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TAMOXIFEN-ASSOCIATION SAFETY REVIEW AND SURVEY

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ABSTRACT

Background: Tamoxifen, a selective estrogen receptor modulator (SERM), is widely used in the treatment and prevention of breast cancer but carries significant safety risks, including a Black Box Warning (BBW) for uterine malignancies, stroke, and pulmonary embolism. Although pharmacists play a critical role in ensuring medication safety, early gaps in pharmacy education regarding BBWs may hinder students' preparedness for clinical decision-making. This study aimed to evaluate the baseline knowledge and perceptions of first-year pharmacy students regarding tamoxifen's therapeutic use, associated risks—particularly uterine sarcoma—and awareness of BBWs. The goal was to identify educational deficiencies and inform curricular improvements to enhance pharmacovigilance and patient safety training. **Methods:** A cross-sectional survey was administered to 47 first-year pharmacy students, assessing demographic data, prior exposure to BBWs, knowledge of tamoxifen-related risks, and opinions on patient monitoring. Statistical analysis was conducted to evaluate associations between academic background and student responses. **Results:** Most participants had prior exposure to BBWs and a background in health sciences. While 86.4% of students correctly identified the higher risk of tamoxifen-induced uterine sarcoma in postmenopausal women, only 31.8% recognized the importance of monitoring abnormal vaginal bleeding even in the absence of severe symptoms. Educational background was significantly associated with risk perception and support for patient monitoring ($p < 0.05$). Overall, participants demonstrated limited knowledge, with an average of 64.1% answering the knowledge-based questions correctly. **Conclusion** First-year pharmacy students demonstrated foundational knowledge of tamoxifen's risks, but critical gaps exist in clinical

application and early symptom monitoring. These findings highlight the need for targeted educational strategies to reinforce BBW interpretation and safety practices. Longitudinal follow-up and expanded studies across institutions are recommended to evaluate the impact of real-world clinical exposure on BBW-related competency.

KEYWORDS: Tamoxifen; Survey; Pharmacy; Black Box Warning; Medication Safety.

INTRODUCTION

Tamoxifen is a selective estrogen receptor modulator (SERM), a class of nonsteroidal compounds that interact with estrogen receptors, in distinct tissue-specific manner. SERMs have demonstrated efficacy for various conditions, including osteoporosis, dyspareunia, and breast cancer, though their use is associated with significant safety risks (Ellis AJ et al. 2015). Evidence suggests that patients with estrogen receptor-positive tumors are more likely to benefit from tamoxifen. As a first generation SERM, tamoxifen carries serious safety concerns, including endometrial cancer, venous thromboembolic events (VTE), and stroke (Burstein HJ, et al. 2014).

Originally synthesized in 1962 as a potential contraceptive, tamoxifen it failed in that indication however, it has since emerged as a highly effective anticancer therapy.[4] Since the early 1970's Tamoxifen has been available as a first-line treatment for metastatic breast cancer in postmenopausal women (IARC Working Group 2012). Over the decades, tamoxifen has become a cornerstone in hormone-receptor-positive breast cancer treatment, with both curative and prophylactic applications (Farrar MC 2023).

Tamoxifen is approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer in both males and females, as an adjuvant therapy following their primary treatment with surgery and radiation, and for the management of ductal carcinoma in situ (DCIS) after surgery and radiation to reduce the risk of invasive breast cancer.[5] It is also indicated for reducing breast cancer risk in high-risk populations such as those with a 5-year risk > 1.67% based on the Gail Model. Despite its therapeutic benefits, tamoxifen has many off label uses that require additional data (Wooltorton E et al. 2002). It is essential to tailor and provide individualized treatment planning due to its safety profile and monitoring parameters.

Tamoxifen carries a Black Box Warning (BBW) for patients DCIS and those at high risk for breast cancer. Life-threatening adverse drug events (ADEs) in the risk reduction setting include uterine malignancies, stroke, and pulmonary embolism. Uterine malignancies consist of both endometrial adenocarcinoma, uterine sarcoma, stroke, pulmonary embolism. In some cases of strokes, pulmonary emboli, and uterine malignancies have been fatal. Tamoxifen citrate tablets are contraindicated in patients with known hypersensitivity to the drug or any of its ingredients, and in those requiring concomitant coumarin-type anticoagulants, and individuals with a history of deep vein thrombosis, or pulmonary embolism (DailyMed 2025).

Common ADEs of tamoxifen includes decreased in platelet counts, typically ranging from to 50,000-100,000mm^3, infrequently lower. Patients with significant thrombocytopenia, rarely, hemorrhagic events have occurred, but it is uncertain if these episodes are due to tamoxifen therapy. Adverse drug reactions (ADRs) to tamoxifen are generally mild and rarely severe enough to lead to treatment discontinuation, they warrant careful monitoring. The most commonly reported ADR is hot flashes.[2]

Clinical trials such as the Italian Tamoxifen Prevention study (n = 5,408) and the Royal Marsden Hospital Tamoxifen Randomization Chemoprevention Trial (n = 2,471) evaluated tamoxifen's potential role in primary prevention of breast cancer in high-risk women (Veronesi U et al. 1999). While these studies demonstrated no significant reduction in breast cancer mortality, they did reveal increased incidences of serious adverse effects, including deep vein thrombosis and pulmonary embolism. These findings further underscore the importance for individualized risk-benefit assessments when prescribing tamoxifen, particularly in preventive settings.

As tamoxifen remains a commonly prescribed high-risk medication, it is essential for pharmacy students to develop a thorough understanding of its therapeutic use, safety profile, and monitoring requirements (Ellis AJ et al. 2015). However, studies suggest that pharmacy education often lacks sufficient emphasis on the practical application of BBWs, especially in the early stages of training. While curricula typically introduce foundational instruction in drug safety concepts and adverse event management, the ability to apply this knowledge in clinical settings remains underdeveloped.

The objective of this study is to evaluate baseline knowledge of first-year pharmacy students regarding tamoxifen, with a specific focus on its BBW and associated safety monitoring practices. By surveying a cohort of students to assess their familiarity with the tamoxifen's clinical use, potential adverse effects, and patient counseling considerations, this research seeks to identify early educational gaps and can inform future targeted curriculum enhancements aimed at strengthening pharmacovigilance and promoting patient safety.

Evidence from other institutions highlights the value of experiential learning on pharmacy education. For instance, faculty assessed the impact of medication error simulations on third-year pharmacy students' ability to recognize and mitigate patient safety risks at a pharmacy school (Frenzel JE et al. 2018). The students participated in three simulation-based scenarios and completed pre- and post-activity questionnaires measuring their knowledge, personal experience, and attitudes with medical errors. The results showed statistically significant improvements in students' ability to identify root causes of errors, recognize contributing factors, and collaborate with a team to prevent recurrence. This study demonstrated that hands-on experiences in a controlled environment, free from real-world patient risk, can effectively enhance students' confidence levels in clinical reasoning and safety practices.

This study addresses a critical gap by evaluating first-year students' baseline understanding of tamoxifen and its BBW. In doing so, it reinforces the need for curriculum enhancements that move beyond theoretical instruction. Research supports the case for integrating targeted, evidence-based learning strategies, such as simulation, case-based learning, and other experiential approaches, to equip students with the skills necessary for safe and effective clinical decision-making.

RESULTS

A total of 47 pharmacy students surveyed with a 93% response rate. The demographic profile of participants is summarized in Table 1, indicating that majority female representation, most participants hold a 4-year bachelor's degree. All the patients have work experience with a majority working in a pharmacy related job, and a significant portion have over 3 years of work experience.

Table 1: Demographic Characteristics of Participants (N=47).

Variables		N (%)
Gender	Male	13 (27.7)
	Female	34 (72.3)
	Non-Binary/Third Gender	0 (0.0)
	Prefer not to say	0 (0.0)
Education (highest level attended)	2 Year college	3 (6.5)
	4 years/BS/BA	31 (67.4)
	MSC/MA or Higher	8 (17.4)
	Other	4 (8.7)
Work experience	Never worked	0 (0.0)
	Worked in Healthcare Related Jobs	8 (17.8)
	Worked in a Pharmacy Related Jobs	27 (60)
	Other	10 (22.2)
If worked, for how many years?	<1	6 (13.6)
	1-3 Years	17 (38.6)
	>3 years	21 (47.7)

Table 2 shows participants familiarity and experience with BBW. A majority participants were familiar with BBW before starting their pharmacy education. Most participants or their family or friends experienced an adverse drug reaction in the past. Most participants had an educational background in health sciences.

Table 2: Participants Familiarity and Experience with Black Box Warning.

Survey Questions	Response Choices	N (%)
Have you heard of Black Box Warning before coming to the pharmacy program?	Definitely not	17 (37)
	Probably yes	5 (10.9)
	Definitely Yes	24 (52.2)
Have you or any members of your family or friends experienced ADR in the past?	Definitely not	9 (20.5)
	Probably Yes	25 (56.8)
	Definitely Yes	10 (22.7)
What was your major as undergraduate Student	Basic or Health Sciences	30 (65.2)
	Social Sciences	1 (2.2)
	Business	1 (2.2)
	Other (Specify)[a]	14 (30.4)
Others[a]: Communications, Biology, Biochemistry, Animal Science, Pre-pharmacy, Chemistry, Biomolecular Science, Pharmaceutical Science/Biology, Biological/Biomedical Science		

The knowledge-based questions on tamoxifen and uterine sarcoma evaluated participants' understanding of key monitoring parameters and associated safety risks. As shown in Table 3, the overall knowledge score was below 70%, indicating a limited knowledge base. While a few questions were answered correctly by many participants, the majority were not. The

highest correct response rate was for the statement that Tamoxifen-induced Uterine Sarcoma is more likely to occur in postmenopausal women than in premenopausal women, indicating strong knowledge in this area. The lowest correct response rate was for monitoring abnormal vaginal bleeding in necessary for patients on Tamoxifen, even before symptoms become severe, highlighting a gap regarding monitoring parameters.

Table 3: Knowledge-Based Questions.

Variables	**Correct Answer**	**Participants with Correct Answer (%)**
1. Tamoxifen can lead to Uterine Sarcoma, due to estrogenic stimulation of the uterine endometrium by the antiestrogen; however, the molecular mechanism underlying the uterotrophic activity of tamoxifen and the uterine cellular compartments that respond to the drug have not been established	True	37 (84.1)
2. The risk of Uterine Sarcoma from Tamoxifen is extremely low, even with prolonged use.	True	21 (47.7)
3. Tamoxifen-induced Uterine Sarcoma is more likely to occur in adult women than in young women	True	31(70.5)
4. Tamoxifen-induced Uterine Sarcoma is more likely to occur in Postmenopausal women than in Premenopausal women.	True	38 (86.4)
5. Monitoring abnormal vaginal bleeding is not necessary for patients on Tamoxifen unless symptoms become severe.	False	14 (31.8)
AVERAGE		**64.1%**

In the opinion-based question found in Table 4 on Tamoxifen related risk factors and examinations. Majority of participants support the continued use of Tamoxifen despite tis BBW. Participants highly value the role of healthcare providers in educating patients about Tamoxifen risks. In general participants generally acknowledge the risks associated with Tamoxifen but still support its use while emphasizing the importance of monitoring, preventive gynecologic exams, and healthcare provider education efforts.

Table 4: Opinion-Based Questions.

Variables	Agree N (%)	Disagree N (%)	Mean + SD
1. Tamoxifen should still be used for breast cancer despite black box warning	40 (85.1%)	4 (8.5%)	14.9 + 11.53
2. Tamoxifen is associated with elevated endometrial cancer risk	40 (85.1%)	3 (6.4%)	13.8 + 10.61
3. Investigate abnormal bleeding and monitor postmenopausal women	36 (76.6%)	8 (17.0%)	14.2 + 11.01
4. Baseline gynecologic exam before starting treatment	41 (87.2%)	3 (6.4%)	14.8 + 11.45
5. Physicians/pharmacists should inform patients of warning signs	39 (83.0%)	5 (10.6%)	14.8 + 11.46

As shown in Table 5, the data set examines the association between the highest level attended and the belief that Tamoxifen Uterine sarcoma is more likely to occur in adult woman than in young women. Those with a higher level of education (MSC/MA or higher) may have a greater awareness of cancer risks, leading to stronger beliefs about Tamoxifen-induced uterine sarcoma risks in adult women. Higher education is linked to greater awareness of and concerns about Tamoxifen related risks. People will lower education levels may be less informed about specific cancer risks, leading to lower agreement with the statement about Tamoxifen-induced uterine sarcoma.

The next dataset examined the association between undergraduate major and support for investigating abnormal vaginal bleeding and close monitorization of postmenopausal women for endometrial hyperplasia or cancer symptoms. Those with a background in basic or health sciences may show higher support for monitoring and investigation compared to those in business or social sciences. Undergraduate major is significantly associated with opinions on the need for investigating abnormal vaginal bleeding and postmenopausal monitoring.

Table 5: Demographics and Opinion Based Questions with Statistical Significance.

Demographics	Opinion Based Questions	P-Values
Education (Highest Level attended)	Tamoxifen induced Uterine sarcoma is more likely to occur in adult women than in young women	0.035
What was your major as an undergraduate student	How much do you support that any abnormal vaginal bleeding should be investigated, and postmenopausal women should be closely monitored for endometrial hyperplasia or cancer symptoms	0.006

DISCUSSION

The result of the study shows that the survey participated had a limited knowledge of Tamoxifen-associated BBWs. However, they showed a high awareness of BBW. Additionally, there was a strong association between education level and knowledge indicating that academic background plays a significant role in drug safety literacy.

An unexpected finding occurred in Question 5 from Table 3, Which assessed knowledge on appropriate monitoring protocols for patients taking Tamoxifen. Only 31.8% of students correctly identified that monitoring for abnormal vaginal bleeding is necessary even in the absence of severe symptoms, indicating a significant gap in clinical safety knowledge. This low correct response rate stands in contrast to the high accuracy observed in the preceding knowledge-based questions, all of which has a correct answer of “true

These findings suggest that pharmacy curricula could benefit from reinforcing the clinical implications of BBWs, particularly the importance of proactive monitoring for adverse effects. Greater emphasis on patient counseling and BBW-related education, especially through case-based learning could strengthen future pharmacists' ability to interpret, communicate, and respond to high-risk medication alerts effectively. This study contributes to the growing need for targeted education on high-risk medications within pharmacy programs and highlights how prior academic background may influence student perceptions and knowledge acquisition.

There are a few limitations to this study. First, the study is limited by its small sample size. Additionally, most participants had prior educational backgrounds in health or science-related fields and were predominantly female. This may reduce the generalizability of the findings to a more diverse student population. The study also relied on self-reported data, which is subject to potential recall bias and social desirability bias. Furthermore, all participants were first-year pharmacy students from the same institution, which may introduce homogeneity in responses due to shared academic experiences and limited clinical exposure. This lack of direct patient care experience may have influenced their ability to fully apply Black Box Warning (BBW) knowledge to real-world scenarios.

Future research should aim to include a larger and more diverse sample across multiple pharmacy schools to enhance the generalizability of findings. Surveys should be distributed across all class years within institutions, to capture developmental trends in BBW-related knowledge, or, if focusing solely on first-year students, studies should involve participants from varied institutional and educational backgrounds. Incorporating performance-based assessments, such as simulations, case-based evaluations, and Objective Structured Clinical Examinations (OSCEs), can provide deeper insights into students' ability to apply BBW knowledge in clinical practice. Additionally, longitudinal studies that follow these students into later years of pharmacy education or into clinical rotations would be valuable to assess whether real-world experiences alter their perceptions, knowledge retention, or patient safety practices regarding BBW.

CONCLUSION

A survey among 47 First year pharmacy students evaluated their baseline and perceptions regarding tamoxifen and its associated BBW, particularly the risk of uterine sarcoma. Findings reveal that while the students demonstrated a strong foundational understanding of

tamoxifen's indication and associated risks, especially among those with prior health science education, critical gaps persist in their clinical application of BBW safety protocols, such as the need for early symptom monitoring. While the survey, limited by sample size and institutional scope, this study adds to the growing evidence that targeted training in the interpretation and application of BBWs is essential to shaping competent, safety-conscious pharmacists. Future research should aim to expand these findings across a broader population and include performance-based evaluations to further assess students' applied knowledge and readiness for clinical practice.

Ethics Approval and Consent to Participate: This study was approved by the institutional Investigational Review Board and was conducted in accordance with ethical standards. As the survey contained no identifiers, formal ethics approval was deemed unnecessary. All participants provided informed consent to participate.

Consent for Publication: Participants provided consent for the publication of findings from this study. The survey did not include any personal identifiers.

Availability of Data and Materials: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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