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Tamoxifen Pharmacovigilance: A survey of current practices and implications for safe use in the future

Demetra Antimisiaris, PharmD, BCGP, FASCP,

Associate Professor at the University of Louisville School of Medicine, Dept. of Pharmacology and Toxicology

Ki-Hwan Gabriel Bae, PhD,

Assistant Professor at the University of Louisville J.B. Speed School of Engineering, Dept. of Industrial Engineering

Laura Morton, MD, and

Assistant Professor at the University of Louisville School of Medicine, Dept. of Family and Geriatric Medicine

Zahara Gully

Candidate for BS in Science in Exercise and a summer research student sponsored by the U of L Dept. of Pharmacology and Toxicology through USPHS grant R25-CA134283

Abstract

Objective—To survey the status of current tamoxifen pharmacovigilance documentation reflecting tamoxifen use in an academic outpatient multispecialty practice in older adults. This data will help provide data to develop improved pharmacovigilance for a growing cohort of older adult users. The data will be utilized by an interdisciplinary team developing new methods of identifying factors for individualized pharmacovigilance in older adults.

Design—Retrospective chart review to gather descriptive and quantitative data on tamoxifen pharmacovigilance.

Setting—Multi specialty clinic.

Patients—93 patients aged 60 and older.

Main Outcome Measures—Quantitative report of tamoxifen monitoring as well as descriptive analysis of individual cases.

Results—We found nineteen cases of serious adverse events possibly related to tamoxifen (thrombi, uterine malignancies). There were fifteen cases with no documentation of pharmacovigilance. All cases had incomplete pharmacovigilance documented. There were two cases of hypercalcemia. There was case of tamoxifen discontinuation due to muscle pain and with chronic muscle pain complaints while receiving tamoxifen. We observed a correlation in older age or high comorbidity burden patients and adverse events patients.

Corresponding Author: Demetra Antimisiaris, PharmD, BCGP, FASCP, University of Louisville, Family and Geriatric Medicine, 501 E. Broadway, Suite 240, Louisville, KY 40202, 502-852-2813, 502-852-0651 (fax), deanti01@louisville.edu.

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Conclusion—Some studies direct the important pharmacovigilance towards prevention of thrombi, uterine malignancies, and hypercalcemia; however, it is not easy to identify recommendations for frequency or focus of monitoring to prevent adverse events for individual older adults based on existing recommendations. The data collected and presented in this survey (study) serves to heighten awareness of tamoxifen pharmacovigilance, and as a starting point for the application of machine learning techniques and modeling to identify patients and individual pharmacovigilance recommendations.

Keywords

Tamoxifen pharmacovigilance; Tamoxifen; Electronic health record; Data; Health record data; Monitoring; Tamoxifen in older adults; Tamoxifen safety; Machine learning; Predictive modeling; Bayesian inference; Predictive analytics

Introduction

Background

The percent of the population of older adults is increasing, and as such, the number of older persons living with breast cancer as a chronic disease is also growing.¹ A medication well known as the cornerstone of long-term breast cancer therapy is tamoxifen (Nolvadex®), having a traditional course of treatment that spans approximately five years. However, since the findings of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) study in 2012, as well as other studies, the updated clinical practice guidelines on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer, expands average length of adjuvant tamoxifen treatment beyond five years and as long as ten years.^{2–6} For older women, the updated clinical practice guidelines suggest that postmenopausal women who have received five years of adjuvant tamoxifen should be offered the choice of continuing tamoxifen or switching to an aromatase inhibitor for ten years with total adjuvant endocrine therapy. This implies that there will be an increase in the number of older women receiving tamoxifen therapy for longer durations of time.

Adverse drug events (ADEs) overall account for a high percentage of hospitalizations of older adults and it is estimated that up to 33 percent of them are due to medication related problems.⁷ One way of preventing ADEs is through adequate monitoring and pharmacovigilance.^{8–11} Regarding tamoxifen pharmacovigilance, there are warnings which provide insight for the monitoring of tamoxifen use highlighted in the prescribing information. In drug databases such as Drug Facts and Comparisons, explicit monitoring recommendations include: gynecological examination, breast examination, mammogram prior to initiation of therapy and at regular intervals, periodic complete blood cell counts including platelets and liver function tests. In addition, explicit contraindications are listed to include concomitant coumarin-type anticoagulant therapy, history of deep vein thrombosis (DVT) or pulmonary emboli (PE).¹² While tamoxifen use is widespread and has been used for decades effectively to treat hormone receptor positive responsive breast cancer without a high incidence of adverse side effects, the side effects associated with tamoxifen use that are potentially life threatening, include thrombi and uterine masses.¹³ As such, pharmacovigilance for the safe use of tamoxifen is warranted, particularly in an aging

population of users. The warnings described in the Food and Drug Administration (FDA) drug monograph and prescribing information is contained in Figure 1.

The increase in prolonged duration of tamoxifen use in older adults based on recent clear evidence of benefit brings attention to the need for heightened pharmacovigilance among older adults using tamoxifen. The current official warnings regarding tamoxifen use were based on data gathered under the previous shorter duration of treatment, which was the standard of care, on a relatively young group of study subjects. The warnings gathered from the National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP P-1) study, cited in the FDA prescribing information, was a multicenter trial, of 13,388 women, comparing tamoxifen to placebo for primary prevention in women at increased risk for developing breast cancer. In this study, six percent of subjects were over seventy years of age, and the duration of the intervention (tamoxifen 20mg daily or placebo), was five years.³ Even within this data, there are age and dose-dependent considerations that point to higher risks of toxicity associated with longer treatment duration and older age. Case studies and related literature about the use of tamoxifen in older adults can provide further information regarding the significance of adverse effects on older adults, and thus can be of value to health care providers in highlighting the need for close pharmacovigilance for tamoxifen use in older adults.^{14–16}

In this paper, we review the status of documentation of tamoxifen pharmacovigilance in a sample of 93 patients, discuss descriptive analysis of our findings as related to potentially higher risk older adult patients, and provide a theoretical framework for further study to help address safe use of tamoxifen for an aging population, in anticipation of increased use in older adults resulting from the clear evidence that extending treatment to ten years is beneficial.

The risk-benefit assessment, and pharmacovigilance parameters for tamoxifen use may be under special consideration with increased use by an aging population. Weighing the risk of recurrence or increased severity of breast cancer versus the known risks of use in persons with significant cardiovascular disease, malignancies and comorbidities presents a challenge. For example, management of the risk of thrombi from tamoxifen use by utilizing seemingly contraindicated medications such as warfarin might be reasonable in many patients. One geriatric pharmacotherapy concept applicable to tamoxifen use, is that the considerations will be highly individualized and include the concomitant medications used, comorbidity burden and severity or recurrence of disease. Our review is aimed at characterizing tamoxifen use and monitoring in older adults by data gathered from retrospective chart reviews.

What are the tamoxifen monitoring parameters?

The prescribing information for Nolvadex®(tamoxifen) contains highlighted warnings for important pharmacovigilance with tamoxifen use (Figure 1).

Official warnings regarding the risks of Novladex® therapy include endometrial cancer, deep vein thrombosis, pulmonary embolism, stroke, cataract formation, and cataract surgery (Table 3 in prescribing information¹⁷). As with most information regarding drug toxicity in

older adults, there is a lack of evidence that can be applied to older adults, in part because it is difficult to study older adults categorically due to their variable individual disease burden and level of frailty. Some resources that offer guidance for geriatric pharmacotherapy include the Beers Criteria and the Screening Tool of Older People's potentially inappropriate prescriptions and the Screening Tool to Alert doctors to Right Treatments (START and STOPP Criteria).^{18,19} One notable guideline, under the endocrine section in the STOPP Criteria, there is caution of the use of estrogens in persons with a history of breast cancer or venous thromboembolism. Tamoxifen is a selective estrogen receptor modulator which possesses both estrogen and antiestrogen actions and is strongly antiestrogen in mammary epithelium, thus the venous thromboembolism and other endocrine cancer risks outside of breast cancer, are of consideration with tamoxifen use.

Additional complications associated with older adults and dose exposure to tamoxifen described in the literature includes reports of coronary thrombus correlating with atrial fibrillation, pulmonary emboli, and femoral thrombosis.^{13,20,21} It has also been documented that increased age is correlated with increased risk of endometrial cancer and duration of tamoxifen use for those exposed to tamoxifen starting over age fifty.^{14,17,22} Traditionally, increased duration of exposure to tamoxifen has been associated with worsening risk-benefit considerations, which explains why tamoxifen treatment has been limited to five years in the past.²³ Hypercalcemia is also a concern with tamoxifen use, but appears to be transient when initiation of therapy occurs.¹⁷ Hypercalcemia has been observed in patients with bone metastases within a few weeks of starting tamoxifen and, if persistent, tamoxifen should be discontinued.^{14,17} Liver function tests should be performed periodically as there has been some association of elevated levels with tamoxifen therapy, but the significance has not been described clearly. In our literature search, we did not find any studies looking at the safety of tamoxifen therapy beyond five years although the ATLAS study looked at the efficacy of treatment over extended periods.

With the aging of the population and recommendations to expand the duration of tamoxifen treatment, health care providers need to define appropriate surveillance of prolonged and safe tamoxifen use to include safety in older adults.¹⁶ We present a survey of current practices surrounding tamoxifen pharmacovigilance in an outpatient healthcare system, which includes primary care and multispecialty clinics. Our findings highlight gaps in tracking of tamoxifen use and safety monitoring; accordingly, we propose a method to develop means for improved monitoring.

A Survey of tamoxifen pharmacovigilance in an outpatient setting

Objective—To characterize and discuss the current state of tamoxifen pharmacovigilance in a sampling of an ambulatory care patient population.

Design—Retrospective chart review to collect quantitative and descriptive tamoxifen use monitoring information. The retrospective review was conducted in two parts simultaneously. One data collector reviewed each chart for documentation of tamoxifen use monitoring parameters such as complete blood count, liver function tests, uterine malignancies, development of thrombotic events (such as deep vein thrombosis, pulmonary

emboli, cardiac stents, cerebrovascular accidents), calcium levels, and reviewed chart for presence of anticoagulants or conditions warranting anticoagulant treatment to describe potential use of tamoxifen in hypercoagulable patients and intentional use with anticoagulants. A more experienced data collector reviewed each chart in depth for adverse events either documented or potentially related to tamoxifen use.

Setting and Patients—The chart review subjects were patients from our university multi-specialty and primary care outpatient practices.

Methods—We requested identification of patients currently taking tamoxifen and sixty years of age and older from the data manager. We requested identification of patients from all the outpatient clinics within a single healthcare system. The confidential and Health Insurance Portability and Accountability Act (HIPAA) protected data provided by our health system IT data specialist yielded 93 patients receiving tamoxifen therapy. A patient identification key was created, numbering each patient sequentially, with the key to patient identification kept separately and securely from the patient numbered list. The data collected includes documentation in the electronic health record (EHR) of drug surveillance parameters described in the FDA drug monograph and other literature describing potential adverse events linked to tamoxifen use. We also collected demographic and disease burden data to look for trends in adverse outcomes, and appropriate monitoring.

We presented our findings to three groups of prescribers during didactic educational sessions to attempt to gain insight into the prescribers' perspectives.

Quantitative documentation of tamoxifen warnings and adverse effects monitoring

Table 1

Quantitative data of documented monitoring and potential complications associated with tamoxifen therapy.

Age	Range=60–100 years old Average 70.5 years Median 74.25 years Two males 91 females
Calcium monitoring	56 percent documented Two patients-elevated calcium levels. See footnote regarding metastatic disease and transient nature of hypercalcemia.*
Complete blood count with platelet monitoring	18 percent
Liver function test monitoring	51 percent documented
Subjects concurrently taking warfarin.	Four patients
Documentation of screens for deep vein thrombosis, pulmonary emboli or cerebrovascular accident.	Three percent of charts reviewed had documentation of “no signs of DVT”.
Documentation of screen for uterine masses.	One percent of charts reviewed had documentation of screen for uterine masses. This chart had a rather complete documentation of tamoxifen use pharmacovigilance by an endocrinologist.
Subjects receiving tamoxifen while experiencing pulmonary emboli.	One patient

Subjects receiving tamoxifen while experiencing a cerebrovascular accident.	Seven patients
Subjects receiving tamoxifen while experiencing a deep vein thrombosis.	One patient
Subjects receiving tamoxifen while undergoing percutaneous coronary stenting.	Two patients

* The subject with very elevated calcium was 100 years of age who had recurrent breast cancer over decades and had recently been prescribed tamoxifen for palliative treatment and the calcium elevation occurred as described in the prescribing information, a few weeks after starting tamoxifen. Of note, the patient had documented bone metastasis. This patient reflects the literature indicating that calcium elevations seem to be limited to initiation of therapy, or in patients with metastatic disease. Another subject, who was 87 years old, had an elevation of calcium with initiation of treatment in 2012 with no subsequent calcium levels recorded.

Descriptive findings for tamoxifen use in high risk patients

Table 2

Descriptive findings regarding tamoxifen use in high risk patients.

There were 45 potentially high risk cases	
Case Description	Comments
24 subjects receiving aspirin, with hypertension (HTN) diagnosis	Tamoxifen can antagonize the antithrombotic effects of aspirin. (Aspirin is sometimes used to reduce the risk of breast cancer). ¹
10 patients with HTN not receiving aspirin	Tamoxifen can increase risk of thromboembolism and hypertension can be an additive risk. Persons with advanced age, with evidence of cardiovascular disease, such as hypertension are recommended to receive low dose aspirin treatment <i>if tolerated</i> , per the American College of Cardiology and American Heart Association Cardiovascular Risk Calculator ¹¹ .
2 subjects receiving aspirin 325mg daily for stroke	One of these subjects had been treated in 2000 with Adriamycin and tamoxifen, but tamoxifen was stopped one week after initiation due to thrombophlebitis incident. In 2014, the subject was treated with aspirin 325 mg and warfarin post-cerebrovascular event, and tamoxifen was stopped again. In 2015, the subject was placed back on tamoxifen plus aspirin 325mg. May be intentional use with anti-coagulant. See discussion section.
Cilostazol (1 subject), Clopidogrel (3 subjects)	These subjects had documented coronary artery disease as indications for the use of these drugs to prevent thrombi. Tamoxifen can antagonize the effect of cilostazol and clopidogrel, but may be intentional use with anticoagulant.
Tamoxifen discontinued due to muscle pain	Tamoxifen generic has been associated with arthralgia; brand name tamoxifen has been substituted successfully ¹¹¹ . The subject had been prescribed rivaroxaban until it was discovered that her lower extremity pain was not a deep vein thrombosis (DVT) but rather, arthralgia related to generic tamoxifen use. Another patient, 66 years of age, had consistent complaints of muscle pain, and trouble walking, which was not attributed to tamoxifen. She was receiving pravastatin and tamoxifen.
Two subjects developed multiple endometrium masses	Subject 1: Removed surgically, gynecology-oncology surgeon noted "been on tamoxifen for two years"; tamoxifen treatment continued post-operatively. Subject 2: tamoxifen discontinued.
Rivaroxaban prescribed for right upper extremity clot	Subject treated by vascular surgery, and had history of past DVT around chest port-after 5 years of tamoxifen treatment. Tamoxifen was not noted as possible contributory factor, and continued, perhaps intentionally.
Subject 1: Percutaneous Intervention: stent to left anterior descending artery-circumflex arteries and 6 years later another stent in right coronary artery. Subject 2: stent in 2014.	Subject 1: treated with tamoxifen for the preceding 9 years. Now receiving aspirin and clopidogrel in addition to tamoxifen. Subject 2: was stented, had atrial fibrillation, followed by a stroke in 2016. Tamoxifen treatment throughout. Received warfarin and propafenone for atrial fibrillation documented back to 2011. Possibly intentional use of tamoxifen, a pro coagulant medication with anticoagulation due to more pressing risk of breast cancer recurrence or worsening.

There were 45 potentially high risk cases	
Case Description	Comments
Patient experiencing a pulmonary emboli two months post-surgery for GI fistula.	Tamoxifen discontinued the day after PE discovered. A warning from the hospital pharmacy regarding tamoxifen and warfarin warning (warning in prescribing information and listed as contraindication in other drug database references such as Drug Facts and Comparisons) ^{iv} . Subject was subsequently placed back on warfarin and tamoxifen, possibly intentionally.

ⁱ Source: Reference 24

ⁱⁱ Source: Reference 14

ⁱⁱⁱ Sources: References 25 and 26

^{iv} Source: Reference 12

Duration of tamoxifen therapy

The range of documented treatment duration of tamoxifen therapy in our sample was one to nine years. Approximately one third of the subjects had an unclear duration of tamoxifen use documented in the EHRs. Those patients were excluded from adverse effect reporting, although we did include all patients in our count of monitoring documentation (for example, calcium levels, and liver function tests).

Discussion

State of tamoxifen pharmacovigilance

The data collected in this study implies that an absence of tamoxifen pharmacovigilance documentation is the normal standard of care. Also, we found fifteen cases with no documentation of monitoring or laboratory studies on record. There are many possible reasons for these findings, some of which are well recognized, including time constraints, barriers to coordination of care, the growing number of providers per patient, and increasing complexity of care regimens. A key limitation to this study is that it is common for providers to not document monitoring unless there is an apparent finding, meaning that otherwise, all is normal, and we have no way of knowing the intent of the individual provider.

For several cases where serious ADEs were reported, the majority of care providers in the chart review appeared to not question the potential role of tamoxifen use in the ADEs, perhaps due to the aforementioned constraints. Tamoxifen was recognized in a couple of cases as a contributory factor and discontinued. In other cases, tamoxifen's possible contribution to ADEs may have been recognized and documented, but the treatment was restarted by subsequent providers who may not have been aware of the documentation in the chart that it had intentionally discontinued. Or, tamoxifen may have been intentionally restarted without documentation of the risk-benefit consideration. The rationale for the use of tamoxifen with a contraindicated medication, such as warfarin, was not observed in chart documentation, yet the intent to utilize tamoxifen with heightened monitoring might have been rational and deliberate as described in medical literature.²⁷

As discussed in earlier sections and illustrated in table two descriptive findings, the use of tamoxifen, a medication linked to hyper coagulation, may be intentional in patients at

heightened risk of thrombotic events if the risk of breast cancer recurrence or worsening condition outweighs protection against thrombi, especially if the patients can be managed with anticoagulants. The practice of unclear documentation of the rationale for the concurrent use of tamoxifen with a contraindicated drug, such as warfarin, could also lead to unintended discontinuation of tamoxifen (or warfarin like medications), if another provider cannot determine the reason for using both. Also, lack of documented rationale for concomitant use of warfarin or other anticoagulant with tamoxifen might cause wasted energy and time addressing warnings from pharmacist, and other providers concerned over the contraindication.

We also found a high rate of tamoxifen use in patients with hypertension not receiving low dose aspirin. It seems counterintuitive not to use low dose aspirin in persons over 65 years of age with hypertension, especially while receiving a potentially pro-thrombic agent, unless the patient cannot tolerate low dose aspirin. The American College of Cardiology and American Heart Association 10-year cardiovascular risk calculator places most people over 65 years of age with hypertension in the category for recommended aspirin therapy.²⁸

There were seven cases of patients who experienced a cerebrovascular accident or stroke, two who underwent percutaneous stent placement, one experienced a pulmonary embolism, one a deep vein thrombosis, and two endometrial malignancies, in our sample of patients while receiving tamoxifen. The two cases of hypercalcemia were in patients over 85 years of age. We are not able to verify any causal association to these potential complications of tamoxifen therapy; however, our aim is to identify the concurrence of these complications in the presence of tamoxifen use to highlight some pharmacovigilance parameters and attempt to characterize risk factors to develop a data driven machine learning method and automated pharmacovigilance algorithm. The goal of the machine learning modeling is to alert providers to patients with elevated risk and overlooked monitoring proactively.

Our small sample seemed to infer that the patients in the eldest group were at risk for adverse events despite having low comorbidity burden, and the younger at risk had high comorbidity burdens. Of the patients experiencing adverse events, the majority were in their sixties with greater than nine comorbidities, while those over 80 years of age had not more than five comorbidities.

We asked providers at our weekly didactics conference, where we presented this and other pharmacovigilance topics, what they thought were the reasons for the absence of pharmacovigilance documentation. We recorded their conversations and found several common points highlighted by a group of six to eight providers:

1. Lack of a designated provider in the health care team who is responsible for comprehensive pharmacotherapy and pharmacovigilance
2. The assumption that one of the many other providers is doing the monitoring, especially the originator of the prescription.
3. Underdeveloped awareness for all the risks of any individual medication when used in complex older patients.

4. It would be difficult to find evidence-based recommendations to account for the safe use of tamoxifen for this group of older adults with complex medical problems and impaired functional status.
5. It would be also a significant task to track comprehensive, appropriate monitoring for tamoxifen use in addition to doing so for other medications.

The incidence of preventable ADEs considering all medications is estimated to be about thirty percent in community dwelling older adults and may potentially be impacted positively by improved monitoring.¹⁰ One limitation of this study is our ability to know whether the documenting providers performed the monitoring necessary to prevent the potential and observed ADEs, but just did not record it in the chart. The practice of documenting normal and abnormal physical exam findings is commonplace, but the practice of documenting the absence of ADEs that the provider checked for is not. In our study, documentation of pharmacovigilance was performed when an abnormal finding arose or there existed a threat to continued medication use. ADEs often are discovered in the emergency department, once severe enough to warrant urgent attention. Emergency department visits by older adults have increased by ten percent in the past decade, and the medications primarily responsible for this increase are familiar to health care providers, and should require robust monitoring for safe use.²⁹ Although we do not have precise data on hospitalizations attributable to tamoxifen use in our sample, our data implies that fifteen of the ninety three subjects (or sixteen percent), were hospitalized while receiving tamoxifen for issues potentially exacerbated by tamoxifen use.

Another limitation is that although we may have observed patients who clearly have had serious ADEs (or were documented to have) due to tamoxifen exposure, we were not able to find documentation regarding why those patients had been continued or discontinued on tamoxifen (for example, the risk benefit statement).

Moreover, we also wondered why the option to change the treatment to an aromatase inhibitor or other options, when actual complications with tamoxifen treatment arose, was not carried out in any of the subjects.^{23,30} Aromatase inhibitors come with their own set of concerns, including changes in lipid profiles that are generally considered to be small and the clinical significance is unclear. In some trials, aromatase inhibitors seem to offer more safety with regards to thrombosis, but there may be a trade off in terms of lack of cardiovascular protection offered by tamoxifen, like estrogen's cardiovascular protective effect (outside the thrombotic effects). The safety of tamoxifen versus aromatase inhibitors may be linked to pre-, peri-, and post-menopausal factors for complex reasons which are beyond the scope of this discussion.³¹

Perhaps we can identify the high-risk patients?

Our descriptive data may provide a glimpse into the patients who are at higher risk of adverse outcomes. The average age of subjects that had documented serious adverse events such as stroke, thrombi, and uterine mass was 78.6 years old, and the median age 80.5 years, while the overall average age of our subjects was 70.5 years of age. We also looked at the disease burden of those with documented serious potential tamoxifen related adverse events,

and concomitant medications used. Our findings suggest that older and (or) complex patients taking tamoxifen with cardiovascular risk should be monitored closely.

The task of hand picking EHR pharmacovigilance data makes it very difficult and time consuming to comprehensively provide pharmacovigilance for each patient using tamoxifen within a healthcare system. Because some cases are present for consults, such as surgical cases often are, it is difficult to expect all providers to document all monitoring safe use parameters for each patient in each EHR. Furthermore, since every EHR from health system to health system is separate, ensuring that at least one of a patient's providers is monitoring all safe use parameters is very difficult. Additionally, we observed a trend in which different providers documented different tamoxifen side effects or risks, implying that each provider views tamoxifen risk through their own lens.

We found in our data collection that the pharmacovigilance for tamoxifen use is very inconsistent, with varying data points correlated with varying ADE outcomes. Therefore, we consulted with the engineering school at our institution to get input from an expert on large complex data sets. We wanted to explore potential enhanced approaches, compared to the traditional medication use evaluation, to develop an automated method of improved pharmacovigilance for tamoxifen use. We discussed the idea that if we could project which patients are at highest risk for tamoxifen ADEs, through expanded data collection, we could then flag these patients at appropriate intervals for pharmacovigilance using EHR alerts so providers would not have to perform unnecessary global tamoxifen pharmacovigilance for every patient and so higher risk patients wouldn't be overlooked for needed monitoring. This would provide a simplified pharmacovigilance algorithm compared to monitoring every parameter discussed in the prescribing information on an ongoing basis. Identification of elevated risk of ADEs for specific patients or population of patients, combined with machine learning methods, could bring efficiency to the challenge of performing appropriate pharmacovigilance and can be tested for impact on prevention of ADEs.

An engineering based approach to implementing pharmacovigilance for drugs similar to tamoxifen (with rare, but high stakes adverse effects) might be to consider *machine learning techniques* using Bayesian inference. By quantifying the risk of a patient having an ADE as probability distribution, Bayesian inference can be used to estimate a true risk profile of drugs prospectively based on recurring characteristics. This is achieved retrospectively in post marketing observational studies, when the risk is updated with additional data or evidence obtained. The underlying idea is to assess a *posterior* (after new evidence) probability of risk based on two parts: the likelihood of observations, that is, how likely the observed evidence would occur given the risk, and a *prior* (before new evidence) probability of risk. As more evidence is collected, the current posterior is in turn used as a prior to estimate a subsequent posterior in an iterative fashion. In other words, in terms of medications such as tamoxifen, where the incidence of serious ADEs is not common, but can be life threatening, and where the risk of such ADE is more common in a subset of patients not well studied (as in high burden multimorbid, over 65 or 70-year-old patients), Bayesian inference can be utilized to collect, collate, and assess the disparate data points that may exist outside the published clinical trials and meta-analysis. Machine learning is a means of making use of each case study to combine data and model risk to help identify

more individualized, efficient and appropriate pharmacovigilance. Older adults tend to be unique individuals in their risk of experiencing ADEs due to their individual level of frailty and comorbidity burden, and mainstream published risk recommendations provide risk information which is difficult to apply to older adults. Machine learning and modeling based on retrospective data, may have some utility in determining prospective, individualized pharmacovigilance parameters for any medication used in older adults.

In a clinical context, suppose the possibility of stroke and thrombi exists as unforeseen future adverse effect of tamoxifen within a patient group of a specific comorbidity, comorbidity burden or a certain demographic. The use of predictive analytics coupled with clinical data mining can uncover such adverse effects more reliably and identify a set of treatment responses or heightened pharmacovigilance for different patient subpopulations. Hence the use of this type of machine learning technique has large potential to effectively individualize pharmacovigilance while reducing monitoring errors and advancing tamoxifen pharmacovigilance as well as pharmacovigilance of any medication. Moreover, with the aid of machine learning methods, the EHR can alert the provider to monitor both potential adverse effects which they may not be aware exists and adverse effects that are highly likely for an individual patient by cueing an increased frequency of monitoring or consideration of alternate therapies for those patients at very heightened risk. This would decrease the overwhelming task of attempting to provide pharmacovigilance for every single patient on every single encounter.

Developing a model for reinforcement of such tamoxifen pharmacovigilance is part of our ongoing research. To that end, our future work is structured as follows:

- EHR database: data records of patients who used tamoxifen are populated and processed in a database system.
- Algorithm development and implementation: machine learning algorithm is designed, developed, and implemented for validation of the use of EHR data.
- Output analysis: output results may uncover complex relationships (for example, drugs, comorbidities, complications, and patient characteristics), and present causal pathways, if statistically significant, captured in the analysis.
- Explanation and evaluation: each attribute of a patient record has an associated positive (or negative) quantile that explains why and to what extent values of predictors are for (or against) a given outcome. This will aid physicians to detect adverse events and to identify predictive risk factors while clinically evaluating proposed pathways to explicate decisions when diagnosing patients.

Conclusion

This study provides a discussion and description of the status of tamoxifen pharmacovigilance with quantitative results demonstrating gaps in ideal documentation of monitoring. Tamoxifen, when treating women with hormone-receptor positive breast cancer, provides a clear benefit, and extended use to ten years is clinically recommended (either tamoxifen or an aromatase inhibitor after five years of tamoxifen treatment). Clinicians

should expect to see an increase in the number of older women being treated with tamoxifen for extended periods of time.

The reasons for the lack of pharmacovigilance documentation are many, yet the descriptive data provides a glimpse at the trends which might be further investigated by healthcare providers regarding the safe use of tamoxifen. The literature that addressed increases in calcium levels in those with metastatic disease or new starts on tamoxifen was consistent with our findings. We found cases of thrombotic events, including stroke, the need for stent placement, deep vein thrombosis, pulmonary emboli, and one myocardial infarction. This seemed to indicate that thrombi are a concern for older persons receiving tamoxifen, yet we also found that many of our patients had cardiovascular risk without any anti-thrombotic treatment concomitant with their tamoxifen use. Although concomitant use of tamoxifen with warfarin and warfarin type anticoagulants is a highlighted warning within the tamoxifen prescribing information, documentation of intentional risk versus benefit for these cases was absent. The concomitant use of tamoxifen with anticoagulants is possibly intentional with the benefit in breast cancer treatment outweighing the manageable risk of hyper coagulation.

We also noted that in the lower age group of older adults, those with serious ADEs potentially linked to tamoxifen use had very high comorbidity burdens while the upper age group of older adults had lower comorbidity burden but quite advanced age. This is consistent with the adages in geriatrics that older adults are highly individual in terms of their health, frailty or vulnerability and not linearly proportionate to age but can often be a function of disease burden. Our findings informed us that there are multiple variables and separate bits of data that may represent trends in risk for individuals. If we aim to develop proactive, individualized means of using pharmacovigilance to prevent ADEs in older adults using tamoxifen, every day healthcare providers should think differently and work beyond our usual environment with other disciplines, including health systems, data analysis experts, and engineers to develop effective interventions towards improved pharmacovigilance and prevention of ADEs.

In our review of the data in a health system, the monitoring of the potential complications of tamoxifen therapy was not consistently documented. Therefore, there were potentially many missed opportunities to provide improved patient care. With minimal pharmacovigilance of tamoxifen therapy, patients can be at an increased risk of developing serious complications such as thromboembolic events and uterine abnormalities including endometrial hyperplasia, polyps, and carcinoma in addition to other less severe adverse effects. This study serves as the foundation for quality improvement projects and upcoming collaboration regarding monitoring for tamoxifen and other similar medication therapies using innovative technology-driven methods. We aim to continue and encourage others to work on interdisciplinary collaborations for future efforts to develop point of care support for providers caring for older adults using existing data and predictive models that may result in identification of high risk patients and automated interventions to ensure that adequate pharmacovigilance occurs. Lastly, this discussion and data set also should serve as a reminder to healthcare providers to be aware of the recommended screening and ongoing monitoring for patients on high-risk medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ADE	Adverse drug events
ATLAS	Adjuvant tamoxifen: longer against shorter
CVA	Cerebrovascular accident
DVT	Deep vein thrombosis
FDA	Food and Drug Administration
EHR	Electronic health record
HIPAA	Health Insurance Portability and Accountability Act
HTN	Hypertension
NSABP P-1	National surgical adjuvant breast and bowel project P-1
PE	Pulmonary Embolism
START	Screening tool to alert to right treatment
STOPP	Screening tool of older people's prescriptions

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WARNING - For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer: Serious and life-threatening events associated with NOLVADEX in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see CLINICAL PHARMACOLOGY-Clinical Studies – Reduction in Breast Cancer Incidence In High Risk Women). Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for NOLVADEX vs 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women-years of 0.17 for NOLVADEX vs 0.0 for placebo)*. For stroke, the incidence rate per 1,000 women-years was 1.43 for NOLVADEX vs 1.00 for placebo**. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for NOLVADEX versus 0.25 for placebo**. Some of the strokes, pulmonary emboli, and uterine malignancies were fatal. Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering NOLVADEX to reduce their risk of developing breast cancer. The benefits of NOLVADEX outweigh its risks in women already diagnosed with breast cancer. *Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See WARNINGS: Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma. **See Table 3 under CLINICAL PHARMACOLOGY-Clinical Studies.

Figure 1.

Reproduction of warning box from the Nolvadex®(tamoxifen) prescribing information.

Source: Reference 14