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Global adverse drug reactions trends of anastrozole, fulvestrant and tamoxifen using vigibase® data

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GLOBAL ADVERSE DRUG REACTIONS TRENDS OF ANASTROZOLE, FULVESTRANT AND TAMOXIFEN USING VIGIBASE® DATA

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Pharmacy (MPharm).

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Johannesburg, 2022.

Declaration

I, Juhi Maharaj, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

____8____ day of ___November___ 20___22___ in ___Johannesburg___

For my mum,
who began her fight with breast cancer shortly
after I took on this research.

Abstract

Introduction:

Breast cancer is the leading cancer subtype and accounts for the most significant number of cancer-related deaths in females. Cancer patients have an elevated risk of experiencing adverse drug reactions before, after, and while on treatment. Pharmacovigilance prioritises drug and patient safety, however, due to extensive under-reporting, more so in low-to-middle income countries, signal detection and the consequent changes to policy and practice are lacking. Thus, there is a need to analyse the global database of individual case safety reports on anastrozole, fulvestrant and tamoxifen, commonly used hormonal agents for treating breast cancer.

Methods:

A quantitative, secondary approach was taken where descriptive and statistical analysis was conducted on data obtained from the Uppsala Monitoring Centre's global individual case safety report database, VigiBase®. A total of 43 411 anonymised reports were analysed, using Microsoft Excel for data organisation, cleaning, and numerical coding. The seriousness of the reported adverse drug reactions was evaluated and categorised. The statistical analysis program STATA was used. Pearson chi-squared analysis was conducted to determine statistical associations. Further binary logistic regression was conducted, using a p-value of < 0.05 to show statistical significance. Comparisons between the reported adverse drug reactions and those listed on the drug's package inserts were also done.

Results:

The majority of the adverse drug reactions were reported from the "Americas" and "Europe". Most of the reports were from females in the "45 – 64 years" age group. The most frequently reported ADR for anastrozole, fulvestrant, and tamoxifen were "arthralgia", "fatigue", and "death" respectively. The type of adverse drug reactions reported from Africa, albeit few, were not entirely similar to the other continents. The adverse drug reactions that were most frequently found to be statistically significant with the demographic variables were "arthralgia" for anastrozole, "malignant neoplasm progression" and "asthenia" for fulvestrant, and "arthralgia" for tamoxifen. Despite most of the adverse drug reactions listed in the medicines package insert, there were other commonly reported reactions not listed in the leaflet.

Conclusion:

Well-known and frequently reported adverse drug reactions have demonstrated statistically significant associations to several age groups and continents. This research can be used to warrant targeted adverse drug reaction monitoring in specific populations to safeguard and better manage patients at greater risk of adverse reactions that impact patient quality of life and have considerable cost implications.

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Table of Contents

List of figures ..... **xi**

List of tables ..... **xii**

List of acronyms and abbreviations ..... **xiv**

CHAPTER 1 ..... **17**

1.1. Background 17

1.2. Establishing pharmacovigilance 17

1.3. The importance of pharmacovigilance 19

1.4. Adverse drug reactions – what are they? 20

1.5. Spontaneous reporting and post-marketing surveillance 21

1.6. The consequences of adverse drug reactions 22

1.7. Cancer chemotherapy and adverse drug reactions 22

1.8. Problem Statement 23

1.9. Research question 23

1.10. Aim and objectives 24

1.11. Significance of study 24

CHAPTER 2 ..... **25**

2.1. Pharmacovigilance – what is it? 25

2.1.1. Setting up a national pharmacovigilance centre 26

2.1.2. Pharmacovigilance indicators 27

2.2. The importance of pharmacovigilance 27

2.2.1. How pharmacovigilance is implemented 28

2.2.1.1. Passive surveillance 28

2.2.1.2. Active surveillance 29

2.2.2. The need for drug safety monitoring 30

2.3. The growth of pharmacovigilance internationally 32
2.3.1. Pharmacovigilance systems in developed countries 33
2.3.2. Pharmacovigilance systems in developing countries..... 35
2.4. Adverse drug reactions 38
2.4.1. How to identify adverse drug reactions, what should be reported and who can report? 39
2.4.2. The impact of adverse drug reactions on patient health and healthcare ……...40
2.4.3. Under-reporting of adverse drug reactions 41
2.5. Cancer in context 42
2.5.1. The global breast cancer burden 43
2.5.2. Breast cancer and its treatment options 44
2.6. Adverse drug reactions in oncology 46
2.6.1. The impact of adverse drug reactions in oncology and why they are important..... 46
2.6.2. Adverse drug reactions related to anastrozole, fulvestrant and tamoxifen ……...47

CHAPTER 3..... 52

3.1. Study Design..... 52
3.2. Data Source 52
3.3. Inclusion and Exclusion Criteria 53
3.3.1. Inclusion Criteria..... 53
3.3.2. Exclusion Criteria..... 53
3.4. Study Population 53
3.5. Data Analysis 54
3.5.1. Descriptive analysis..... 56
3.5.2. Statistical analysis 57
3.5.3. Package insert comparison 57

3.5.4. Characterising the seriousness of the ADRs 58
3.6. Statistical Analysis 58
3.7. Bias, validity, and reliability 59
3.7.1. Bias 59
3.7.2. Validity 60
3.7.3. Reliability 60
3.8. Ethical Considerations 61
CHAPTER 4 62
4.1. Study population 62
4.2. Drug-related ADRs categorised per UN continent 63
4.2.1. Anastrozole-related ADRs 66
4.2.2. Fulvestrant-related ADRs 66
4.2.3. Tamoxifen-related ADRs 66
4.3. Statistical associations of ADRs with demographic characteristics 70
4.3.1. Anastrozole 71
4.3.1.1. Age groups 72
4.3.1.2. UN continents 72
4.3.1.3. Gender 72
4.3.2. Fulvestrant 73
4.3.2.1. Age groups 74
4.3.2.2. UN continents 74
4.3.2.3. Gender 74
4.3.3. Tamoxifen 74
4.3.3.1. Age groups 77
4.3.3.2. UN continents 77
4.3.3.3. Gender 78

4.4. Comparing the ADRs reported on VigiBase® to those listed on the drugs package insert 78

4.5. Article submitted to the Journal of Oncology Pharmacy Practice in fulfilment of objective 4 91

CHAPTER 5 113

5.1. Description and categorisation of anastrozole, fulvestrant and tamoxifen related ADRs 113

5.1.1. Demographic data and report characteristics 113

5.1.2. Categorisation of the top 10 ADRs for anastrozole, fulvestrant and tamoxifen 115

5.1.2.1. Anastrozole 115

5.1.2.2. Fulvestrant 116

5.1.2.3. Tamoxifen 116

5.1.3. Continental categorisation of ADRs for anastrozole, fulvestrant and tamoxifen 118

5.2. Statistically significant ADRs 120

5.2.1. Anastrozole 121

5.2.2. Fulvestrant 122

5.2.3. Tamoxifen 123

5.3. Package insert comparison 126

5.3.1. Anastrozole 126

5.3.2. Fulvestrant 127

5.3.3. Tamoxifen 128

5.4. Study limitations 129

5.5. Study recommendations 130

CHAPTER 6 132

6.1. Conclusion 132

6.2. Disclosure 134

6.3. Conflict of interest 134

REFERENCES 135

Annexure 1 153

Ethical clearance certificate 153

APPENDIX 1 154

List of figures

Chapter 2

Figure 2.1 Pharmacovigilance indicators..... 28

Chapter 3

Figure 3.1 Raw data headings with a brief description as provided by UMC..... 55

Chapter 4

Figure 4.1 The percentage of ADRs reported by each UN continent for anastrozole. 64
Figure 4.2 The percentage of ADRs reported by each UN continent for fulvestrant. 65
Figure 4.3 The percentage of ADRs reported by each UN continent for tamoxifen.. 65

Chapter 5

Figure 5.1 (a) Incidence rates of breast cancer in 2020 120
Figure 5.1 (b) Mortality rates of breast cancer in 2020 120

List of tables

Chapter 1

Table 1.1 Classification of adverse drug reactions 21

Chapter 2

Table 2.1. Adverse drug reactions and side effects of anastrozole, fulvestrant and tamoxifen adapted from the package inserts of Arimidex® 1mg, Faslodex® and Nolvadex-D® 20mg. 49

Chapter 3

Table 3.1. Timeframe of adverse drug reaction reports for the three core chemotherapeutic agents. 54
Table 3.2. The number of duplicates removed according to MedDRA system organ class……...54

Table 3.3. The difference in the number of ICSRs after the removal of blank reports ……....55

Table 3.4. An overview of the study objectives and their related methodologies 55
Table 3.5. CIOMS adverse drug reaction frequency criteria..... 57
Table 3.6. Data coding values used for statistical analysis 59
Table 3.7. The types of bias that could influence the study and how they were accounted for 59
Table 3.8. The possible threats to the validity of the study how validity was upheld 60
Table 3.9. The possible threats to the reliability of the study and how reliability was upheld 61

Chapter 4

Table 4.1. Study population, number of reports and ICSR characteristics of anastrozole, fulvestrant and tamoxifen..... 62
Table 4.2. The top 10 ADRs for anastrozole, fulvestrant and tamoxifen 64

Table 4.3. The top 10 ADRs in each UN continent for anastrozole 67
Table 4.4. The top 10 ADRs in each UN Continent for fulvestrant 68
Table 4.5. The top 10 ADRs in each UN Continent for tamoxifen 69
Table 4. 6. The numerical coding of the top 10 ADRs for anastrozole, fulvestrant and tamoxifen..... 70
Table 4.7. Results of the Pearson chi-2 analysis for anastrozole, fulvestrant and tamoxifen..... 71
Table 4.8. Binary logistic analysis of the top 10 ADRs for anastrozole and their association with demographic data 73
Table 4.9. Binary logistic analysis of the top 10 ADRs for fulvestrant and their association with demographic data 75
Table 4.10. Binary logistic analysis of the top 10 ADRs for tamoxifen and their association with demographic data 76
Table 4.11. Comparison between the ADRs reported in VigiBase® (n) with the ADRs reported in each of the drugs package inserts 80

List of acronyms and abbreviations

95% CI	95% Confidence Interval
ADRs	Adverse drug reactions
AI(s)	Aromatase inhibitor(s)
AIA	Aromatase inhibitor induced arthralgia
AIDs	Acquired immunodeficiency syndrome
AMRH	African Medicines Regulatory Harmonisation
ART	Antiretroviral therapy
ARVs	Antiretrovirals
ATM	Access to medicines
CDER	Centre for Drug Evaluation and Research
CEM	Cohort event monitoring
Chi-2	Chi-squared
CIOMS	Council for International Organisations for Medical Sciences
COVID-19	Coronavirus disease 2019
DoH-PvPHP	NDoH Pharmacovigilance Centre for Public Health Programmes
DVT	Deep vein thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
EML	Essential Medicines List
EPI	Extended Programme for Immunisation
ER	(O)estrogen receptor
EU	European Union
FAERS	FDA Adverse Event Reporting System
FDG	Fluorodeoxyglucose
GDP	Gross Domestic Profit
HCP(s)	Healthcare professional(s)
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hormone receptor
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual case safety report
LLT	Low level term
LMICs	Low- and middle- income countries
MAH(s)	Market authorisation holder(s)
MedDRA	Medical Dictionary for Regulatory Authorities
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MRSA	Medicines and Related Substances Act
NADEMC	National Adverse Drug Events Monitoring Centre
NC	National pharmacovigilance centres
NCD(s)	Non-communicable disease(s)
NDoH	National Department of Health
NEPAD	New Partnership for African Development
NMPs	New medicinal products
OR	Odds Ratio
PE	Pulmonary embolism
PET	Positron emission tomography
PgR	Progesterone receptor
PHPs	Public health programmes
PI(s)	Package insert(s)
PIDM	Programme for International Drug Monitoring
PMS	Post-marketing surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PSURs	Periodic Safety Update Reports
PT(s)	Preferred term(s)
PTC(s)	Pharmacy and Therapeutics Committee(s)
PTS	Post-thrombotic syndrome
PV	Pharmacovigilance
PVSF	Pharmacovigilance Sans Frontiers
QoL	Quality of life
RA(s)	Regulatory authority/authorities
RCORE	Regional centres for regulatory excellence

SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
SERM(s)	Selective (O)estrogen Receptor Modulator(s)
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SJS	Stevens-Johnson Syndrome
SOC(s)	System organ class(es)
SRS(s)	Spontaneous reporting system(s)
SSFFCs	Substandard, Spurious, Falsely labelled, Falsified Counterfeits
TB	Tuberculosis
TSR	Targeted spontaneous reporting
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organisation
US FDA	United States Food and Drug Administration
US	United States
USAID	United States Agency for International Development
UTI(s)	Urinary tract infection(s)
VTE	Venous thromboembolism
WHA	World Health Assembly
WHO	World Health Organisation

CHAPTER 1
Introduction

Chapter Overview

This chapter looks at the emergence of pharmacovigilance and the role of the World Health Organisation in establishing the global individual case safety report database, VigiBase®. The importance of pharmacovigilance is highlighted and the definitions of commonly used terms relating to adverse drug reactions are distinguished. The role of spontaneous reporting systems and the specific impact of chemotherapy-associated adverse drug reactions are also briefly discussed.

1.1. Background

In the 1950s, thalidomide was marketed as a safe and effective treatment for nausea and a sedative for pregnant women (1). By 1961, the drug was banned in most countries due to malformations in the limbs of foetuses, a condition called phocomelia, that had been exposed to thalidomide in utero (1,2). To avoid such a tragedy in the future, emphasis was placed on systematically testing pharmaceutical products before their release onto the market (1,2). This sparked concern over the long-term safety profiles of medicines and the need for safety monitoring after a drug's release onto the market became apparent. This concept now falls within the scope of pharmacovigilance (PV). The World Health Organization (WHO) defines PV as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" (3).

1.2. Establishing pharmacovigilance

The consequences of the thalidomide tragedy were recognised and addressed at the 16th World Health Assembly (WHA) held in 1963 whereby resolution 16.36 – Clinical and Pharmacological Evaluation of Drugs – was proposed and members were invited to arrange for the systematic collection of information relating to serious adverse drug reactions (ADRs) that were identified either during the drug development process or

once the drug was released onto the market for general use by the public (4). Other WHA resolutions in 1965, 1966 and 1967 (5) led to the establishment of the WHO Programme for International Drug Monitoring (PIDM) in 1968 to prevent drug disasters like that of thalidomide, and the concept of PV emerged (6).

Within a decade of the WHO PIDM operating, the WHO Collaborating Centre for International Drug Monitoring, commonly known by its field name, Uppsala Monitoring Centre (UMC), was established in 1978. The UMC is tasked with improving global PV status, providing technical support, contributing to capacity building in countries, and establishing and maintaining VigiBase®. VigiBase® is the WHO's global individual case safety report (ICSR) database which houses ICSRs received from national pharmacovigilance centres (NCs) of WHO PIDM member countries and associate members (6–8). VigiBase® is the oldest and largest ICSR database which, as of September 2021, has a record 28 million ICSRs which can be attributed to an influx of reports relating to the Coronavirus disease 2019 (COVID-19) vaccines (9). As of October 2021, 149 permanent member countries and 23 associate members are contributing to the database (10). VigiBase® data can be used to analyse and assess global patterns of ADRs which plays an important role in signal detection and monitoring of ADRs (11). The UMC collects and collates all ICSRs from WHO PIDM members and associate members to generate signals to mitigate the risk of previously unknown ADRs, ensuring they are identified timeously (12).

The WHO continued to establish PV collaborating centres to grow the global PV community. Low- and middle- income countries (LMICs), such as those on the African continent, did not view PV as a priority due to the general lack of access to medicines (ATM), thus, emphasis was placed on attaining medicines instead. This led to a delayed response from the LMICs to the global initiatives to ensure patient safety (8,13). The growth of PV in Africa started with Morocco and South Africa (SA) joining the WHO PIDM in 1992 (8). To aid countries in developing and growing PV across the African continent, organisations such as the WHO, Global Fund, and the United States Agency for International Development (USAID) funded training and capacity building initiatives for PV. In 2007, Pharmacovigilance Sans Frontiers (PVSF), a group of consultants with interest in drug safety in Africa, was established. In 2009, the WHO Collaborating Centre for Advocacy and Training was set up in Ghana to provide the

necessary PV technical support and training to other African countries (8). Further developments resulted in the establishment of the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices in Morocco in 2011. These advances saw a substantial increase in the number of African countries that joined the WHO PIDM (13–15). As of September 2015, 35 of 54 African countries are full WHO PIDM members (8).

To meet the requirements of a WHO PIDM member country, the country in question needs to have an established NC, be competent in the spontaneous ADR reporting procedures and must fulfil the ICSR reporting requirements (submit ICSRs quarterly, if not, more frequently) (16). Additionally, the WHO has specific requirements for functional PV systems, including having a national ADR reporting system, a national ICSR database and an NC with sufficient funding, staff and clear roles and structures (17). In the wake of PV, many NCs were established in conjunction with national regulatory authorities (RAs), who are also tasked with granting market authorisation for new medicinal products (NMPs). This authorisation is based on meeting the governing legislature, guidelines and regulations specific to the RA. Market authorisation holders are required by certain RAs to submit ADR and safety reports periodically. Additionally, healthcare professionals (HCPs) may also be required to submit ADR reports as part of their scope of practice (18). Pharmacovigilance aims to ensure the safe and effective use of medicines and medicinal products and undertake post-marketing surveillance (PMS) of drugs for any safety, quality, or effectiveness issues that the drug may exhibit (5).

1.3. The importance of pharmacovigilance

Pharmacovigilance ensures the continuous safety of medicines by identifying their associated risks. It informs regulatory actions such as labelling changes, safety alerts, drug recalls or withdrawals and allows for appropriate medicine use when communicated effectively (19). Awareness surrounding ADRs is crucial since reporting ADRs helps to determine whether additional investigations need to be undertaken, if educational initiatives need to be held, and if changes to package inserts, scheduling status or manufacturing processes need to be made (20). The scope of PV includes the study of ADRs and their related reporting procedures. It also

encompasses medication errors, abuse and misuse of medications, overdose, drug-drug interactions, lack of efficacy, and Substandard, Spurious, Falsely labelled, Falsified Counterfeits (SSFFCs) (21,22). All these categories are concerned with quality and safety of the drug which, if compromised, poses a risk to patient safety. Thus, PV can be considered a highly complex and crucial aspect of drug safety.

1.4. Adverse drug reactions – what are they?

It is important to differentiate between the terms “adverse drug reaction”, “adverse event”, “adverse effect”, and “side effect”. The WHO defines ADRs as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (12,23). Adverse drug reactions can be classified into 6 types of reactions, namely, type A through to type F, each with an accompanying mnemonic as seen in Table 1.1 adapted from Edwards and Arson (24). An adverse event is defined as “any untoward medical occurrence that is temporarily associated with the use of a medicinal product but is not necessarily causally related” and a side effect is an “unintended effect occurring at a normal dose and is related to the pharmacological properties of the drug” (23,24). The Council for International Organisations for Medical Sciences (CIOMS), established in 1949 by the WHO and the United Nations Educational, Scientific and Cultural Organisation (UNESCO), is actively involved in PV (25). In 1968 the CIOMS set up its first working group on PV, a Working Group on International Reporting of Adverse Drug Reactions, with the aim of “coordinating and standardizing international adverse drug reporting by pharmaceutical manufacturers to regulatory authorities” (26). The WHO, the CIOMS and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) were the organisations involved in creating the definitions for the field of PV (23). The CIOMS states that the terms “adverse reaction”, “adverse effect”, “suspected adverse (drug) reaction” and “undesirable effect” are synonymous with “adverse drug reaction”. Additionally, “adverse experience” is synonymous with “adverse event” (27).

Table 1.1 Classification of adverse drug reactions

Type of reaction	Mnemonic	Features
Type A: Dose-related	Augmented	Common, predictable
Type B: Non-dose-related	Bizarre	Uncommon, unpredictable, high mortality
Type C: dose-related and time-related	Chronic	Uncommon, usually related to cumulative dose
Type D: Time-related	Delayed	Uncommon, occurs sometime after drug use
Type E: Withdrawal	End of use	Uncommon, occurs soon after cessation of drug use
Type F: Unexpected treatment failure	Failure	Common, dose-related, may be due to drug interaction

(24)

1.5. Spontaneous reporting and post-marketing surveillance

Traditionally, PV and PMS relied on spontaneous reporting systems that primarily received physicians' reports. This later progressed to include reports submitted by other HCPs and more recently, patients (18). Spontaneous reporting is still the most common system of ADR reporting for the early detection of ADRs (28). A spontaneous report is an unsolicited communication, received by RAs or pharmaceutical companies from a HCP or consumer and details a suspected adverse reaction that occurred in a patient using one or more medicinal products (27). Some of the advantages of spontaneous reporting systems (SRSs) include the following (29–31):

- their low cost and time efficiency,
- SRSs include reports for all drugs that are used across the entire population compared to specific drugs in predefined populations as seen in clinical trials, and
- SRSs detect rare, new and serious ADRs.

However, spontaneous reporting has limitations, the most important of which is under-reporting (30,32–33).

1.6. The consequences of adverse drug reactions

Adverse drug reactions have been found to be associated with increased morbidity and mortality, with ADRs also contributing to hospitalisations and increased healthcare costs (34,35). Adverse drug reactions negatively impact the patients quality of life, resulting in decreased confidence in medications and HCPs and ultimately lead to poor treatment outcomes (36). Studies have found antineoplastic agents to be one of the most common drug classes associated with ADRs (30,37,38), with the antineoplastic and immunosuppressive drug classes being responsible for 6% of fatal ADRs (39). Non-communicable diseases (NCDs), such as cancer, have been cited by the WHO to become the leading cause of death by 2030 (40).

1.7. Cancer chemotherapy and adverse drug reactions

Cancer ranks as the second leading cause of death globally, with the annual cancer economic cost estimated at US$ 1.16 trillion in 2010 (41). Approximately 70% of deaths from cancer occur in LMICs (42) due to weak and poorly resourced healthcare systems (13). Chemotherapy forms part of a multimodal approach in the treatment of cancer (43). Cancer chemotherapy involves a multi-drug regimen of antineoplastic agents, pre-treatments and palliative care that utilises other medications to manage side effects and ADRs, such as anti-emetics and analgesics. This renders cancer patients more vulnerable to ADRs due to polypharmacy (44,45). Some of the ADRs associated with cancer chemotherapy include nausea and vomiting due to emetogenicity of the drugs, as well as diarrhoea and anorexia (46). These effects of chemotherapy can lead to malnourishment and organ dysfunction in cancer patients, which, in turn, can affect the drug's pharmacokinetics resulting in drug toxicity (47). Additionally, the high toxicity and narrow therapeutic index of the chemotherapeutic agents themselves compounds the high incidence of ADRs (48,49). Adverse drug reactions specifically related to chemotherapy have been linked to an increased mortality rate, an escalation in the cost of therapy (50), an increase in the length of stay and cost associated with hospitalisation (30) and found to negatively impact on the quality of life (QoL) of patients (51). These factors, coupled with the extensive under-reporting of ADRs in general and in the field of oncology in particular (44–46,52), underscore the necessity for PV and the prioritisation of patient safety.

1.8. Problem Statement

The under-reporting of ADRs has been widely acknowledged in literature (8,20,53–55). The reasons for under-reporting vary between studies, but poor reporting has been frequently attributed to the lack of PV knowledge and training, time constraints, and indiscernibility of the causative agent of an ADR (28,29,56,57). In addition, LMICs and developing countries are faced with financial constraints, poor infrastructure, lack of resources such as reporting forms and HCPs that are inadequately equipped with the knowledge on how, when and where to report ADRs (8,13,58). Additionally, there is a growing incidence of cancer in LMICs (59). Poor reporting patterns in LMICs, coupled with the increasing incidence of cancer in these countries and the under-reporting of chemotherapy related ADRs, emphasise the extent to which PV is needed. Under-reporting of ADRs is a major issue that hinders signal detection, thus having a knock-on effect on regulatory action and patient safety that heavily relies on signal generation (8). With the high incidence of ADRs, patient safety is compromised (53,60).

Breast cancer is the most prevalent cancer globally, is the most commonly diagnosed cancer in females and is responsible for the most cancer-related deaths in females (Sung et al., 2021). More specifically, hormone receptor (HR) positive breast cancer, which warrants the use of routine anti-hormonal agents such as anastrozole, fulvestrant and tamoxifen, is the most commonly occurring breast cancer subtype. In LMICs, access to essential medicines is a problem, with state of the art, novel medicines usually not being an option in resource-scare settings (8,13). Thus, there is a reliance on such routine medicines. Little is known about post-marketing side effects and ADRs of drugs in such a setting, hence conducting analysis from VigiBase® can provide vital information for practice and further research in LMICs.

1.9. Research question

What are the demographic profiles and the patterns of ADRs that have been reported to VigiBase® for anastrozole, fulvestrant and tamoxifen?

1.10. Aim and objectives

This study aims to analyse and describe anastrozole, fulvestrant, and tamoxifen related ADRs as reported by national pharmacovigilance systems to VigiBase®, a World Health Organization International Drug Monitoring Program database.

Study objectives:

- To identify, describe and categorise anastrozole, fulvestrant and tamoxifen related ADRs.
- To assess the associations of age and gender with the top 10 adverse drug reactions for anastrozole, tamoxifen and fulvestrant.
- To assess and compare the adverse drug reactions identified from the study with the package insert of the drugs.
- To describe anastrozole, fulvestrant and tamoxifen related ADRs and characterize their seriousness.

1.11. Significance of study

Well known adverse reactions and safety signals are widely published, however, analysis of comprehensive information on the ADRs of anastrozole, fulvestrant and tamoxifen from a single global source has not been performed. With a rising incidence of cancer in LMICs, and underdeveloped PV systems, providing a concise overview of the frequently reported and serious ADRs associated with commonly used cancer drugs for the most prevalent cancer (breast cancer) in LMICs could be beneficial to HCPs. Reporting on global patterns of ADRs on the above-mentioned drugs can assist HCPs in evidence-based evaluation of ADRs and eventually aid in reducing hospital stays and associated healthcare costs, and improve clinical outcomes (37,61). Identifying at-risk populations for specific ADRs can lead to the use of alternative treatments, if available, and better management of the patient as well as inform policy and improve patient safety. Additionally, the use and analysis of a population database can be beneficial in evaluating potential ADRs (31).

CHAPTER 2
Literature review

Chapter overview

This chapter discusses the importance of pharmacovigilance, national pharmacovigilance systems and its growth throughout the world. To further illustrate the magnitude and scope of pharmacovigilance, adverse drug reactions, their implications on health, and under-reporting will be explained. More specifically, the chapter looks at the adverse drug reactions within the field of oncology, with particular attention to anastrozole, fulvestrant and tamoxifen, three drugs used in the treatment of hormone receptor positive breast cancer.

2.1. Pharmacovigilance – what is it?

Pharmacovigilance is primarily concerned with drug and patient safety. It is a multi-faceted field that involves drug safety monitoring, evidence-based regulatory adjustments, educational initiatives and global collaboration and harmonisation (62). The concept of drug regulation and pharmaceutical testing of medicines for their safety in patients resulted from the thalidomide tragedy that mainly affected the western world in the 1960s (1,2). This led to the establishment of the WHO PIDM and thereafter, many WHO collaborating centres that aided in the dissemination of PV, its methodologies, and its principles throughout the world (62). Medicines and medical devices cost up to 6% and 45% of country's national health budget for developed and developing countries, respectively. With drug-related issues such as ADRs being common and costly, the need for a system that monitors the safety of drugs to ensure patient safety can be considered a "cost-effective commitment of resources" (5).

The WHO has largely promoted pharmacovigilance through reports and guidelines which assist national health departments in establishing NCs and expanding their roles in drug safety and surveillance. The WHO considers it necessary for an NC to be supported by a regulatory body that will consider the NC's data and undertake the necessary related actions (63). It is the responsibility of the individual national health

departments to adhere to these guidelines so as to conform to international standards and ensure a successful and efficient PV system. The WHO and the UMC provide support and assistance to countries wanting to develop their national PV programs and set up a monitoring system (63). National PV centres aid in creating public awareness surrounding drug safety. This enables the role of PV as a regulatory activity due to its influence over clinical practice and public health policy implementation (62).

2.1.1. Setting up a national pharmacovigilance centre

The WHO, along with The Global Fund, have established “Minimum Requirements for a Functional National Pharmacovigilance System” which states that the following needs to be present within any national PV system: an NC with designated staff, funding and collaboration with the WHO PIDM; a national spontaneous reporting system and accompanying ADR reporting form; a national ADR report database; a national advisory committee to provide technical assistance and a proper communication strategy (17).

According to the UMC guideline (63), the ideal setting for establishing an NC would be within a national drug regulatory authority, but a clinical department in a hospital or academic environment such as a university is also suitable. Setting up a centralised system with a main national centre that receives and manages all reports. Although a decentralised approach is possible, this requires strong communication and collaboration and may be more costly due to the need for more staff and facilities (63). On the other hand, since an NC requires reliable communication and collaboration, starting the centre locally and later expanding to national level may allow for an easier transition into the PV system (63). Pharmacovigilance goes hand in hand with drug regulation so governmental support is crucial for nationwide co-ordination, collaboration, and communication for a robust PV system. The second step is to establish connections with key stakeholders and have HCPs inform them of the purpose and importance of PV, followed by developing an ADR reporting form and disseminating information about PV and the accompanying terms and methods. The minimum requirements for a reporting form includes patient details such as age, sex, and medical history. Information regarding the ADR experienced, the suspected drugs and other drugs the patient was using, and the reporter details are also needed (63). The recruitment and education of staff and the development of an ICSR database

follows. Lastly, the principles and requirements of PV and ADR reporting must be widely communicated to promote their importance (63).

Once established, the NC must ensure it fulfils the main functions of a PV system as laid out by The Global Fund and the WHO. These functions include the promotion of PV, collecting and managing ADR reports, and, if applicable, harmonising existing ADR report collection activities within the country. Identifying medicine safety signals, medicine quality issues that may result in ADRs and issues with unregulated prescribing and dispensing are also key functions of a PV system. Undertaking risk assessments and risk mitigation options, effectively communicating information related to medicine safety such as correcting misinformation and providing PV information in the interest of public health and, lastly, developing and maintaining drug utilisation information (17).

2.1.2. Pharmacovigilance indicators

The WHO has detailed PV indicators, which are measures of inputs, processes, outputs, outcomes, and impacts of development that establish how well a PV system is achieving its objectives. Figure 2.1 illustrates the indicators and their respective outcomes. The indicators should be able to determine strengths, weaknesses, achievements and growth or the lack thereof as well as assess PV activities, and capacity, provide tools for supervision of activities and tools to measure the impact of PV interventions (64).

2.2. The importance of pharmacovigilance

Pharmacovigilance aims to, with the use of medicines and medical devices, improve patient safety and care, improve public health, encourage the safe and rational use of medicines, assess the risk, benefit, harm and efficacy of medicines and promote training and education regarding PV (62). Pharmacovigilance ensures the continuous safety of medicines by identifying their associated risks, it informs regulatory actions such as labelling changes, safety alerts, drug recalls or withdrawals and allows for

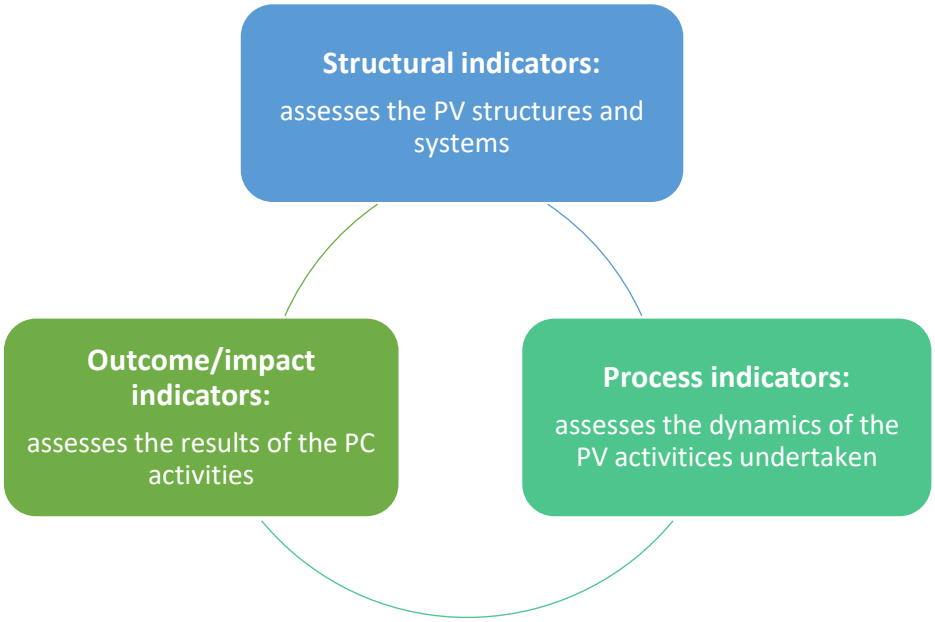


Figure 2.1 Pharmacovigilance indicators

appropriate medicine use when communicated effectively (19). Pharmacovigilance should have a strong affiliation to regulatory authorities to inform them of safety issues that could further require regulatory intervention (62). Additionally, awareness surrounding ADRs is crucial since reporting ADRs helps to determine whether additional investigations need to be undertaken, if educational initiatives need to be held, and if changes to package inserts, scheduling status and manufacturing processes need to be made (20).

2.2.1. How pharmacovigilance is implemented

The main focus of PV is on ADR reporting and PMS in order to detect safety signals, however, the scope of PV includes, issues related to SSFFCs, medication errors, off-label use of medicines, medicine abuse or misuse, poisoning, overdose and drug-drug and drug-food interactions as these also pose a threat to patient safety (22,62,64). There are many different signal detection systems that can be used, however, the most used is spontaneous reporting.

2.2.1.1. Passive surveillance

Spontaneous reporting is a form of passive surveillance and is defined as “a communication to a regulatory authority or pharmaceutical company by a healthcare

professional or patient describing a suspected ADR" (12). Spontaneous reporting systems are considered the cornerstone of PV as it is crucial in signal detection (62). Spontaneous reporting systems are the easiest and most commonly used drug surveillance systems, it is also cost-effective and useful in early signal detection (28,65). It enables the collection of safety information for all drugs on the market and the entire population (33). Additionally, SRSs provide vast amounts of data from a 'real-world' perspective (66) and are the only reporting systems that allow for continuous drug safety monitoring throughout the drugs' existence on the market (67). Lastly, spontaneous reporting can detect rare ADRs that occur temporally after the initial use of a drug (31). However, spontaneous reporting has many limitations such as under-reporting, duplicated reports, the influence of the media on reporting, and the inability to detect ADRs that have a delayed onset (68), as well as the uncertainty regarding the causality of the ADR and the frequency of the ADR (18). Spontaneous reporting is also limited when it comes to determining the incidence and frequency of ADRs since the denominator value is not known (65). These limitations demonstrate a need for other forms of drug safety surveillance such as active surveillance.

2.2.1.2. Active surveillance

Active surveillance, on the other hand, consists of targeted monitoring for specific ADRs or events and involves cohort event monitoring (CEM), targeted spontaneous reporting (TSR) systems and pregnancy exposure registries (64). Active surveillance involves the active, continuous monitoring of a specific population for ADRs. It can provide incidence estimations and possible risk factors associated with an ADR (69). Actively surveying data can aid in identifying at risk populations and discovering interactions not previously investigated (70). Numerous active surveillance initiatives have been implemented across North America, Europe, and Australia to decrease reliance on SRSs (32), however, these systems have not been widely implemented in LMICs (69).

Public health programs (PHPs) are aimed at decreasing morbidity and/or mortality by treating large proportions of the population for a specific disease. In many developing countries, NCDs and infectious diseases impose a large burden on the healthcare systems. With the use of medicines within the PHPs, PV is essential to safeguard the patient from potential harm (5). For example, in SA, many TSR systems were launched

over the years, mainly focusing on the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) epidemic, to expand on national PV in SA. A decentralised approach was taken for TSR of antiretrovirals (ARVs) and was found to be successful (53) and expanded as part of the National Department of Health (NDoH) PV Centre for PHPs in 2011 (71). This decentralised system allowed for multi-disciplinary teams to review ADR reports associated with ARVs and helped identify trends in antiretroviral therapy (ART) (72). By 2013/2014, this programme expanded to include the North West province and was supported by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS), which is funded by the USAID (73). Financial support from USAID, the WHO, The Global Fund etc. enabled capacity building and promoted PV training not just in SA but in the rest of the continent (13).

2.2.2. The need for drug safety monitoring

Post-marketing surveillance is defined as “the practice of monitoring safety and effectiveness of pharmaceutical products or other consumable medical products after it has been released on the market with the objectives to decrease mortality and morbidity associated with adverse events and improving understanding of effectiveness in real-world situations” (74). Pre-marketing studies aim to establish the drug’s toxicity profile but fall short when detecting important ADRs. Thus, PMS bridges that gap by identifying uncommon ADRs that could be serious as well as unrecognised ADRs (62,75) and potential safety signals (76). A signal is defined as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”. Generally, more than one ICSR is required to generate a signal but it is dependent on the quality of the report and the seriousness of the event (63). A signal may present as an increase in the frequency or the severity of an ADR or an ADR not previously known within a particular population. Once a signal is identified, further investigations need to be carried out to determine whether the signal is of concern and how to manage it thereafter (77). Signal generation is a crucial part of PV, however, poor reporting hinders signal detection and generation and, in essence, PV as a whole (8). Hence, PMS, which is the collection and identification of information regarding medicines once the regulatory authority has approved them for use by the public, is an integral component of pharmacovigilance (75). Post-marketing surveillance plays a role in

confirming whether a medicine is safe for use by a greater population than that of the clinical trial (12). This provides more realistic results as it identifies rare ADRs (78).

The WHO has emphasised the need for a PV system that is reliable to promote the rational, safe and cost-effective use of drugs within all countries (62). Pre-clinical trials cannot be considered predictive of human safety thus, clinical trials are necessary. Despite extensive drug safety studies conducted in pre-marketing/clinical trials, the data obtained is incomplete (63). Toxicities and ADRs need to be investigated post-marketing even if ADRs had already been identified during clinical trials (79). Although clinical trials determine the safety of newly introduced drugs, it is usually the common ADRs that are identified (80). This is because clinical trials are subject to strict inclusion and exclusion criteria (79), whereas, in reality, patients may be part of a special population group such as the elderly, who are at an increased risk of ADRs as a result of concomitant treatment which predisposes the patient to drug interactions, medical errors and comorbidities (49,81). Additionally, rare but serious ADRs that require a much larger sample size may not be detected in clinical trials (62). It has been reported that 30 000 people would have to use a drug to detect an ADR that occurs in only every one in 10 000 people (82). Thus, clinical trials are limited due the use of a small number of specific patients, short follow up durations and the exclusion of special populations, limiting heterogeneity (61). Additionally, information regarding potential drug-drug interactions and the effect of the drug in patients with co-morbidities may not be deduced from these trials (63). Clinical trials lack sufficient power to reliably identify ADRs that are uncommon or rare as well as to detect ADRs that have a delayed onset or are due to long-term use of the drug as a result of short follow up times (31). Therefore, the need for PMS and drug safety monitoring is essential to understand the safety profile of the drug in a ‘real-world’ setting (61) since PMS can provide a more accurate description of a drug’s safety profile, thus bridging the gap between clinical trials and clinical practice (83). Post marketing surveillance can also aid in decreasing morbidity, mortality, healthcare costs and the length of stay in hospitals (84).

International PMS is useful as it provides drug safety information that may not have been recognised yet in a country. However, drug safety monitoring conducted in the country of origin of the drug does not take into consideration certain factors such as

traditional and genetic differences that patients may exhibit in another country (63). Developing countries have unique disease burdens and socioeconomic circumstances (85). Clinical trials are largely confined to developed countries; thus, their safety outcomes cannot be assumed for people in developing countries like African countries (86). The need to have PMS in these LMICs is warranted by the lack of inclusion of these populations in clinical trials, thus, the drug's safety within this population may be undocumented (13). However, with poor PV systems, there is a risk of drug use in local populations not being adequately monitored (86). Therefore, not only is it necessary for PMS of all drugs, but it is also necessary for PMS to be conducted in all countries. Safety data from individual countries has great educational value and its relevance can allow for specific regulatory actions to be considered nationally (63).

2.3. The growth of pharmacovigilance internationally

The thalidomide tragedy in the 1960s was the event that sparked concern over drug safety. Countries such as Australia, Japan, Germany and other European countries bore the brunt of the tragedy (1) while developing countries such as those in Africa were protected as a result of their poor ATM (13). The field of PV has grown throughout the years, particularly in Africa where in the space of 10 years (2000 to 2010), the number of WHO PIDM member countries increased from five to 24, with an additional nine associate members (13). This number increased to a total of 35 member countries in 2015 (8). This can be attributed to the work of the WHO and UMC (13). Recently, due to the Coronavirus disease 2019 (COVID-19) pandemic, there has been an increase in PV awareness because of the fast-tracking of vaccine approval in the interest of public health (87). The growth was recognised through the rapid increase of ADR reports sent to the UMC for VigiBase® (9).

Many LMICs have ramped up their efforts to partake in PV activities (22,88). However, the divide between developed and under-developed/developing countries remains an issue, with the inequality between these countries greatly disadvantaging the people of the latter. There are many reasons why developing countries, or LMICs, have had a delayed response, if any, to drug safety and, in essence, PV. One of these reasons is poor ATM, with an estimated 50–80% of the African population with inadequate ATM

(13). As a result, PV was not seen as a priority; the focus was rather on attaining medicines that could treat the vast burden of disease within the countries which saw ADR monitoring and drug safety taking a back seat. With the financial help of international organisations such as The Global Fund, USAID, and through the implementation of PHPs, ATM increased (8,15,88). However, despite an increase in ATM in resource-limited countries, the development of PV activities and practices has not been proportionate (22,83). Poor legislation and uncoordinated supply chains (8), a lack of basic infrastructure and personnel, insufficient training and education of HCPs and weak policies resulted in the setback of early detection, assessment, and management of drug safety problems (58). Resource constraints and overburdened healthcare systems (22) are also contributing factors to weak PV systems. The need for PV and safety monitoring in these resource-scarce settings is necessary because of the difference between the morbidity profiles and burden of disease which has largely been undocumented (13).

2.3.1. Pharmacovigilance systems in developed countries

The PV and PMS systems in developed countries have been in existence since the WHO established the PIDM following the thalidomide tragedy in the 1960s (13). In 2012, developed or high-income countries such as the United States (US), the United Kingdom (UK), Australia, Canada and European countries, contributed 85% of ADR reports in the study, with middle-income and low-income countries contributing the remaining 15% of reports (89). Now, 45% of reports in VigiBase® come from the US and 20% from the European Union (EU) (9).

One of the first PV systems targeted at mitigating ADRs was the Yellow Card scheme in the UK which came into existence in 1964. Thereafter, several other initiatives aimed at improving ADR reporting and awareness were launched as an extension of the Yellow Card scheme. The scheme is based on voluntary spontaneous reporting from HCPs with the intention of, as with all spontaneous reporting systems, detecting rare but serious ADRs that may not be identified during clinical trials due to small sample populations. The Medicines and Healthcare Products Regulatory Agency (MHRA) has additional initiatives where reporting is mandatory. These include black triangle products wherein newly released products are marked with an inverted black triangle. This requires all suspected ADRs for such products to be reported despite

the severity of the ADR. Additionally, all serious ADRs, ADRs resulting in death, disability or incapacitation and congenital abnormalities, and medically significant ADRs for such black triangle products, must also be reported. When a Yellow Card is completed with all the appropriate information, it is submitted to the MHRA, an acknowledgement of receipt is sent to the reporter and the data is stored on the MHRA database. Regulatory action can be recommended to the MHRA by the Pharmacovigilance Expert Advisory Group (75,90).

The PV activities within the EU are managed mainly by the European Medicines Agency (EMA) as well as the European Commission and EU member states. The EMA has a Pharmacovigilance Risk Assessment Committee (PRAC) that monitors and assesses the safety profiles of human medicines as well as evaluating possible safety signals as received from EudraVigilance. EudraVigilance is the EMAs database of suspected ADRs from medicines that have been authorised for use in the European Economic Area (EEA). Each EU member state also has its own national regulatory authority (91,92).

In Canada, Health Canada is the national regulatory authority wherein Canada's PMS program, the Canada Vigilance Program, now known as MedEffect Canada, is operated. It was established in 1965 and relied on voluntary reports from consumers and HCPs. The reports can be submitted either to Health Canada directly or to the market authorisation holder. Pharmaceutical manufacturers are also required, by Health Canada, to submit periodic safety update reports (PSURs) at regular intervals to demonstrate continuous drug safety. MedEffect Canada has an online database, Adverse Reaction Online, which houses ADR data for drugs and natural products. Health Canada uses the MedDRA terminology in their ADR reports to allow for easy transfer of information as set out by the ICH. Promoting education amongst the healthcare community via the MedEffect website and a monthly newsletter which is shared with HCPs and details safety information are two of the initiatives Health Canada has undertaken to improve communication and PV awareness (75).

In the US, the United States Food and Drug Administration (US FDA) is responsible for the country's PV program, ensuring the use of safe and effective medicines. The US was the first country to have regulations specific to drug safety. The Centre for

Drug Evaluation and Research (CDER) falls under the FDA. The CDER houses the Office of Surveillance and Epidemiology which is where the Office of Pharmacovigilance and Epidemiology is located. The Division of Pharmacovigilance manages drug and, therefore, patient safety, signal detection, safety communications and regulatory actions. The FDA receives reports that have been voluntarily submitted by HCPs, patients, and consumers either to pharmaceutical manufacturers or via the FDA MedWatch safety information and adverse event reporting program. These reports are stored in the FDA Adverse Event Reporting System (FAERS) which is a spontaneous report database. Majority of the reports are received from manufacturers due to the mandate to submit ADR reports (92,93). It was the work of the FDA, more specifically, Dr Frances Kelsey, in the 1960s that prevented the approval for thalidomide to be used in pregnant women which helped avoid the tragedy in the country (1).

2.3.2. Pharmacovigilance systems in developing countries

In general, healthcare systems in resource-limited countries are over-burdened and fragmented compared to those in developed countries. There is usually a divide between the public and private sector, with the former having primary, secondary and tertiary facilities (15). Low-to-middle income countries are burdened with many non-communicable diseases and infectious diseases that are targeted through PHPs. However, with a lack of PV to monitor the safety of the drugs used in these PHPs, populations are left vulnerable (15). The following points are ways in which PV can improve in LMICs (15):

- include adjustments to curricula at universities to establish a basic PV knowledge for HCPs,
- stronger regulatory requirements,
- standardising the report format to the ICH-E2b format for easier ICSR upload to VigiFlow,
- establishing a PV system within a hospital or university to avoid political changes that may accompany the ministry or department of health in LMICs due to volatile political circumstances,
- focusing on counterfeit medicines which are of particular importance in LMICs,
- engaging patients in ADR reporting,

- incentivising ADR reporting for HCPs which may, in turn, allow HCPs to provide better care to patients which can improve treatment outcomes, and,
- making it mandatory for market authorisation holders (MAHs) and HCPs to report ADRs.

Studies have found a low contribution of ADR reports to VigiBase® from LMICs. Africa was found to contribute less than 1% of ADR reports in VigiBase® in September 2015. Just over 15% of reports come from LMICs, which is an improvement from 5% over the past decade (9). In LMICs, PV can be considered a new concept in comparison to the developed countries who have well established PV systems (22). There are many factors that hinder the development of a robust and well-functioning PV system in LMICs. Multiple studies have found these factors to be a lack of funding, infrastructure, training, PV knowledge, personnel such as HCPs, and cumbersome reporting forms as well as language barriers and issues relating to submitting ADR reports (8,15,58,83). A study looking at the PV systems in 55 LMICs (22) found similar limitations to PV. Other finding from the study include: seven countries did not have a PV system; only 23 of the 55 countries had a budget for PV activities, with the majority of these budgets allocated as part of the health budget and not dedicated to PV; most PV centres were not adequately staffed; in 33 countries, market authorisation holders are legally required to report suspected ADRs and in 25 countries, they are legally required to submit PSURs. The study found gaps in the PV systems and concluded that these LMICs need to establish PV systems that serve and prioritise that country's unique needs (22).

The development of PV in LMICs like many countries in Africa may be attributed to the work of the WHO and the establishment of WHO collaborating centres in Morocco and Ghana, as mentioned in section 1.2., to expand PV activities on the continent. The collaborating centres aimed to assist in training and supporting NCs (15). A study evaluating the organisational capacity of NCs in Africa found factors that limit the country's PV activities. Many PV centres in Africa were established with the aid of international organisations that influenced the PV activities conducted in that country. Heavy reliance on other stakeholders may lead to uncertainty regarding the future of PV initiatives. Additionally, the lack of consistent governmental support leaves

populations vulnerable to drug-related problems that could be mitigated by well-functioning PV systems (88). However, PV amongst African countries continues to grow. Collaboration between African countries led to the establishment of the African Medicines Regulatory Harmonisation (AMRH) in 2009 by the New Partnership for African Development (NEPAD), to collectively tackle challenges faced by national regulatory authorities such as limited technical capacity, weak legislation and delayed medicine registration and subsequent approval. The main aim of AMRH is to enable access to safe, efficacious, affordable medicines of quality by rectifying and optimising medicines registration processes (94). Further growth resulted in two regional centres for regulatory excellence (RCORE) in Kenya and Ghana (15).

South Africa was one of the first African countries to join the WHO PIDM in 1992. Based on the number of reports submitted to UMC from WHO PIDM member countries in Africa, SA ranks number one, with 28 609 ICSRs in by 2015. However, when taking how long a country has been a WHO PIDM member as well as the population size into consideration, SA ranks further down with 27.22 ICSRs per million person-years (8). The South African NDoH established the National Adverse Drug Events Monitoring Centre (NADEMC) in 1987 and South Africa became one of the first African countries to join the WHO PIDM in 1992 after meeting member criteria (95). The NADEMC, which is a satellite unit of and operates under the South African Health Products Regulatory Authority (SAHPRA), collates reported data, and assesses the risks and causality of the ADRs. South Africa has two programmatic units that work in collaboration with the Regulatory Pharmacovigilance unit of SAHPRA, namely the Extended Programme for Immunisation (EPI) unit and the NDoH Pharmacovigilance Centre for Public Health Programmes (DoH-PvPHP) (12). Recently, SAHPRA launched the MedSafety mobile application that can be used by HCPs and patients to report ADRs and look up drug safety information.

In SA, the healthcare sector is divided into the private sector, accounting for 27% of the population, and public sector which attends to the majority of the population (96). The ADR reporting procedures for the two sectors differ. The public sector encompasses state-funded hospitals that report ADRs via the facility's Pharmacy and Therapeutics Committees (PTCs). The PTCs, which are established at the various

levels of the public healthcare sector, promote rational use of medicines and implement policies to aid in the management of the different stages of drug supply (97). Private sector includes private hospitals and pharmacies, as well as the pharmaceutical industry. The number of reports received from the public sector is high in comparison to that of the private sector due to the increased number of ARV submissions (19).There is not much evidence surrounding the reporting systems of the private sector but in industry, there is a robust PV system in place.

South Africa had legal requirements regarding ADR reporting (19). Section 2B - functions of the authority - of the Medicines and Related Substances Act (MRSA) (Act 101 of 1965), which governs the registration of medicines in South Africa, states under subsection (1) that “evidence of existing and new adverse events, interactions, information about PMS and vigilance is being monitored, analysed and acted upon”. Regulation 37 of the MRSA legally requires the pharmaceutical manufacturer of a drug to report suspected ADRs to the council (previously MCC, now SAHPRA) (98). ADR reports from the pharmaceutical industry and HCPs can be sent to SAHPRA, the NADEMC or can be sent to the pharmaceutical manufacturer of the drug suspected of causing the ADR. Reports can be sent through via email, fax or using the Essential Medicines List (EML) Clinical Guidance mobile application. All reports are then sent to UMC by entering the data into the VigiFlow ICSR management system by SAHPRA staff (12).

Despite the efforts and progress that has been made in SA, research has found that the ADR reporting rate is low, and the national PV system is not yet functioning optimally due to a lack of human, financial and technical resources (19).

2.4. Adverse drug reactions

Adverse drug reactions are an associated risk with the use of all medications (61). They have economic implications and a significant impact on clinical outcomes in clinical practice. It is estimated that ADRs may cost the US $30.1 billion annually (61). In the US, the incidence of serious and fatal ADRs are high, with fatal ADRs estimated to be between the fourth to sixth leading cause of death (99). Some developed countries have recorded hospital admissions due to ADRs, accounting for > 10% of all

hospital admissions. However, data on ADRs in developing countries is limited but is estimated to be worse than that of developed countries (82).

2.4.1. How to identify adverse drug reactions, what should be reported and who can report?

It can be difficult to differentiate between certain disease states and ADRs. To identify a drug-related problem, HCPs need to determine whether the reaction did in fact follow the use of the drug in question. The time interval between the initial use of the drug and the onset of the reaction also needs to be established (82). The concept of a "dechallenge" is when a drug is withdrawn from a patients' regimen to determine if the drug in question is the cause of the adverse event. A negative dechallenge means that the adverse event persisted when the drug was withdrawn and a positive dechallenge means that there was either a partial or complete resolution of the adverse event when the drug was withdrawn. A "rechallenge" on the other hand is when a drug is reintroduced into the patients' therapeutic regimen but only following a positive dechallenge. A negative rechallenge means that the drug failed to produce similar signs and symptoms as before when it was reintroduced and a positive rechallenge means that, when reintroduced, there was a reoccurrence of the signs and symptoms (12). Both dechallenges and rechallenges, which aid in establishing a possible link between drug and adverse event, require the patient to be monitored, thus, they may only be possible in an inpatient setting. A HCP also needs to evaluate any other possible causes of the ADR and consult the relevant literature and resources before reporting the ADR to the relevant authority (82).

Many products are included in PV, not just medicines. Herbal and traditional medicines, medical devices, blood products, biologicals, vaccines and complementary medicines are all subject to PV and safety monitoring (64). It is important to report all suspected ADRs that may be considered of clinical importance. Cases for when an ADR should be reported include: when a new drug enters the market, all suspected ADRs must be reported regardless of their severity or seriousness; when there is an increase in the frequency of an ADR; all serious and unusual ADRs for well-known or common drugs; any ADR that is suspected to be due to drug-drug, drug-food or drug-food supplements as well as complementary and herbal remedies; ADRs associated

with drug overdose, withdrawal or abuse; ADRs occurring when a drug is used during pregnancy or lactation and lastly, when there is a lack of efficacy of a drug (82).

Healthcare professionals have a pivotal role in PV as the success of spontaneous reporting is largely dependent on HCPs contribution to ADR reporting (62). Healthcare professionals are ideally placed within the healthcare sector to identify and report ADRs due to their everyday interaction with patients (82). Healthcare professionals, consumers, and patients can report suspected ADRs to the relevant RAs or the NCs. These reports will be collated and evaluated before being sent off to the ICSR database, VigiBase®, for further analysis. Pharmaceutical manufacturers also submit PSURs and suspected ADRs to the RA (64). National regulatory agencies may require HCPs to report ADRs, however, there are usually no consequences if ADRs go unreported. Pharmaceutical manufacturers in certain countries are also required to report suspected ADRs via PSURs to RAs (18).

2.4.2. The impact of adverse drug reactions on patient health and healthcare

Adverse drug reactions are known to be a risk associated with the use of any medicine (37,61,84). Adverse drug reactions have been found to be associated with increased morbidity and mortality, with ADRs also contributing to hospitalisations and increased healthcare costs (34,35). Hospitalisation costs were found to be significantly higher in patients hospitalised due to an ADR compared to those who were not (37). Adverse drug reactions negatively impact the patients QoL which can result in decreased confidence in medications and HCPs, ultimately leading to poor treatment outcomes (36). Additionally, the costs related to ADR-associated morbidity and mortality may exceed the cost of the drugs themselves (61), thus, increasing the burden on healthcare systems (100).

Several studies conducted in SA paint a bleak picture of the extent of ADRs in the country. Studies have found that 6.3% (34) and 8.4% (60) of patients admitted to hospital were admitted directly due to an ADR. Furthermore, the reporting rate of ADRs was 14%, which is more than double what was found in other studies, and the mortality rate of community-acquired ADRs was 1.5%, which is 5-10-fold higher than when compared to the UK and US (34). Another study found that ADRs contributed to 2.9% of the deaths and 16% of all deaths recorded were related to ADRs (101). A

questionnaire completed by HCPs across hospitals in the Gauteng province revealed that the spontaneous reporting rate by HCPs was only 16% (56). The use of traditional and herbal medicines, self-medication (54) in conjunction with over-burdened healthcare systems and a high prevalence of noncommunicable and infectious diseases increases the burden of ADRs and drug-related harm in SA (13).

2.4.3. Under-reporting of adverse drug reactions

The drug-induced human suffering and related financial risks associated with ADRs are why PV and PMS are necessary. However, under-reporting greatly undermines signal detection and safety monitoring which can result in underestimating the extent of a drug-related problem. Countries with developed PV centres may only report 10% of serious ADRs (63), thus, the under-reporting of ADRs is a global issue faced in all countries (62). A systematic review conducted to estimate the extent of under-reporting from spontaneous reporting systems estimated an overall under-reporting rate of > 90% for countries such as France, the UK, Sweden and the US. Furthermore, it was estimated that only 6% of all ADRs are in fact reported (29). Since the absolute number of ADRs experienced is unknown, and considering the high estimated under-reporting rate, the real risk associated with a drug is unknown. Reasons for under-reporting include not knowing the reporting requirements, the inability to access reporting forms, a lack of time, indiscernibility of the causative agent of the ADR, lacking in the understanding of reporting and not reporting ADRs that are well known (29).

Under-reporting of ADRs is a major issue since ADRs significantly contribute to patient morbidity and hospitalisation, over-burdening the healthcare systems (34). Multiple studies and surveys conducted have looked into the reasons behind under-reporting in an African setting. The most common reasons include poor PV knowledge; lack of understanding of the reporting procedure, where to submit/report ADRs, and what to report; inadequately trained HCPs; lethargy, complacency, lack of interest and indifference; lack of knowledge regarding the causality of ADRs; fear of litigation; lack of capacity, resources and infrastructure and reporting procedures that are time-consuming, not user-friendly and forms that are inaccessible (13,19,102,22,53–57,71,73). There is also a misconception among HCPs regarding the difference between a side effect and an ADR, which highlights the lack of in-depth PV knowledge

(102). Two studies found an awareness rate of the reporting procedure to be 57.5% (56) and 18.9% (71), respectively, which depicts a significant gap in PV knowledge of HCPs. The African population accounts for 15% of the global population and due to the high number of infectious diseases and increased incidence of non-communicable diseases, the population is exposed to an array of drugs that should, in theory, reflect a high number of ADR reports even if it was just for agents used to treat those specific diseases. As of September 2015, Africa's ICSR contribution to UMC was only 0.88% (103 499 of 11.82 million) of the total number of ICSRs reported to VigiBase®.

2.5. Cancer in context

Cancer is the second global leading cause of death resulting in approximately 10 million deaths in 2020. It is estimated that roughly 70% of cancer-related deaths (103) and 60% of cancer cases occur in LMICs. Research has found that cancer will be responsible for 17.5 million deaths by 2050 (104). Non-communicable diseases, such as cancer, have been cited by the WHO to become the leading cause of death by 2030 (40). The global cancer incidence and mortality is growing and can be attributed to an aging population and population growth (105). Risk factors associated with cancer include physical inactivity, poor diet, tobacco use, alcohol consumption, air pollution (42), obesity, overexposure to sunlight and radiation, and infectious agents (104).

In 2020, 19.3 million new cancer cases and 10 million cancer deaths were recorded worldwide. The number of cancer-related deaths were higher than the number of cases in Asia and Africa due to different cancer types and higher fatality rates. The most commonly diagnosed cancer in men was prostate cancer and lung cancer had the highest mortality whereas, breast cancer was most diagnosed and had the highest mortality in women. Overall, female breast cancer was the most diagnosed cancer in 2020 with 2.26 million new cases, accounting for 11.7% of all cancer cases. This was followed by lung, colorectal, prostate and stomach cancers. Lung cancer was the leading cause of cancer deaths with 18% of the total deaths, followed by colorectal, liver, stomach, and female breast cancer. The cancer incidence rate and the mortality rate was 19% and 43% higher for men respectively (105).

The economic burden that cancer imposes on the country affects the patient and healthcare systems due to productivity lost as a result of morbidity, premature mortality, and increased healthcare costs. In 2017, the estimated healthcare cost for cancer was US$161.2 billion in the US. Additional costs associated with productivity loss from morbidity and premature mortality were estimated at US$30.3 billion and US$150.7 billion, respectively. The overall economic cancer burden in the US amounted to 1.8% of the country's gross domestic profit (GDP). The economic burden of productivity lost due to premature mortality in South Africa, Brazil, India, and China (transitioning countries) is estimated to cost 0.49%, 0.21%, 0.36% and 0.34% of the GDP respectively (106).

Cancer is a growing problem in Africa as a result of an increase in the risk factors that are associated with economic transition and lifestyles seen in high-income countries such as smoking, obesity, physical inactivity, excessive alcohol intake, air pollution and reproductive behaviours which increase the risk of cancer (104,107). The number of new cancer cases in Africa is estimated to increase by 70% between 2010 and 2030 due to the growth of the population and the ageing population (104,107,108). The public health priority in African countries lies with HIV/AIDS, tuberculosis (TB), and malaria (8,13,109), however, cancer is responsible for more deaths globally each year than the abovementioned diseases combined (110).

2.5.1. The global breast cancer burden

Breast cancer accounts for one in every four cancer cases and one in every six cancer-related deaths in women. It is ranked as the number one cancer in 159 of 185 countries. The highest breast cancer incidence rates were in Australia/New Zealand, North America, and northern and western Europe and the lowest in eastern and middle Africa, central America, and south-central Asia. Mortality rates on the other hand, are higher in transitioning countries (105). The incidence rate of breast cancer in Africa, Asia and South America are rising due to changes in lifestyle like a decreased physical activity that leads to increased body weight, later childbearing, and having fewer children. Simultaneously, mortality rates in sub-Saharan Africa have increased and are now the highest in the world (105).

The incidence rate and mortality rate of breast cancer in Africa in 2020 was 8.5% and 12.5%, respectively (111). The age-standardised incidence and mortality rate per 100 000 in southern Africa for breast cancer in 2020 was 50.4 and 15.7, respectively (105). The number of new breast cancer cases in South Africa in 2020 was 14.3% of the total number of cancer cases in the country (112). Breast cancer is the leading cancer in females with South Africa having one of the highest incidence rates in Africa due to high prevalence of risk factors (109). These risk factors include early menarche, late childbearing, fewer children, and increased detection and urbanisation (107,109). Age and environment have been found to have the highest relative risk for breast cancer in a South African study with the use of hormone replacement therapy (HRT), oral contraceptives and the presence of diabetes mellitus also being risk factors (113).

2.5.2. Breast cancer and its treatment options

Prevention has become a key part of the management of breast cancer. Preventable risk factors include decreased alcohol consumption, increased physical activity, avoiding post-menopausal obesity, and encouraging breast feeding. Studies have found that the use of HRT that consisted of oestrogen and progesterone doubled the risk of developing breast cancer in comparison to oestrogen-only HRT which only increased the patients breast cancer risk by 30% (114). The presence of BRCA1 and BRCA2 genes with germline mutations can predispose a person to a lifetime breast cancer risk of up to 80% (115). Screening for early detection of breast cancer can be done usually by mammography. The use of magnetic resonance imaging (MRI) is typically used to define the size and location of the tumour as well as to assess spread to the contralateral breast. Positron emission tomography (PET) scans using fluorodeoxyglucose (FDG) is useful in identifying the stage of breast cancer (115).

Biological tumour markers, namely the oestrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER-2) and Ki-67, can discern the subtypes of breast cancer which in turn determines the treatment regimen a patient will be on (116). Hormone receptor positive breast cancer expresses the ER and/or PgR, and is the most common type of breast cancer with approximately 70% of breast cancers being ER positive (114,117). Human epidermal growth factor receptor 2 positive breast cancer has an overexpression of HER-2 growth factor receptor and offers poor prognosis. Lastly, a triple negative subtype, which also has a

poor prognosis, expresses neither the hormone receptors nor the HER-2 receptors. Typically, neoadjuvant therapy, surgery and adjuvant therapy options are available. The purpose of neoadjuvant therapy is to decrease the tumour size to allow for easier surgical removal. Neoadjuvant therapy can be hormonal for HR-positive breast cancers, involve the use of targeted therapies such as monoclonal antibodies for HER-2 positive breast cancer and can be chemotherapy based for triple negative breast cancer (116,117). However, neoadjuvant use of hormone therapy in premenopausal women has not been established (116). Surgical interventions can be either breast conserving surgery, which is the preferred option, or a mastectomy. Following surgery, adjuvant therapy options are considered. Chemotherapy, hormone therapy, radiation or a combination can be used based on the subtype, metastases, stage, and risk of recurrence. Radiation is usually required after surgery (115,117) to control metastatic disease and prevent the proliferation of residual tumour cells (118).

Regarding hormonal therapy for HR-positive breast cancer, treatment usually consists of agents targeting oestrogen production or oestrogen receptors. Selective oestrogen receptor modulators (SERMs) such as tamoxifen and raloxifene have been the gold standard for many years. Selective oestrogen receptor modulators exert their effect by preventing the binding of oestrogen to the ER, thus, reducing its effect (119). More recently, 3rd generation aromatase inhibitors (AIs) such as anastrozole, exemestane and letrozole have entered the market. Aromatase inhibitors work by preventing the conversion of androgens into oestrogen via the aromatase enzyme, thus, lowering the levels of oestrogen in the body (117). These agents are typically used in postmenopausal women however, tamoxifen can be used in premenopausal women as well. The use of AIs cannot prevent the production of oestrogen from the ovaries, thus, AIs are only used in postmenopausal women (117). Both tamoxifen and anastrozole can be used for early stage and metastatic breast cancer in postmenopausal women (120). As an adjuvant, these endocrine drugs decrease breast cancer recurrence and mortality with long-term treatment. They are used for five years however, individuals with a high risk of recurrence may require more prolonged treatment (121). Tamoxifen was considered the first-line adjuvant treatment for advanced, HR-positive breast cancer in postmenopausal women (118), however, the use of anastrozole as initial treatment is preferred due better tolerability, less adverse effects and greater reduction in recurrence (121). Anastrozole was found to

have significant improvements relating to time-to-recurrence, disease free survival, time-to-distant-recurrence and a reduction in incidence of contralateral breast cancer (122). Fulvestrant is an oestrogen receptor antagonist or down regulator and can be used for HR-positive and HER-2 negative breast cancer (123). Fulvestrant competitively binds to the OR with a greater affinity than that of tamoxifen. It is typically used in metastatic breast cancer in postmenopausal women with disease progression following initial endocrine treatment. It is also effective in tamoxifen-resistant disease (124).

Breast cancer is the leading cancer in SA, accounting for 14.3% and 8.2% of all cancer cases and deaths respectively, and 27.1% of cases in women in 2020 (112). Women in southern Africa have the highest incidence of breast cancer compared to the rest of the continent, which can be attributed to early menarche and late childbearing (109,125). The tertiary and quaternary level EML used in the public healthcare sector in SA has approved the use of many antineoplastics and immunomodulating agents for cancer treatment. Two of the three drugs in this study, namely anastrozole and tamoxifen, have been approved for use and are indicated for adjuvant and metastatic breast cancer as stated on the EML (126).

2.6. Adverse drug reactions in oncology

Adverse drug reactions in oncology are high (38,46). Studies have found antineoplastic agents to be one of the most common drug classes associated with ADRs (30,37), with the antineoplastic and immunosuppressive drug classes being responsible for 6% of fatal ADRs (39). The incidence of ADRs related to chemotherapeutic agents is higher than that of other drugs (127,128). A study found high income countries reported more ADRs for the “antineoplastic and immunomodulating agents” therapeutic class than other countries (89).

2.6.1. The impact of adverse drug reactions in oncology and why they are important

All chemotherapeutics can potentially illicit an adverse drug reaction, but the severity of the reaction varies between patients (129). With regards to spontaneous reporting, HCPs may not report ADRs with a known causality which hinders the ability to

determine the frequency of an ADR (32). More specifically, in the field of oncology, under-reporting of ADRs is prevalent since doctors have been found to not pay as much attention to ADRs that are expected when using a specific drug and when these ADRs do not require treatment changes or additional supportive care (130). Thus, spontaneous reporting of ADRs is seen as inefficient due to the extent of under-reporting that exists (45) since oncology healthcare workers tend to underestimate the incidence of chemotherapy-associated toxicities (51). The treatment of cancer is usually a combination of chemotherapeutic agents to reduce the risk of resistance arising against a single agent (131). Cancer therapy is considered to be complex as it involves combination chemotherapy, palliative care and possibly the use of complimentary and herbal medicines to manage the side effects associated with therapy (79). Chemotherapeutics have narrow therapeutic windows and are usually not specific to malignant cells, causing effects that are an extension of their action. This results in other fast-dividing cells such as those found in hair follicles, the gastro-intestinal tract, bone marrow cells and cells of the reproductive system (51,131) also being effected. It has been found that the longer a person's life expectancy, the greater the risk of developing cancer (79) and there is an increased incidence of ADRs in the elderly (127) which compounds the ADR risk. Therefore, it is easy for HCPs to overlook ADRs in oncology patients as they are considered inevitable or normal; part of the treatment process; or may be mistaken for underlying clinical conditions (46,49,79).

2.6.2. Adverse drug reactions related to anastrozole, fulvestrant and tamoxifen

When clinical trials are conducted, common ADRs and side effects are identified (80). The study populations during clinical trials have limited heterogeneity. Many individuals who will use the drug in a 'real-world' setting may have comorbidities, a larger range in age and may be taking other prescription and non-prescription medications. These variables, which largely are unaccounted for, all have the potential to interact with a drug approved for use after successful clinical trials. Thus, the current approval processes, which are concerned with drug safety and efficacy, cannot fully determine the drugs risk (70). Rare but serious ADRs that require a much larger sample size may not be detected in clinical trials (62). The ADRs detected from clinical trials as seen in the drug's package insert for the hormonal therapies anastrozole, fulvestrant and tamoxifen, are tabulated in Table 2.1 below.

Studies have found that arthralgia is a common ADR associated with the use of anastrozole (121,122). Literature has shown arthralgia is associated with decreased adherence to treatment or even treatment discontinuation in severe cases because of its negative impact on patient QoL and daily functioning (132,133). Anastrozole has an increased risk of fractures as compared to tamoxifen. Urinary tract infections (UTIs), hypertension and osteoporosis or osteopenia are also side effects of anastrozole (121). Additionally, anastrozole use increases serum lipid levels more than tamoxifen (120). Other side effects associated with anastrozole include hot flushes, headaches, asthenia and gastrointestinal effects such as nausea, abdominal pain, diarrhoea and constipation (134). Tamoxifen has an increased risk of uterine cancer associated with its use (135). Tamoxifen is classified as a Class I human carcinogen by the International Agency for Research on Cancer (IARC) due to the development of secondary endometrial cancer (119). Tamoxifen is also associated with the risk of venous thromboembolic and cerebrovascular events such as pulmonary embolism (PE) and deep vein thrombosis (DVT). Fulvestrant is typically well tolerated. Some common side effects associated with its use includes vasodilation, headaches, pain, asthenia and nausea (124).

Table 2.1. Adverse drug reactions and side effects of anastrozole, fulvestrant and tamoxifen adapted from the package inserts of Arimidex® 1mg, Faslodex® and Nolvadex-D® 20mg.

Drug	**Anastrozole**		**Fulvestrant**		**Tamoxifen**	
CIOMS frequency criteria	**MedDRA SOC**	**ADR**	**MedDRA SOC**	**ADR**	**MedDRA SOC**	**ADR**
Very Common ≥ 10%	Gastro-intestinal	Nausea	General disorders and administration site conditions	Injection site reactions, asthenia	Vascular	Hot flushes
	General	Asthenia	Hepatobiliary disorders	Elevated liver enzymes ALT, AST, ALP)	Reproductive and breast	Menstruation suppression
	Musculoskeletal, connective tissue and bone	Arthralgia/Joint stiffness, arthritis	Gastrointestinal disorders	Nausea		
	Nervous system	Headache	Immune system disorders	Hypersensitivity reactions: angioedema and urticaria		
	Skin and subcutaneous tissue	Rash	Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain		
	Vascular	Hot flushes	Skin and subcutaneous tissue disorders	Rash		
			Vascular disorders	Hot flushes		
Common ≥ 1% and < 10%	Gastro-intestinal	Diarrhoea; vomiting	Nervous system disorders	Headache	Vascular	Ischaemic cerebrovascular events; Thromboembolic events, including deep vein thrombosis and pulmonary embolism

Drug	Anastrozole		Fulvestrant		Tamoxifen	
CIOMS frequency criteria	**MedDRA SOC**	**ADR**	**MedDRA SOC**	**ADR**	**MedDRA SOC**	**ADR**
	Hepatobiliary disorders	Increase in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase	Hepatobiliary disorders	Elevated bilirubin	Reproductive and breast	Vaginal bleeding; Vaginal discharge; Pruritus vulvae; Endometrial changes (including hyperplasia and polyps)
	Metabolism and nutrition	Anorexia; hypercholesterolaemia	Blood and lymphatic system	Reduced platelet count	Gastrointestinal	Gastrointestinal intolerance
	Musculoskeletal, connective tissue and bone	Bone pain; myalgia	Gastrointestinal disorders	Vomiting, diarrhoea	Dermatologic	Alopecia; Skin rash
	Nervous system	Carpal tunnel syndrome; somnolence; sensory disturbances (including paraesthesia, taste loss and taste perversion)	Metabolism and nutrition disorders	Anorexia	Nervous	Headache; Light-headedness
	Reproductive system and breast	Vaginal dryness; vaginal bleeding	Infections and infestations	Urinary tract infections	General	Tumour flare; Fluid retention; Drug related fatigue
	Skin and subcutaneous tissue	Hair thinning (alopecia); allergic reactions			Metabolic and nutritional	Weight gain
					Musculoskeletal	Leg cramps
Uncommon ≥ 0.1% and < 1%	Hepatobiliary disorders	Increase in gamma-GT and bilirubin; hepatitis	Hepatobiliary disorders	Elevated gamma-GT	Ophthalmologic	Cataracts; Retinopathy
	Metabolism and nutrition	Hypercalcaemia (with or without an increase in parathyroid hormone)			Reproductive and breast	Uterine fibroids; Endometrial cancer

Drug	Anastrozole		Fulvestrant		Tamoxifen	
CIOMS frequency criteria	**MedDRA SOC**	**ADR**	**MedDRA SOC**	**ADR**	**MedDRA SOC**	**ADR**
	Musculoskeletal, connective tissue and bone	Trigger finger			General	Hypersensitivity, including angioedema
	Skin and subcutaneous tissue	Urticaria			Investigations	Thrombocytopenia; Leukopenia; Neutropenia; Anaemia; Changes in liver enzymes; Elevated triglycerides
Rare ≥ 0.01% and < 0.1%	Skin and subcutaneous tissue	Erythema multiformae; anaphylactoid reaction, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)			Ophthalmologic	Corneal changes; Optic neuropathy; Optic neuritis
					Reproductive and breast	Uterine sarcoma (mostly malignant mixed Mullerian tumours); Endometriosis; Ovarian cysts
					Gastrointestinal	Pancreatitis
					Hepatic and biliary	Fatty liver; Cholestasis; Hepatitis
					Investigations	Hypercalcaemia (not including tumour flare)
Very rare < 0.01%	Skin and subcutaneous tissue	Stevens-Johnson syndrome; angioedema			Pulmonary	Interstitial pneumonitis
					Dermatologic	Erythema multiforme; Stevens-Johnson syndrome; Bullous pemphigoid

CHAPTER 3
Methodology

Chapter overview

This chapter details the methods that were undertaken to carry out the study. The source of the data, the data characteristics and how the data was analysed is further explained. The methods used to achieve each study objective are briefly explained and tabulated. Lastly, ways in which the reliability and validity of the study were maintained are outlined and the types of bias that may be encountered during the study listed.

3.1. Study Design

A quantitative, cross-sectional approach involved secondary data analysis from a pre-established, global ICSR database, VigiBase®.

3.2. Data Source

The ICSR data was purchased from the UMC in 2020 via a research grant. The data consisted of ICSRs for anastrozole, fulvestrant and tamoxifen (referred to as the core drugs) where the drug was reported as “suspect” and “interacting”. The terms “suspect” and “interacting” identifies the drug in question as either suspected of causing the ADR or that the ADR is suspected to be due to a drug-drug interaction (136). The ICSRs included concomitant drugs (reported as “concomitant”) that a patient was on at the time of the ADR to aid in determining causality of the ADR which could be because of possible drug-drug interactions. Individual case safety reports were pulled based on this study’s core drugs being “suspect” and “interacting” thus, entire ICSRs (with the same unique report ID) were provided. This meant that other drugs listed as “suspect” and “interacting” that were not the core drugs also formed part of the data since it was related to a report ID that had at least one report containing at least one of the core drugs. Since a single patient (corresponding to a single report ID/ICSR) may experience more than one ADR, each report ID may feature multiple times resulting in a greater number of ADRs than ICSRs.

3.2.1. VigiBase®

The initial data set comprised 43 411 ICSRs from UMC's database, VigiBase®: 15 207 (35.03%) for anastrozole, 7 448 (17.16%) for fulvestrant and, 20 756 (47.81%) for tamoxifen. The study research team assisted in determining what information to be included and excluded in the various categories of information. The reports were not restricted to specific countries as long as the text was in English to obtain a data set representing the current situation at the UMC.

3.3. Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were applied:

3.3.1. Inclusion Criteria

- All ICSRs where only the core drugs are reported as "suspect" or "interacting".

3.3.2. Exclusion Criteria

- Duplicated ADRs for a single patient.
- All drugs that were listed as "concomitant".
- Reports where the Medical Dictionary for Regulatory Authorities (MedDRA) system organ class (SOC) and MedDRA preferred terms (PTs) are blank (indicated by a dash "-").

3.4. Study Population

Table 3.1 shows the timeframes for which the ICSRs were obtained which ranged from the date of inception of the drugs onto the market until 30 August 2020. The 43 411 ICSRs equated to 636 866 lines (individual ADRs) on Microsoft Excel. Figure 3.1 details the categorical variables that were provided in the database. The demographic variables include predetermined age groups (0 – 27 days, 28 days – 23 months, 2 – 11 years, 12 – 17 years, 18 – 44 years, 45 – 64 years, 65 – 74 years, ≥ 75 years, and blank/unknown), gender (female, male, not applicable and blank/unknown) and United Nations (UN) continent (Africa, Americas, Asia, Europe, and Oceania).

Table 3.1. Timeframe of adverse drug reaction reports for the three core chemotherapeutic agents.

Drug	First Report Recorded	Last Report Recorded
Anastrozole	1996/04/19	2020/08/30
Fulvestrant	1999/12/21	2020/08/30
Tamoxifen	1976/09/30	2020/08/30

3.5. Data Analysis

The UMC provided the ICSR data in a report format on Microsoft Excel; thus, version 16 of Microsoft Excel was used to clean the data. Duplicated ADR reports were found in the database due to a single ADR report for the same patient being reported by multiple notifiers with different indications for the same drug and different tradenames and seriousness classifications. Duplicated ADR reports were removed from Excel. This did not change the number of ICSRs but decreased the number of individual ADRs or lines on Excel. Table 3.2 shows the number of duplicated ADRs removed under each MedDRA SOC for each drug.

Table 3.2. The number of duplicates removed according to MedDRA system organ class

Drug	Anastrozole	Fulvestrant	Tamoxifen
Number of duplicated ADRs removed	7 196	7 379	5 060

To isolate specific sets of data, the data were filtered for only the drugs reported as “suspect” and “interacting” under the “Basis’ heading. Only the core drugs were extracted according to the “WHOPreferredName” heading which is synonyms with the drugs’ generic names (i.e., anastrozole, fulvestrant and tamoxifen). The MedDRA terminologies used in the database are a standardised form of medical terminology used to enable the global sharing of regulatory information (MedDRA, n.d.). The MedDRA SOC and the subsequent MedDRA PT fields that were blank (indicated with a dash “-“) were not used in the analysis as these fields should describe the ADR, and thus, they did not elaborate on the ADR experienced. Table 3.3 shows the changes in the number of ICSRs once the blank MedDRA SOCs and PT were deleted. Table 3.4 provides an overview of the study objectives and briefly explains the methods imployed to meet the objective.

Table 3.3. The difference in the number of ICSRs after the removal of blank reports

Drug	Number of ICSRs for the raw data	Number of ICSRs for the clean data	Number of ICSRs with blank MedDRA SOCs and PTs
Anastrozole	15 207	15 197	10 (0.07%)
Fulvestrant	7 448	7 448	0 (0%)
Tamoxifen	20 756	20 656	100 (0.5%)

Heading	Description text
ReportID	Unique number identifying each case report
FirstDateDatabase	Date (YYYYMMDD) when the report was first entered in VigiBase.
ReportUpdatedDate	Date (YYYYMMDD), the last time the same report was entered in VigiBase e.g. due to an update.
UN_Continent	Continent of the primary source, according to the United nations
WHO_Region	Region of the primary source, according to the World health organization
Reported Serious case	Refers to if the case was reported serious or not (Y=yes, N=no, - = unknown)
Seriousness	Seriousness criteria of case
ReportType	Report type text
Reporter(s)	Reporter type text
Age Group	AgeGroup of patient at time of onset of reaction/event
Gender	Gender text
WHODrugTradename	WHODrug coded Trade name of reported drug
WHODrugPreferredBaseName	WHODrug coded Preferred base text
WHODrugPreferredSaltName	WHODrug coded Preferred salt text
Basis	Characterization of drug role text
Amount	Dosage regimen: Amount
AmountUnit	Dosage regimen: Amount unit text
Frequency	Dosage regimen: Frequency. Number of (time) units in the interval
FrequencyUnit	Dosage regimen: Frequency unit text. Definition of the interval
DrugTreatmentDuration	Calculated duration of drug intake. Always in the base unit days
RouteOfAdministration	Coded route of administration of drug
IndicationText	Reason for drug use. Indication can be decoded from MedDRA, ICD-8, ICD-9 or ICD-10.
MeddraSOC_name	MedDRA System Organ Class (SOC)
MeddraPT_name	MedDRA Preferred Term (PT)
MeddraLLT_name	MedDRA Low Level Term (LLT)
Outcome	Outcome text
DechallengeAction	Dechallenge action
DechallengeOutcome	Dechallenge outcome
ReactionDuration	Calculated duration of reaction. Always in the base unit days
RechallengeAction	Rechallenge action
RechallengeOutcome	Rechallenge outcome
TimeToOnset	Calculated time to onset. Based on drug start date and reaction start date. Always in the base unit days
Preferred_ReportId	Suspected duplicate clusters are identified by the preferred Report ID

Figure 3.1 Raw data headings with a brief description as provided by UMC.

Table 3.4. An overview of the study objectives and their related methodologies

Objectives	Study endpoint	Methods for data analysis
Objective 1 To identify, describe and categorise anastrozole, fulvestrant and tamoxifen related ADRs	Quantify the demographic profile (age, gender, UN continent), top 10 MedDRA SOCs and top 10 ADRs for each drug.	Using pivot tables and filtering the data to isolate specific variables for easier quantification.
Objective 2 To assess the associations of age and gender with the adverse drug reactions for	To determine possible significant associations between demographics and the top 10 ADRs.	Conduct chi-2 and binary logistic regression analysis using STATA, a statistical analysis program

anastrozole, tamoxifen and fulvestrant.		
Objective 3 To assess and compare the adverse drug reactions identified from the study with that of the South African drugs' package insert for each of the chosen drugs.	To determine whether the ADRs listed on the package insert are similar or different to the ADRs in the database	Evaluate and quantify the ADRs from the VigiBase® data and use it as the basis for comparison with the ADRs and side effects listed in the drugs package insert
Objective 4 To describe anastrozole, fulvestrant and tamoxifen related ADRs and characterize their seriousness.	To determine the most common serious ADRs and characterise their seriousness and implications for a patient	Filtering and isolating the serious ADRs, quantifying the common ADRs and characterising them according to seriousness sub-categories

3.5.1. Descriptive analysis

The data were identified, described, and categorised as follows: quantifying the demographic data (UN continent, age group and gender) by using percentage and frequency statistics and quantifying the ADRs based on their seriousness and the frequency of the individual ADRs. To quantify the demographic data, pivot tables were utilised. The data was selected, a pivot table was inserted with the category being analysed (i.e., "UN_Continent") and the report ID included as rows of the pivot table. All sub-categories (i.e., a sub-category for UN continent - Africa) had to be individually quantified by highlighting all the report IDs within the sub-category. The count/number of report IDs that had been selected was displayed at the bottom of the Excel sheet. This count corresponded to the number of ICSRs (number of patients) in that category. This was done for each drug and each demographic variable.

The details of the ADRs can be found in the "MeddraSOC_name", "MeddraPT_name" and "MeddraLLT_name" columns. As seen in Figure 1 above, the MedDRA SOC is the standardised MedDRA system organ class which encompasses the following 27 classes: blood and lymphatic disorders; cardiac disorders; congenital, familial, and genetic disorders; ear & labyrinth disorders; endocrine disorders; eye disorders; gastrointestinal disorders; general disorders & administration site conditions; hepatobiliary disorders; immune system disorders; infections & infestations; injury, poisoning & procedural complications; investigations; metabolism & nutrition disorders; musculoskeletal & connective tissue disorders; neoplasms benign, malignant & unspecified (incl. cysts & polyps); nervous system disorders; pregnancy, puerperium & perinatal conditions; product issues; psychiatric disorders; renal &

urinary disorders; reproductive system & breast disorders; respiratory, thoracic & mediastinal disorders; skin & subcutaneous tissue disorders; social circumstances; surgical & medical procedures; and vascular disorders. These SOCs are selected based on the organ class in which the ADR occurred. The MedDRA PT specifies what the ADR was (e.g., myocardial infarction) and the MedDRA low-level term (LLT) can be considered the layman's term for the ADR (e.g., heart attack) but, in most cases, the PT and the LLT are the same. The top 10 MedDRA SOCs in which the ADRs occurred were quantified and categorised by the UN continents from which the ADRs were reported. This was done for each drug. Additionally, the top 10 most commonly occurring ADRs for each drug were quantified. Based on the CIOMS frequency criteria, the common ADRs for each core drug were determined.

3.5.2. Statistical analysis

To determine possible significant associations between demographic data and individual ADRs, statistical analysis was conducted using STATA. See section 3.6 on statistical analysis.

3.5.3. Package insert comparison

To compare the ADRs that were identified from the study with that of the drugs' package inserts (PIs), further analysis of the data was done. The MedDRA PT, which is a description of the ADR that was observed, was used as the basis for ADR comparison. The PIs for anastrozole, fulvestrant, and tamoxifen were obtained from the SAHPRA online repository of package inserts, and all PIs of all products with the active pharmaceutical ingredient in this study which are registered in SA were used for the comparison. The PIs listed the side effects/adverse reactions based on SOCs and determined their frequency based on the CIOMS frequency criteria as seen in Table 3.5. The MedDRA SOCs and their corresponding ADRs mentioned in the PIs were compared to those listed under the same MedDRA SOCs from the database.

Table 3.5. CIOMS adverse drug reaction frequency criteria

Very common	≥ 10%
Common	≥ 1% and < 10%
Uncommon	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1%
Very rare	< 0.01%

3.5.4. Characterising the seriousness of the ADRs

To describe and characterise the seriousness of the ADRs, only the serious ADRs (indicated by a “yes” under the “serious” category) were filtered. The demographic data for the serious ADRs were quantified. The ICH defines a serious ADR as “any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect” (137). Thus, the serious sub-categories in the database were “death”, “life threatening”, “congenital anomaly/birth defect”, “caused/prolonged hospitalisation”, “disabling/incapacitating” Combinations of these sub-categories were used by reporters which resulted in 36 possible seriousness sub-categories. This proved to be tedious and thus, it was decided that only the main sub-categories were used for analysis, as well as two additional sub-categories, “unknown/blank” and “other”. The serious ADRs were filtered further to isolate the individual seriousness sub-categories and the top 3 ADRs were quantified for each drug. Based on the CIOMS frequency criteria in Table 7 above, all common serious ADRs were also quantified for each drug.

3.6. Statistical Analysis

To meet the second objective of establishing an association between the ADRs based on the MedDRA PTs and the demographics (age groups, UN continent and gender), version 16 of STATA, a statistical analysis program, was used. The ADRs for each drug were quantified and the top 10 isolated. The column headings in the database are categorical variables, with each variable housing specific sets of information that will be assigned a numerical value, AKA nominal data, which can be considered as coding the data as detailed in Table 3.6. Pearson Chi-squared (Chi-2) analysis was done to determine if there was a statistically significant association (p-value < 0.05) between the ADRs and demographic variables. Further binary logistic regression was done to determine the strength of the association. A p-value of < 0.05 was considered as significant.

Table 3.6. Data coding values used for statistical analysis

Variable	Sub-categories of each variable	Codes
UN Continent	Africa, Asia, Americas, Europe, Oceania	Africa = 1, Asia = 2, Americas = 3, Europe = 4, Oceania = 5
Age Group	0 – 27 days, 28 days – 23 months, 2 – 11 years, 12 – 17 years, 18 – 44 years, 45 – 64 years, 65 – 74 years and ≥ 75 years, blank/unknown	0 – 27 days = 1, 28 days – 23 months = 2, 2 – 11 years = 3, 12 – 17 years = 4, 18 – 44 years = 5, 45 – 64 years = 6, 65 – 74 years = 7 and ≥ 75 years = 8, blank/unknown = 9
Gender	Female, male, not applicable, unknown	Female = 1, Male = 2, blank/unknown = 3, not applicable = 4
MedDRA PT	Based on ADR observed for individual drugs	See Table 4.6

3.7. Bias, validity, and reliability

3.7.1. Bias

Bias can be defined as “systematic error introduced into sampling or testing by selecting or encouraging one outcome or answer over others” and/or “to give a settled and often prejudiced outlook to” (138). Bias directly affects the validity and reliability of a study and can be prevented through measures as stipulated in Table 3.7.

Table 3.7. The types of bias that could influence the study and how they were accounted for

Type of bias	Definition according to this study	How bias was avoided
Design bias	Poor study design that may favour the researchers aim and hypothesis.	The study was designed to be conducted as exploratory, inductive research.
Implementation bias	When the approved protocol and methods are not adhered to.	The methodology was performed without deviations from the approved protocol
Data collection bias	When a researchers personal views influence the way data is collected.	All data used were from the provided database and the application of inclusion and exclusion criteria were consistent for each drug
Analysis bias	The researcher may look for data that supports their beliefs or hypothesis and disregards data that does not.	All data were cleaned, coded, and statistically analysed using the same methods for each drug
Reporting bias	When only favourable results that confirm or support the study hypothesis are reported.	All data was used in analysis (based on the inclusion and exclusion criteria) and all the results were reported as per the study objectives.

(139)

3.7.2. Validity

Validity speaks to the accuracy of a measure or method. All methods that are valid (accurate) are also reliable. The types of validity and how they were accounted for are detailed in Table 3.8.

Table 3.8. The possible threats to the validity of the study how validity was upheld

Threat	Definition	Applicability to the current study	How the threat was mitigated
Content validity	The extent to which the methods cover all aspects of the topic being measured	The methodology must be sufficient and thorough to cover all objectives	All objectives are addressed in the methodology thus ensuring that all content is covered
Construct validity	The extent to which the methods measure the topic being investigated	The methods must be able to produce results that align to the intended study objectives	The methods were designed to ensure they provided results that could be used to speak to the study objectives e.g., using the drugs package insert to draw a comparison between pre-established ADRs and observed ADRs will achieve the objective
Criterion validity	The extent to which the methods used can obtain the results	The methods must be able to adequately achieve the results that they are set out to achieve	The methods that were used to determine the results were effective in achieving them e.g., using binary logistic regression analysis produced results that determined associations between ADRs and demographic data

(140,141)

3.7.3. Reliability

Reliability refers to the consistency of a measure or method. It determines whether the results obtained using that measure or method will be the same if applied under the same conditions. All results that are reliable (reproducible) may not be valid or accurate. The types of reliability and how they are accounted for are detailed in Table 3.9.

Table 3.9. The possible threats to the reliability of the study and how reliability was upheld

Threat	Definition	Applicability to the current study	How the threat was mitigated
Homogeneity	The extent to which the methods carried out will obtain the same results i.e., the consistency of the method	The same method had to be applied to each objective for each drug	The methods applied to each drug for each objective were the same e.g., the data for all drugs were managed and analysed in the same way each time
Stability	The extent to which the results are consistent when the method is repeated	The methods were designed to ensure they could be repeated	The methods were detailed enough to allow for replicability of the study
Equivalence	The extent of the consistency when the same methods are implemented	The same methods had to be applied for each drug	All data were statistically analysed using the same methods for each drug. e.g., the variables from the raw data were not changed for each drug and thus allowed for consistent analysis

(140,141)

3.8. Ethical Considerations

Medical ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (study no. M210851) on 21 September 2021. The data from the VigiBase® database did not include any identifiable patient information and was thus, anonymous. The data was coded for statistical analysis (see section 3.6.).

CHAPTER 4
Results

Chapter Overview

This chapter looks at the results obtained from the study. The results are listed in order of the objectives for the study. The first table in this chapter looks at the study population for each drug against demographic data (UN continent, age group and gender) and the report type and notifier. This is followed by tables looking at the top 10 ADRs for each UN continent for each drug. The significant associations between the top 10 ADRs and demographics are shown in tables according to each drug. The ADRs found in VigiBase® and the ADRs in the drugs package insert are compared as per the frequency criteria of the ADRs. Lastly, the seriousness of the ADRs is characterised and described according to the CIOMS frequency criteria.

4.1. Study population

Table 4.1. details the study population and report characteristics. The majority of the ICSRs are contributed by the Americas, followed by Europe for all three drugs. This is a characteristic of VigiBase® data since most ICSRs received for the database are from the US and Europe (9). These three drugs are mainly used in postmenopausal women, therefore, the trend that is shown in Table 9 has the majority of the ICSRs being from females within the “45 – 64 years” and “65 – 74 years” is expected.

Table 4.1. Study population, number of reports and ICSR characteristics of anastrozole, fulvestrant and tamoxifen

	Drug Name		
Continent	**Anastrozole (n = 15 197)**	**Fulvestrant (n = 7 448)**	**Tamoxifen (n = 20 656)**
Africa	101 (0.66%)	19 (0.26%)	214 (1.04%)
Americas	9 781 (64.36%)	3 924 (52.69%)	9 534 (46.16%)
Asia	636 (4.19%)	620 (8.32%)	2 340 (11.33%)
Europe	4 302 (28.31%)	2 749 (36.91%)	8 024 (38.85%)
Oceania	377 (2.48%)	136 (1.83%)	544 (2.36%)
Age Groups			
0 – 27 days	4 (0.02%)	-	4 (0.02%)
28 days – 23 months	2 (0.01%)	1 (0.01%)	10 (0.05%)
2 – 11 years	24 (0.16%)	-	14 (0.07%)
12 – 17 years	25 (0.16%)	-	12 (0.06%)

18 – 44 years	338 (2.22%)	277 (3.72%)	2 011 (9.74%)
45 – 64 years	4 896 (38.22%)	1 893 (25.42%)	7 277 (35.23%)
65 – 74 years	3 487 (22.95%)	1 490 (20.00%)	3 562 (17.24%)
≥ 75 years	2 366 (15.57%)	975 (13.09%)	2 772 (13.42%)
Unknown/blank	4 055 (26.68%)	2 812 (37.76%)	4 994 (24.17%)
Gender			
Female	14 448 (95.07%)	6 875 (92.31%)	19 377 (93.81%)
Male	278 (1.83%)	80 (1.07%)	632 (3.06%)
Not Applicable/unknown/blank	471 (3.10%)	493 (6.62%)	647 (3.13%)
Report Type			
Other	41 (0.27%)	7 (0.09%)	109 (0.53%)
PMS/special monitoring	24 (0.16%)	199 (2.67%)	67 (0.32%)
Report from a study	829 (5.46%)	1 136 (15.25%)	857 (4.15%)
Spontaneous	14 091 (92.72%)	5 991 (80.44%)	19 163 (92.77%)
Not available to sender (unknown)/blank	212 (1.40%)	115 (1.54%)	460 (2.23%)
Notifier			
Consumer/Non health professional	5 326	1 749	3 013
Lawyer	19	2	36
Other health professional	1 168	1 481	1 247
Pharmacist	1 315	574	1 696
Physician	4 118	3 133	7 116
Unknown/blank	3 421	835	7 833

Report type is an indication of how the report was submitted. Spontaneous reporting is the cornerstone of PV, and most reports from VigiBase® are submitted via SRSs; thus, the majority (> 80%) of ICSRs for each drug is from spontaneous reporting is understandable. The notifier identifies the individual that reported the ADR. Due to duplicated reports because of reports for the same patient being submitted by multiple people, this information is not reliable. Additionally, when the duplicated reports were removed, there was no way to control which of the duplicated reports would be removed. In other words, a duplicated report could have been removed wherein a physician or a pharmacist or a consumer was the notifier, thus, the notifier data was altered.

4.2. Drug-related ADRs categorised per UN continent

The top 10 ADRs for anastrozole, fulvestrant and tamoxifen are identified in Table 4.2. The common ADRs amongst the three drugs include arthralgia, nausea, and fatigue. All the top 10 ADRs were reported at a frequency > 1%. Therefore, according to the CIOMS frequency criteria, all these ADRs are commonly occurring. It is important to highlight that “death” was the most reported ADR for tamoxifen.

Table 4.2. The top 10 ADRs for anastrozole, fulvestrant and tamoxifen

Anastrozole (n = 52 256)		Fulvestrant (n = 28 624)		Tamoxifen (n = 48 150)	
Arthralgia	2 513 (4.63%)	Fatigue	852 (2.98%)	Death	1 388 (2.88%)
Hot flush	1 134 (2.09%)	Malignant neoplasm progression	816 (2.85%)	Arthralgia	772 (1.60%)
Fatigue	964 (1.78%)	Neutropenia	643 (2.25%)	Nausea	763 (1.58%)
Nausea	914 (1.68%)	Nausea	632 (2.21%)	Fatigue	675 (1.40%)
Headache	781 (1.44%)	Dyspnoea	393 (1.37%)	Hot flush	674 (1.40%)
Pain in extremity	773 (1.42%)	Injection site pain	389 (1.36%)	Rash	600 (1.25%)
Alopecia	731 (1.35%)	Arthralgia	383 (1.34%)	Malignant neoplasm progression	571 (1.19%)
Bone pain	683 (1.26%)	Diarrhoea	380 (1.33%)	Pulmonary embolism	536 (1.11%)
Pain	674 (1.24%)	Metastases to bone	338 (1.18%)	Visual impairment	517 (1.07%)
Myalgia	655 (1.21%)	Asthenia	335 (1.17%)	Deep vein thrombosis	484 (1.01%)

Figures 4.1, 4.2, and 4.3 describe the percentage of ADRs contributed by each UN continent. These values are different from those in Table 4.1 due to the number of ICSRs being calculated for Table 4.1 and the number of ADRs calculated for Figures 4.1 – 4.3. This is on account of the difference in the number of individuals that

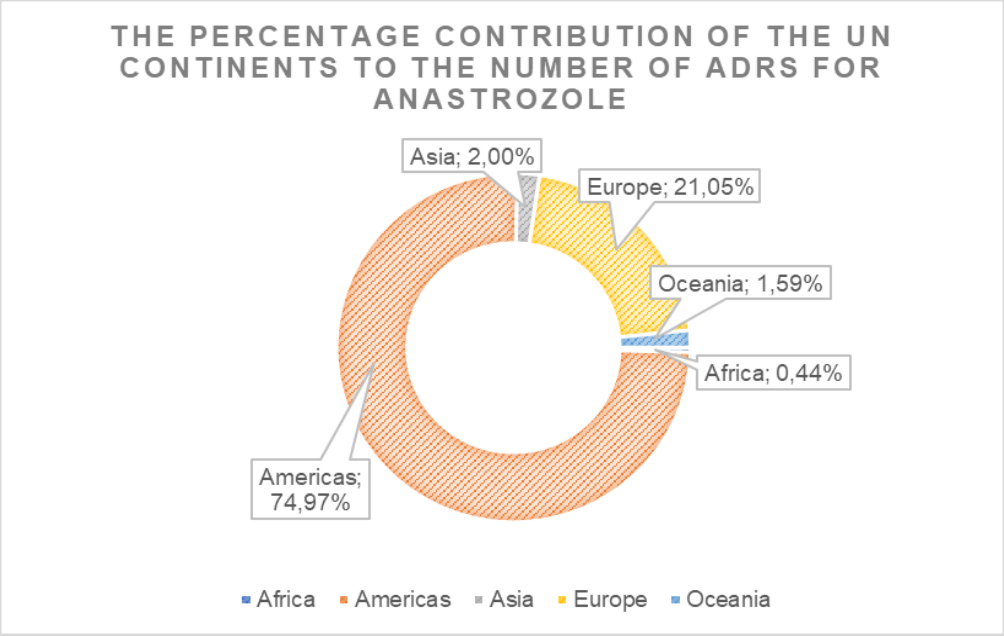


Figure 4.1 The percentage of ADRs reported by each UN continent for anastrozole.

experienced ADRs and the number of ADRs experienced, respectively. Despite Africa contributing to 16.72% of the global population (142), the continent's contribution to ADR reports is < 1% for anastrozole, fulvestrant and tamoxifen.

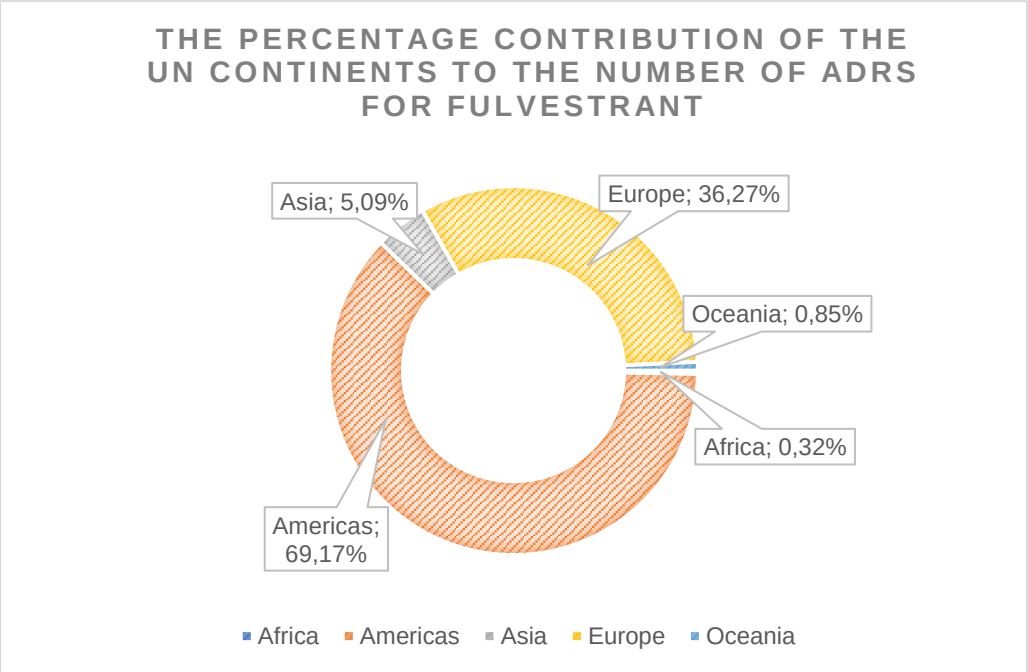


Figure 4.2 The percentage of ADRs reported by each UN continent for fulvestrant

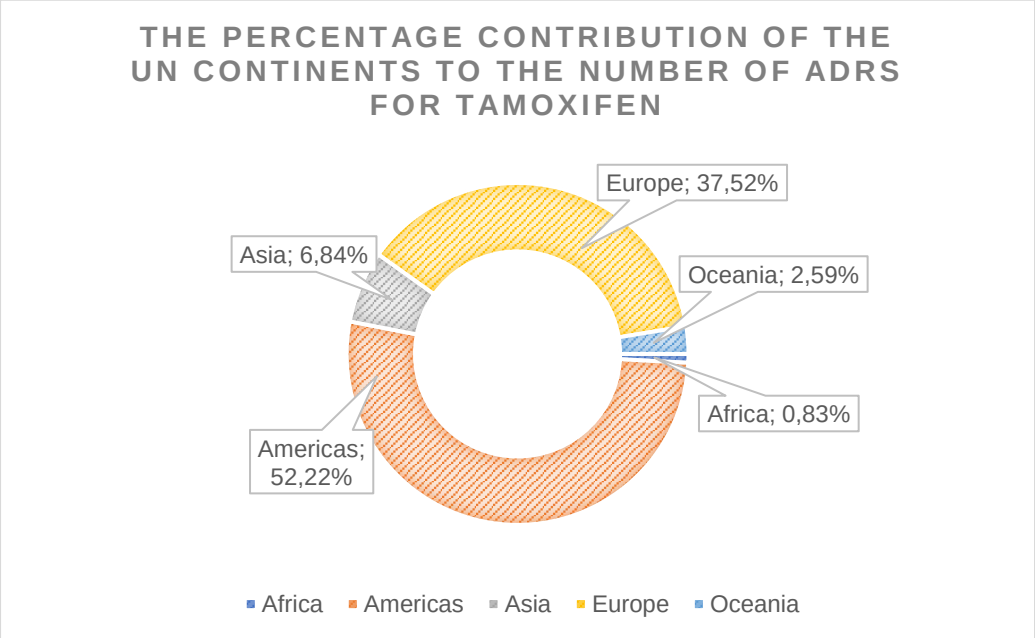


Figure 4.3 The percentage of ADRs reported by each UN continent for tamoxifen

Tables 4.3, 4.4 and 4.5 further categorise the data into the top 10 ADRs for each UN continent for anastrozole, fulvestrant and tamoxifen, respectively. When looking at

the top 10 ADRs for each drug in Table 4.2 compared to the top 10 ADRs for each UN continent, similarities can be seen with the Americas. This may, however, be attributed to the Americas contributing the greatest number of ADR reports for each drug

4.2.1. Anastrozole-related ADRs

The most common ADR for all the UN continents for anastrozole (Table 4.3), excluding Africa, was “arthralgia”. Arthralgia falls under the MedDRA SOC “Musculoskeletal and connective tissue disorders”; other musculoskeletal disorders that may be related to “arthralgia” include “bone pain”, “myalgia” and “pain in extremity”, which are all ADRs that also feature prominently amongst the UN continents. The high combined number of reports for Oceania that relate to disease progression, recurrence, and metastases (n = 69, 8.02%).

4.2.2. Fulvestrant-related ADRs

Table 4.4 looks at the ADR distribution across the UN continents for fulvestrant, with “malignant neoplasm progression” being common amongst all UN continents except for Africa. Nearly 45% of ADR reports from Oceania are for “malignant neoplasm progression”, with another 13.5% due to “disease progression” and “metastasis” and “death”. “Death” also features prominently in Asia.

4.2.3. Tamoxifen-related ADRs

Tamoxifen is known to have a less favourable side effect profile than anastrozole. Some of the ADRs that feature in Table 4.5 for tamoxifen and not for anastrozole include “endometrial cancer”, “deep vein thrombosis”, “pulmonary embolism” and “uterine cancer”. The Americas account for 1 341 of 1 388 (96.61%) of the deaths reported for tamoxifen. Despite the Americas contributing 52.22% of the ADR reports for tamoxifen, the proportion of ADRs for “death” is concerning.

Table 4.3. The top 10 ADRs in each UN continent for anastrozole

UN Continents									
Africa (n = 218)		**Americas (n = 40 676)**		**Asia (n = 1 083)**		**Europe (n = 11 419)**		**Oceania (n = 860)**	
Headache	11 (5.05%)	Arthralgia	1 635 (4.02%)	Arthralgia	66 (6.09%)	Arthralgia	748 (6.55%)	Arthralgia	56 (6.51%)
Bone pain	10 (4.59%)	Hot flush	938 (2.31%)	Myalgia	35 (3.23%)	Nausea	282 (2.47%)	Disease progression	22 (2.56%)
Arthralgia	8 (3.67%)	Fatigue	753 (1.85%)	Interstitial lung disease	29 (2.68%)	Headache	225 (1.97%)	Bone density decreased	20 (2.33%)
Fatigue	7 (3.21%)	Pain in extremity	628 (1.54%)	Rash	19 (1.75%)	Pruritus	193 (1.69%)	Hot flush	19 (2.21%)
Osteoporosis	6 (2.75%)	Nausea	598 (1.47%)	Metastases to bone	17 (1.57%)	Myalgia	189 (1.66%)	Nausea	18 (2.09%)
Pruritus	5 (2.29%)	Pain	561 (1.38%)	Bone pain	15 (1.39%)	Fatigue	189 (1.66%)	Metastases to bone	13 (1.51%)
Back pain	4 (1.83%)	Alopecia	540 (1.33%)	Nausea	14 (1.29%)	Diarrhoea	183 (1.60%)	Malignant neoplasm progression	13 (1.51%)
Oedema peripheral	4 (1.83%)	Headache	523 (1.29%)	Pyrexia	14 (1.29%)	Alopecia	171 (1.50%)	Depression	12 (1.40%)
Alopecia	4 (1.83%)	Insomnia	520 (1.28%)	Pruritus	13 (1.20%)	Hot flush	166 (1.45%)	Breast cancer metastatic	11 (1.28%)
Rash	4 (1.83%)	Bone pain	501 (1.23%)	Headache	13 (1.20%)	Bone pain	156 (1.37%)	Breast cancer recurrent	10 (1.16%)

Table 4.4. The top 10 ADRs in each UN Continent for fulvestrant

UN Continent									
Africa (n = 81)		**Americas (n = 17 725)**		**Asia (n = 1 304)**		**Europe (n = 9 295)**		**Oceania (n = 219)**	
Tumour marker increased	5 (6.17%)	Fatigue	581 (3.28%)	Malignant neoplasm progression	37 (2.84%)	Neutropenia	488 (5.25%)	Malignant neoplasm progression	95 (43.38%)
Drug ineffective	5 (6.17%)	Nausea	380 (2.14%)	Asthenia	35 (2.68%)	Malignant neoplasm progression	356 (3.83%)	Disease progression	20 (9.13%)
Vomiting	4 (4.94%)	Malignant neoplasm progression	328 (1.85%)	Death	35 (2.68%)	Fatigue	257 (2.76%)	Metastases to bone	5 (2.28%)
Hepatic steatosis	3 (3.70%)	Arthralgia	274 (1.55%)	Cough	31 (2.38%)	Nausea	239 (2.57%)	Product dose omission	3 (1.37%)
Bone pain	3 (3.70%)	Injection site pain	244 (1.38%)	Neutrophil count decreased	30 (2.30%)	Metastases to bone	156 (1.68%)	Liver function test abnormal	3 (1.37%)
Pain	3 (3.70%)	Diarrhoea	233 (1.31%)	Dyspnoea	22 (1.69%)	Leukopenia	152 (1.64%)	Neuropathy peripheral	2 (0.91%)
Hepatic enzyme increased	3 (3.70%)	Pain	229 (1.29%)	White blood cell count decreased	21 (1.61%)	Dyspnoea	150 (1.61%)	Metastasis	2 (0.91%)
Dyspnoea	3 (3.70%)	White blood cell count decreased	225 (1.27%)	Platelet count decreased	21 (1.61%)	Anaemia	142 (1.53%)	Skin lesion	2 (0.91%)
Renal impairment	2 (2.47%)	Neoplasm progression	222 (1.25%)	Neoplasm progression	20 (1.53%)	Diarrhoea	141 (1.52%)	Death	2 (0.91%)
Stomatitis	2 (2.47%)	Dyspnoea	216 (1.22%)	Drug ineffective	20 (1.53%)	Metastases to liver	133 (1.43%)	Myocardial infarction	2 (0.91%)

Table 4.5. The top 10 ADRs in each UN Continent for tamoxifen

UN Continent									
Africa (n = 399)		**Americas (n = 25 145)**		**Asia (n = 3 293)**		**Europe (n = 18 064)**		**Oceania (n = 1 249)**	
Pruritus	20 (5.01%)	Death	1 341 (5.33%)	Uterine cancer	152 (4.62%)	Arthralgia	410 (2.27%)	Malignant neoplasm progression	47 (3.76%)
Vaginal discharge	15 (3.76%)	Nausea	403 (1.60%)	Hot flush	115 (3.49%)	Hot flush	313 (1.73%)	Disease progression	47 (3.76%)
Arthralgia	13 (3.26%)	Vasodilatation	398 (1.58%)	Retinopathy	80 (2.43%)	Fatigue	285 (1.58%)	Metastases to bone	39 (3.12%)
Hot flush	13 (3.26%)	Fatigue	357 (1.42%)	Pruritus	79 (2.40%)	Nausea	279 (1.54%)	Breast cancer metastatic	38 (3.04%)
Headache	12 (3.01%)	Pain	324 (1.29%)	Rash	67 (2.03%)	Malignant neoplasm progression	273 (1.51%)	Nausea	29 (2.32%)
Vertigo	12 (3.01%)	Rash	313 (1.24%)	Endometrial cancer	64 (1.94%)	Pulmonary embolism	270 (1.49%)	Breast cancer recurrent	19 (1.52%)
Rash	10 (2.51%)	Arthralgia	295 (1.17%)	Insomnia	55 (1.67%)	Endometrial cancer	245 (1.36%)	Alopecia	18 (1.44%)
Nausea	9 (2.26%)	Depression	290 (1.15%)	Ovarian hyperstimulation syndrome	51 (1.55%)	Deep vein thrombosis	215 (1.19%)	Metastases to liver	16 (1.28%)
Vomiting	7 (1.75%)	Weight increased	279 (1.11%)	Alopecia	50 (1.52%)	Myalgia	214 (1.18%)	Pruritus	16 (1.28%)
Visual impairment	7 (1.75%)	Visual impairment	266 (1.01%)	Dizziness	46 (1.40%)	Endometrial hyperplasia	213 (1.18%)	Deep vein thrombosis	15 (1.20%)

4.3. Statistical associations of ADRs with demographic characteristics

Pearson Chi-squared (chi-2) analysis was first conducted to determine if there were any significant associations between the top 10 ADRs and the demographic variables “UN continent”, “age group” and “gender”. The numerical coding of the top 10 ADRs for each drug can be seen in Table 4.6.

Table 4. 6. The numerical coding of the top 10 ADRs for anastrozole, fulvestrant and tamoxifen

Anastrozole		Fulvestrant		Tamoxifen	
Arthralgia	1	Fatigue	1	Death	1
Hot flush	2	Malignant neoplasm progression	2	Arthralgia	2
Fatigue	3	Neutropenia	3	Nausea	3
Nausea	4	Nausea	4	Fatigue	4
Headache	5	Dyspnoea	5	Hot flush	5
Pain in extremity	6	Injection site pain	6	Rash	6
Alopecia	7	Arthralgia	7	Malignant neoplasm progression	7
Bone pain	8	Diarrhoea	8	Pulmonary embolism	8
Pain	9	Metastases to bone	9	Visual impairment	9
Myalgia	10	Asthenia	10	Deep vein thrombosis	10

Pearson chi-2 analysis showed a p-value of < 0.05 for all variables for drugs (apart from the “gender” variable for fulvestrant) when the chi-2 analysis was run against the top 10 ADRs and UN continent and age group as depicted in Table 4.7. Binary logistic regression analysis was then conducted to determine the strength of the significant association for the individual ADRs for each drug. Tables 4.8, 4.9, and 4.10 show only the ADRs that were significantly associated with specific age groups, genders, and

UN continents for anastrozole, fulvestrant and tamoxifen, respectively. The younger age groups (“0 – 27 days”, “28 days – 23 months”, “2 – 11 years”, and “12 – 17 years”) were combined to form a new “< 18 years” age group due to few ADR reports being recorded for these age groups in the top 10 ADRs for each drug. Two of the variables under gender, “not known” and “not applicable” were excluded from this analysis due to their negligible numbers – 155 of 9 822 (1.58%) ADRs for anastrozole, 199 of 5 161 (3.86%) for fulvestrant, and 229 of 6 980 (3.28%) for tamoxifen.

Table 4.7. Results of the Pearson chi-2 analysis for anastrozole, fulvestrant and tamoxifen

Drug/demographics	Pearson Chi-2	df	P-value
Anastrozole			
UN continent	377.1627	36	0.000
Age group	130.3165	45	0.000
Gender	18.2846	9	0.032
Fulvestrant			
UN Continent	895.4866	36	0.000
Age group	195.2656	36	0.000
Gender	13.0774	9	0.159
Tamoxifen			
UN Continent	$1.7x10^3$	36	0.000
Age group	$2.0x10^3$	45	0.000
Gender	84.0135	9	0.000

To ensure uniformity of the statistical analysis, the reference value/base level for each variable was manually assigned. The “Americas” was chosen as the base level/reference value for the UN continents variable since it was the next available variable that had data for all the ADRs and all the drugs. Additionally, the “Americas” was the UN continent with the greatest number of ADR reports and ICSRs. Similarly, “females” was the chosen base level for gender. The “≥ 75 years” age group was the assigned base level for the age groups since it had data for all the ADRs for all the drugs. Despite other age groups also having data for all drugs and ADRs, this age group was chosen because it was on the end of the spectrum and not a middle value. Initially, STATA automatically assigned the first coded value as

the statistical comparison, however, not all the data had recorded reports for all the age groups/UN continents, e.g., there were no reports for the” <18 years” age group for fulvestrant and some ADRs had no reports recorded for “Africa”. This was done for all the drugs and not just the drugs or ADRs with incomplete data, thus accounting for any possible bias. The complete statistical results for all ADRs can be found in appendix 1.

4.3.1. Anastrozole

Table 4.8 shows the statistically significant ADRs (p-value > 0.05) from the top 10 ADRs for anastrozole (as seen in Table 4.6) based on demographic data (age groups, UN continents and gender). The base levels/reference values for the variables are

indicated in the table for comparison purposes. The ADR “arthralgia” was the most associated ADR with the demographic variables overall.

4.3.1.1. Age groups

All the age groups had at least one ADR significantly associated. The ADR “arthralgia” was found to be significantly associated with all the age groups greater than 18 years, making it the ADR most associated with the age groups. The older age groups had more ADRs that were significantly associated compared to the younger age groups. The “45 – 64 years” (odds ratio (OR) 1.59; 95% confidence interval (95% C)I 1.36 – 1.86; p = 0.000) “65 – 74 years” (OR 1.30; 95% CI 1.10 – 1.53; p = 0.003), and “blank/unknown” (OR 1.32; 95% CI 1.11 – 1.58; p = 0.002) age groups show a strong association with developing arthralgia in comparison to the “≥ 75 years” base level. The “45 – 64 years” age group had the most significantly associated ADRs, with it being the only demographic variable to be associated with “alopecia. The “blank/unknown” age group was also found to have a statistically significant association with “nausea” (OR 0.68; 95% CI 0.54 – 0.86; p = 0.001).

4.3.1.2. UN continents

All UN continents were found to have significant associations with ADRs, with Europe having the greatest number of associations. Africa was significantly associated with “headache” (OR 3.70; 95% CI 1.87 – 7.32; p = 0.000) and “bone pain” (OR 3.44; 95% CI 1.70 – 6.97; p = 0.001) despite the low numbers of ICSRs/ADRs reported from the continent. Asia had a strong association with “myalgia” (OR 3.73; 95% CI 2.54 – 5.49; p = 0.000) and exhibited a greater odds of developing myalgia in comparison to the “Americas”. The ADR “arthralgia” was the most common ADR significantly associated with the UN continents and showed strong associations with Europe (OR 1.53; 95% CI 1.38 – 1.70; p = 0.000) and Oceania (OR 1.99; 95% CI 1.42 – 2.79; p = 0.000).

4.3.1.3. Gender

The male population only made up 1.83% of the total number of ICSRs (see Table 4.1) from the database but was found to be strongly associated with “myalgia” (OR 1.95; 95% CI 1.11 – 3.43; p = 0.021) and “fatigue” (OR 2.04; 95% CI 1.01 – 4.12; p = 0.048).

Table 4.8. Binary logistic analysis of the top 10 ADRs for anastrozole and their association with demographic data

Demographic variable/ADR	Odds ratio (95% Confidence Interval)	p-value (<0.05)
Age groups	**≥ 75 years reference**	
< 18 years		
Pain in extremity	6.42 (2.07 – 19.92)	0.001
18 – 44 years		
Arthralgia	1.53 (1.05 – 2.22)	0.025
45 – 64 years		
Arthralgia	1.59 (1.36 – 1.86)	0.000
Fatigue	0.81 (0.65 – 1.00)	0.047
Nausea	0.62 (0.50 – 0.76)	0.000
Alopecia	0.65 (0.51 – 0.82)	0.000
65 – 74 years		
Arthralgia	1.30 (1.10 – 1.53)	0.003
Nausea	0.80 (0.64 – 0.99)	0.038
Blank/unknown		
Arthralgia	1.32 (1.11 – 1.58)	0.002
Nausea	0.68 (0.54 – 0.86)	0.001
UN continents	**Americas reference**	
Africa		
Headache	3.70 (1.87 – 7.32)	0.000
Bone pain	3.44 (1.70 – 6.97)	0.001
Asia		
Arthralgia	1.69 (1.24 – 2.31)	0.001
Hot flush	0.30 (0.15 – 0.60)	0.001
Fatigue	0.25 (0.10 – 0.61)	0.002
Myalgia	3.73 (2.54 – 5.49)	0.000
Europe		
Arthralgia	1.53 (1.38 – 1.70)	0.000
Hot flush	0.50 (0.42 – 0.59)	0.000
Fatigue	0.76 (0.64 – 0.90)	0.001
Nausea	1.54 (1.33 – 1.80)	0.000
Headache	1.36 (1.15 – 1.61)	0.000
Pain in extremity	0.58 (0.47 – 0.71)	0.000
Pain	0.46 (0.36 – 0.58)	0.000
Myalgia	1.41 (1.17 – 1.68)	0.000
Oceania		
Arthralgia	1.99 (1.42 – 2.79)	0.000
Bone pain	0.089 (0.012 – 0.64)	0.016
Gender	**Females reference**	
Males		
Fatigue	1.95 (1.11 – 3.43)	0.021
Myalgia	2.04 (1.01 – 4.12)	0.048

4.3.2. Fulvestrant

Table 4.9 shows the statistically significant ADRs that were found to be associated with the demographic variables for fulvestrant. “Malignant neoplasm progression” is the ADR most often associated with the variables.

4.3.2.1. Age groups

The top 10 ADRs for fulvestrant did not contain any reports in the "< 18 years" age group despite there is one report in the database (see Table 4.1). The "18 – 44 years" age group was strongly associated with "neutropenia" (OR 1.72; 95% CI 1.09 – 2.71; p = 0.019) and "metastases to bone" (OR 1.85; 95% CI 1.00 – 3.41; p = 0.048). "Metastases to bone" (OR 1.83; 95% CI 1.22 – 2.72; p = 0.003) was also strongly associated with the "45 – 64 years" age group along with "malignant neoplasm progression" (OR 1.41; 95% CI 1.06 – 1.89; p = 0.020). The "blank/unknown" age group also had an association with "malignant neoplasm progression" (OR 1.93; 95% CI 1.46 – 2.55; p = 0.000).

4.3.2.2. UN continents

The only ADR associated with Africa was "dyspnoea" (OR 16.19; 95% CI 2.68 – 97.69; p = 0.002). "Malignant neoplasm progression" was significantly associated with Asia (OR 1.67; 95% CI 1.11 – 2.53; p = 0.015), Europe (OR 1.40; 95% CI 1.18 – 1.66; p = 0.000), and Oceania (OR 50.73; 95% CI 26.43 – 97.39; p = 0.000). Asia was also strongly associated with "metastases to bone" (OR 1.74; 95% CI 1.03 – 2.93; p = 0.037) and "asthenia" (OR 3.85; 95% CI 2.55 – 5.82; p = 0.000). Europe was statistically associated with the most ADRs including "neutropenia" (OR 5.83; 95% CI 4.71 – 7.21; p = 0.000) and "metastases to bone" (OR 1.27; 95% CI 1.00 – 1.61; p = 0.048).

4.3.2.3. Gender

The only ADR associated with the male population was "malignant neoplasm progression" (OR 2.57; 95% CI 1.28 – 5.15; p = 0.008) which was found to be strongly associated in comparison with females.

4.3.3. Tamoxifen

The statistically significant ADRs associated with the demographic variables for tamoxifen are detailed in Table 4.10. Tamoxifen had the greatest number of significantly associated ADRs from all three drugs for the age groups.

Table 4.9. Binary logistic analysis of the top 10 ADRs for fulvestrant and their association with demographic data

Demographic variable/ADR	Odds ratio (95% Confidence Interval)	p-value (<0.05)
Age groups	**≥ 75 years reference**	
< 18 years	No data available	
18 – 44 years		
Neutropenia	1.72 (1.09 – 2.71)	0.019
Injection site pain	0.29 (0.11 – 0.73)	0.008
Metastases to bone	1.85 (1.00 – 3.41)	0.048
Asthenia	0.33 (0.16 – 0.68)	0.003
45 – 64 years		
Malignant neoplasm progression	1.41 (1.06 – 1.89)	0.020
Metastases to bone	1.83 (1.22 – 2.72)	0.003
Asthenia	0.56 (0.40 – 0.77)	0.000
65 – 74 years		
Asthenia	0.70 (0.51 – 0.96)	0.026
Blank/unknown		
Malignant neoplasm progression	1.93 (1.46 – 2.55)	0.000
Asthenia	0.31 (0.22 – 0.46)	0.000
UN continents	**Americas reference**	
Africa		
Dyspnoea	16.19 (2.68 – 97.69)	0.002
Asia		
Fatigue	0.26 (0.14 – 0.49)	0.000
Malignant neoplasm progression	1.67 (1.11 – 2.53)	0.015
Nausea	0.44 (0.24 – 0.82)	0.010
Dyspnoea	1.72 (1.07 – 2.77)	0.025
Arthralgia	0.29 (0.12 – 0.72)	0.008
Metastases to bone	1.74 (1.03 – 2.93)	0.037
Asthenia	3.85 (2.55 – 5.82)	0.000
Europe		
Fatigue	0.51 (0.43 - 0.60)	0.000
Malignant neoplasm progression	1.40 (1.18 – 1.66)	0.000
Neutropenia	5.83 (4.71 – 7.21)	0.000
Nausea	0.79 (0.66 – 0.95)	0.011
Injection site pain	0.70 (0.56 – 0.88)	0.002
Arthralgia	0.49 (0.38 – 0.62)	0.000
Metastases to bone	1.27 (1.00 – 1.61)	0.048
Asthenia	0.72 (0.56 – 0.93)	0.012
Oceania		
Fatigue	0.097 (0.023 – 0.40)	0.001
Malignant neoplasm progression	50.73 (26.43 – 97.39)	0.000
Nausea	0.080 (0.011 – 0.58)	0.012
Gender	**Females reference**	
Males		
Malignant neoplasm progression	2.57 (1.28 – 5.15)	0.008

Table 4.10. Binary logistic analysis of the top 10 ADRs for tamoxifen and their association with demographic data

Demographic variable/ADR	Odds ratio (95% Confidence Interval)	p-value (<0.05)
Age groups	**≥ 75 years reference**	
< 18 years		
Arthralgia	20.63 (1.92 – 221.88)	0.012
18 – 44 years		
Death	0.073 (0.048 – 0.11)	0.000
Arthralgia	8.02 (5.06 – 12.70)	0.000
Nausea	2.82 (2.03 – 3.91)	0.000
Fatigue	3.09 (2.14 – 4.45)	0.000
Hot flush	6.29 (3.81 – 10.37)	0.000
Rash	1.58 (1.09 – 2.30)	0.016
Malignant neoplasm progression	2.35 (1.46 – 3.79)	0.000
Pulmonary embolism	0.52 (0.33 – 0.82)	0.005
Visual impairment	1.69 (1.12 – 2.53)	0.011
Deep vein thrombosis	0.41 (0.25 – 0.65)	0.000
45 – 64 years		
Death	0.10 (0.084 – 0.13)	0.000
Arthralgia	8.21 (5.46 – 12.34)	0.000
Nausea	2.00 (1.54 – 2.58)	0.000
Fatigue	2.37 (1.77 – 3.16)	0.000
Hot flush	5.25 (3.53 – 8.21)	0.000
Rash	1.58 (1.20 – 2.07)	0.001
Malignant neoplasm progression	2.47 (1.07 – 3.57)	0.000
Visual impairment	1.73 (1.29 – 2.32)	0.000
Deep vein thrombosis	0.72 (0.55 – 0.93)	0.014
65 – 74 years		
Death	0.33 (0.28 – 0.40)	0.000
Arthralgia	2.74 (1.24 – 4.32)	0.000
Nausea	1.97 (1.49 – 2.59)	0.000
Fatigue	1.89 (1.38 – 2.60)	0.000
Hot flush	2.29 (1.39 – 3.79)	0.001
Rash	1.54 (1.15 – 2.08)	0.004
Malignant neoplasm progression	1.85 (1.24 – 2.78)	0.003
Visual impairment	1.64 (1.19 – 2.26)	0.002
Blank/unknown		
Death	0.047 (0.034 – 0.065)	0.000
Arthralgia	7.05 (4.62 – 10.77)	0.000
Nausea	1.48 (1.11 – 1.99)	0.009
Fatigue	1.48 (1.11 – 1.99)	0.009
Hot flush	10.51 (6.70 – 16.48)	0.000
Malignant neoplasm progression	5.61 (3.87 – 8.13)	0.000
Pulmonary embolism	0.70 (0.51 – 0.97)	0.031
Deep vein thrombosis	0.46 (0.32 – 0.64)	0.000
UN continents	**Americas reference**	
Africa		
Arthralgia	2.23 (1.18 – 4.22)	0.014
Hot flush	3.16 (1.66 – 6.03)	0.000
Rash	2.21 (1.10 – 4.45)	0.026

Asia		
Death	0.013 (0.0019 – 0.096)	0.000
Fatigue	0.28 (0.15 – 0.50)	0.000
Hot flush	4.62 (3.51 – 6.08)	0.000
Rash	2.56 (1.88 – 3.47)	0.000
Europe		
Death	0.043 (0.031 – 0.059)	0.000
Arthralgia	1.84 (1.55 – 2.17)	0.000
Hot flush	1.80 (1.49 – 2.18)	0.000
Malignant neoplasm progression	1.71 (1.40 – 2.08)	0.000
Pulmonary embolism	2.06 (1.70 -2.49)	0.000
Deep vein thrombosis	1.69 (1.38 – 2.07)	0.000
Oceania		
Death	0.043 (0.015 – 0.12)	0.000
Nausea	1.80 (1.19 – 2.74)	0.006
Malignant neoplasm progression	7.07 (4.82 – 10.37)	0.000
Gender	**Females reference**	
Males		
Arthralgia	0.28 (0.14 – 0.58)	0.001
Pulmonary embolism	2.16 (1.44 – 3.23)	0.000
Visual impairment	0.41 (0.19 – 0.88)	0.022
Deep vein thrombosis	3.42 (2.37 – 4.95)	0.000

4.3.3.1. Age groups

All age groups were also strongly associated with “arthralgia” in comparison to the “Americas” with “arthralgia” being the only ADR associated with the “< 18 years” age group (OR 20.63; 95% CI 1.92 – 221.88; p = 0.012). The “18 – 44 years” age group was significantly associated with all of the top 10 ADRs; the “45 – 64 years” age group with nine and the “65 – 74 years” age group with eight. The ADR “malignant neoplasm progression” was strongly associated with all the age groups apart from the “< 18 years” age group.

4.3.3.2. UN continents

Europe had the greatest number of significantly associated ADRs and was the only continent that was associated with “pulmonary embolism” (OR 2.06; 95% CI 1.70 - 2.49; p = 0.000) and “deep vein thrombosis” (OR 1.69; 95% CI 1.38 – 2.07; p = 0.000). “Death” was associated with all UN continents apart from Africa, and “malignant neoplasm progression” was only found to be associated with Europe (OR 1.71; 95% CI 1.40 – 2.08; p = 0.000) and Oceania (OR 7.07; 95% CI 4.82 – 10.37; p = 0.000).

4.3.3.3. Gender

The two ADRs that were strongly associated with the male population were “pulmonary embolism” (OR 2.16; 95% CI 1.44 – 3.23; p = 0.000) and “deep vein thrombosis” (OR 3.42; 95% CI 2.37 – 4.95; p = 0.000).

4.4. Comparing the ADRs reported on VigiBase® to those listed on the drugs package insert

The results in Table 4.11 show a comparison between multiple package inserts for each drug and the ADRs reported in VigiBase®. The package inserts found for anastrozole were for Arimidex® 1 mg tablet (manufactured by AstraZeneca), Sandoz Anastrozole 1 mg tablet (manufactured by Sandoz, a division of Novartis), Mylan Anastrozole 1 mg film-coated tablet (manufactured by Mylan) and Teva Anastrozole 1 mg film-coated tablet (manufactured by Teva pharmaceuticals). The SAHPRA online PI and PIL repository had four PIs for fulvestrant; three from AstraZeneca, namely, Faslodex 250 mg/5 ml injection and Faslodex 50 mg/ml solution for injection and Faslodex 500mg/5ml injection, and Fastelev 250mg/5ml solution for injection manufactured by Teva Pharmaceuticals. Lastly, for tamoxifen, the PIs for Nolvadex-D 20 mg tablet (manufactured by AstraZeneca), Tamoxihexal 10 and 20 mg tablets (manufactured by Sandoz, a division of Novartis), Tamoplex 20 mg tablet (manufactured by Teva pharmaceuticals) and Kessar 20 mg tablet (manufactured by Pfizer). The side effects and adverse effects noted in the PIs were combined based on the MedDRA SOCs and their frequencies detailed as seen in the PIs. The frequencies “frequent”, “less frequent” and “frequency unknown” did not have a frequency criterion like the CIOMS frequency criteria. The ADRs in blue reported under the VigiBase® sections show the ADRs that were reported with either a higher value than those that were mentioned in the PIs or reported and stood out against the rest of the ADRs reported under that specific MedDRA SOC. The percentages calculated for the ADRs were calculated based on the number of ADRs reported for each drug. If an ADR was listed under a certain MedDRA SOC and did not feature, the ADR is searched for, and, if found, it is noted under a different MedDRA SOC.

For most of the ADRs, they were already noted in the drug’s PIs. This could be because the ADRs are commonly known to be associated with that drug’s use and the

ADR was reported. However, because of under-reporting and that the ADR is already known, the incidence of the ADR may be underestimated in the VigiBase® data. On the other hand, commonly occurring, serious and rare ADRs that are not known to be associated with a drug may not have been reported, thus, hindering the primary role of spontaneous ADR reporting - signal detection. None of the ADRs in VigiBase® were of a frequency of > 10% (very common) as stated in the drug's PIs, which may be as a result of the extensive under-reporting of ADRs.

Table 4.11. Comparison between the ADRs reported in VigiBase® (n) with the ADRs reported in each of the drugs package inserts

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
Blood and lymphatic: **Less frequent –** anaemia; leukopenia; thromboembolism; thrombophlebitis	Anaemia (108 – 0.21%) Leukopenia (70 – 0.13%) Neutropenia (126 – 0.24%) Thrombophlebitis (10) and thrombophlebitis superficial (7) under vascular disorders	**Blood and lymphatic:** **Common** - Reduced platelet count **Less frequent** – reduced platelet count	Thrombocytopenia (179 – 0.63%) Anaemia (225 – 0.79%) Leukopenia (197 – 0.69%) Neutropenia (643 – 2.25%)	**Blood and lymphatic system:** **Frequent** – anaemia **Less frequent** – thrombocytopenia; leukopenia; neutropenia; agranulocytosis; haemorrhagic episodes	Anaemia (145 – 0.30%) Thrombocytopenia (263 – 0.55%) Leukopenia (142 – 0.29%) Neutropenia (85 – 0.18%) Agranulocytosis (17 – 0.04%)
Gastrointestinal: **Very common** – Nausea **Common** - Diarrhoea; vomiting **Frequent** – constipation; dry mouth; abdominal pain	Nausea (914 – 1.75%) Diarrhoea (507 – 0.97%) Vomiting (334 – 0.64%) Constipation (200 – 0.38%) Dry mouth (170 – 0.33%) Abdominal pain (156 – 0.30%) Abdominal pain lower (14 – 0.03%) Abdominal pain upper (183 – 0.35%)	**Gastrointestinal:** **Very common** – Nausea **Common** - Vomiting, diarrhoea	Nausea (632 – 2.21%) Vomiting (243 – 0.85%) Diarrhoea (380 – 1.33%)	**Congenital, familial and genetic:** **Less frequent** – porphyria cutanea tarda	Porphyria (5 – 0.01%) Porphyria non-acute (5 – 0.01%) Congenital anomaly (15 – 0.03%)
General: **Very common** – Asthenia **Common** – Fatigue **Frequent** – pain; pelvic pain **Less frequent** – flu syndrome	Asthenia (571 – 1.09%) Fatigue (964 – 1.85%) Pain (674 – 1.29%) Malaise (418 – 0.80%) Pelvic pain (28) under reproductive system and breast disorders	**General:** **Very common** - Injection site reactions; asthenia **Frequent** – sciatica; peripheral neuropathy **Less frequent** – injection site haemorrhage; injection site	Injection site bruising (38 – 0.13%), discomfort (24 – 0.08%), extravasation (11 – 0.04%), haematoma (31 – 0.11%), haemorrhage (32 – 0.11%), hyperaesthesia (10 – 0.03%), induration (42 – 0.15%), inflammation (11 – 0.04%), injury (14), irritation (10 – 0.03%), mass (97), necrosis (22 – 0.08%), nerve damage (10 – 0.03%), nodule	**Eye:** **Rare** - Corneal changes; Optic neuropathy; Optic neuritis **Frequent** – cataracts; retinopathy **Less frequent** – visual disturbances (including blurred vision and loss of visual acuity); corneal changes; optic neuropathy	Corneal degeneration (7 – 0.01%), deposits (6 – 0.01%), disorder (7 – 0.01%), opacity (16 – 0.03%) Optic neuropathy (6 – 0.01%) Cataracts (264 – 0.55%) Retinopathy (148 – 0.31%) Vision blurred (140 – 0.29%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
		haematoma; neuralgia	(34 – 0.12%), oedema (10 – 0.03%), pain (389 – 1.36%), pruritis (57 – 0.20%), rash (22 – 0.08%), reaction (44 – 0.15%), scar (13 – 0.05%), swelling (58 – 0.20%), ulcer (10 – 0.03%), warmth (11 – 0.04%) **(Injection site reaction total 990 – 3.46%)** Asthenia (335 – 1.17%) Death (257 – 0.90%) Disease progression (288 – 1.00%) Drug ineffective (177 – 0.62%) Fatigue (852 – 2.98%) Gait disturbance (136 – 0.48%) Pain (302 – 1.06%) Malaise (177 – 0.62%) Pyrexia (151 – 0.53%) Neuralgia (28) and sciatica (61) under nervous system disorders		Visual acuity reduced (39 – 0.08%) Visual impairment (517 – 1.07%) Retinal disorder (140 – 0.29%) Optic neuritis (43) under nervous system.
Hepatobiliary: **Common** - Increase in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase	Hyperbilirubinemia (6 – 0.01%) Hypertransaminasaemia (3) Hepatitis (27 – 0.05%) Hepatitis acute (8 – 0.02%)	**Hepatobiliary:** **Very common** - Elevated liver enzymes (ALT, AST, ALP) **Common** - Elevated bilirubin	Hypertransaminasaemia (4 – 0.01%) Hyperbilirubinemia (10 – 0.03%) Hepatic failure (34 – 0.12%) Hepatitis (8 – 0.03%) Hepatic lesion (26 – 0.09%)	**Gastrointestinal:** **Common** - Gastrointestinal intolerance **Rare** – Pancreatitis **More frequent** – nausea	Pancreatitis (62 – 0.13%) Pancreatitis acute (38 – 0.08%) Nausea (763 – 1.58%) Vomiting (329 – 0.68%) Diarrhoea (273 – 0.57%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
Uncommon - Increase in gamma-GT and bilirubin; hepatitis	Hepatitis cholestatic (7 – 0.01%) Hepatitis toxic (4) Chronic hepatitis (4) Hepatitis fulminant (1) **(Hepatitis total 60 – 0.11%)** Hepatic steatosis (22 – 0.04%) Jaundice (26 – 0.05%) Liver disorder (24 – 0.05%) Hepatic function abnormal (27 – 0.05%)	**Uncommon** - Elevated gamma-GT **Less frequent** – hepatic failure; hepatitis	Hepatic function abnormal (21 – 0.07%)	**Frequent** – vomiting; diarrhoea; constipation **Less frequent** – pancreatitis **Frequency unknown** – abdominal cramps	Constipation (157 – 0.33%) Abdominal pain (231 – 0.48%)
Metabolism and nutrition: **Common** - Anorexia; hypercholesterolaemia **Uncommon** - Hypercalcaemia (with or without an increase in parathyroid hormone), anorexia, hypercholesterolaemia **Less frequent** – increased appetite; weight gain	Decreased appetite (256 – 0.50%) Abnormal loss of weight (2) Cachexia (2) Hypercholesterolaemia (50 – 0.10%) Hyperlipidaemia (24 – 0.05%) Hypertriglyceridemia (10 – 0.02%) Dyslipidaemia (3) Hypercalcaemia (29 – 0.06%) Increased appetite (24 – 0.05%) Abnormal weight gain (2)	**Immune system:** **Very common -** Hypersensitivity reactions (angioedema and urticaria) **Less frequent** – anaphylactic reactions	Hypersensitivity (89 – 0.31%) Drug hypersensitivity (43 – 0.15%) Anaphylactic reaction (18 – 0.06%)	**General:** **Common** - Tumour flare; Fluid retention; Drug related fatigue **Uncommon –** Hypersensitivity (including angioedema) **Frequency unknown** – oedema; severe increase in bone and tumour pain	Fatigue (675 – 1.40%) Oedema (102 – 0.21%) Oedema peripheral (225 – 0.47%) Pain (457 – 0.95%) Asthenia (253 – 0.53%) Death (1 388 – 2.88%) Disease progression (281 – 0.58%) Malaise (229 – 0.48%) Tumour flare (1) and tumour pain (2) under neoplasms benign, malignant, and unspecified. Fluid retention (53) under metabolism and nutrition. Angioedema (50) under skin and subcutaneous

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
					tissue. Hypersensitivity (84) under immune system.
Musculoskeletal and connective tissue: **Very common** - Arthralgia/Joint stiffness, arthritis **Common** - Bone pain; myalgia **Uncommon** - Trigger finger **Frequent** – back and bone pain; bone fractures; osteoporosis	Arthralgia (2 513 – 4.81%) Arthritis (469 – 0.90%) Joint stiffness (224 – 0.43%) Bone pain (683 – 1.31%) Myalgia (655 – 1.25%) Trigger finger (234 – 0.45%) Back pain (404 – 0.77%) Osteoporosis (272 – 0.52%) Joint swelling (199 – 0.38%) Muscle spasms (271 – 0.52%) Muscular weakness (206 – 0.39%) Pain in extremity (773 – 1.48%) Facture (62) under injury, poisoning and procedural complications	**Infections and infestations:** **Common -** Urinary tract infections **Frequent –** pharyngitis	Urinary tract infection (78 – 0.27%) Urinary tract infection bacterial (3 – 0.01%) Pharyngitis (8 – 0.03%) Pneumonia (101 – 0.35%) Nasopharyngitis (64 – 0.22%) Herpes zoster (36 – 0.13%)	**Hepatobiliary:** **Rare -** Fatty liver; Cholestasis; Hepatitis **Frequent –** changes in liver enzymes; fatty liver **Less frequent –** cirrhosis of the liver; cholestasis; hepatic failure; hepatocellular injury; hepatic necrosis **Frequency unknown –** hepatoxicity, alterations of liver function parameters, serum lipid changes, cholestasis, hepatitis, jaundice, steatosis, liver cell necrosis, liver cell damage, liver failure	Cholestasis (10 – 0.02%) Hepatitis (98 – 0.20%) Hepatitis acute (6 – 0.01%) Hepatitis cholestatic (20 – 0.04%) (Hepatitis total 124 – 0.26%) Hyperbilirubinemia (25 – 0.05%) Hypertransaminasaemia (2) Hepatic cirrhosis (87 – 0.18%) Hepatic failure (34 – 0.07%) Hepatocellular injury (35 – 0.07%) Hepatic necrosis (13 – 0.03%) Hepatotoxicity (12 – 0.02%) Hepatic function abnormal (187 – 0.39%) Jaundice (59 – 0.12%) Jaundice cholestatic (14 – 0.03%) Hepatic steatosis (170 – 0.35%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
Nervous system: **Very common -** Headache **Common -** Carpal tunnel syndrome; somnolence; sensory disturbances (including paraesthesia, taste loss and taste perversion) **Frequent** – dizziness **Less frequent** – anxiety; confusion; insomnia; nervousness	Headache (781 – 1.49%) Capral tunnel syndrome (203 – 0.39%) Somnolence (100 – 0.19%) Sensory disturbance (7 – 0.01%) Sensory loss (5) Paraesthesia (363 – 0.69%) Taste disorder (27 – 0.05%) Dizziness (496 – 0.95%) Hypoesthesia (322 – 0.62%) Anxiety (287), "confusional" state (116), insomnia (606) and nervousness (72) under psychiatric disorders	**Metabolism and nutrition:** **Common** - Anorexia	Decreased appetite (238 – 0.83%)	**Immune system:** **Frequent** - hypersensitivity reactions (including urticaria, angioedema and dyspnoea)	Drug hypersensitivity (63 – 0.13%) Hypersensitivity (84 – 0.17%) Angioedema (50) and urticaria (192) under skin and subcutaneous tissue. Dyspnoea (425) under respiratory, thoracic and mediastinal.
Psychiatric: **Frequent -** depression	Depression (480 – 0.92%) Depressed mood (90 – 0.17%) **(Depression total 570 – 1.09%)**	**Musculoskeletal and connective tissue:** **Very common** - Joint and musculoskeletal pain **Frequent** – back pain	Musculoskeletal pain (79 – 0.28%) Back pain (249 – 0.87%) Arthralgia (383 – 1.34%) Bone pain (188 – 0.66%) Myalgia (165 – 0.58%) Pain in extremity (225 – 0.79%)	**Injury, poisoning and procedural complications:** **Less frequent** – radiation recall/recall phenomenon	Recall phenomenon (9 – 0.02%) Off label use (114 – 0.24%) Fall (83 – 0.17%)
Reproductive system and breast: **Common** - Vaginal dryness; vaginal bleeding	Vulvovaginal dryness (117 – 0.22%) Vaginal haemorrhage (158 – 0.30%)	**Nervous system:** **Common** - Headache	Headache (269 – 0.94%) Dizziness (232 – 0.81%)	**Investigations:** **Uncommon** - Thrombocytopenia; Leukopenia; Neutropenia; Anaemia; Changes in liver	Neutrophil count decreased (19 – 0.04%) Platelet count decreased (43 – 0.09%) Red blood cell count decreased (15 – 0.03%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
				enzymes; Elevated triglycerides **Rare** - Hypercalcaemia (not including tumour flare) **Frequent** – hypertriglyceridemia **Frequency unknown** – weight gain	Transaminases increased (20 – 0.04%) Aspartate aminotransferase increased (146 – 0.30%) Alanine aminotransferase increased (143 – 0.30%) Hepatic enzyme increased (85 – 0.18%) Blood triglycerides increased (39 – 0.08%) Weight increased (467 – 0.97%) Hypertriglyceridemia (86) under metabolism and nutrition.
Respiratory, thoracic and mediastinal: **Frequent –** chest pain; dyspnoea; cough; pharyngitis **Less frequent –** bronchitis, sinusitis or rhinitis	Dyspnoea (400 – 0.77%) Cough (304 – 0.58%) Bronchitis chronic (4) Rhinitis allergic (6 – 0.11%) Pharyngitis (8), pharyngitis streptococcal (4), bronchitis (47), sinusitis (53) and rhinitis (8) under infections and infestations	**Reproductive system and breast disorders:** **Less frequent** – vaginal moniliasis; leucorrhoea; vaginal haemorrhage	Vaginal haemorrhage (12 – 0.04%) Pelvic pain (12 – 0.04%) Vulvovaginal dryness (12 – 0.04%) Breast mass (11 – 0.04%) Breast pain (24 – 0.08%)	**Metabolism and nutrition:** **Common** - Weight gain **More frequent** – fluid retention **Less frequent** – hypercalcaemia (in patients with bony metastases) **Frequency unknown** - anorexia	Fluid retention (53 – 0.11%) Hypercalcaemia (80 – 0.17%) Decreased appetite (153 – 0.32%)
Skin and subcutaneous tissue: **Very common** - Rash	Rash (421 – 0.81%) Rash erythematous (39 – 0.07%) Rash macular (31 – 0.06%)	**Respiratory, thoracic and mediastinal:**	Cough (321 – 1.12%) Dyspnoea (393 – 1.37%) Pleural effusion (118 – 0.41%)	**Musculoskeletal and connective tissue:** **Common** - Leg cramps **Frequent** - myalgia	Myalgia (402 – 0.83%) Arthralgia (772 – 1.60%) Muscle spasms (327 – 0.68%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
Common - Hair thinning (alopecia); allergic reactions **Uncommon** - Urticaria **Rare** - Erythema multiformae; anaphylactoid reaction, cutaneous vasculitis (Including some reports of Henoch-Schönlein purpura) **Very rare** - Stevens-Johnson syndrome; angioedema **Frequent** – sweating **Less frequent –** pruritis	Rash maculopapular (30 – 0.06%) Rash papular (18 – 0.03%) Rash pruritic (66 – 0.13%) **(Rash total 605 – 1.16%)** Alopecia (731 – 1.40%) Urticaria (177 – 0.34%) Urticaria chronic (2) Urticaria papular (4) Erythema (157 – 0.30%) Erythema multiformae (29 – 0.06%) Cutaneous vasculitis (6 – 0.01%) Henoch-Schönlein purpura (7 – 0.01%) Stevens-Johnson syndrome (7 – 0.01%) Angioedema (32 – 0.06%) Hyperhidrosis (211 – 0.40%) Pruritis (446 – 0.85%)	**Common** – cough; dyspnoea	Pulmonary embolism (86 – 0.3%)		Pain in extremity (280 – 0.58%) Bone pain (240 – 0.50%)
Vascular: **Very common**: Hot flushes	Hot flush (1 134 – 2.17%) Flushing (69 – 0.13%) Hypertension (309 – 0.59%)	**Skin and subcutaneous tissue:** **Very common** - Rash	Rash (261 – 0.91%) Rash erythematous (17 – 0.06%), pruritic (29 – 0.1%) **(Rash total 307 – 1.07%)** Pruritis (204 – 0.71%) Alopecia (296 – 1.03%)	**Neoplasms benign, malignant, and unspecified (including cysts and polyps):** **Frequent** – uterine fibroids; endometrial cancer **Less frequent** – uterine sarcoma (mostly mixed Mullerian tumours); tumour flare	Endometrial cancer (462 – 0.96%) Sarcoma uterus (33 – 0.07%) Tumour flare (1) Malignant neoplasm progression (571 – 1.19%) Breast cancer (371 – 0.77%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
				Frequency unknown – hepatocellular cancer	Metastases to bone (337 – 0.70%) Uterine cancer (281 – 0.58%)
		Vascular: **Very common** - Hot flushes **Frequent** – venous thromboembolism	Hot flush (190 – 0.66%) Venous thrombosis (4 – 0.01%) Hypertension (105 – 0.37%)	**Nervous system:** **Common** - Headache; Light-headedness **Frequent** – ischaemic cerebrovascular events; stroke; sensory disturbances (including paraesthesia and dysgeusia) **Less frequent** – optic neuritis	Headache (482 – 1.00%) Ischaemic stroke (26 – 0.05%) Cerebrovascular accident (102 – 0.21%) Cerebrovascular disorder (129 – 0.27%) Sensory disturbance (10 – 0.02%) Dysgeusia (91 – 0.19%) Paraesthesia (218 – 0.45%) Optic neuritis (43 – 0.09%) Dizziness (401 – 0.83%) Hypoesthesia (119 – 0.25%) Neuropathy peripheral (130 – 0.27%)
				Psychiatric disorders: **Frequency unknown** – depression; confusion	Depression (475 – 0.99%) “Confusional” state (99 – 0.21%) Insomnia (343 – 0.71%) Anxiety (168 – 0.35%)
				Reproductive and breast:	Amenorrhoea (78 – 0.16%) Vaginal haemorrhage (361 – 0.75%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
				Very common - Menstruation suppression **Common** - Vaginal bleeding; Vaginal discharge; Pruritus vulvae; Endometrial changes (including hyperplasia and polyps) **Uncommon** – Uterine fibroids; Endometrial cancer **Rare** - Uterine sarcoma (mostly malignant mixed Mullerian tumours); Endometriosis; Ovarian cysts **Frequent** – menstrual irregularities (including amenorrhoea) **Less frequent** – vaginal polyps, cystic ovarian swelling	Vaginal discharge (203 – 0.42%) Pruritis genital (38 – 0.08%) Endometrial hyperplasia (341 – 0.71%) Endometrial disorder (118 – 0.25%) Uterine polyp (220 – 0.46%) Endometriosis (48 – 0.10%) Ovarian cysts (134 – 0.28%) Vaginal polyp (3) Uterine haemorrhage (124 – 0.26%)
				Respiratory, thoracic, and mediastinal: **Very rare** - Interstitial pneumonitis **Less frequent** – interstitial pneumonitis **Unknown** - cough	Interstitial lung disease (53 – 0.11%) Cough (148 – 0.31%) Dyspnoea (425 – 0.88%) Pulmonary embolism (536 – 1.11%)
				Skin and subcutaneous tissue:	Alopecia (379 – 0.79%) Rash (600 – 125%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
				Common – Alopecia; Skin rash **Very rare** - Erythema multiforme; Stevens-Johnson syndrome; Bullous pemphigoid **Frequent** – dry skin **Less frequent** – angioedema; cutaneous vasculitis; cutaneous lupus erythematous	Rash erythematous (64 – 0.13%), macular (14 – 0.03%), maculo-papular (79 – 0.16%), papular (20 – 0.04%), pruritic (36 – 0.07%) **(Rash total 813 – 1.69%)** Erythema multiformae (32 – 0.07%) Stevens-Johnson syndrome (21 – 0.04%) Dry skin (106 – 0.22%) Angioedema (50 – 0.10%) Cutaneous vasculitis (10 – 0.02%) Cutaneous lupus erythematous (2) Urticaria (192 – 0.40%) Pruritis (468 – 0.97%) Hyperhidrosis (213 – 0.44%)
				Vascular: **Very common** - Hot flushes **Common** - Ischaemic cerebrovascular events; Thromboembolic events, including deep vein thrombosis, microvascular	Hot flush (674 – 1.40%) Flushing (116 – 0.24%) Thrombophlebitis (111 – 0.23%) Thrombosis (161 – 0.33%) Deep vein thrombosis (484 – 1.01%) Vasodilation (398 – 0.83%)

Anastrozole (Arimidex 1 mg tablet, Sandoz Anastrozole 1 mg tablet, Mylan Anastrozole 1 mg film-coated tablet and Teva Anastrozole 1 mg film-coated tablet)		Fulvestrant (Faslodex 250 mg/5 ml injection and solution for injection, Faslodex 500mg/5ml injection, Fastelev 250mg/5ml solution for injection)		Tamoxifen (Nolvadex-D 20 mg tablet, Tamoxihexal 10 and 20 mg tablets, Tamoplex 20 mg tablet and Kessar 20 mg tablet)	
Package Insert	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**	**Package Insert**	**VigiBase® Data**
				thrombosis, and pulmonary embolism **Less frequent** – thrombophlebitis; thromboembolism	Pulmonary embolism (536) under respiratory, thoracic, and mediastinal.

4.5. Article submitted to the Journal of Oncology Pharmacy Practice in fulfilment of objective 4

Serious Adverse Drug Reactions of Anti-Hormonal Agents Used in Breast Cancer as Reported in VigiBase®

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Abstract

Background: Cancer-related adverse drug reactions are regarded as a part of patient therapy and are therefore overlooked and underreported. With cancer being the most common cause of death globally in 2020, there is a need for a comprehensive overview of the serious adverse drug reactions associated with commonly used cancer drugs as reported to the WHO global individual case safety report database, VigiBase®. This study aims to describe anastrozole, fulvestrant and tamoxifen related ADRs and characterize their seriousness as reported by national pharmacovigilance systems.

Methods: A total of the 43 411 individual case safety reports from VigiBase® were provided in the database. They were then anonymised, and the serious adverse drug reactions were isolated. The serious adverse drug reactions were described and the common adverse drug reactions for each drug were quantified. Additionally, the top three adverse drug reactions for each seriousness sub-category were quantified.

Results: Nearly 40% (38.14%) of individual case safety reports were reported as serious. Majority of serious reports were from the Americas and Europe for the three drugs, with most reports falling within the “45-64 years” age group. The common serious adverse drugs reactions that were quantified showed that the adverse drug reactions “arthralgia”, “fatigue”, “nausea”, “breast cancer” and “malignant neoplasm progression” were mutual between the three drugs. The most reported serious adverse drug reaction for anastrozole was “arthralgia” (3.45%) and for fulvestrant (4.02%) and tamoxifen (2.65%) was “malignant neoplasm progression”.

Conclusion: This study has found that commonly reported serious adverse drug reactions for anastrozole, fulvestrant and tamoxifen are documented throughout published literature. These adverse drug reactions have significant impact on patient quality of life, healthcare costs and general patient wellbeing, which can inform policy, practice, and support the movement for targeted safety monitoring of breast cancer patients.

Key words: adverse drug reactions, VigiBase®, anastrozole, fulvestrant, tamoxifen, global

1. Introduction/Literature review

The thalidomide tragedy, that left many new-borns in the 1950s with phocomelia, is largely known as the event that was the catalyst for systematic evaluation of pharmaceutical products prior to their release onto the market, namely post marketing surveillance, which falls within the scope of pharmacovigilance (PV) (1). The World Health Organization (WHO) defines PV as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem” (143). Pharmacovigilance activities include collecting and managing medicine safety data, evaluating Individual Case Safety Reports (ICSRs) to detect new “signals”, management of potential risks associated with the use of medicines, and communicating and informing stakeholders and patients (49). Despite the lacking knowledge and poor practices of healthcare practitioners (HCPs) regarding adverse drug reaction (ADR) reporting (28), the Coronavirus disease 2019 (COVID-19) pandemic and the consequential fast-tracking of vaccine approvals for emergency use has shed light on PV and its central role in drug development, manufacturing and regulatory affairs (87).

Pharmacovigilance ensures the continuous safety of medicines through identifying risks associated with their use; it informs regulatory actions such as labelling changes, safety alerts, drug recalls or withdrawals and can promote the appropriate use of medicines (19). Consistent vigilance and awareness surrounding ADRs and their related reporting procedures is vital as it aids in determining whether additional investigations are required, if educational initiatives need to be held, and if changes need to be made to package inserts, scheduling status and manufacturing processes (20). Furthermore, the importance of PV is becoming more apparent as the rates of ADRs resulting in patient morbidity and mortality are increasing (34) For instance, two separate studies conducted in South Africa (SA), a developing country, found that 6.3% of patients admitted to hospital was directly due to an ADR (34) and that ADRs had resulted in the deaths of 2.9% of hospital admissions (101).

The WHO defines ADRs as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (12). There is always the possibility that the use of a drug can result in an ADR. Antineoplastic agents have been identified as one of the main classes of drugs that are associated with ADRs (30,37,61,128). Studies have found that ADRs are common in oncology patients (38,46). One study observed that antineoplastic agents accounted for 21.8% of all ADRs experienced in hospitalised patients (144). Cancer treatment is already complex due to the frequent use of combination chemotherapy, palliative care and, possibly, the use of complimentary and herbal medicines to manage

side effects associated with therapy (79). These combination therapies can result in polypharmacy, which is a factor tied to ADR-related deaths in hospital settings (39).

It is estimated that 70% of cancer-related deaths (42) and 60% of cancer cases occur in low-to-middle income countries (LMICs), many of which are found in Africa. Cancer is a growing problem in Africa due to an increase in the risk factors that are associated with economic transition and lifestyles as seen in high-income countries which increase the risk of cancer. These risk factors include smoking, obesity, physical inactivity, excessive alcohol intake, and air pollution (104,107). However, the public health priority of LMICs for cancer is low due to a lack of resources as well as the prioritisation of other public health problems, namely human immunodeficiency virus (HIV), tuberculosis (TB), and malaria (109).

In 2020, cancer was the second leading cause of death with approximately 10 million deaths globally, with breast cancer accounting for 2.26 million cases and 685 000 deaths. The incidence and mortality rate of breast cancer for Southern Africa in 2020 was 50.4 per 100 000 and 15.7 per 100 000 respectively, with Africa contributing to 8.3% of all breast cancer cases and 12.5% of all breast cancer deaths globally (111). Breast cancer-specific risk factors include reproductive factors such as early menarche, late childbearing, having fewer children, as well as an increase in breast cancer awareness, screening, and diagnosis (107,109).

Breast cancer can be treated with hormonal therapy, which is dependent on whether the cancer is oestrogen receptor (OR) or progesterone receptor (PgR) positive or negative (145). Hormone receptor positive (HR+) breast cancer therapy consists of systemic or local treatment options that can be used both as adjuvant or neoadjuvant therapy (116). Seventy percent of breast cancers are OR-positive and the frequency increases as age increases (114). Initially, tamoxifen, a selective oestrogen receptor modulator (SERM), was considered the first-line adjuvant treatment for advanced, HR+ breast cancer (118), however, due to the advantageous side effect profile of aromatase inhibitors (AIs), 3rd generation AIs such as anastrozole, have largely become the preferred first-line adjuvant treatment option for early-stage HR-positive breast cancer (121,146,147). Anastrozole was found to have better tolerability, fewer serious adverse effects and a lower rate of cancer recurrence than tamoxifen (121). Both anastrozole and tamoxifen are used in early and advanced hormone sensitive (hormone receptor positive) breast cancer in postmenopausal women (120). Fulvestrant, an oestrogen receptor antagonist or down regulator, is another treatment option that can be used for HR+ and human epidermal growth factor receptor 2 (HER-2) negative breast cancer (123). The known adverse effects associated with the use of these drugs is as follows: anastrozole is associated with arthralgias, bone thinning and bone fractures, tamoxifen with strokes, vasomotor symptoms, thromboembolic disorders and an increased

risk of uterine tumours and ovarian cysts and fulvestrant with hypersensitivity and injection site reactions (117,148).

The 22nd (2021) WHO Model List of Essential Medicines lists anastrozole and tamoxifen as essential medicines under section 8.2. Antineoplastics and supportive medicines, subsection 8.2.4. Hormones and antihormones, indicated for early stage and metastatic breast cancer (149). Locally, the South African national tertiary and quaternary level essential medicines list (EML) used in the public healthcare sector in SA, which serves approximately 70% of the country's population (96), has approved the use of several antineoplastics and immunomodulating agents for the treatment of cancer. Two of the three drugs in this study, namely anastrozole and tamoxifen, have been approved for use and are indicated for adjuvant and metastatic breast cancer as stated in the national EML (126). An application for fulvestrant to be added to the WHO Model List of Essential Medicines was submitted in January 2021 (150). The inclusion of these drugs in both global and national EMLs demonstrates the value and the necessity of pursuing research in this field.

Although known adverse reactions and safety signals are widely published, analysis of comprehensive information on the ADRs of anastrozole, fulvestrant and tamoxifen from a single global source has not been conducted. With a rising incidence of cancer in LMICs, coupled with underdeveloped PV systems, providing a comprehensive overview of the serious ADRs associated with commonly used cancer drugs could be beneficial to HCPs working in resource-scarce settings. Reporting on global patterns of ADRs on the above-mentioned drugs can assist HCPs in evidence-based evaluation of ADRs and eventually assist in reducing hospital stays, improve clinical outcomes, and reduce healthcare costs (37,61). Thus, this study thus aims to describe anastrozole, fulvestrant and tamoxifen related ADRs and characterize their seriousness as reported by national PV systems to VigiBase®, a World Health Organisation Program for International Drug Monitoring (WHO PIDM) database.

2. Methods

2.1. Study Design and data source

A quantitative, cross-sectional approach was taken involving secondary analysis of VigiBase® data. VigiBase® is the WHO's global ICSR database of suspected ADRs to a medicinal product, which was developed and is managed and maintained by the Uppsala Monitoring Centre (UMC) in Sweden (151). The UMC is the WHO collaborating centre for international drug monitoring, which provides support to the WHO PIDM (www.who-umc.org) (6). VigiBase® is the world's largest repository of ICSRs with 28 million reports as of September 2021 from over 120 countries (152). VigiBase® is compatible with multiple standardised medical terminologies for ICSR submissions such as the WHO Drug Dictionary

(WHO-DD), WHO Adverse Reaction Terminology (WHO-ART), Medical Dictionary for Regulatory Activities (MedDRA) and International Classification of Diseases (ICD) (6). The standard terminology for ADR reports is MedDRA (153), which is a standardised form of medical terminology that enables global sharing of regulatory information (154).

2.2. Study Population

VigiBase® data for anastrozole, fulvestrant and tamoxifen were purchased from the UMC in 2020. The ICSRs are made up of ADR reports submitted from all WHO PIDM member countries. As of October 2021, there are 149 permanent member countries and 23 associate members contributing to the database (10). A total of 43 411 ICSRs were obtained from the database; 35.03% of which were for anastrozole, 17.17% for fulvestrant, and 47.81% for tamoxifen. The ICSRs are based on the number of unique report IDs i.e., individual patients, that were recorded in the database from the time the drug was released onto the market to August 2020. The demographic variables that formed part of the database included predetermined age groups, gender, and United Nations (UN) continent.

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion Criteria

- All data where only the core chemotherapeutic drugs (i.e., anastrozole, fulvestrant and tamoxifen) for this study were reported as “suspect” or “interacting” drugs were included. The terms “suspect” and “interacting” mean that the drug is suspected of causing the ADR and that the ADR is suspected to be due to a drug interaction respectively (136).
- All ADRs that were reported as serious (indicated by a “yes” under the serious variable). A serious ADR, according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), is defined as “any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect” (137).

2.3.2. Exclusion Criteria

- Duplicated ADR reports were removed prior to analysis.
- Reports where the MedDRA system organ class (SOC) and MedDRA preferred terms (PTs) are blank (indicated by a dash “- “).

2.4. Data Analysis

The data were provided in a report format on Microsoft Excel sheets; thus, cleaning and filtering the data based on exclusion and inclusion criteria was done using Microsoft Excel. The “blank” and “not applicable” gender categories were combined due to their low percentages. For each drug, only the serious ADRs were filtered, isolated and the common ADRs quantified based on the Council for International Organizations for Medical Sciences (CIOMS) frequency criteria for ADRs as seen in Table I (155). According to the ICH definition of a serious ADR, the ADRs for each drug were filtered to further characterise them into their seriousness sub-categories and the top 3 ADRs were quantified for each category.

Table I. CIOMS ADR frequency criteria

Very common	≥ 10%
Common	≥ 1% and < 10%
Uncommon	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1%
Very rare	< 0.01%

2.5. Ethical considerations

Medical ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (study no. M210851) on 21 September 2021. The data from the VigiBase® database did not include any identifiable patient information and was thus, anonymous. The data was coded for the purpose of statistical analysis.

3. Results

Table II details the demographic data/study population for the VigiBase® data based on the number of ICSRs. Of the 43 411 ICSRs that were obtained from VigiBase®, 16 556 ICSRs (38.14%) were reported as serious. From the 16 556 ICSRs, there were 65 549 ADRs. It is important to note that there is a difference between the number of ICSRs and the number of ADRs. A single patient, identified by a unique report ID that is used to calculate the number of ICSRs, can experience multiple ADRs resulting in a larger number of ADRs compared to ICSRs. The Americas (North and South) contributed the most ICSRs for each drug apart from tamoxifen, where Europe was the largest contributor of ICSRs. Both Africa and Oceania have low numbers (1% and below) of ICSRs. For all three drugs, majority (> 90%) of the serious ICSRs were seen in females, contributing to 94.48%, 93.50% and 91.68% of the serious ICSRs for anastrozole, fulvestrant and tamoxifen respectively (see Table II). The “45 – 64 years” followed by the “65 – 74 years” age groups had the highest proportions of ICSRs. Most (> 50%) of the

ICSRs for the three drugs were reported in individuals ≥ 45 years of age. The majority of ICSRs falling within the older age groups was expected since increasing age is known to be a factor that is related to cancer incidence (113,156). However, age groups that were “unknown” featured prominently in the data.

Table II. Demographic data of all serious adverse drug reactions for anastrozole, fulvestrant and tamoxifen

Demographic/Drug	Anastrozole (n = 6 162)	Fulvestrant (n = 4 094)	Tamoxifen (n = 6 300)
UN Continent			
Africa	16 (0.26%)	15 (0.37%)	41 (0.65%)
Americas	3 947 (64.05%)	1 931 (47.17%)	2 069 (32.84%)
Asia	308 (5.00%)	451 (11.02%)	980 (15.56%)
Europe	1 865 (30.27%)	1 656 (40.45%)	3 158 (50.13%)
Oceania	26 (0.42%)	41 (1.00%)	52 (0.83%)
Gender			
Female	5 822 (94.48%)	3 828 (93.50%)	5 776 (91.68%)
Male	115 (1.87%)	53 (1.29%)	264 (4.19%)
Blank/Not applicable	225 (3.65%)	213 (5.20%)	260 (4.13%)
Age Group			
0 – 27 days	-	-	1 (0.02%)
28 days – 23 months	1 (0.02%)	-	5 (0.08%)
2 – 11 years	16 (0.26%)	-	7 (0.11%)
12 – 17 years	6 (0.10%)	-	6 (0.95%)
18 – 44 years	139 (2.26%)	168 (4.10%)	698 (11.08%)
45 – 64 years	1 982 (32.16%)	1 122 (27.41%)	2 202 (34.95%)
65 – 74 years	1 461 (23.71%)	809 (19.76%)	852 (13.52%)
≥ 75 years	993 (15.14%)	526 (12.85%)	557 (8.84%)
Unknown	1 564 (25.38%)	1 469 (35.88%)	1 972 (31.30%)

Table III shows all reported serious ADRs that are common (≥ 1%) for each drug. The data analysed did not have any serious ADRs that fell within the “very common” CIOMS frequency criteria (≥ 10%). From the common ADRs, “arthralgia”, “fatigue”, “nausea”, “breast cancer” and “malignant neoplasm progression” were identified as mutual ADRs for all three drugs. Tamoxifen and fulvestrant also shared the serious ADR “metastases to bone”. Most of these ADRs are known to be associated with their respective drugs. However, for fulvestrant, disease progression and metastases seem to dominate the serious ADRs.

Table IV depicts the distribution of the top three ADRs across their seriousness sub-categories. The seriousness sub-category “congenital anomaly/birth defect” was not included in the analyses due to its negligible contribution. The ADRs in blue font for anastrozole bring attention to the common nature of the ADR “arthralgia” and associated symptoms. For fulvestrant, “malignant neoplasm progression” and “metastases” are in blue font to show their frequency in the data. Lastly, for tamoxifen, “pulmonary embolism”, “deep vein thrombosis” and other uterine and vaginal related ADRs are highlighted with blue font due to their serious nature.

Table III. Common adverse drug reactions as per the CIOMS frequency criteria

Anastrozole (n = 27 493)		**Fulvestrant (n = 18 176)**		**Tamoxifen (n = 19 880)**	
Arthralgia	948 (3.45%)	Malignant neoplasm progression	731 (4.02%)	Malignant neoplasm progression	527 (2.65%)
Fatigue	406 (1.48%)	Neutropenia	514 (2.83%)	Breast cancer	311 (1.56%)
Hot flush	382 (1.39%)	Fatigue	413 (2.27%)	Metastases to bone	291 (1.46%)
Nausea	332 (1.21%)	Metastases to bone	334 (1.84%)	Pulmonary embolism	264 (1.33%)
Malignant neoplasm progression	313 (1.14%)	Nausea	319 (1.76%)	Arthralgia	250 (1.26%)
Breast cancer	309 (1.12%)	Death	254 (1.40%)	Fatigue	230 (1.16%)
Pain in extremity	308 (1.12%)	Metastases to liver	244 (1.34%)	Uterine cancer	216 (1.09%)
Bone pain	283 (1.03%)	Dyspnoea	244 (1.34%)	Nausea	201 (1.01%)
		Breast cancer metastatic	222 (1.22%)		
		Diarrhoea	216 (1.19%)		
		Asthenia	203 (1.12%)		
		Disease progression	189 (1.04%)		
		Breast cancer	189 (1.04%)		
		Arthralgia	181 (1.00%)		

Table IV. The top 3 adverse drug reactions characterised by the main seriousness sub-categories

Drug	Caused/prolonged hospitalisation	Death	Disabling/ incapacitating	Life threatening	Other	Blank
Anastrozole	Arthralgia – 86 of 3 184 (2.70%)	Death – 98 of 325 (30.15%)	Arthralgia – 134 of 1 092 (12.27%)	Pulmonary embolism – 9 of 158 (5.70%)	Arthralgia – 592 of 16 659 (3.55%)	Arthralgia – 24 of 419 (5.73%)
	Dyspnoea – 56 of 3 184 (1.76%)	Sudden death – 5 of 325 (1.54%)	Pain in extremity – 38 of 1 092 (3.48%)	Acute myeloid leukaemia – 4 of 158 (2.53%)	Hot flush – 285 of 16 659 (1.71%)	Alopecia – 12 of 419 (2.86%)
	Pulmonary embolism – 48 of 3 184 (1.51%)	Breast cancer – 5 of 325 (1.54%)	Myalgia – 34 of 1 092 (3.11%)	Fatigue – 3 of 158 (1.90%)	Malignant neoplasm progression – 265 of 16 659 (1.59%)	Fatigue – 10 of 419 (2.37%)
Fulvestrant	Nausea – 69 of 1 877 (3.68%)	Death – 206 of 583 (35.33%)	Neuropathy peripheral – 5 of 157 (3.18%)	Dyspnoea – 6 of 121 (4.96%)	Malignant neoplasm progression – 617 of 10 829 (5.70%)	Metastases to bone – 7 of 153 (4.58%)
	Fatigue – 43 of 1 877 (2.29%)	Malignant neoplasm progression – 20 of 583 (3.43%)	Pain - 5 of 157 (3.18%)	Hypersensitivity – 4 of 121 (3.31%)	Neutropenia – 426 of 10 829 (3.93%)	Asthenia – 6 of 153 (3.92%)
	Vomiting – 41 of 1 877 (2.18%)	Neoplasm progression – 14 of 583 (2.40%)	Fatigue - 5 of 157 (3.18%)	Drug ineffective – 3 of 121 (2.48%)	Metastases to bone – 278 of 10 829 (2.57%)	Pleural effusion – 5 of 153 (3.27%)
Tamoxifen	Pulmonary embolism – 111 of 2 804 (3.96%)	Death – 27 of 318 (8.49%)	Arthralgia – 35 of 797 (4.39%)	Pulmonary embolism – 24 of 243 (9.88%)	Malignant neoplasm progression – 472 of 11 335 (4.16%)	Hepatic function abnormal – 14 of 172 (8.14%)
	Deep vein thrombosis – 83 of 2 804 (2.96%)	Acute myeloid leukaemia – 9 of 318 (2.83%)	Fatigue – 22 of 797 (2.76%)	Deep vein thrombosis – 12 of 243 (4.94%)	Breast cancer – 274 of 11 335 (2.42%)	Alopecia – 7 of 172 (4.07%)
	Endometrial hyperplasia – 57 of 2 804 (2.03%)	Neutropenic sepsis – 9 of 318 (2.83%)	Myalgia – 21 of 797 (1.63%)	Uterine cancer – 8 of 243 (3.29%)	Metastases to bone – 245 of 11 335 (2.16%)	Vaginal haemorrhage – 4 of 172 (2.33%)

4. Discussion

4.1. Demographic data

The demographic findings shown in Table II are consistent with published literature. A previous VigiBase® study found that high-income countries reported more ADRs for antineoplastic and immunomodulating agents than lower income countries (89). Additionally, developed countries such as the United States and European countries report more ADRs in general (9), which can be attributed to their robust PV systems. The same can be deduced for this study since the majority of ICSRs were reported from Europe and the Americas. However, there is a large disparity between economic status of countries and to a greater extent between continents, which is what our findings are based on. The low ICSR numbers for Africa were expected. Underreporting of ADRs has largely rendered signal detection and post-marketing surveillance (PMS) which are crucial to drug safety. Underreporting is a worldwide issue, however, to a greater extent in LMICs (86). Developing countries such as those located in Africa have weak PV systems among other factors that limit PV activities and ADR reporting (8,13). Additionally, cancer is not seen as a priority in African countries due to the burden of non-communicable diseases (NCDs) and infectious diseases such as malaria, HIV and TB (8,13,107). However, globally, cancer causes more deaths each year than the three diseases combined (110). The cancer incidence is growing in LMICs due to the growth and ageing of the population and other factors previously mentioned (104,107,108,110).

Since these hormonal agents are primarily used in premenopausal and postmenopausal women, it was expected that the majority of the ICSRs would be reported in females and that males would contribute a low percentage of the ICSRs. Additionally, it has been stated in other studies that females are at an increased risk of developing ADRs which may possibly be due to the different stages females go through such as pregnancy, menarche and menopause which result in changes in the pharmacokinetic (PK) activities in the body (157,158).

Most ICSRs were reported for the older populations, who are particularly predisposed to ADRs due to age-related changes in PK and pharmacodynamics (PD), multimorbidity and polypharmacy (159,160). Polypharmacy in itself also increases the risk of ADRs (144) which compounds the ADR risk for elderly populations. Other studies have found that there is a higher incidence of breast cancer with increasing age (103,107,124). This may account for why there are less ICSRs in the “18 – 44 years” age group as compared to the “45 – 64 years”, “65 – 74 years” and “≥75 years” age groups. The number of ICSRs for anastrozole and tamoxifen are similar, however, there is a notable difference between the percentage of ICSRs for the “18 – 44 years” age group. This may be attributed to the limited use of anastrozole in premenopausal women due to the drugs mechanism of action. Since anastrozole is an AI, it primarily inhibits the aromatase enzyme from converting androgens produced in the adrenal glands to oestrogen. Thus, the oestrogen produced by the ovaries are unaffected, which renders the use of AIs ineffective in premenopausal women (117). This may explain why this age group accounts for only 2.26% of the anastrozole ICSRs and 11.08% of the tamoxifen ICSRs.

4.2. Common ADRs

Most of the serious ADRs identified from the VigiBase® database for the chemotherapeutic agents as seen in Table III are known to be associated with that specific drugs' use, with many of them identified during clinical trials and appearing on the drugs professional information leaflets. However, the seriousness of the reaction is not diminished by the fact that the ADRs are well known and reported to VigiBase®. Cancer is an incurable disease and only few drugs are available to halt the uncontrolled proliferation of cells within the body (161). Thus, treatment options are limited despite the ongoing research and drug development within the oncology field, resulting in patients having to contest with serious ADRs as part of their treatment regimen (44,46,130).

Hormonal therapies such as anastrozole and tamoxifen are indicated for long-term use to reduce the risk of breast cancer recurrence and decrease the incidence of contra-lateral spread (132). Thus, their role in breast cancer management is pivotal. Anastrozole, or more accurately, AIs, are commonly associated with arthralgia and related musculoskeletal symptoms such as bone pain, pain in the extremities and myalgia (162). Thus, "arthralgia" being the most common serious ADR for anastrozole is consistent with other findings (121,132,163).

The common serious ADRs reported for tamoxifen in Table III include the ADRs "pulmonary embolism" and "uterine cancer". Tamoxifen use is known to be associated with thromboembolic and cerebrovascular events such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and an increased risk of uterine cancer (119,121,135). Thus, our findings are congruent with current published literature. The addition of hormonal therapy such as tamoxifen to chemotherapy increases the risk of venous thromboembolism (VTE) (164). Cancer patients are at an increased risk of thrombosis due to several factors such as surgery and hospitalisation. Chemotherapy and metastases further increase the VTE risk and hormonal treatments have been found to increase the thrombosis risk by 50% (165). In addition to the complexities associated with VTE and cancer, the long-term effects of DVT has significant impact on patient QoL and daily functioning of patients (166,167). In hospitals within the United States (US), DVT and PE admissions accounted for > $11 billion in hospital charges. The overall in-patient mortality was 0.7% and 2.7% for DVT and PE respectively, with PE being associated with greater length-of-stay and hospital costs than DVT (168).

The serious ADRs "disease progression", "metastases to bone", "metastases to liver" and "breast cancer metastatic" were found to be associated with fulvestrant use. Fulvestrant is typically used as a second-line hormonal treatment option following the use of tamoxifen or AIs such as anastrozole in the case of disease recurrence or metastases. The use of fulvestrant can also be due to the resistance developing against anastrozole or tamoxifen, thus limiting their use. However, fulvestrant does not exhibit cross-resistance with tamoxifen or steroidal AIs like anastrozole, making it a viable option for patients who have previously been on endocrine therapies as well as those who have not (169,170). Fulvestrant is indicated for use in OR-positive, locally advanced or metastatic breast cancer for patients with disease relapse on or after adjuvant anti-oestrogen therapy or disease progression on anti-

oestrogen therapy (91). This may explain the nature of the ADRs as mentioned above. Typically, fulvestrant is well tolerated, thus, the reports in VigiBase® may not be a true reflection of the ADRs associated with fulvestrant, but rather of the patients' state of health while on the drug.

4.3. Seriousness categorisation of the reported ADRs

Table IV further characterises the serious ADRs into the 5 main sub-categories as defined by the ICH - caused/prolonged hospitalisation, congenital anomaly/birth defect, life threatening, disabling/incapacitating, and death. The data also had two additional sub-categories: "other" and "blank". When an ADR is reported, the reporter/notifier determines whether the ADR is serious or not and then further describes the seriousness as above. Thus, combinations of these sub-categories were present in the ICSR data which resulted in a possible 36 seriousness sub-categories for the three drugs.

The ADR "arthralgia" features in most of the seriousness sub-categories for anastrozole. Studies have found that aromatase inhibitor induced arthralgia (AIA) largely impacts patients' quality of life (QoL) and can result in treatment discontinuation or poor adherence (133,171–173). A systematic review by Murphy et al. demonstrated that more than two thirds of patients did not complete their recommended 5-year adjuvant treatment plan (172). Moreover, side effects were found to be a common barrier to treatment continuation (172). This subsequently renders the treatment less effective since early discontinuation and non-adherence of the long-term treatment were identified as independent predictors of mortality (173). This poses a significant issue for patients on treatment if the ADR is not addressed and managed appropriately.

Under the "life threatening" sub-category for fulvestrant, "drug ineffective" was reported in 3 of 121 (2.48%) serious ADRs in the sub-category. A lack of efficacy of a drug is one of the circumstances under which ADR should be reported (82). Due to the poor nature of ADR reporting, there may be a larger proportion of ineffective use of fulvestrant. In contrast, the data from VigiBase® has not been verified and thus, further investigations need to be done. The ADR "pulmonary embolism" is part of the top three serious ADRs as reported for both anastrozole and tamoxifen and "deep vein thrombosis" for tamoxifen only. Both DVT and PE are associated with significant patient morbidity and mortality, resulting in great economic burden (168), with mortality rates for VTE being highest in cancer patients (165). Studies have also found a poorer prognosis and higher incidence of mortality in cancer patients with DVT as well as a higher risk of DVT recurrence in comparison to DVT patients without cancer (174,175). As mentioned above, DVT and PE also have significant cost and QoL implications that can affect clinical outcomes. Additionally, anastrozole has an advantageous side effect profile over tamoxifen (121,122) which may explain the less serious ADRs for anastrozole.

It is concerning to see that the ADR "malignant neoplasm progression" is commonly reported for all three drugs. However, it is important to note that the data obtained from VigiBase® and the UMC is based on suspected ADRs that have been reported by HCPs and consumers. Additional causality assessments need to be done for a definitive causal relationship between the drug and the ADR to be

established. “Death” was the most common ADR in the “death” seriousness sub-category for all three drugs. The cause of death, however, is not stipulated in the ICSR. This makes it difficult to determine whether the use of the drug is the cause of death through an unknown mechanism, if an ADR involving the drug was the cause of death, or if the death was entirely non-drug related.

The purpose of post marketing surveillance (PMS) is to detect ADRs that may be less common but are serious in nature (82). The ADRs in blue font in Table IV are the ADRs commonly associated with the drug’s use according to literature (117,148). Thus, it was expected that these ADRs would feature prominently. However, the similarities between the common ADRs in Table III and the characterised serious ADRs in Table IV suggest that the serious ADRs are, in fact, well known and prevalent amongst patients. Due to the toxicity of chemotherapeutic agents, many HCPs consider side effects and ADRs to be inevitable or part of the treatment (46,79) which could be a contributing factor to why ADRs in oncology are underreported (45). Since oncology ADRs are underreported, and, when coupled with the underreporting of ADRs overall, the actual number of serious ADRs may be significantly higher than what the data shows. An increase in the frequency of known ADRs is another circumstance that warrant an ADR to be reported (82). Therefore, if HCPs are over-looking certain ADRs on the basis that they are known, an increase in frequency of an ADR may not be detected and the true extent of serious ADRs may not be known. This counteracts signal detection, which could aid in regulatory actions such as amendments to labelling to ensure patient safety (19).

The outcomes of this research can be useful when implementing patient treatment regimens: highlighting the ADRs that are reported as serious by the patient gives insight into how patients perceive and tolerate their treatment. This may help the patients treating doctor understand the implications of the treatment they prescribe which has significant effect on the patient’s QoL and prospect of their treatment. This research also highlights the fact that ADRs well known to medical professionals may not necessarily be acceptable to patients and thus, must not be considered synonymous with the treatment. Taking the seriousness of the ADRs into account can change the outlook on how treatments affect patients and how they can be managed to improve or maintain patient QoL while undergoing long-term treatment.

5. Limitations

A key limitation in this research is that ADRs are typically underreported. Underreporting of ADRs is widely acknowledged as a limitation to PV activities, post marketing surveillance and signal detection (63). Additionally, since the source of the ADR reports are mainly from spontaneous reporting systems, there is a possibility of ICSR duplication. Thus, the results of the study may not be an accurate representation of the extent of ADRs. Lastly, the seriousness of the reported ADRs has been determined by the notifier/reporter, therefore, the ADR may not conform to the “serious” definition as defined by the ICH.

6. Conclusion

Well known ADRs for anastrozole, fulvestrant and tamoxifen have been commonly reported in the data. In addition, these ADRs dominate the seriousness sub-categories in the data despite ADRs being routinely underreported. Adverse drug reactions that have considerable impact on patient QoL, daily functioning and have significant cost implications such as DVT, PE and arthralgia are ADRs that, albeit may not be preventable in this case, should be identified early on and managed in a way that safeguards patients in their treatment, improves clinical outcomes and informs treatment regimens.

Disclosure

The data obtained from the UMC comes from a variety of sources and is based on suspected ADR reports and the probability that the suspected ADR is drug-related is not the same in all cases. This research is in no way the opinion of the WHO or UMC.

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Conflict of interest

The author(s) declare(s) there are no conflicts of interest

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CHAPTER 5
Discussion

Chapter Overview

This chapter interprets and explains the results that were detailed in Chapter 4. This chapter will elucidate the results of the demographic data and compare them with the current literature that exists for these studied chemotherapeutic drugs. The results of the top ten ADRs for the studied drugs will be deliberated and literature that is similar and dissimilar to the results will be described. The ADR reporting comparatives between the continents and reasoning behind the differences will be provided.

5.1. Description and categorisation of anastrozole, fulvestrant and tamoxifen related ADRs

The data had been analysed to describe the demographic profile of each of the drugs' and to then categorise the top 10 ADRs from each drug as per the UN continent from which the ADR was reported. Lastly, the top 10 reported ADRs for each drug were identified and quantified.

5.1.1. Demographic data and report characteristics

Most ICSRs were received from the Americas and Europe, which is consistent with VigiBase® data (9). The percentage distribution of the global population across the continents is as follows: Asia – 59.40%, Africa – 17.20%, Europe – 9.59%, North America – 7.60%, South America – 5.53%, therefore, the Americas (13.13%), Australia – 0.55%, and Antarctica – 0% (176). In a perfect world, the ICSR data should ideally reflect the percentage population, however, this is not the case. Access to medicines is a factor that has significantly impacted healthcare systems and disease burden. Many LMICs had poor ATMs, which left the populations vulnerable to diseases that could be treated or even prevented. As a result, the priority was to secure a steady flow of medicines, whether it be through local manufacture, importation or as part of global aid initiatives. With the focus on ATM, PV and PMS were not a concern. Only in recent years have LMICs joined the WHO PIDM, set up NCs and partaken in ADR

reporting (8,13,22,88). Higher-income countries report more than lower income-countries, which could be why the Americas and Europe dominate the ICSRs (89). However, the data analysed was separated into UN continents, which groups North and South America, for example, into a single continent. The economic, social, and political climates vary greatly, not only between continents but also between countries and possibly between different regions within a country (89), therefore, the fact that higher income countries report more than lower-income countries cannot be generalised for the UN continents.

It is well known that cancer incidence increases as age increases, owing to the larger proportion of ICSRs in the older age groups (177). Additionally, pharmacodynamic changes in the elderly and an increase in the number of medications used in older populations may also contribute to the greater number of ICSRs from the older age groups (160). A high proportion of ICSRs (27.39% of all ICSRs) has been reported under the "unknown/blank" category of the age groups. This could be attributed to the poor ADR reporting practices from HCPs, which have been widely documented (28,33,54,56), that has resulted in incomplete ICSRs.

The study population primarily comprised of females (93.99% of all ICSRs) between the ages of 45 and 74 years (61.76% of all ICSRs). The drugs reviewed in this study are mainly used in postmenopausal women, thus, these results were expected. The use of anastrozole, fulvestrant and tamoxifen is not well documented in males. However, literature has noted their use in increasing male height in precocious puberty, delaying puberty (178), male breast cancer and off-label use (179). This may account for the small percentage of ICSRs for males. It is important to note the difference between "sex" and "gender". The data that was provided had the variable "gender", which is a socially constructed characteristic as determined by the individual, rather than "sex", which is determined biologically (180) and is usually the characteristic included in study populations.

The report characteristics included in this study were "report type" and "notifier". The most common "report type" in the data was spontaneous reporting, accounting for 90.63% of all ICSRs for anastrozole, fulvestrant and tamoxifen. Pharmacovigilance mainly relies on SRSs for ADR reporting due to its convenience, affordability, ability to

detect signals and large population and drug coverage. However, due to the limitations of spontaneous reporting, the main limitation being under-reporting, the data may not be entirely accurate. Spontaneous reporting cannot determine the incidence and frequency of ADRs because the actual denominator value of the ADR is unknown; additionally, the causality of the ADR cannot be confirmed from SRSs (18,65,68). Other “report types” such as active surveillance systems and clinical trial studies, do not contribute nearly as much as SRSs, as seen in Table 9. It is encouraging to see a low number of “unknown/blank” report types compared to the “unknown/blank” fields for the “age groups” and “notifier” variables.

The “notifier” characteristic shows that physicians and consumers/non health professionals were the main contributors to ICSRs. Healthcare professionals such as physicians and pharmacists are encouraged to report ADRs especially because of their knowledge regarding medicines (63). Studies have shown that there are many limitations to ADR reporting amongst HCPS such as fear of litigation, inadequate knowledge on reporting procedures, time constraints, and poor PV knowledge overall (8,13). Pharmacists, however, did not play a significant role in ICSR reporting despite their scope of practice and ideal placement in healthcare (33,84,102). Pharmacists, the custodians of medicine, could be the primary source of ADR reporting due to their role in drug safety (84).

5.1.2. Categorisation of the top 10 ADRs for anastrozole, fulvestrant and tamoxifen

Identifying and categorising the top 10 ADRs for each core drug provides a more comprehensive overview of the ADRs that are most often reported and, by extension, the most likely ADRs that are experienced by patients.

5.1.2.1. Anastrozole

The top 10 ADRs reported for anastrozole (Table 4.2) account for 18.80% (9 822 of 52 256) of the total number of ADRs for anastrozole. Arthralgia, the most commonly reported, is frequently associated with anastrozole and AIs in general (121). Various trials have reported the incidence of arthralgia associated with the treatment of AIs to range between 5.4% - 35.6% (132,181) with other studies suggesting an incidence of up to 50% (172,182,183). Aromatase inhibitor-induced arthralgia (AIA) is a condition

that is associated with the use of AIs such as anastrozole, however, due to the lack of a clear definition for AIA, the incidence between studies varies due to the inclusion of different terms/conditions such as “myalgia”, “joint pain”, “joint stiffness” etc. (132,163). Another study stated that the terms/conditions “myalgia”, “fibromyalgia” and “neuropathy” are not considered to be part of the definition of “arthralgia”. Additionally, arthralgia does not involve inflammation and swelling of the joints, which is synonymous with arthritis (181). Another term, AI-associated musculoskeletal syndrome, has also been used to describe the conditions associated with AI use (163).

Despite the increased incidence of arthralgia associated AIs, other conditions may also contribute to arthralgia in this population, including menopause. It is widely known that oestrogen has protective effects on bone, which may explain why the deficiency of oestrogen brought on by the menopausal state could explain the increase of arthralgia and other musculoskeletal symptoms such as bone fractures, osteoporosis, and arthritis in postmenopausal women. Certain disease states such as auto-immune diseases (rheumatoid arthritis), gout and osteoarthritis are also causes that may result in arthralgia (132,163,181).

5.1.2.2. Fulvestrant

Fulvestrant is indicated for OR positive and HER-2 negative locally advanced or metastatic breast cancer in postmenopausal women not previously on anti-oestrogen therapy and locally advanced or metastatic breast cancer in postmenopausal who have disease progression after previous anti-oestrogen therapy (184). Keeping this in mind, the presence of the ADRs “malignant neoplasm progression” and “metastases to bone” in the top 10 ADRs for fulvestrant may not be as a result of the drug itself but rather the progression of the disease in the patient. This could have occurred either during or prior to initiating the drug in the patient’s treatment regimen. Studies looking at fulvestrant’s tolerability have stated that the drug is well tolerated and had noted “injection site pain”, “nausea”, “arthralgia” and “asthenia” as effects related to the drug’s use (124,185,186).

5.1.2.3. Tamoxifen

The most reported ADR for tamoxifen is “death”. There is no way to determine whether the deaths that were reported as ADRs of tamoxifen are, due to the explicit use of the

drug. There are many confounding factors that may contribute to the death of a patient such as duration of therapy, dosage, concomitant drugs, disease stage etc., none of which are available in the database. More so, additional analysis, such as causality assessments, would need to be conducted to draw a conclusion regarding death and tamoxifen use.

It is widely known that tamoxifen, when used at doses for the prevention or treatment of breast cancer, is associated with an increased incidence of thromboembolic events that include DVT and PE and secondary endometrial cancer (119,121,187). Thus, the presence of “deep vein thrombosis” and “pulmonary embolism” in the top 10 ADRs for tamoxifen is no surprise. Despite the extensive use of tamoxifen in its treatment, breast cancer was not found to be one of the cancer types associated with higher rates of VTE, however, metastatic cancer was (188). A study found that 4.1% of cancer patients were diagnosed with VTE (188,189). Cancer patients are also at an increased risk of thrombosis due to several factors such as surgery and hospitalisation and the effects of malignant tumour cells activating coagulation pathways. Active chemotherapy and metastases further increase the VTE risk and hormonal treatments have been found to increase the thrombosis risk by 50% (165). This may explain the increased reporting of DVT and PE in the data.

Tamoxifen use is also associated with arthralgia, although to a lesser extent than anastrozole, which may be why the percentage of arthralgia ADRs reported is not as extensive as that for anastrozole (121). The ADR “malignant neoplasm progression” also features in the top 10 ADRs for tamoxifen, however, a conclusion cannot be drawn as to whether this progression is directly due to the use of tamoxifen. Other reasons for disease progression could be due to tamoxifen resistance or, simply due to the nature of the tumour. Tamoxifen resistance results in the drug no longer effective in its treatment of breast cancer. This can be attributed to the partial oestrogenic agonistic properties of the drug that also contribute to the increased incidence of secondary cancer. This can lead to the growth of the tumour rather than its suppression (124).

5.1.3. Continental categorisation of ADRs for anastrozole, fulvestrant and tamoxifen

The reported ADRs were further categorised as per the UN continent to gain insight into whether specific ADRs are more prevalent in certain geographical locations. However, many factors can influence health in a given setting, such as socioeconomic conditions, the burden of disease, quality, cost and accessibility of healthcare and medicines, the influence and prevalence of counterfeit medications, knowledge surrounding health, traditional healers and natural/herbal remedies, availability of HCPs, medicine shortages etc., all of which can play a role in the extent of ADR reporting (8,13). More so, these factors can vary significantly between continents, countries, and even cities. These confounding factors are not known within the context of this study and thus should be considered.

Figures 4.1, 4.2, and 4.3 all depict a similar trend. The greatest number of ADRs for all three drugs were reported by the Americas, followed by Europe, Asia, Oceania and lastly, Africa. This was largely expected due to robust PV systems in developed countries which has created an awareness surrounding ADR reporting. It has also been reported that high-income countries have more excellent ADR reporting rates than low-income countries. Additionally, high-income countries reported the most ADRs for the class of “antineoplastics ad immunomodulating agents”, which may be attributed to better access to such medicines (89). New Zealand and Australia, which are part of Oceania, are high-income countries but their contribution to the number of reported ADRs is slightly greater than that of Africa. This may be due to the relatively small population in those countries, which can translate to lesser reports when compared to other high-income countries such as those in Europe. It is important to note that the UN continent “Americas” includes both North and South America, which have vastly different burdens of disease, socio-economic statuses, genetic profiles, PV knowledge, healthcare systems etc. Thus, these results need to be interpreted with caution.

With the Americas contributing 65% of the reported ADRs on average, the ADRs from the Americas for each drug as seen in Tables 4.3, 4.4 and 4.5 are similar to the top 10 ADRs of each drug in Table 4.2. The benefit of having a large contribution of ADRs from the Americas is the insight it provides regarding common ADRs associated with

using those specific drugs in a ‘real-world’ setting (63,79). Clinical trials, which establish a drug’s safety profile, are conducted under specified conditions which may exclude certain populations resulting in homogeneity (61,80). This may not always be beneficial when it comes to ADRs due to many factors such as age, economic and health status, sex, genetics, comorbidities etc. that significantly influence both ADRs and the risk of experiencing an ADR (70). Additionally, ADRs related to “long latency diseases like cancer are difficult to detect on account of the short duration of the study” (160).

The types of ADRs reported from Europe are comparable to those of the Americas and the overall top 10 ADRs for the specific drug. These ADRs are also commonly reported in current literature, which may be due to clinical trial data being based on these populations. The profile of ADRs for Oceania shows a large proportion of ADRs to be related to disease progression and metastases. This may be attributed to the incidence rate of breast cancer for Australia and New Zealand being the greatest in the world in 2020 at 95.5 per 100 000 (world average 47.8 per 100 000). Additionally, two albeit small subregions of Oceania, namely Melanesia and Polynesia, had the greatest and second greatest breast cancer mortality rates in the world in 2020 (27.5 and 22.3 per 100 000 respectively) (111).

The ADR profile for Africa is slightly different to the rest of the UN continents and the overall top 10 ADRs for the specific drug. Despite the very low contribution of ADR reports to the database, these ADRs are not entirely comparable to what is being seen in the rest of the world. Thus, the idea that the common ADRs experienced when using these chemotherapeutic drugs are not reported may not be the case for Africa. However, due to the low numbers of ADR reports from Africa, conclusions cannot be drawn regarding the nature of the ADRs in that population. As a result of the poorly functioning PV systems, if any, that hinder ADR reporting and signal detection, LMICs have lower reporting rates than high-income countries (89). Figures 5.1 below, taken from the 2020 breast cancer fact sheet from Globocan, the WHO and IARC, shows a geographical comparison between the incidence (a) and mortality (b) rates for breast

cancer in 2020. Despite Africa having comparatively low incidence rates to Europe, Australia and North America, the majority of highest mortality rates is found in Africa.

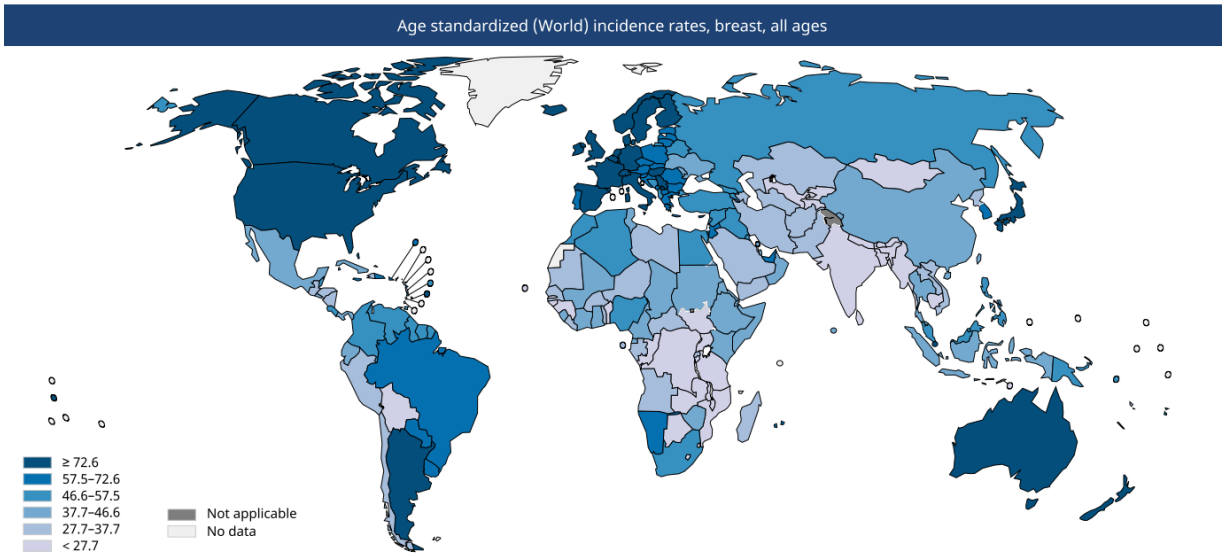


Figure 5.1 (a) Incidence rates of breast cancer in 2020 (111)

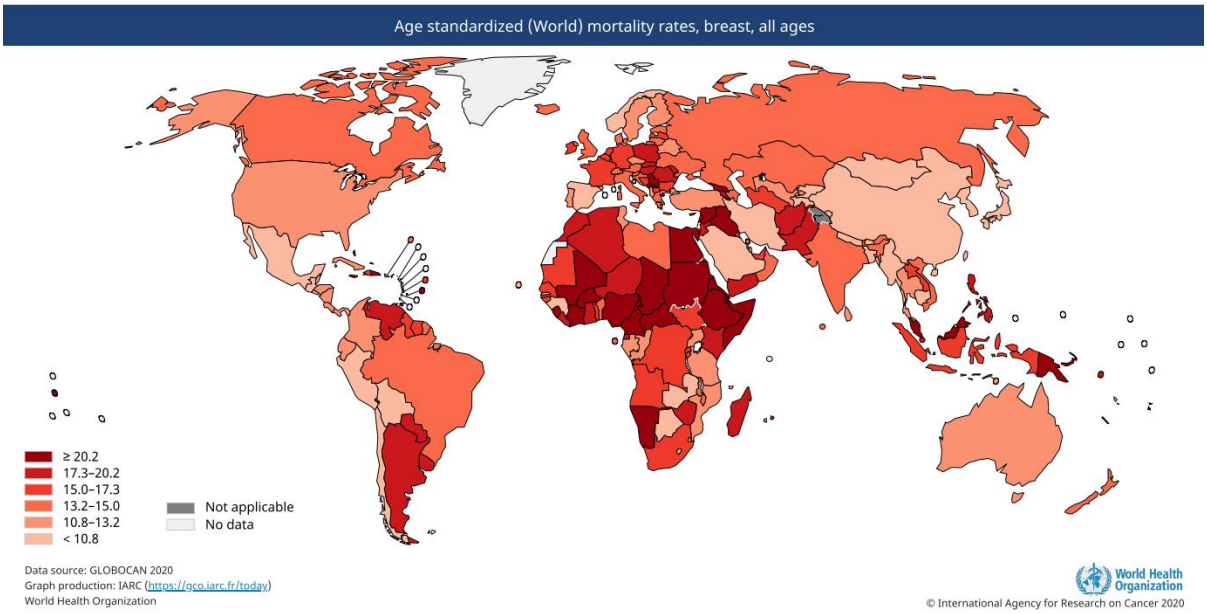


Figure 5.1 (b) Mortality rates of breast cancer in 2020 (111)

5.2. Statistically significant ADRs

The statistical analysis conducted on the data was aimed at establishing any associations between the demographic variables UN Continent, age group and gender. Determining statistically significant associations between specific ADRs and population characteristics can help identify patient populations that are at an increased

risk of experiencing a specific ADR. This information could be used to engage in targeted ADR monitoring/PMS which will allow for better patient care.

The statistical analysis program STATA assigned reference values to which the binary regression results are compared. The reference values were the first variable for each demographic characteristic, i.e., Africa for “UN continent”; < 18 years for “age group”; and female for “gender”. Africa was the reference value for “UN continent” and, since the number of reports for Africa was very low in comparison to the rest of the “UN continents” (see Table 4.1), the majority of the 95% CI’s are large, indicating a great degree of uncertainty in the results. For Oceania, however, there was also a relatively low number of reports, which may be why some of the 95% CIs for the ADRs significantly associated with this variable are narrow. The same logic for the UN continents can be applied to the “age group”. the “gender” variable on the other hand, female, was the reference value, which accounts for the majority of the ADR/ICSR reports.

5.2.1. Anastrozole

Table 4.8 shows the statistically significant ADRs associated with the demographic variables for anastrozole. The ADR with the most significant associations across all the demographics was “arthralgia”. This was followed by “fatigue” and “nausea” tied for the second most significantly associated ADR and “myalgia” third. Previous studies have highlighted the high prevalence of ADRs associated with the musculoskeletal system in patients on AIs such as anastrozole (121,122,132,162,163). It has also been noted that joint symptoms increase with increasing age (190). Additionally, the post-menopausal status of women have been found to be an independent predictor that is associated with increased musculoskeletal symptoms (162). As mentioned before, drugs like anastrozole are primarily used in postmenopausal women, thus, may explain the presence of “arthralgia” as a significantly associated ADR.

The statistically significant association of arthralgia across the different age groups and UN continents is an important finding not only because it is commonly associated with the use of anastrozole but also because of its associated effects on the affected populations. Studies have found that AIA negatively impacts patients’ QoL and daily functioning leading to poor adherence and/or treatment discontinuation (132,133,171–

173,191). A systematic review demonstrated that more than two-thirds of patients did not complete the recommended 5-year adjuvant therapy and side effects were found to be a barrier to treatment continuation (172). This subsequently renders the treatment less effective since early discontinuation and non-adherence of the long-term AI treatment were identified as independent predictors of mortality (173).

The term AIA is commonly used when referring to arthralgia associated with of AIs. However, there is no widely accepted definition of AIA yet, thus, the way in which the condition is categorised remains unclear (132). One must note that there are many disease states that can cause arthralgia including menopause, due to oestrogen deficiency. In contrast to arthritis, arthralgia is not an inflammatory disease and does not include other musculoskeletal symptoms such as myalgia. Thus, it is not possible to know whether the ADRs reported as “arthralgia” were misconstrued as other ADRs such as “myalgia”, “bone pain” or “pain in extremity”. This may have contributed to the significant association of arthralgia with multiple age groups and UN continents.

Other side effects associated with anastrozole include hot flushes, headaches, asthenia and gastrointestinal effects such as nausea, abdominal pain, diarrhoea and constipation (134). As seen in Table 4.8, “nausea” has been reported as statistically significant for the “45 – 64 years” (OR 0.62; 95% CI 0.50 – 0.76; p = 0.000), “65 – 74 years” (OR 0.80; 95% CI 0.64 – 0.99; p = 0.038), and “blank/unknown” age groups (OR 0.68; 95% CI 0.54 – 0.86; p = 0.001) and for the UN continent “Europe” (OR 1.54; 95% CI 1.33 – 1.80; p = 0.000).

5.2.2. Fulvestrant

The statistically significant ADRs associated with demographics for fulvestrant were detailed in Table 4.9. The two ADRs with the most significant associations with the demographic variables were “malignant neoplasm progression” and “asthenia”. Other serious ADRs that showed significant associations were “metastases to bone” and “neutropenia”. Typically, fulvestrant has been documented as a well-tolerated drug. It exhibits minimal serious side effects, with the most common side effects being hot flushes, nausea, asthenia and injection site reactions (124).

Fulvestrant acts by competing with oestradiol and binds to the OR with a higher affinity (192). The bound OR-fulvestrant complex is unstable, resulting in the complex's accelerated degradation (186). Fulvestrant does not demonstrate any oestrogenic activity and has been found to be effective in patients that have developed tamoxifen resistance (124). There is a risk of resistance to endocrine therapy, which may warrant the use of cytotoxic chemotherapy for the treatment of HR-positive breast cancer. Thus, there is a need for alternate endocrine therapies that do not exhibit cross-resistance with existing treatments. These alternate therapies can be implemented sequentially to extend the time to chemotherapy. Fulvestrant has been approved and licensed by both the US FDA and European Union for "the treatment of hormone receptor-positive advanced breast cancer in postmenopausal women with disease progression following anti(o)estrogen therapy" and "for the treatment of postmenopausal women with E(O)R-positive advanced breast cancer, for disease relapse on or after anti(o)estrogen therapy or disease progression on therapy with an anti(o)estrogen" (193).

This may be the reason for its use in advanced breast cancer following previous hormonal therapies. Due to its indication, there may be an increased likelihood that patients on fulvestrant have metastatic disease. This could explain the nature of the ADRs (malignant neoplasm progression and metastases to bone).

Other ADRs that showed significant associations included "dyspnoea", "nausea", "fatigue", "injection site pain", and "arthralgia". A trial looking at the use of fulvestrant in breast cancer patients with advanced disease after treatment with an AI found the following toxicities to be "at least likely related to treatment" in 76 of the 77 patients: fatigue, hot flashes, nausea, injection site reactions, anorexia, arthralgias, diarrhoea, alopecia, neurosensory difficulties, and dyspnoea. Despite these observations, treatment was reported as well tolerated (185).

5.2.3. Tamoxifen

Table 4.10 detailed the statistically significant ADRs associated with the demographic variables for tamoxifen. All the age groups except for "< 18 years" age group had several significantly associated ADRs. The "18 – 44 years" age group showed significant associations with all of the top 10 ADRs and the "45 – 64 years" age groups

had nine out of ten significantly associated ADRs. The UN continent “Europe” had the most ADRs significantly associated. The ADR with the most significant associations was “arthralgia” followed by “death”, “malignant neoplasm progression”, and “hot flush”. The ADRs “deep vein thrombosis” and “pulmonary embolism”, which are known to be associated with tamoxifen use, also featured prominently in the data. Despite arthralgia being more commonly associated with AIs, it is also an ADR prevalent with tamoxifen use, albeit to a lesser extent (121,122).

There is concern surrounding “death” featuring so prominently within the reported ICSRs, however, there is insufficient data to conclude whether the deaths are directly due to tamoxifen itself or if other factors such as disease stage/progression status, drug-drug interactions, comorbidities etc. had influence in these reported deaths. More so, causality assessments and other further analyses would have to be conducted to determine if tamoxifen use causes death. The same applies to the ADR “malignant neoplasm progression”; there is no way to determine, with the data from this study, if the disease progression is directly a result of tamoxifen use or due to other confounding factors. As mentioned in section 5.2.2.3, tamoxifen resistance is a phenomenon that can occur and therefore leads to disease progression. That does not translate to malignant neoplasm progression due to tamoxifen use.

The ADRs of concern, which also happens to be well-known ADRs associated with tamoxifen, are DVT and PE. Tamoxifen is a drug with the risk of VTE associated with its use. The term VTE comprises DVT and PE, which are associated with significant patient morbidity and mortality, resulting in an economic burden due to the substantial use of health resources (168). Thrombosis occurs due to vasculature obstruction either in the peripheral veins or within the pulmonary arteries resulting in DVT and PE respectively (164,189). Proximal DVTs are associated with chronic diseases involving the cardiac and respiratory systems and cancer. Other risk factors include inactivity, prolonged bed rest, paralysis, stroke , heart failure, previous VTE, increasing age, hormonal treatment, oral contraceptives, obesity, pregnancy, surgery, female sex, age ≥ 65 years, chemotherapy, and cancer (164,165,189,194,195).

The association between cancer and VTE is widely known (164). With PE contributing to one in seven cancer deaths, VTE is the second leading cause of death in cancer

patients. If survived, the likelihood of developing chronic complications such as post-thrombotic syndrome (PTS) and recurrent VTE is evident (196). Cancer patients on active treatment are at a greater risk of developing VTE, with a 5% and 17.6% incidence of VTE in patients receiving chemotherapy for early-stage breast cancer and metastatic breast cancer, respectively (197). Studies have found a higher incidence of mortality and poorer prognosis in cancer patients with DVT and a higher risk of DVT recurrence (174,175). Mortality rates for venous thrombosis are highest in patients with cancer. Genetic factors such as gene mutations also play a role in VTE incidence across populations (165). Patients with distant metastases had a doubled incidence of VTE compared to those without metastases (164,195).

Despite this pre-existing association between cancer and VTE, there is a further increase in the risk of VTE in cancer patients directly due to chemotherapy. More so, the addition of hormonal therapy such as tamoxifen to chemotherapy further increases the VTE risk (164). The data that was provided did not specify whether patients had been on chemotherapy as well as hormonal therapy, thus, it cannot be determined if these results were influenced by such. However, another study has found that cancer treatment, whether chemotherapy or hormonal therapy, increases the risk for VTE (196). This may explain the increased incidence of DVT and PE in the reported VigiBase® data.

Deep vein thrombosis is associated with serious morbidity (PTS and bleeding due to anticoagulation treatment) and may even progress to pulmonary embolism-associated mortality (198). In addition to the complexities associated with VTE and cancer, the long-term effects of DVT have a significant impact on patient QoL and the daily functioning of patients (166,167). Another study has shown similarities between health-related quality of life (HRQoL) of DVT patients and population norms, however, patients diagnosed with PE exhibited a poorer HRQoL due to the lasting effects of PE (199). In addition to the significant impact on VTE patients QoL, the costs associated with VTE and its complications also need to be considered (196). Studies have found better survival after DVT than after PE (200). In hospitals within the US, DVT and PE admissions accounted for > $11 billion in hospital charges, with DVT averaging approximately US$30 000 and PE US$37 000 per admission. The overall in-patient mortality was 0.7% and 2.7% for DVT and PE respectively, with PE being associated

with greater length-of-stay and hospital costs than DVT. The majority of the re-admissions for DVT (4.2% of the total number of admissions) and PE (4.0% of the total number of admissions) occurred within the first 60 days of the initial incident (168).

In contrast, DVT diagnosis has been found to be a potentially indicative sign of cancer (201), thus, the incidence of DVT in cancer patients may be unknown. Malignant cells can activate pro-coagulation pathways, increasing VTE risk (196). A study found 12.1% of participants with venous thrombosis had diagnosed malignancy, with an overall odds ratio of 4.3 (95% CI, 3.3-5.6) compared to the participants without malignancy(175). Furthermore, the risk of VTE was highest during the first three months after the cancer diagnosis, with the risk declining. Participants with haematological malignancies were at greatest risk of VTE, followed by lung and gastrointestinal cancers. Participants with distant metastases had a higher VTE risk than those without metastases and even more so in those without cancer (175,202). Cancer patients with VTE have a higher risk for VTE recurrence and anticoagulant-associated bleeding than VTE patients without cancer (203). Cancer patients with malignancy of the bone, ovary, brain, and pancreas exhibited the most significant incidence of VTE. Despite this, the largest number of VTE cases were in patients with breast, prostate, lung, and colon cancer (195).

5.3. Package insert comparison

The comparisons between each of the drugs package inserts and the VigiBase® data helped to bring ‘real-world’ data and clinical trial data together to get a more holistic understanding of the ADRs associated for a drug. These findings must be interpreted with caution due to the substantial under-reporting of ADRs which greatly influences the frequency of the reported ADRs. As a result of this under-reporting, the reported incidence of the ADRs may be underestimated and thus, the true incidence is not known.

5.3.1. Anastrozole

For anastrozole (n = 52 256), neutropenia was not listed as a side effect in the PI, however, it was reported more often than anaemia and leukopenia which were listed. Nausea was listed as very common and vomiting and diarrhoea as common, however,

based on the CIOMS frequency criteria, the number of reports for nausea would classify it as a common ADR (914 of 52 256 – 1.75%) and diarrhoea (507 of 52 256 – 0.97%) and vomiting (334 of 52 256 – 0.64%) as uncommon. Dry mouth, constipation and abdominal pain were listed as frequent, but the VigiBase® data did not reflect the same frequency. Fatigue and pain were reported more than asthenia but were not listed within the same frequency criteria as asthenia. An increase in hepatic enzymes such as the aminotransferases and alkaline phosphatase were not reported as common as stipulated in the PI, however, hepatitis was reported more often despite it being listed as an uncommon ADR. The frequency of the combined reports of hepatitis (47 of 52 256 – 0.09%) fell within the rare range.

Anorexia was a common side effect but did not feature in the ADR reports. Decreased appetite was reported but at a frequency of 0.49% (256 of 52 256 ADRs), which is classified as uncommon (≥ 0.1% and < 1%). For the musculoskeletal and connective tissue SOC, pain in extremity was reported at a frequency of 1.48% (773 of 52 256 ADRs) but did not appear in any of the drug's PIs. Under the skin and subcutaneous tissue disorder, Stevens-Johnson syndrome (SJS) and angioedema are listed as very rare (< 0.01%) in the drugs' PI. However, SJS was reported at a frequency of 0.013% (7 of 52 256 ADRs) and angioedema at 0.061% (32 of 52 256 ADRs) which are classified as rare ADRs (≥ 0.01% and < 0.1%).

5.3.2. Fulvestrant

For fulvestrant (n = 28 624), thrombocytopenia was listed as a common side effect but was only reported at a frequency of 0.62% (179 of 28 624 ADRs – uncommon), however, neutropenia (643 of 28 624 ADRs – 2.25%) was reported more than thrombocytopenia and would be classified as a common ADR but does not feature in the drug's PI. A combination of the injection site reactions reported on VigiBase® amounts to 1 000 ADR reports (1 000 of 28 264 – 3.49%) which is a common ADR. Fatigue is not listed as an ADR for fulvestrant in the drug's PI, but it has been reported in VigiBase® at a frequency of 2.98% (852 of 28 624 ADRs) which translates to a commonly occurring ADR. Death, drug ineffective and disease progression also feature prominently under the general SOC, which is concerning as these ADRs could warrant further investigation. Despite hypersensitivity reactions being listed as very common, they were not frequently reported to VigiBase®. Dizziness under the nervous

system SOC and alopecia under the skin and subcutaneous tissue SOC were also reported in VigiBase® but did not feature in the drug's PI.

5.3.3. Tamoxifen

For tamoxifen (n = 48 150), under the blood and lymphatic SOC, thrombocytopenia was reported more than anaemia, but anaemia was listed as frequent and thrombocytopenia as less frequent. Both ADRs fall within the uncommon frequency criteria, with anaemia at 0.30% (145 of 48 150 ADRs) and thrombocytopenia at 0.55% (263 of 48 150 ADRs). Visual impairment was reported most frequently for eye disorders with a frequency of 1.07% (517 of 48 150 ADRs), which is classified as common. However, they did not feature as an ADR in the drug's PI, and if included as part of the "visual disturbances" ADR, it was reported more frequently that stipulated. Under the General disorders SOC, tumour flare did not feature. Death (1 388 of 48 150 ADRs – 2.88%) was the most reported ADR for tamoxifen overall and was listed within the general disorders SOC. The ADR was reported as death, but the cause of death is not known. Off-label use (114 of 48 150 – 0.24%) of the drug was reported under the injury, poisoning and procedural complications SOC but does not specify the effect the off-label use of the drug had on the patient. Arthralgia (772 of 48 150 ADRs – 1.60%) was reported at nearly double the rate of myalgia (402 of 48 150 ADRs – 0.83%) but was not listed on the drug's PI. Secondary cancer such as endometrial (462 of 48 150 ADRs – 0.96%) and uterine (281 of 48 150 ADRs – 0.58%) cancer have been reported, however, malignant neoplasm progression (571 of 48 150 ADRs – 1.19%) and metastases to bone (337 of 48 150 ADRs – 0.70%) have also stood out in the VigiBase® reports.

Pulmonary embolism (536 of 48 150 ADRs – 1.12%) was reported under the respiratory, thoracic and mediastinal SOC, but on the drug's PI, is considered a vascular complication. Erythema multiformae (32 of 48 150 – 0.066%) and SJS (21 of 48 150 – 0.044%) are listed as very rare side effects according to the drug's PI but according to VigiBase® reports, these ADRs are considered rare. Additionally, angioedema (50 of 48 150 ADRs – 0.010%) is not on the drug's PI but has more reports than SJS and erythema multiformae and would be classified as an uncommon ADR according to the CIOMS frequency criteria. Urticaria also features in the VigiBase® database at a frequency of 0.40% (192 of 48 150 ADRs) which should also

be considered an uncommon but serious ADR to be aware of. Lastly, deep vein thrombosis (494 of 48 150 ADRs – 1.03%) and pulmonary embolism (536 of 48 150 ADRs – 1.12%) have been listed and reported as common ADRs.

5.4. Study limitations

This study had several limitations, the most important being underreported and incomplete data. Adverse drug reactions are widely underreported due to lack of knowledge, resources, time and understanding surrounding the role of ADR reporting. Despite the VigiBase® data being a global source, there is still significant under-reporting from certain WHO PIDM member countries that contribute to the database. Additionally, the main form of ADR reporting for VigiBase® is spontaneous reporting, which, despite its benefits, is disadvantaged by under-reporting. This hinders signal detection, which leads to poor ADR data generation which is crucial to informing policy and practice. In addition to under-reporting, the quality of the ICSRs also limits how data can be analysed. As seen in the results, a large proportion of ICSRs that had "blank/unknown" age groups due to missing or incomplete ICSRs which speaks to the poor reporting practices from HCPs.

The presence of duplicated reports introduces inaccuracy. Since the database only provided UN continent-specific data, there was no way in which the results could be generalised to a specific country. This issue is heightened by the disparities in socioeconomic climate, quality of healthcare, medicines and healthcare services accessibility etc. between countries within a continent, also making it difficult to draw accurate conclusions based on UN continent. Reporting bias, which influences the number of ADRs reported, coupled with under-reporting, does not provide an accurate estimate of the prevalence of ADRs. Additionally, the true incidence of ADRs are unknown due to the denominator value, which is usually based on consumption data, is also unknown (29).

Drug-drug interactions were not looked at in this study, which leaves a gap in the research since ADRs can be as a result of an interaction and not necessarily due to a single drug by itself. Not all MedDRA SOCs were analysed in the comparison of the

core drugs PI which could have resulted in ADRs with high incidences being overlooked.

5.5. Study recommendations

Under-reporting of ADRs is a growing concern that negatively affects PV. The need for optimally functioning PV systems in all countries will increase medicine safety and contribute to evidence-based treatment plans that will assist HCPs in ensuring patient safety. It is known that LMICs are disadvantaged due to their poor PV systems and lack of training and awareness regarding PV. Therefore, greater international collaboration is necessary to establish and standardise PV systems so all countries have a means to which ADRs can be reported, documented, and analysed. This can lead to more ADR reporting and better signal detection.

An increase in the education and training of HCPs on PV and ADRs can aid in identifying and subsequently reporting ADRs. Early identification and treatment of ADRs can be used to improve patient care and QoL as well as ensuring unnecessary healthcare costs are avoided. An increase in reporting will also allow for a more accurate picture on the true incidence of ADRs and assists in signal detection.

In addition to under-reporting of ADRs, missing data from ICSRs needs to be addressed. Poor reporting practices affect the quality of the report, which also plays a role in timeous signal detection. It could be suggested that mass rollout of user-friendly guides, videos or social media campaigns on ADR reporting by organisations such as the WHO, UMC and regulatory bodies in each country could assist in ICSR discrepancies and also inform HCPs of the processes to follow when reporting ADRs.

There are discrepancies in what is reported as an ADR. Due to the overlapping of definitions for ADRs, side effects, adverse effects, adverse events and adverse drug events, confusion exists surrounding what is considered an ADR. A similar approach can be taken to educate HCPs and the public on the differences and how they can be identified.

There is a need for constant review and update of PIs to ensure PMS data can be used to provide a more accurate description of ADRs and side effects that have not been listed on the drugs PI. This is largely because clinical trial data and 'real-world' data differ significantly in terms of the number of patients using the drug, the comorbidities of these patients, genetic variety, concomitant drugs, and age.

Consideration for population-specific ADR monitoring might prove beneficial to the patient, especially in the oncology setting where patients are at a much greater risk of serious ADRs. This can assist in ensuring the patient is well informed of the ADRs they are at risk of experiencing, how it can be prevented, if possible, and how to manage the ADR to ensure patient safety, financial security and maintenance of patient QoL.

This research has highlighted, amongst other things, that there is an inherent need for PMS of drugs to ensure patient safety and improve patient outcomes. The findings in this study can also prove useful in informing PV policy change to place greater emphasis on ADR monitoring in patients that are high risk and implement training courses on PV for HCPs. Implementing such changes can reduce hospital costs and ADR-related morbidity and mortality as discussed above.

CHAPTER 6
Conclusion

6.1. Conclusion

This study examined the ADRs for hormonal therapies used in the treatment of HR-positive breast cancer that were reported to the global ICSR database, VigiBase®. The study analysed ADRs reported to VigiBase® to characterise the nature and seriousness of the ADRs related to anastrozole, fulvestrant and tamoxifen as well as to determine any statistical significance between the reported ADRs and demographic variables.

This study provided insight into ADRs as experienced in a 'real-world' setting. As discussed in Chapter 2, clinical trial data that is used to determine the safety profile of a drug typically does not have a population diverse enough to accurately determine the side effect profile of a drug and the potential for and nature of ADRs that might be experienced. Thus, analysing data from a global database that primarily relies on spontaneous ADR reporting systems to obtain reports (allowing for data from all populations throughout the lifespan of a drug) allowed for a more accurate picture to be drawn regarding the drug's ADR profile. The analysis found that most of the ICSRs were reported from two of the five UN continents, namely "Americas" and "Europe". Most ICSRs occurred within the "45 – 64 years" and "Unknown/blank" age groups. This sheds light on the quality of ICSRs, which also speaks to the inadequacy surrounding PV systems and their role in drug and patient safety.

The top 10 ADRs for each drug mainly consisted of well-known and commonly associated ADRs for that specific drug, however, there were ADRs that stood out against the rest. Fulvestrant and tamoxifen had "malignant neoplasm progression" as one of the top 10 ADRs. This would require further investigation due to the severity of the ADR as it links to the efficacy of the drugs. Serious and common ADRs, such as DVT and PE for tamoxifen and arthralgia for anastrozole, featured prominently in the data. Given that ADRs are already extensively underreported, the true frequency of these ADRs may be much greater than what was found.

Oceania was found to have ADRs related to disease progression and metastases which requires further investigations despite the region having a high breast cancer incidence rate. Africa had very few ADRs reported which has been previously discussed in several other studies. This study looked at global data to determine whether the ADRs reported from other parts of the world could also be applicable to Africa, a continent ravaged by a lack of health resources, funding, and HCPs, inadequate and insufficient facilities and poor PV knowledge and training. However, ADRs that were reported from the continent were not always similar to ADRs reported from the rest of the world. This warrants further research since a detailed overview of the ADRs experienced in patients from Africa may allow for a more targeted approach to ADR management.

For anastrozole, “arthralgia” was the most reported ADR, and it was also found to be significantly associated with several age groups and UN continents. Similarly, malignant neoplasm progression and asthenia were significantly associated with age groups and UN continents for fulvestrant and DVT, PE, and malignant neoplasm progression for tamoxifen. In addition to these ADRs being frequently reported, they also have a substantial impact on patient QoL, healthcare costs, and treatment outcomes. This information could prove useful to HCPs since there could be a more focused approach to populations at risk of developing these ADRs. Additionally, improving HCP and patient awareness and knowledge about these ADRs and their associated implications can allow for earlier detection, treatment, and possibly prevention.

There were discrepancies between the PIs that were used for comparison against the ADRs in the database and the reported ADRs. There were instances where ADRs that were reported in VigiBase®, at a frequency similar to or greater than ADRs that were included in the PI, were not listed in the PI. It was also found that ADRs listed in the PI did not feature in VigiBase® data. This finding warrants regular updates of drug PIs based on PMS and ‘real-world’ ADR report data from databases such as VigiBase®.

To our knowledge, this is the first study conducted on these specific drugs that used VigiBase® as a data source. The findings from this study were supported by published literature and can be used as a basis for further investigations related to ADRs, improvements to PV systems and as a source of information for targeted, population-specific ADR monitoring.

6.2. Disclosure

The data obtained from the UMC comes from a variety of sources and is based on suspected ADR reports and the probability that the suspected ADR is drug-related is not the same in all cases. This research is in no way the opinion of the WHO or UMC.

6.3. Conflict of interest

The author(s) declare(s) there are no conflicts of interest.

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Annexure 1

Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Juhi Maharaj

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M210851

NAME: (**Principal Investigator**)	Miss Juhi Maharaj
DEPARTMENT:	Pharmacy and Pharmacology
PROJECT TITLE:	Global Adverse Drug Reaction Trends of Anastrozole, Fulvestrant and Tamoxifen Using VigiBase Data
DATE CONSIDERED:	27/08/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr N. Padayachee, Dr K. Mensah and Dr P. Yamoah
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/09/2021

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 21 September 2021

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 1

Tables 1.1. – 3.2. show the binary logistic regression analysis results for all of the top 10 ADRs analysed

Table 1.1. The binary logistic regression analysis of the top 10 ADRs for anastrozole and their association with demographic data

Variables	1. Arthralgia		2. Hot flush		3. Fatigue		4. Nausea		5. Headache	
	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)
UN Continent										
Americas	Reference		Reference		Reference		Reference		Reference	
Africa	0.56 (0.25 – 1.25)	0.154	0.45 (0.14 – 1.44)	0.176	1.21 (0.51 – 2.87)	0.659	0.23 (0.032 – 1.69)	0.149	3.70 (1.87 – 7.32)	0.000
Asia	1.69 (1.24 – 2.31)	0.001	0.30 (0.15 – 0.60)	0.001	0.25 (0.10 – 0.61)	0.002	1.01 (0.58 – 1.76)	0.963	0.99 (0.56 – 1.75)	0.967
Europe	1.53 (1.38 – 1.70)	0.000	0.50 (0.42 – 0.59)	0.000	0.76 (0.64 – 0.90)	0.001	1.54 (1.33 – 1.80)	0.000	1.36 (1.15 – 1.61)	0.000
Oceania	1.99 (1.42 – 2.79)	0.000	0.95 (0.58 – 1.54)	0.827	0.62 (0.33 – 1.19)	0.154	1.52 (0.92 – 2.51)	0.103	0.83 (0.42 – 1.64)	0.590
Age group										
≥75 years	Reference		Reference		Reference		Reference		Reference	
<18 years	0.96 (0.27 – 3.46)	0.949	-	-	1.54 (0.41 – 5.79)	0.523	-	-	1.53 (0.33 – 7.02)	0.586
18 – 44 years	1.53 (1.05 – 2.22)	0.025	0.72 (0.40 – 1.31)	0.289	0.87 (0.50 – 1.51)	0.628	0.74 (0.43 – 1.27)	0.270	1.32 (0.80 – 2.22)	0.304
45 – 64 years	1.59 (1.36 – 1.86)	0.000	1.10 (0.90 – 1.34)	0.356	0.81 (0.65 – 1.00)	0.047	0.62 (0.50 – 0.76)	0.000	0.90 (0.71 – 1.14)	0.383
65 – 74 years	1.30 (1.10 – 1.53)	0.003	1.00 (0.81 – 1.24)	0.987	1.00 (0.80 – 1.25)	0.997	0.80 (0.64 – 0.99)	0.038	0.90 (0.70 – 1.16)	0.433
Blank/unknown	1.32 (1.11 – 1.58)	0.002	0.96 (0.77 – 1.21)	0.730	0.94 (0.74 – 1.19)	0.594	0.68 (0.54 – 0.86)	0.001	0.93 (0.72 – 1.22)	0.612
Gender										
Female	Reference		Reference		Reference		Reference		Reference	
Male	0.88 (0.51 – 1.49)	0.623	0.38 (0.14 – 1.04)	0.059	1.95 (1.11 – 3.43)	0.021	1.32 (0.66 – 2.67)	0.434	1.18 (0.56 – 2.49)	0.671

Table 1.2. The binary logistic regression analysis of the top 10 ADRs for anastrozole and their association with demographic data

Variables	6. Pain in extremity		7. Alopecia		8. Bone pain		9. Pain		10. Myalgia	
	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)
UN Continent										
Americas	Reference		Reference		Reference		Reference		Reference	
Africa	0.69 (0.21 – 2.23)	0.534	1.15 (0.41 – 3.21)	0.794	3.44 (1.70 – 6.97)	0.001	0.51 (0.12 – 2.13)	0.358	0.34 (0.046 – 2.44)	0.280
Asia	0.53 (0.27 – 1.05)	0.067	0.59 (0.29 – 1.21)	0.149	1.14 (0.67 – 1.95)	0.633	0.75 (0.40 – 1.39)	0.360	3.73 (2.54 – 5.49)	0.000
Europe	0.58 (0.47 – 0.71)	0.000	0.99 (0.83 – 1.18)	0.909	0.90 (0.74 – 1.09)	0.267	0.46 (0.36 – 0.58)	0.000	1.41 (1.17 – 1.68)	0.000
Oceania	0.60 (0.29 – 1.22)	0.159	0.72 (0.35 – 1.47)	0.361	0.089 (0.012 – 0.64)	0.016	0.87 (0.45 – 1.66)	0.670	1.00 (0.51 – 1.98)	0.996
Age group										
≥75 years	Reference		Reference		Reference		Reference		Reference	
<18 years	6.42 (2.07 – 19.92)	0.001	0.63 (0.081 – 4.98)	0.665	-	-	1.70 (0.37 – 7.91)	0.498	-	-
18 – 44 years	0.98)0.52 – 1.82)	0.937	0.48 (0.23 – 1.01)	0.052	1.50 (0.84 – 2.69)	0.174	0.95 (0.50 – 1.83)	0.887	0.86 (0.42 – 1.76)	0.674
45 – 64 years	0.90 (0.71 – 1.15)	0.409	0.65 (0.51 – 0.82)	0.000	1.20 (0.93 – 1.56)	0.167	0.88 (0.69 – 1.13)	0.317	1.20 (0.91 – 1.57)	0.189
65 – 74 years	1.12 (0.87 – 1.43)	0.377	0.81 (0.63 – 1.02)	0.078	0.98 (0.74 – 1.30)	0.887	0.88 (0.67 – 1.14)	0.324	1.08 (0.81 – 1.43)	0.605
Blank/unknown	1.04 (0.80 – 1.36)	0.744	0.89 (0.69 – 1.14)	0.365	1.11 (0.83 – 1.49)	0.472	1.03 (0.78 – 1.35)	0.841	1.02 (0.75 – 1.39)	0.884
Gender										
Female	Reference		Reference		Reference		Reference		Reference	
Male	0.62 (0.25 – 1.51)	0.290	1.13 (0.51 – 2.50)	0.758	0.16 (0.022 – 1.18)	0.073	1.04 (0.47 – 2.31)	0.928	2.04 (1.01 – 4.12)	0.048

Table 2.1. The binary logistic regression analysis of the top 10 ADRs for fulvestrant and their association with demographic data

Variables	1. Fatigue		2. Malignant neoplasm progression		3. Neutropenia		4. Nausea		5. Dyspnoea	
	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)
UN Continent										
Americas	Reference		Reference		Reference		Reference		Reference	
Africa	0.94 (0.10 – 8.40)	0.953	-	-	5.95 (0.66 – 53.73)	0.112	-	-	16.19 (2.68 – 97.69)	0.002
Asia	0.26 (0.14 – 0.49)	0.000	1.67 (1.11 – 2.53)	0.015	1.71 (0.94 – 3.12)	0.078	0.44 (0.24 – 0.82)	0.010	1.72 (1.07 – 2.77)	0.025
Europe	0.51 (0.43 - 0.60)	0.000	1.40 (1.18 – 1.66)	0.000	5.83 (4.71 – 7.21)	0.000	0.79 (0.66 – 0.95)	0.011	0.90 (0.72 – 1.13)	0.374
Oceania	0.097 (0.023 – 0.40)	0.001	50.73 (26.43 – 97.39)	0.000	0.27 (0.037 – 1.95)	0.194	0.080 (0.011 – 0.58)	0.012	0.30 (0.072 (1.21)	0.091
Age group										
≥75 years	Reference		Reference		Reference		Reference		Reference	
<18 years	-	-	-	-	-	-	-	-	-	-
18 – 44 years	1.08 (0.70 – 1.65)	0.736	1.41 (0.88 – 2.26)	0.157	1.72 (1.09 – 2.71)	0.019	0.83 (0.48 – 1.42)	0.486	0.91 (0.50 – 1.65)	0.755
45 – 64 years	0.93 (0.73 – 1.19)	0.588	1.41 (1.06 – 1.89)	0.020	0.81 (0.60 – 1.10)	0.181	1.11 (0.84 – 1.48)	0.451	1.03 (0.74 – 0.1.43)	0.872
65 – 74 years	1.00 (0.78 – 1.27)	0.973	1.00 (0.74 – 1.36)	0.997	0.90 (0.66 – 1.23)	0.520	1.17 (0.88 – 1.55)	0.278	0.94 (0.67 – 1.32)	0.728
Blank/unknown	0.94 (0.74 0 1.21)	0.646	1.93 (1.46 – 2.55)	0.000	(1.14 (0.86 – 1.52)	0.351	1.90 (0.82 – 1.44)	0.550	0.79 (0.56 – 1.12)	0.185
Gender										
Female	Reference		Reference		Reference		Reference		Reference	
Male	1.08 (0.51 – 2.28)	0.838	2.57 (1.28 – 5.15)	0.008	1.54 (0.53 – 4.45)	0.430	1.07 (0.45 – 2.57)	0.870	0.57 (0.14 – 2.35)	0.433

Table 2.2. The binary logistic regression analysis of the top 10 ADRs for fulvestrant and their association with demographic data

Variables	6. Injection site pain		7. Arthralgia		8. Diarrhoea		9. Metastases to bone		10. Asthenia	
	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)
UN Continent										
Americas	Reference		Reference		Reference		Reference		Reference	
Africa	-	-	-	-	-	-	-	-	-	-
Asia	0.95 (0.54 – 1.68)	0.855	0.29 (0.12 – 0.72)	0.008	0.44 (0.19 – 1.00)	0.050	1.74 (1.03 – 2.93)	0.037	3.85 (2.55 – 5.82)	0.000
Europe	0.70 (0.56 – 0.88)	0.002	0.49 (0.38 – 0.62)	0.000	0.80 (0.64 – 1.00)	0.050	1.27 (1.00 – 1.61)	0.048	0.72 (0.56 – 0.93)	0.012
Oceania	-	-	-	-	-	-	1.11 (0.44 – 2.79)	0.829	-	-
Age group										
≥75 years	Reference		Reference		Reference		Reference		Reference	
<18 years	-	-	-	-	-	-	-	-	-	-
18 – 44 years	0.29 (0.11 – 0.73)	0.008	0.87 (0.46 – 1.67)	0.683	1.26 (0.70 – 2.27)	0.443	1.85 (1.00 – 3.41)	0.048	0.33 (0.16 – 0.68)	0.003
45 – 64 years	1.06 (0.77 – 1.46)	0.726	0.92 (0.65 – 1.30)	0.628	0.80 (0.55 – 1.16)	0.237	1.83 (1.22 – 2.72)	0.003	0.56 (0.40 – 0.77)	0.000
65 – 74 years	0.77 (0.55 – 1.09)	0.136	1.21 (0.87 – 1.69)	0.265	1.39 (0.99 – 1.96)	0.061	1.08 (0.70 – 1.67)	0.714	0.70 (0.51 – 0.96)	0.026
Blank/unknown	0.77 (0.55 – 1.09_	0.138	0.87 (0.61 – 1.23)	0.428	1.02 (0.71 – 1.45)	0.930	1.32 (0.88 – 1.99)	0.180	0.31 (0.22 – 0.46)	0.000
Gender										
Female	Reference		Reference		Reference		Reference		Reference	
Male	-	-	0.49 (0.12 – 2.06)	0.334	0.57 (1.4 – 2.38)	0.440	0.36 (0.049 – 2.61)	0.311	1.81 (0.70 – 4.69)	0.224

Table 3.1. The binary logistic regression analysis of the top 10 ADRs for tamoxifen and their association with demographic data

Variables	1. Death		2. Arthralgia		3. Nausea		4. Fatigue		5. Hot flush	
	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)
UN Continent										
Americas	Reference		Reference		Reference		Reference		Reference	
Africa	-	-	2.23 (1.18 – 4.22)	0.014	1.16 (0.54 – 2.47)	0.710	0.89 (0.38 – 2.10)	0.793	3.16 (1.66 – 6.03)	0.000
Asia	0.013 (0.0019 – 0.096)	0.000	0.94 (0.65 – 1.35)	0.739	1.08 (0.76 – 1.52)	0.677	0.28 (0.15 – 0.50)	0.000	4.62 (3.51 – 6.08)	0.000
Europe	0.043 (0.031 – 0.059)	0.000	1.84 (1.55 – 2.17)	0.000	1.01 (0.85 – 1.19)	0.953	1.09 (0.92 – 1.30)	0.307	1.80 (1.49 – 2.18)	0.000
Oceania	0.043 (0.015 – 0.12)	0.000	0.90 (0.49 – 1.65)	0.730	1.80 (1.19 – 2.74)	0.006	0.98 (0.57 – 1.69)	0.940	1.02 (0.52 – 1.98)	0.958
Age group										
≥75 years	Reference		Reference		Reference		Reference		Reference	
<18 years	-	-	20.63 (1.92 – 221.88)	0.012	5.46 (0.55 – 53.91)	0.146	5.22 (0.53 – 51 92)	0.158	-	-
18 – 44 years	0.073 (0.048 – 0.11)	0.000	8.02 (5.06 – 12.70)	0.000	2.82 (2.03 – 3.91)	0.000	3.09 (2.14 – 4.45)	0.000	6.29 (3.81 – 10.37)	0.000
45 – 64 years	0.10 (0.084 – 0.13)	0.000	8.21 (5.46 – 12.34)	0.000	2.00 (1.54 – 2.58)	0.000	2.37 (1.77 – 3.16)	0.000	5.25 (3.53 – 8.21)	0.000
65 – 74 years	0.33 (0.28 – 0.40)	0.000	2.74 (1.24 – 4.32)	0.000	1.97 (1.49 – 2.59)	0.000	1.89 (1.38 – 2.60)	0.000	2.29 (1.39 – 3.79)	0.001
Blank/unknown	0.047 (0.034 – 0.065)	0.000	7.05 (4.62 – 10.77)	0.000	1.48 (1.11 – 1.99)	0.009	2.69 (1.97 – 3.67)	0.000	10.51 (6.70 – 16.48)	0.000
Gender										
Female	Reference		Reference		Reference		Reference		Reference	
Male	0.77 (0.49 – 1.22)	0.265	0.28 (0.14 – 0.58)	0.001	0.77 (0.48 – 1.23)	0.270	1.39 (0.93 – 2.10)	0.110	0.54 (0.29 – 1.00)	0.051

Table 3.2. The binary logistic regression analysis of the top 10 ADRs for tamoxifen and their association with demographic data

Variables	6. Rash		7. Malignant neoplasm progression		8. Pulmonary embolism		9. Visual impairment		10. Deep vein thrombosis	
	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)	OR (95% CI)	p-value (<0.05)
UN Continent										
Americas	Reference		Reference		Reference		Reference		Reference	
Africa	2.21 (1.10 – 4.45)	0.026	-	-	-	-	1.69 (0.75 – 3.80)	0.202	0.36 (0.050 – 2.65)	0.318
Asia	2.56 (1.88 – 3.47)	0.000	0.60 (0.36 – 1.01)	0.053	0.95 (0.57 – 1.59)	0.836	1.31 (0.88 – 1.93)	0.179	0.69 (0.37 – 1.28)	0.239
Europe	0.92 (0.76 – 1.12)	0.421	1.71 (1.40 – 2.08)	0.000	2.06 (1.70 -2.49)	0.000	1.12 (0.92 – 1.37)	0.260	1.69 (1.38 – 2.07)	0.000
Oceania	0.97 (0.54 – 1.73)	0.906	7.07 (4.82 – 10.37)	0.000	0.80 (0.39 – 1.65)	0.546	0.76 (0.38 – 1.51)	0.433	1.62 (0.93 – 2.82)	0.088
Age group										
≥75 years	Reference		Reference		Reference		Reference		Reference	
<18 years	-	-	7.55 (0.74 – 77.59)	0.089	-	-	-	-	-	-
18 – 44 years	1.58 (1.09 – 2.30)	0.016	2.35 (1.46 – 3.79)	0.000	0.52 (0.33 – 0.82)	0.005	1.69 (1.12 – 2.53)	0.011	0.41 (0.25 – 0.65)	0.000
45 – 64 years	1.58 (1.20 – 2.07)	0.001	2.47 (1.07 – 3.57)	0.000	1.00 (0.76 – 1.30)	0.973	1.73 (1.29 – 2.32)	0.000	0.72 (0.55 – 0.93)	0.014
65 – 74 years	1.54 (1.15 – 2.08)	0.004	1.85 (1.24 – 2.78)	0.003	1.22 (0.92 – 1.62)	0.165	1.64 (1.19 – 2.26)	0.002	1.01 (0.77 – 1.33)	0.928
Blank/unknown	1.17 (0.86 – 1.61)	0.319	5.61 (3.87 – 8.13)	0.000	0.70 (0.51 – 0.97)	0.031	1.30 (0.93 – 1.83)	0.125	0.46 (0.32 – 0.64)	0.000
Gender										
Female	Reference		Reference		Reference		Reference		Reference	
Male	0.82 (0.48 – 1.40)	0.462	1.48 (0.93 – 2.36)	0.101	2.16 (1.44 – 3.23)	0.000	0.41 (0.19 – 0.88)	0.022	3.42 (2.37 – 4.95)	0.000