

Original Research

Evaluation of Kosovo pharmacists' knowledge of tamoxifen-induced psychiatric disorders in comparison with reported side effects in the WHO pharmacovigilance database

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Abstract

Background: Tamoxifen is a widely prescribed selective estrogen receptor modulator (SERM) used for the treatment and prevention of hormone receptor-positive breast cancer. While tamoxifen has proven effective in lowering the chance of cancer recurrence, current data point to a possible link between tamoxifen treatment and unfavorable psychological consequences. **Objective:** In this study, the World Health Organization (WHO) pharmacovigilance database will be analyzed to determine the frequency and kind of psychiatric disorders linked to the use of the tamoxifen as well as Kosovo pharmacists' awareness of these reported adverse effects. **Methods:** The WHO pharmacovigilance database, VigiBase, was queried for adverse drug reaction reports related to tamoxifen use between 1978 and 2022. A cross-sectional survey of 70 community pharmacies operating in Kosovo was conducted as part of the data collection between January 1 and March 1, 2023, with the goal of comparison. **Results:** The search of VigiBase yielded a total of 1746 reported cases of psychiatric disorders. The data were further classified based on the type of psychiatric adverse effect, including depressive disorders, anxiety disorders, cognitive impairment, and other psychiatric symptoms. Depressive disorders were the most frequently reported adverse event, accounting for 30% of the cases. Anxiety disorders and sleep disorders were also prevalent, comprising 11% and 7% of the reported cases, respectively. Other psychiatric symptoms such as mood swings, insomnia, and confusion were observed in 32% of the cases. In Kosovo, 30% of pharmacist's linked tamoxifen with depression, 25% with anxiety, 56% with sleep disorders, 53% insomnia, and 18% confusion. **Conclusions:** Based on the WHO pharmacovigilance database and knowledge of Kosovo pharmacists for these documented adverse effects, this study analyzes tamoxifen-induced psychiatric disorders. The findings show how attentive healthcare professionals must be to any potential psychiatric side effects of tamoxifen therapy. The safety and effectiveness of tamoxifen treatment for patients with breast cancer should be improved with more study into the underlying processes and the development of methods for prevention, early diagnosis, and management of these side effects.

Keywords: tamoxifen; pharmacovigilance; side effects; psychiatric disorders; kosovo

INTRODUCTION

Affected people, their families, and society bear a heavy weight of pain, sickness, death, and lost productivity as a result of psychiatric diseases. They significantly increase the prevalence of chronic health issues, adversely impact physical well-being in general, and exacerbate acute illnesses.^{1,2} Anxiety and depressive disorders were the most prevalent, followed by bipolar disorders, disruptive behavior and dissociative disorders, neurodevelopment disorders, bipolar disorder, etc. In 2019, 1 in every 8 individuals, or 970 million people worldwide, were suffering with a mental condition.³ Health systems are severely underfunded and have not yet provided for the requirements of those with mental illnesses. Around

the world, there is a huge gap between the demand for therapy and its availability; when it is given, it is frequently of low quality. For instance, only 33% of those with depression and 29% of those with psychosis obtain official mental health care, respectively.^{4,5} Type 2 diabetes,⁶⁻¹⁰ coronary heart disease,¹¹ migraine,¹² and other diseases have been linked to psychiatric disorders.

Various drugs have been related to and often cause drug-induced psychiatric disorders. For newly introduced medications, depression is a frequently reported adverse effect.¹³ Additionally, a number of earlier investigations looked at connections between drug use and psychiatric disorders.¹⁴⁻²² It has been challenging to get agreement on the part that medications play in the genesis of psychiatric disorders.

Recent researches have found links between tamoxifen, a competitive inhibitor of estradiol binding to the estrogen receptor,²³ used to treat breast cancer, and psychiatric illnesses. Tamoxifen users had a considerably increased risk of endometrial cancer, according to Fisher et al.²⁴ Despite the fact that the absolute risks were low, a meta-analysis of clinical trials indicates that tamoxifen raises the risk of stroke in women with breast cancer.²⁵ The limited absorption of tamoxifen as a preventative medication may be due to tamoxifen toxicity, which includes venous thromboembolic

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events (VTE) and endometrial cancer.²⁶ Reduced quality of life and treatment discontinuation are also brought on by the emergence of menopausal symptoms during tamoxifen medication, including vasomotor symptoms, sexual, and gynecologic abnormalities.^{27,28} Patients on tamoxifen fared worse than controls on cognitive tests. Cognitive side effects of tamoxifen can significantly affect a patient's everyday life and general well-being.²⁹ The use of tamoxifen has also been linked to frequent adverse effects like sleeplessness and vivid nightmares. Tamoxifen usage was linked to increased sleep disruption among breast cancer survivors, which affected both the quality and amount of their sleep, according to a 2008 research by Cella et al. Sleep difficulties can increase patients' mood disorders and cognitive deficits, creating a vicious cycle of poor mental health.³⁰

Studying adverse drug reactions (ADRs) reported to national pharmacovigilance networks might be one strategy to address psychiatric disorders globally.^{31,32} In fact, since the middle of the 1960s, national pharmacovigilance systems from over 130 nations across the world have transmitted ADRs to the World Health Organization (WHO) Uppsala Monitoring Center (UMC), which are then recorded in VigiBase, the WHO Global Individual Case Safety Report database.³³

The goal of this study was to evaluate the distribution and key features of reports of psychiatric disorders according to various geographic locations by using VigiBase. Additionally, a questionnaire was utilized to assess the pharmacists' knowledge of reported potential side effects of tamoxifen in Kosovo as well as their experience with ADRs counseling.

METHODS

Study design, sample, and setting

Anonymized reports of alleged adverse drug reactions (ADRs) experienced by patients are stored in VigiBase. Up to the first of March 2013, 23686 possible adverse effects of tamoxifen had been recorded. Since 1978, Uppsala Monitoring Center (UMC) has created the pharmacovigilance database known as VigiBase on behalf of the World Health Organization (WHO).³³ The MedDRA (Medical Dictionary for Regulatory Activities), WHO ICD (International Classification of Disease), and WHO Drug (Medical Product Dictionary) classification systems are connected to the VigiBase database system.

Psychiatric disorders were chosen once cases - defined in this study as reports involving tamoxifen - were identified. The number, proportion, gender, age, region, and disorders involved were all listed as broad trends and characteristics that were used to define the reports. Results were then given as a descriptive analysis of reports as a result of this.

A cross-sectional study was undertaken from January 1 to March 1 of 2023 to compare the reported potential side effects from VigiBase with the expertise of pharmacists in Kosovo for these ADRs. Participants in this study were licensed pharmacists working in community pharmacies in Kosovo's five largest municipalities (Prishtinë, Pejë, Prizren, Gjiilan, and

Gjakovë). This study used an anonymous, self-completed survey that was verified and delivered. Participants were requested to complete the written questionnaire after giving their consent at the start of the survey using the convenience sampling approach. The pharmacy professionals that took part in this survey were picked at random.

Questionnaire development

The WHO, Center for Disease Control and Prevention (CDC), Kosovo Pharmacists' Chamber, National Institute of Public Health, Ministry of Health, and other Kosovo government public health guidelines as well as information from the International Pharmaceutical Federation (FIP) served as the foundation for the questionnaire's development. After it was developed, each draft of the questionnaire was reviewed for content validity by three pharmacists (two Ph.D. holders and one Master of Pharmacy - Mr.Ph.). In order to ensure clarity and eliminate any ambiguity in the questions, a discussion was held after this. As a result, just a few questions were added or removed. The four-part survey was written in both English and Albanian, with the first component evaluating pharmacists' familiarity with tamoxifen. Part 2 tested pharmacists' understanding of tamoxifen adverse drug reactions. Part 3 examined how pharmacists counsel patients with adverse drug reactions, and Part 4 to gather data on the demography of pharmacists. Five experts and an official English/Albanian translator were invited to comment on the items' grammar, vocabulary selection, placement, and scoring in order to assure the qualitative content validity evaluation.

Sample size

For the purposes of this study, a minimum sample size of 70 pharmacists was deemed to be representative.

RESULTS

Evaluation of reported potential side effects of tamoxifen in the WHO pharmacovigilance database

The most frequent adverse drug reactions (ADRs) were general disorders and administration site conditions (13%), neoplasms benign, malignant, and unspecified (9%), musculoskeletal and connective tissue disorders (7%), nervous system disorders (7%), psychiatric disorders (4%), and others among the 23686 reports provided and registered in VigiBase between 1 January 1978 and 1 March 2023 (Figure 1). In the category of reported potential side effects for mental disorders, depression was more prevalent than insomnia, anxiety, sleep disorder, confusional state, depression mood, suicidal ideation, mood swings, nervousness, and reduced libido (Figure 2).

Patients between the ages of 46 and 64 made up the majority of tamoxifen's reported potential adverse effects. Similarly, there were proportionately more reports among patients 75 and older than among those under 17 years old (Figure 3). Figure 4 shows that women (93%) reported more ADRs than males (3%). America was the primary source of reports, followed by Europe, Asia, Oceania, and then Africa (Figure 5).



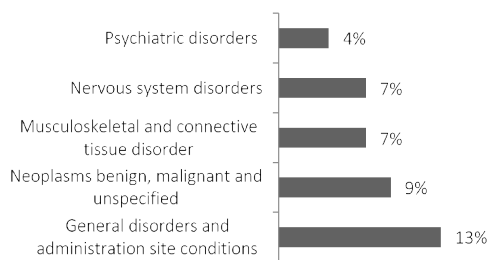


Figure 1. The most frequent reported potential side effects

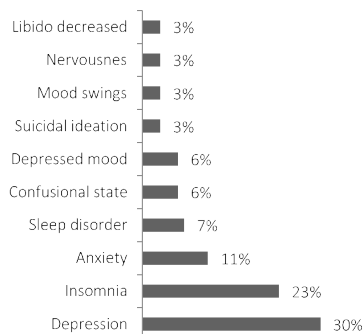


Figure 2. Distribution of ADRs in psychiatric disorders group

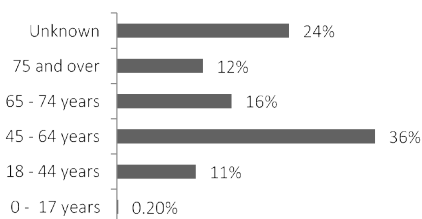


Figure 3. Age group distribution

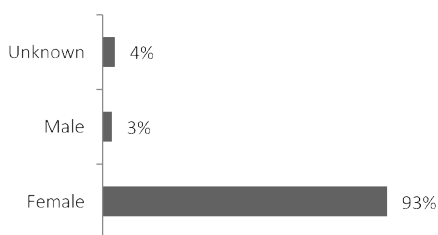


Figure 4. Patients sex distribution

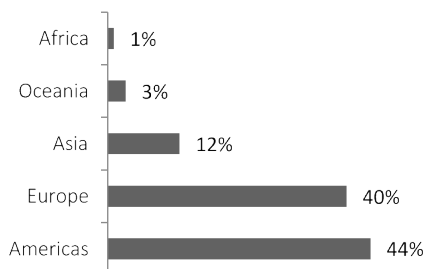


Figure 5. Geographical distribution

Sample characteristics for evaluation of Kosovo pharmacists' knowledge of tamoxifen-induced psychiatric disorders

The sample for this study included 70 pharmacists from 5 major municipalities of Kosovo. The study sample's median age was 33 (SD=9.9). 75.7% of the pharmacists who took part in the study were female (n=53), and they all held master's degrees. Fifty-nine (84%) of those were employees, while the remaining were pharmacy owners. The majority of pharmacist's – more than two-thirds – were employed by independent community pharmacies. Refer to Table 1 for further information.

Table 1. Socio-demographic characteristics of the study sample (n=70)		
Parameters	Mean (SD)	n (%)
Age (years)	33 (9.9)	
Gender		
○ Male		17 (24)
○ Female		53 (75.7)
Education level		
○ Master (Mr.ph.)		70 (100)
Job status		
○ Employee		59 (84)
○ Owner		11 (16)
Site work		
○ Independent community pharmacy		58 (83)
○ Chain community pharmacy		12 (17)
Experience as community pharmacists	7.5 (7.8)	
Municipalities:		
○ Prishtinë		17 (24.3)
○ Pejë		12 (17.1)
○ Prizren		15 (21.4)
○ Gjilan		12 (17.1)
○ Gjakovë		14 (20)

Pharmacists' knowledge tamoxifen-induced psychiatric disorders

100% of the participants were aware of tamoxifen's permitted uses. 60 (86%) of respondents said tamoxifen might be used as a preventative strategy. All pharmacists who were asked about the dose recommended 20–40 mg/day orally (PO), and 49 (70%) of them indicated taking tamoxifen without meals. All pharmacists concur that patients should be counseled on adherence to tamoxifen therapy, and 96% said dietary changes should be the primary emphasis of any recommended lifestyle changes or precautions. Table 2 provides information on pharmacists' understanding of tamoxifen indications, dosage and administration, interactions, and counseling points.

Out of the overall sample, 21 pharmacists (30%) are aware that using tamoxifen might increase the risk of developing depression. 37 of the pharmacists who participated in the research connected tamoxifen usage to insomnia. According to the study, 25% of pharmacists are aware that using tamoxifen increases the risk of anxiety. All pharmacists (100%) knew the particular signs and symptoms of anxiety and when to seek medical assistance. 56% of pharmacists were aware of how tamoxifen affected the likelihood of developing sleep disturbances. It was discovered that 18% of pharmacists are



Knowledge Area	Assessment Questions	Answer n (%)
Indications and Uses	Do you know approved indications for tamoxifen?	Yes: 70 (100) No: 0 (0)
	Can tamoxifen be used as a preventive measure?	Yes: 60 (86) No: 10 (14)
	Are there any off-label uses for tamoxifen?	Yes: 5 (77) No: 65 (93)
Dosage and Administration	What is the recommended dosage of tamoxifen for different indications?	20 - 40 mg/day: 70 (100) Other: 0 (0)
	How should tamoxifen be taken (e.g., with or without food)?	With: 21 (30) Without: 49 (70)
Counseling Points	Should pharmacists advise patients regarding adherence to tamoxifen therapy?	Yes: 70 (100) No: 0 (0)
	Are there any specific lifestyle modifications or precautions that patients should be aware of?	Yes: 67 (96) No: 3 (4)

aware of the possibility of developing confusional condition when using tamoxifen. 90% of them comprehend the proper counseling and management techniques for preventing confusional states. Only two pharmacists had an elevated likelihood of having suicidal thoughts when taking tamoxifen. While 84% of pharmacists were aware of the proper counseling techniques for reducing mood swings, 25% of pharmacists responded positively to the statement that there is an increased risk of mood swings while using tamoxifen. In the respondents, 41% of pharmacists connected tamoxifen usage to a higher chance of experiencing anxiety, and 80% of pharmacists were aware of the right counseling and management techniques for preventing anxiety. Of the 70 pharmacists who made up the entire sample, 13% are aware of the possibility of having a

lower libido while taking tamoxifen. Refer to Table 3 for further details.

The outcomes of the pharmacists' practice delivering information on ADRs counseling are an intriguing aspect of our study. ADRs are counseled about menstruation abnormalities by providing enough information about the cause and the next actions, according to 100% of respondents. According to pharmacists, there are a lot of patients with cataracts, and 90% of them provide ADRs guidance regarding the causes of lens clouding in the eye. Bone density loss occurs often, especially as people age, and all participants provide advice regarding the danger of osteoporosis and reduced bone density. Since there are several causes of liver dysfunction or injury, 84% of pharmacists offer advice on ADRs that cause hepatotoxicity. 60% of pharmacists said that they offer practice regarding ADRs for a higher risk of blood clots, and 100% of them responded favorably when asked whether they offer practice regarding ADRs counseling for hot flashes, a sense of nausea or vomiting, or exhaustion. Table 4 shows the practice of pharmacists giving ADRs advice.

DISCUSSION

In this study, the pharmacists' knowledge of tamoxifen-induced psychiatric disorders was investigated, and data from the WHO database for pharmacovigilance was compared.

Based on WHO database for pharmacovigilance, the most often reported adverse drug reactions (ADRs) for tamoxifen were general disorders, which made up 13% of all reported ADRs. 9% of the reported ADRs were neoplasms, including benign, malignant, and undefined neoplasms. This raises the possibility that tamoxifen and other malignancies or tumors may be connected. 7% of reported ADRs were musculoskeletal and connective tissue diseases. These could include joint stiffness, muscular soreness, or other musculoskeletal system-related problems. 7% of the reported ADRs were neurological

ADR Category	Description	Pharmacists with positive answer n (%)
Depression	Description of depression and its occurrence in patients taking tamoxifen	21 (30)
Insomnia	Description of insomnia and its association with tamoxifen	37 (53)
Anxiety	Understanding the increased risk of anxiety with tamoxifen use	18 (25)
	Understanding of potential symptoms of anxiety and when to seek medical attention	70 (100)
Sleep disorder	Awareness of tamoxifen's impact on the risk of sleep disorders	39 (56)
Confusional state	Understanding the increased risk of confusional with tamoxifen use	12 (18)
	Understanding of appropriate counseling and management strategies for confusional state prevention	63 (90)
Suicidal ideation	Understanding the increased risk of suicidal ideations with tamoxifen use	2 (2)
Mood swings	Understanding the increased risk of mood swings with tamoxifen use	25 (36)
	Understanding of appropriate counseling for mood swings prevention	59 (84)
Nervousness	Understanding the increased risk of nervousness with tamoxifen use	29 (41)
	Understanding of appropriate counseling and management strategies for nervousness prevention	56 (80)
Libido decreased	Understanding the increased risk of libido decreased with tamoxifen use	9 (13)



ADR	Description	Pharmacists with positive answer on practice providing about ADRs counseling n (%)
Menstrual Irregularities	Changes in menstrual cycle patterns	70 (100)
Cataracts	Clouding of the lens in the eye	63 (90)
Bone Density Loss	Decreased bone density and osteoporosis risk	70 (100)
Hepatotoxicity	Liver damage or dysfunction	59 (84)
Thromboembolic Events	Increased risk of blood clots	42 (60)
Hot Flashes	Sudden, intense feeling of heat	70 (100)
Nausea/Vomiting	Feeling of sickness and/or vomiting	70 (100)
Fatigue	Extreme tiredness and lack of energy	70 (100)

diseases. This group may include neurological symptoms including headaches, vertigo, or mental difficulties. 4% of the reported ADRs were due to psychiatric disorders. This implies that tamoxifen may affect mental health, perhaps resulting in illnesses like depression or anxiety. Depression was the most common of the reported potential side effects for psychiatric disorder. This suggests that compared to other mental health-related side effects such as insomnia, anxiety, sleep difficulties, confusional state, and mood swings, tamoxifen may be more associated with depression. Suicidal thoughts, anxiousness, and a decrease in libido are some other documented possible adverse effects for psychiatric disorders that are addressed in the research. Patients between the ages of 46 and 64 made up the majority of those with reported possible tamoxifen side effects, according to the age distribution of reported ADRs. This shows that people in this age range may be more likely to experience drug-related adverse drug reactions (ADRs). Contrarily, reports of adverse effects were proportionally lower in children under the age of 17 compared to older age groups, suggesting that pediatric populations may be more seldom affected by these consequences. The gender breakdown of reported ADRs reveals that women made up 93% of all cases, while males accounted for only 3%. This gap between the sexes shows that women may be more susceptible to side effects from taking tamoxifen. America was the main source of reports on the adverse drug reactions (ADRs) associated with tamoxifen, followed by Europe, Asia, Oceania, and then Africa. This distribution shows that the bulk of reported side effects came from these areas.

For evaluation of above-mentioned reported potential side effects, in our study a sample of 70 pharmacists from five major Kosovo municipalities was used to assess the pharmacists' knowledge of tamoxifen-induced psychiatric disorders. The reason to focus in this is the effects of psychiatric diseases have on people, families, and society as a whole make them very important. They directly affect people's happiness, physical health, social connections, education, productivity, financial burden, public health, and stigma reduction. It is essential to get to know them before attempting to deal with them.

The study sample's pharmacists had a 33-year median age. The median age was followed by a standard deviation (SD) of 9.9 years. 53 participants, or 75.7% of the pharmacists in the

study sample, were female. The fact that every pharmacist participating in the study had a master's degree shows the participants had a high level of education. Eighty-four percent (n=59) of the pharmacists in the survey were employees, while the remaining were pharmacy owners. This indicates that the vast majority of pharmacists held jobs as staff members in pharmacies. In the research, independent community pharmacies employed more than two thirds of the pharmacists. This shows that the sample of pharmacists worked most frequently in independent community pharmacies.

Only two of the pharmacists in our sample had an elevated likelihood that patients in tamoxifen therapy may develop suicidal thoughts. 25 pharmacists responded affirmatively to the question about the potential for mood swings while using tamoxifen, and 84% of pharmacists were aware of the proper counseling techniques to use in this situation. Among the respondents, 41% of pharmacists connected tamoxifen usage to an elevated chance of developing anxiety, and 80% of pharmacists were aware of the proper counseling and management techniques for avoiding anxiety. Of the 70 pharmacists who made up the entire sample, 13% are aware of the possibility of having a lower libido while taking tamoxifen. All participating pharmacists concurred that patients should get advice on following tamoxifen treatment, highlighting the need of patient education and drug adherence. The majority of pharmacists (96%) thought that any advised lifestyle adjustments or precautions related to tamoxifen medication should be focused primarily on food changes. This implies that food advice is crucial when talking to patients about tamoxifen.

The study indicates that pharmacists' knowledge of certain adverse drug reactions (ADRs) connected to tamoxifen use varies. The probable increased risk of experiencing depression (30%), sleeplessness (37%), anxiety (25%), confusional condition (18%), mood swings (25%), and decreased libido (13%) when certain pharmacists knew using tamoxifen. The fact that all pharmacists (100%) were aware of the warning signs and symptoms of anxiety and when to seek medical attention shows that they are aware of the anxiety-related issues with tamoxifen medication.

Additionally, this study shows the professional background by pharmacists to inform and counsel patients about drug-related



adverse drug reactions. On atypical menstruation, cataracts, osteoporosis, hepatotoxicity, and an elevated risk of blood clots, pharmacists offered guidance. On each subject, the precise percentages of pharmacists who offer assistance are indicated. The information shows that, in this point, pharmacists are knowledgeable about a variety of ADRs connected to the use of drugs and engage in counseling activities.

CONCLUSIONS

Pharmacists are expected to take the initiative in educating patients on reported potential side effects. However, Kosovo pharmacists' perceived responsibility and confidence to adequately advise patients about tamoxifen-induced psychiatric illnesses are undervalued, and their impact to improve patients' psychiatric health is not enough. Education is the key to helping Kosovo pharmacists promote tamoxifen-induced psychiatric disorders. The pharmacists must be aware of the specific requirements. However, there is always space for improvement in terms of ensuring that all pharmacists are consistently informed. Pharmacists are essential in patient counseling, sharing information on adverse drug reactions, and encouraging patient education and adherence to all medications, including tamoxifen therapy. Therefore, to supplement this occasionally ignored area of health; additional researches that take into account the perspectives of both patients and pharmacists on psychiatric diseases are needed. Long-term research must also be conducted to ascertain how participants' opinions and degree of participation are impacted by education.

DECLARATIONS

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Universum International College, Alma Mater Europaea Campus College "Rezonanca" and UBT College - Higher

Education Institution committees approved this study.

CONSENT FOR PUBLICATIONS

Not applicable

AVAILABILITY OF DATA AND MATERIAL

All data generated or analyzed during the study are included in this publication

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COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationship that could influence the work reported in this paper.

AUTHORS' CONTRIBUTIONS

Valon Ejupi contributed to the concept and design of the study. Valon Ejupi and Ardian Rugova both contributed to the data analysis. Valon Ejupi and Ardian Rugova participated in the literature review and writing of the manuscript and data interpretation. Sulltane Havolli provided revision to the scientific content and made significant contribution to drafting the paper for its intellectual contribution. All authors contributed to critical revision and final approval of the manuscript and agreed to take responsibility for the manuscript's content.

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