International Classification of Disease version 9 (ICD-9) codes 174.0-174.9). We did not include patients during their first year of eligibility for prescription drug coverage (age 65) to avoid incomplete medication records.

For each patient, we determined the total duration of tamoxifen therapy by aggregating the total days supplied for all tamoxifen prescriptions. We restricted our analysis to women whose tamoxifen use encompassed at least 80% of the total number of days between the first and last tamoxifen prescriptions. In addition, we restricted our analysis to women co-prescribed a single SSRI antidepressant (paroxetine, fluoxetine, sertraline, citalopram, or fluvoxamine) during tamoxifen therapy. We also included venlafaxine, which inhibits serotonin reuptake as well as norepinephrine reuptake at higher doses.[32] We did not study

duloxetine or escitalopram because they were not insured benefits of the provincial formulary during the study period.

For analytical purposes, we defined the index date as the date on which tamoxifen was last dispensed, plus an additional 60 days. This allowed us to completely ascertain the total duration of tamoxifen therapy and the extent to which co-prescription of interacting medications occurred during the course of treatment. Moreover, it allowed us to adequately characterize the mortality consequences of the drug interaction between SSRIs and tamoxifen, which are delayed and largely anticipated after tamoxifen therapy has ceased. This differs from the vast majority of clinically important drug interactions, which typically have immediate clinical consequences.[29][31][33]

In the primary analysis, patients were followed from the index date until death from breast cancer or the end of the study period (December 31, 2007), whichever occurred first. A secondary analysis considered death from any cause, including breast cancer. For each patient, we quantified the duration of tamoxifen therapy and the proportion of this time that was characterized by concomitant SSRI therapy. Because we anticipated that the consequences of CYP2D6 inhibition during tamoxifen therapy would be delayed, we excluded women who switched from one SSRI to another while taking tamoxifen. Consequently, all women in our analysis were 66 years or older, newly treated with tamoxifen for

breast cancer, and treated with a single SSRI antidepressant during tamoxifen therapy.

The primary outcome was death from breast cancer (ICD9 codes 174.0 to 174.9 and ICD10 codes C50.0 to 50.9). We used Cox proportional hazards regression to examine the effect of SSRI co-prescribing on survival following cessation of tamoxifen. In each analysis, we expressed exposure as the proportion of time on tamoxifen that was characterized by overlapping SSRI therapy.

For each SSRI, we estimated hazard ratios and 95% confidence intervals associated with increasing proportions of co-prescribing of that same drug with tamoxifen, thereby restricting our analyses to within-drug comparisons. Consequently, the analysis explored the relationship between a continuous measure (proportion of overlap between each SSRI and tamoxifen) and breast cancer mortality, without need for a reference group. The regression model was adjusted for age, year of tamoxifen initiation, duration of tamoxifen therapy, timing of tamoxifen in relation to the date of breast cancer diagnosis (within one year of diagnosis or thereafter), socioeconomic status, co-morbidity in the year prior to tamoxifen completion,[34] and co-prescription of other CYP2D6 inhibitors (bupropion, quinidine, thioridazine, amiodarone, cimetidine, and chloroquine) during tamoxifen therapy. The proportional hazards assumption was verified using Schoenfeld residuals.[35] All analyses were performed using SAS version 9.1

(SAS Institute, Cary N.C.) and used a two-tailed Type I error rate of 0.05 as the threshold for statistical significance.

RESULTS

We identified 24,430 women aged 66 years and older who started tamoxifen therapy during the 13 year study period (Appendix 1). Of these, 7489 (30.6%) received at least one antidepressant during tamoxifen therapy. After excluding those treated with no SSRI or with multiple SSRIs, those with poor adherence to tamoxifen therapy, and those with unknown cause of death, the primary analysis included 2430 women (Table 1). The median age in the year prior to tamoxifen initiation was 74 years (interquartile range 70 to 79 years).

Most patients (n=2025, 83.3%) initiated tamoxifen therapy within one year of breast cancer diagnosis. The median duration of tamoxifen therapy was 4.0 years (interquartile range 2.2 to 5.0 years), ranging from 3.2 years (interquartile range; 1.4 to 4.8 years) in women who also received fluoxetine to 4.2 years (interquartile range 2.5 to 5.1) among women who also received citalopram (Appendix 2). Paroxetine was the most commonly prescribed SSRI (n=630; 25.9%) followed by sertraline (n=541; 22.3%), citalopram (n=467; 19.2%), venlafaxine (n=365; 15.0%) fluoxetine (n=253; 10.4%) and fluvoxamine (n=174; 7.2%).   Overall, 735 patients (30.2%) received at least one other non-SSRI antidepressant, including 445 (18.3%) who received a cyclic antidepressant, 209

(8.6%) who received other antidepressants, and 81 (3.3%) who received both. The distribution of these patients was relatively comparable across the various SSRI groups (Appendix 3).

Main analyses

In total, 1074 women (44.2%) died by the end of follow-up, including 374 women (15.4%) in whom breast cancer was recorded as the cause of death. In the primary analysis, we found an increased risk of death from breast cancer among women who received paroxetine, an irreversible CYP2D6 inhibitor, in combination with tamoxifen. After adjusting for potential confounders, absolute increases of 25%, 50% and 75% in the proportion of time on tamoxifen that was characterized by overlapping use of paroxetine were associated with relative increases of 24%, 54% and 91% in the risk of death from breast cancer, respectively (Table 2 and Figure 1). In contrast, we found no increased risk of breast cancer mortality associated with exposure to the other SSRIs during tamoxifen therapy. Interestingly, we observed a nonsignificant trend toward reduced breast cancer mortality among venlafaxine users (table 2), which may reflect the common practice of using venlafaxine for tamoxifen-related hot flashes,[36] a potential predictor of better outcomes in women receiving tamoxifen.[37]

To test the robustness of our conclusions, we replicated our analyses using death from any cause (including breast cancer) as the outcome of interest

(n=1074). After adjusting for potential confounders, we found that absolute

increases of 25%, 50% and 75% in paroxetine exposure during tamoxifen

therapy were associated with relative increases of 13%, 28% and 46%,

respectively, in the risk of death from any cause (table 3 and fig 2). In contrast,

we found no such increased risk in all-cause mortality associated with exposure

to the other SSRIs in women receiving tamoxifen for breast cancer. Finally, we

conducted an additional analysis including 226 women whose cause of death

was unknown (total n=1300). This analysis again yielded consistent results,

showing an increased risk of death only with paroxetine.

Estimate of Absolute Risks

To better characterize the absolute risks imparted by use of paroxetine with

tamoxifen, we generated absolute risk estimates from our primary analysis using

methods described elsewhere[38] and applied previously.[39] These estimates were

obtained using a 5-year time horizon from the end of tamoxifen therapy, and their

reciprocal is the number needed to treat to harm (NNTh).

As compared to patients with minimal (1%) overlap of paroxetine with tamoxifen,

use of paroxetine for 41% of tamoxifen therapy (the median duration of overlap in

our sample) would result in one additional breast cancer death at 5 years for

every 19.8 treated patients. Similarly, relative to patients a 1% overlap, use of

paroxetine for the entire duration of tamoxifen (100% overlap) would result in an additional death for every 6.9 patients treated.

DISCUSSION

Using population-based healthcare data, we found that women with breast cancer who received paroxetine in combination with tamoxifen were at increased risk for death due to breast cancer and death from any cause. The increased risk was directly related to the extent of co-prescribing, consistent with the hypothesis that irreversible CYP2D6 inhibition by paroxetine can reduce or abolish the considerable survival advantage conferred by long-term tamoxifen therapy in patients with breast cancer. We found no such risk with other antidepressants. Our findings are consistent with an emerging body of literature indicating the critical role of CYP2D6 in the metabolic activation [4 5 15] and clinical effectiveness of tamoxifen.[9-14]

Our findings have major implications for clinical practice, particularly in light of the frequency of combination therapy. The prevalence of depression among women with early breast cancer is roughly twice that of the general female population and is particularly high around the time of diagnosis.[40] In our study, 30% of women who initiated tamoxifen therapy also received antidepressant therapy, and paroxetine was the most commonly used agent. Patients may also take SSRIs for other indications. Up to 80% of women treated with tamoxifen

experience hot flashes,[41] and clinical trials have demonstrated the efficacy of SSRIs for their treatment.[20]

Our findings differ from previous research reporting no significant association between SSRI treatment and adverse outcome in women receiving tamoxifen. Insufficient statistical power, utilization of a case-control design, and assessment of a single SSRI with weak CYP2D6-inhibiting activity[18 42-44] may have hampered the ability of these studies to detect clinically important differences in outcome. In the context of drug interactions, case-control studies are better suited to the study of short-term risks resulting from drug interactions rather than long-term risks.[25 29 31 33 45]

Some limitations of our study merit emphasis. We could not ascertain the indication for antidepressant therapy, but our finding of an increased mortality risk with paroxetine has strong biologic plausibility and is not readily explained by selection bias. Some women taking tamoxifen may have been prescribed newer antidepressants for treatment of tamoxifen-related hot flashes,[20] which have been associated with better response to therapy.[37] These observations may underlie the trend toward lower breast cancer mortality observed with venlafaxine, which exhibits minimal CYP2D6 inhibition and is commonly used for hot flashes, which are postulated to predict better response to tamoxifen.[46-48]

We lacked information on breast cancer stage, which is an important predictor of outcome. However, because we conducted a within-SSRI analysis, this is unlikely to bias our findings. There is no reason why women with more advanced breast cancer should be preferentially prescribed paroxetine as compared to other antidepressants. We cannot exclude the possibility that individuals who received longer durations of paroxetine while taking tamoxifen had more severe disease, although this seems clinically implausible.[21][49]

Approximately 7% of individuals exhibit no functional CYP2D6 activity [7] and are therefore unable to convert tamoxifen to endoxifen. These individuals may experience fewer tamoxifen-associated hot flashes, and may have better adherence to tamoxifen but poorer response to the drug.[50] Although we do not have genotype information on our study subjects, the inclusion in our analysis of patients with loss-of-function polymorphisms will tend to minimize the clinical consequences of drug-induced CYP2D6 inhibition, and can only attenuate the ability of our analysis to discriminate among SSRIs.

The finding of an increased risk of death from any cause in women co-prescribed paroxetine is anticipated and has at least two contributing explanations. First, breast cancer is the most common cause of death in these patients, and an association between paroxetine use and total mortality is therefore expected. Second, it is probable that many deaths not specifically ascribed to breast cancer reflect remote effects of the disease (such as pulmonary embolism or cardiac

tamponade) or the disease itself, particularly when no cause of death was recorded. Importantly, all of these limitations apply to all antidepressants, and cannot explain the differential mortality risk observed with paroxetine therapy.

Finally, it is important to note that although studies differ on the degree to which various SSRIs inhibit CYP2D6, there is consensus that both fluoxetine and its metabolite are strong inhibitors of CYP2D6.[51][52] However, we found no association between increasing use of fluoxetine and breast cancer death among women taking tamoxifen. The reasons for this are unclear, but may reflect the relatively small number of women exposed to fluoxetine in our study sample. Our results should not be viewed as evidence that fluoxetine is safely used in combination with tamoxifen.

In conclusion, our findings indicate that the choice of antidepressant can significantly influence survival in women receiving tamoxifen for breast cancer. This observation is consistent with the critical role of CYP2D6 in the metabolic activation of tamoxifen, and highlights a drug interaction that is extremely common, widely underappreciated and uniformly avoidable. Tamoxifen is a crucial element of therapy for patients with hormone receptor-positive breast cancer regardless of age or breast cancer stage. When co-prescription of tamoxifen with an antidepressant is necessary, preference should be given to antidepressants that exhibit little or no inhibition of CYP2D6.

Table 1   Cohort Characteristics by Antidepressant Group

	Paroxetine n=630	Fluoxetine n=253	Sertraline n=541	Fluvoxamine n=174	Citalopram n=467	Venlafaxine n=365
Age (year) group *						
66-70	55 (8.7)	35 (13.8)	37(6.8)	10 (5.8)	32 (6.9)	49 (13.4)
71-75	159 (25.2)	79 (31.2)	119 (22.0)	34 (19.5)	118 (25.3)	153 (41.9)
76-80	181 (28.7)	68 (26.9)	153 (28.3)	51 (29.3)	125 (26.8)	83 (22.7)
81-85	124 (19.7)	49 (19.4)	110 (20.3)	42 (24.1)	106 (22.7)	51 (14.0)
86+	111 (17.6)	22 (8.7)	122 (22.6)	37 (21.3)	86 (18.4)	29 (8.0)
Tamoxifen initiation †						
≤365 days	517 (82.1)	184(72.7)	439 (81.2)	142 (81.6)	412 (88.2)	331 (90.7)
>365 days	113 (17.9)	69 (27.3)	102 (18.9)	32 (18.4)	55 (11.8)	34 (9.3)
Drugs dispensed ‡	12 (8 to 16)	12 (8 to 16)	12 (8 to 15)	11 (7 to 17)	12 (8 to16)	10 (7 to15)
Income quintiles§						
1 (lowest)	130 (20.6)	58 (22.9)	106 (19.6)	35(20.1)	109 (23.3)	69 (18.9)
2	138 (21.9)	52 (20.6)	131 (24.2)	33 (19.0)	92 (19.7)	73 (20.0)
3	143 (22.7)	49 (19.4)	99 (18.3)	31 (17.8)	87(18.6)	69 (18.9)
4	111 (17.6)	43 (17.0)	93 (17.2)	38 (21.8)	86 (18.4)	81 (22.2)
5 (highest)	106 (16.8)	49 (19.4)	108 (20.0)	32 (18.4)	92 (19.7)	71(19.5)
Missing	**	**	**	**	**	**
Year of diagnosis						
1964-1973	7 (1.1)	**	**	**	**	**
1974-1983	22 (3.5)	23 (9.1)	21 (3.9)	**	7 (1.5)	**
1984-1992	50 (7.9)	30 (11.9)	50 (9.2)	18 (10.3)	20 (4.3)	15 (4.1)
1993-2005	551 (87.5)	196 (77.5)	465 (86.0)	150 (86.2)	435 (93.2)	345 (94.5)
Tamoxifen duration‖	4.2 (2.3-5.0)	3.2 (1.4-4.8)	3.9 (2.1-4.9)	3.6 (1.7-5.0)	4.2 (2.5-5.1)	4.1 (2.5-4.9)

* Frequency (percent) by age group in the year prior to tamoxifen cessation by antidepressant group.

† Frequency (percent) starting tamoxifen within a year or greater from breast cancer diagnosis by antidepressant group.

‡ Median number of drugs (interquartile range) dispensed in the year prior to tamoxifen completion by antidepressant group.[34]

§ Income quintiles used to estimate socioeconomic status by antidepressant group.

‖ Median duration of tamoxifen use in years (interquartile range) by antidepressant group.

** Cell sizes ≤ 5 are suppressed in accordance with Ontario privacy legislation

Table 2 Antidepressant Exposure and Risk of Death From Breast Cancer Among Women Receiving Tamoxifen

Antidepressant (n)	Death due to breast cancer (n)	Increase in proportion of co-treatment*	Unadjusted HR and 95% CI	Adjusted HR and 95% CI [†]
Paroxetine (n=630)	105			
		0.25	1.17 (1.01 to 1.35)	1.24 (1.08 to 1.42)
		0.50	1.36 (1.02 to 1.82)	1.54 (1.17 to 2.03)
		0.75	1.59 (1.03 to 2.46)	1.91 (1.26 to 2.89)
Fluoxetine (n=253)	71			
		0.25	0.96 (0.81 to 1.13)	0.97 (0.82 to 1.15)
		0.5	0.92 (0.66 to 1.27)	0.94 (0.67 to 1.32)
		0.75	0.88 (0.54 to 1.43)	0.91 (0.55 to 1.51)
Sertaline (n=541)	115			
		0.25	0.96 (0.84 to 1.09)	1.00 (0.88 to 1.14)
		0.5	0.92 (0.71 to 1.19)	1.00 (0.77 to 1.29)
		0.75	0.88 (0.60 to 1.30)	0.99 (0.67 to 1.47)
Fluvoxamine (n=174)	38			
		0.25	1.04 (0.85 to 1.26)	0.98 (0.81 to 1.19)
		0.5	1.08 (0.73 to 1.60)	0.96 (0.66 to 1.40)
		0.75	1.12 (0.62 to 2.01)	0.94 (0.53 to 1.66)
Citalopram (n=467)	29			
		0.25	0.95 (0.71 to 1.26)	1.10 (0.82 to 1.47)
		0.5	0.90 (0.51 to 1.59)	1.21 (0.68 to 2.16)
		0.75	0.85 (0.36 to 2.01)	1.33 (0.56 to 3.17)
Venlafaxine (n=365)	16			
		0.25	0.61(0.37 to 0.99)	0.67 (0.41 to 1.09)
		0.5	0.37(0.14 to 0.98)	0.45 (0.17 to 1.20)
		0.75	0.22 (0.05 to 0.97)	0.30 (0.07 to 1.31)

*   Absolute increases in the proportion of time on tamoxifen therapy during which an antidepressant was co-prescribed.

†   Adjusted for age in the year prior to tamoxifen cessation, year of tamoxifen initiation, duration of tamoxifen therapy, timing of tamoxifen in relation to date of breast cancer diagnosis (within one year of diagnosis or thereafter), socioeconomic status, co-morbidity [34] in the year prior to tamoxifen cessation and receipt of other CYP2D6 inhibiting medications (bupropion, quinidine, thioridazine, amiodarone, cimetidine or chloroquine) during tamoxifen therapy.

Table 3 Antidepressant Exposure and Risk of Death From Any Cause Among Women Receiving Tamoxifen

Antidepressant (n)	Death from any cause (n)	Proportion of co-treatment[*]	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [†]
Paroxetine (n=630)	296			
		0.25	1.12 (1.02 to 1.23)	1.13 (1.05 to 1.23)
		0.5	1.25 (1.04 to 1.51)	1.28 (1.11 to 1.50)
		0.75	1.40 (1.06 to 1.86)	1.46 (1.15 to 1.84)
Fluoxetine (n=253)	149			
		0.25	0.97 (0.86 to 1.10)	0.98 (0.89 to 1.09)
		0.5	0.95 (0.75 to 1.20)	0.97 (0.79 to 1.19)
		0.75	0.92 (0.64 to 1.32)	0.95 (0.70 to 1.29)
Sertraline (n=541)	321			
		0.25	1.02 (0.95 to 1.09)	1.06 (0.97 to 1.16)
		0.5	1.04 (0.90 to 1.19)	1.12 (0.94 to 1.34)
		0.75	1.05 (0.86 to 1.30)	1.19 (0.91 to 1.56)
Fluvoxamine (n=174)	112			
		0.25	1.05 (0.93 to 1.18)	1.00 (0.89 to 1.12)
		0.5	1.09 (0.86 to 1.39)	1.00 (0.80 to 1.26)
		0.75	1.15 (0.80 to 1.64)	1.00 (0.71 to 1.41)
Citalopram (n=467)	135			
		0.25	0.98 (0.86 to 1.12)	1.07 (0.92 to 1.23)
		0.5	0.96 (0.74 to 1.25)	1.14 (0.85 to 1.51)
		0.75	0.94 (0.64 to 1.40)	1.21 (0.79 to 1.86)
Venlafaxine (n=365)	61			
		0.25	0.96 (0.80 to 1.15)	1.04 (0.87 to 1.24)
		0.5	0.92 (0.64 to 1.33)	1.08 (0.76 to 1.54)
		0.75	0.89 (0.51 to 1.54)	1.13 (0.66 to 1.92)

[*]   Absolute increases in the proportion of time on tamoxifen therapy during which antidepressant was co-prescribed.

[†]   Adjusted for age in the year prior to tamoxifen cessation, year of tamoxifen initiation, duration of tamoxifen therapy, timing of tamoxifen in relation to date of breast cancer diagnosis (within one year of diagnosis or thereafter), socioeconomic status, co-morbidity [34] in the year prior to tamoxifen cessation and receipt of other CYP2D6 inhibiting medications (bupropion, quinidine, thioridazine, amiodarone, cimetidine or chloroquine) during tamoxifen therapy.

Fig 1 Risk of breast cancer mortality associated with increasing proportions of antidepressant use during tamoxifen therapy
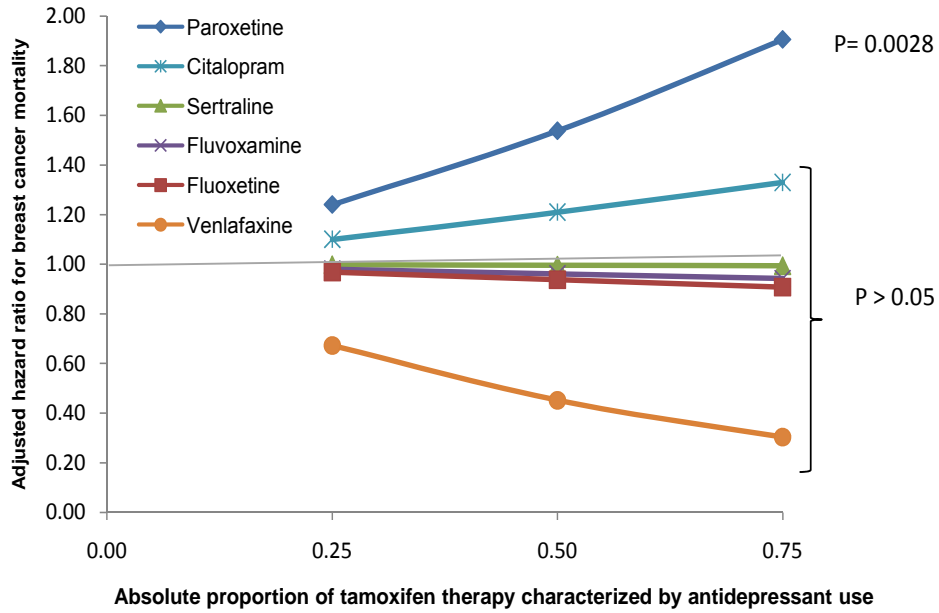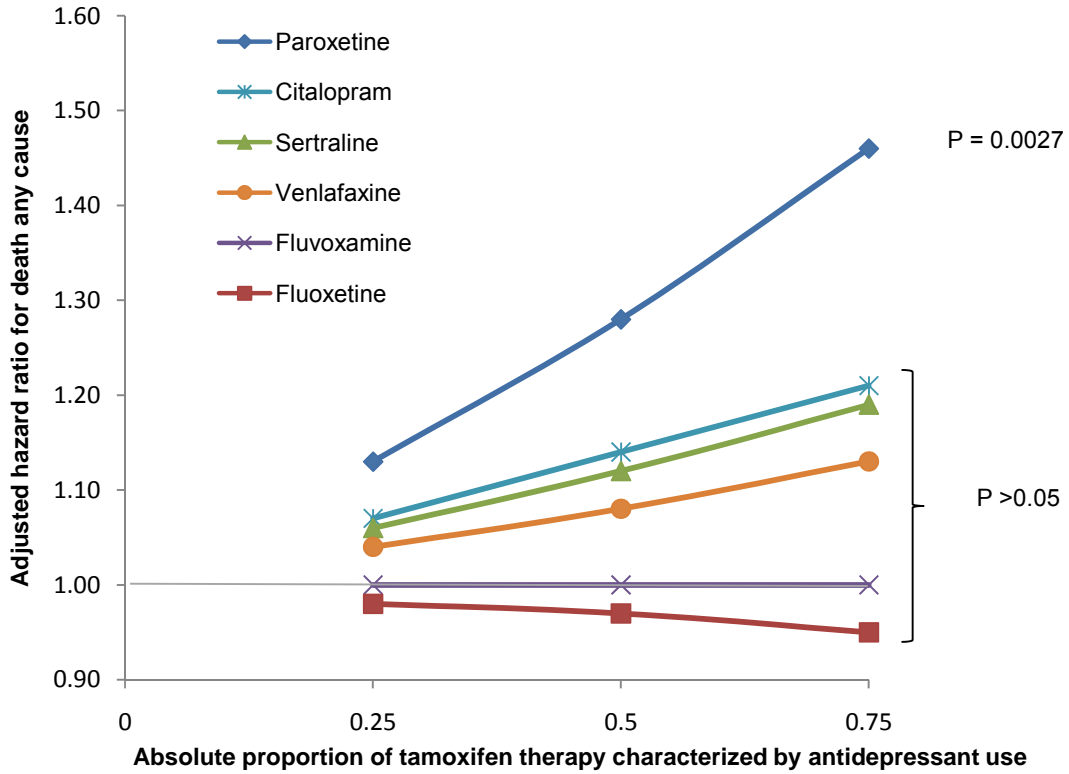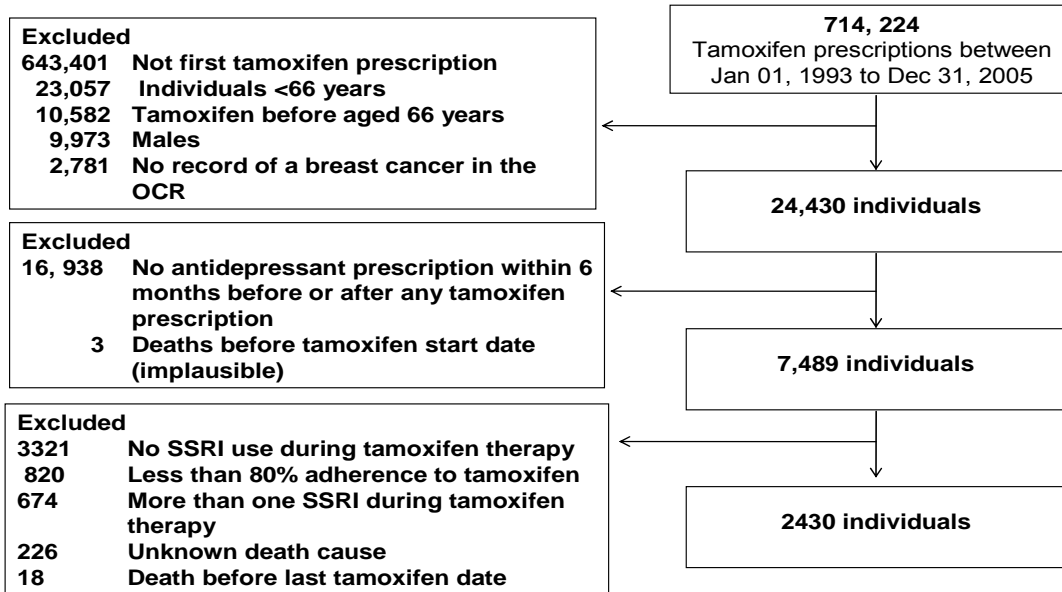

Figure shows the adjusted risk of breast cancer mortality associated with absolute increases of 25%, 50% and 75% in the percentage of time on tamoxifen during which each antidepressant was co-prescribed Increasing co-prescription of paroxetine (an irreversible inhibitor of CYP2D6) are associated with a statistically significant increase in breast cancer mortality

Fig 2 All-cause mortality associated with increasing proportions of antidepressant use during tamoxifen therapy

Figure shows the adjusted risk of any cause mortality associated with absolute increases of 25%, 50% and 75% in the percentage of time on tamoxifen during which each antidepressant was co-prescribed Increasing co-prescription of paroxetine (an irreversible inhibitor of CYP2D6) are associated with a statistically significant increase in any cause mortality

Appendix 1 Cohort Assembly

714, 224
Tamoxifen prescriptions between
Jan 01, 1993 to Dec 31, 2005

Excluded
643,401	Not first tamoxifen prescription
23,057	Individuals <66 years
10,582	Tamoxifen before aged 66 years
9,973	Males
2,781	No record of a breast cancer in the OCR

24,430 individuals

Excluded
16, 938	No antidepressant prescription within 6 months before or after any tamoxifen prescription
3	Deaths before tamoxifen start date (implausible)

7,489 individuals

Excluded
3321	No SSRI use during tamoxifen therapy
820	Less than 80% adherence to tamoxifen
674	More than one SSRI during tamoxifen therapy
226	Unknown death cause
18	Death before last tamoxifen date

2430 individuals

Appendix 2 Characteristics of Tamoxifen and Antidepressant Use

Drug (N=2430)	Median duration (in years) of SSRI use (IQR)	Median time (years) from start of tamoxifen therapy to start of SSRI (IQR)	Median proportion of time on tamoxifen with overlapping SSRI exposure (IQR)
Paroxetine (n=630)	0.99 (0.24 to 2.62)	0.52 (0.11 to1.88)	0.41 (0.08 to 0.80)
Fluoxetine (n=253)	0.78 (0.22 to 2.55)	0.16 (0.04 to 0.70)	0.50 (0.13 to 0.87)
Sertraline (n=541)	0.74 (0.17 to 2.24)	0.57 (0.11 to 2.03)	0.30 (0.06 to 0.77)
Fluvoxamine (n=174)	0.45 (0.16 to1.38)	0.38 (0.07 to 1.81)	0.23 (0.06 to 0.68)
Citalopram (n=467)	0.90 (0.16 to1.94)	119 (0.19 to 3.02)	0.27 (0.06 to 0.63)
Venlafaxine (n=365)	0.57 (0.08 to 2.30)	0.69 (0.20 to 2.0)	0.24 (0.04 to 0.72)

Appendix 3 Other Antidepressant Use Among Women Receiving SSRI Treatment during Tamoxifen Therapy

Drug (N=2430)	SSRI only (%)	SSRI and a tricyclic* antidepressant (%)	SSRI and other[†] antidepressant (%)	SSRI, tricyclic, and other antidepressant (%)
Paroxetine (630)	451(71.6)	116 (18.4)	43 (6.8)	20 (3.2)
Fluoxetine (253)	179 (70.8)	55 (21.7)	9 (3.6)	9 (3.6)
Sertraline (541)	384 (71.0)	92 (17.0)	49 (9.1)	16 (3.0)
Fluvoxamine (174)	122 (70.1)	37 (21.3)	12 (6.9)	**
Citalopram (467)	317 (67.9)	80 (17.1)	54 (11.6)	16 (3.4)
Venlafaxine (365)	248 (68.0)	62 (17.0)	39 (10.7)	16 (4.4)

* Tricyclic antidepressants include clomipramine, doxepine, amitriptyline,   desipramine, imipramine, and nortripyline

[†] Other antidepressants bupropion, maprotiline, moclobemide, phenelzine, tranylcypromine, tryptophan, mirtazapine, trazodone, nefazodone

** Cell sizes $\leq$ 5 are suppressed in accordance with institutional privacy policies

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Role of each author:

- Catherine M. Kelly (guarantor): study concept, design, data extraction, analysis, manuscript writing
- David N. Juurlink: study concept, design, analysis, supervision, manuscript writing
- Tara Gomes: study design, analysis of data
- Minh Duong-Hua: data extraction and analysis
- Kathleen I. Pritchard: study design, supervision
- Peter C. Austin: study design and analysis of the data
- Lawrence F. Paszat: study concept, design, analysis, supervision

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Dr. Kathy Pritchard:

During the past three years KIP has been a consultant for Sanofi-Aventis, AstraZeneca, Roche, Pfizer, Ortho-Biotech, YM Biosciences, Novartis, Abraxis, Amgen and GlaxoSmithKline (GSK). KIP has received research funding either directly through per case funding for studies, or indirectly through the National Cancer Institute of Canada Clinical Trials Group, contracted with pharmaceutical companies including AstraZeneca, YM Biosciences, Bristol Myers, Squibb, Sanofi-Aventis, Amgen, Ortho-Biotech, Pfizer, Novartis, GlaxoSmithKline and Ortho Biotech. KIP has received honoraria or been part of Speaker's Bureaus from companies form Sanofi-Aventis, AstraZeneca, Pfizer, Roche, YM Biosciences and Novartis. KIP has given paid expert testimony for Sanofi-Aventis, AstraZeneca and GlaxoSmithKline. KIP has been a member of Advisory Committees for Sanofi-Aventis, AstraZeneca, Ortho-Biotech, Roche, Pfizer, Novartis, YM Biosciences and GlaxoSmithKline.

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