

A RETROSPECTIVE REVIEW OF THE UTILIZATION OF BENZODIAZEPINES  
AND Z-DRUGS IN SELECTED PRIVATE COMMUNITY PHARMACIES IN  
NAMIBIA: 2017-2022

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## ABSTRACT

**Background:** Overuse of benzodiazepines and Z-drugs is a considerable global public-safety concern. In Namibia, despite the rising burden of mental illnesses, there is a paucity in data regarding the utilization of benzodiazepines and Z-drugs.

**Aim:** The study aimed to determine the patterns and factors associated with the utilization of benzodiazepines and Z-drugs in community pharmacies to guide medicine policy reforms.

**Methods:** A descriptive multicenter longitudinal study as per the World Health Organisation (WHO) medicine utilization design. The consumption data on benzodiazepines and Z-drugs were retrospectively abstracted from the Unisolv® dispensing software in selected pharmacies over a six-year period, 2017-2022. Consequently, key informants were interviewed to identify the drivers of the use of benzodiazepines and Z-drugs. Data were exported to SPSS v25 for analysis of the patterns and factors of use of benzodiazepines and Z-drugs.

**Results:** Of the 10 selected-pharmacies, a total of 867 168 medicines were dispensed over the six-year review period and 2% of these were benzodiazepines and Z-drugs (n=17 840/867 168). Benzodiazepines (BZD) were the most dispensed (56%, n=9993/17 840), mainly to male patients (53.6%). The consumption of benzodiazepines and Z-drugs was highest with Zolpidem (6.07 DDDs/1000 population) compared to other benzodiazepines and Z-drugs. Over 54% of the dispensing encounters of benzodiazepines and Z-drugs were repeat prescriptions of Z-drugs. From 2017 to 2022, the consumption of Z-drugs increased but declined for benzodiazepines. Stakeholders identify the thematic drivers of the use of benzodiazepines and Z-drugs as irrational prescribing, marketing, and patient drug dependency.

**Conclusion:** Whilst, the consumption of benzodiazepines and Z-drugs in Namibia is lower than global estimates, there is an increase in the use of benzodiazepines and Z-drugs in the private health sector. There is a need for a regulatory framework and an education strategy to empower pharmacists' led interventions towards safe use of new benzodiazepines and Z-drugs in the community pharmacies.

KEYWORDS:

Dependency

Defined Daily Dose

Community pharmacies

Benzodiazepine and Z-drugs

Anatomical Therapeutic Chemical

## TABLE OF CONTENT

<b>ABSTRACT</b> .....	<b><i>i</i></b>
<b>TABLE OF CONTENT</b> .....	<b><i>iii</i></b>
<b>LIST OF TABLES</b> .....	<b><i>v</i></b>
<b>LIST OF FIGURES</b> .....	<b><i>vi</i></b>
<b>LIST OF ABBREVIATIONS AND ACRONYMS</b> .....	<b><i>vii</i></b>
<b>ACKNOWLEDGEMENTS</b> .....	<b><i>viii</i></b>
<b>DEDICATION</b> .....	<b><i>ix</i></b>
<b>INTRODUCTION</b> .....	<b><i>1</i></b>
<b>1.1 Background</b> .....	<b><i>1</i></b>
<b>1.2 Problem statement</b> .....	<b><i>3</i></b>
<b>1.3 Study objectives</b> .....	<b><i>5</i></b>
<b>1.4 Justification of the Study</b> .....	<b><i>6</i></b>
<b>1.4 Significance of the Study</b> .....	<b><i>6</i></b>
<b>LITERATURE REVIEW</b> .....	<b><i>9</i></b>
<b>2.1 Search strategy</b> .....	<b><i>9</i></b>
<b>2.2. Patterns of use of benzodiazepines and Z-drugs</b> .....	<b><i>9</i></b>
<b>2.3 Trends in utilization of benzodiazepines and Z-drugs</b> .....	<b><i>10</i></b>
<b>2.4 Drivers of utilization of newer versus older benzodiazepines and Z-     drugs</b> .....	<b><i>11</i></b>
<b>2.5 Conceptual framework</b> .....	<b><i>12</i></b>
.....	<b><i>12</i></b>
<b>2.6 Summary of gaps in current literature</b> .....	<b><i>13</i></b>
<b>METHODOLOGY</b> .....	<b><i>14</i></b>
<b>3.1 Research design and setting</b> .....	<b><i>14</i></b>
<b>3.2 Population</b> .....	<b><i>14</i></b>
<b>3.3 Selection criteria</b> .....	<b><i>15</i></b>
<b>3.4 Sample Size Estimation and Sampling Technique</b> .....	<b><i>15</i></b>
<b>3.5 Research Instrument</b> .....	<b><i>16</i></b>
<b>3.6 Research Procedure</b> .....	<b><i>16</i></b>
<b>3.7 Data Analysis and Management</b> .....	<b><i>17</i></b>
<b>3.8 Reliability and validity</b> .....	<b><i>20</i></b>

3.9 Research Ethics.....	20
<b>RESULTS.....</b>	<b>23</b>
4.1 Characteristics of the study population .....	23
4.2 Patterns of utilization of benzodiazepines and Z-drugs in private pharmacies.....	25
4.3 Trends of consumption of benzodiazepines and Z-drugs .....	31
4.4 Factors associated with the use of new classes of benzodiazepines and Z-drugs in Namibia .....	33
<b>DISCUSSION.....</b>	<b>38</b>
5.1 Patterns of utilization of benzodiazepines and Z-drugs.....	39
5.2 Trends of consumption of benzodiazepines and Z-drugs .....	42
5.3 Factors associated with the use of new classes of benzodiazepines and Z-drugs- .....	43
5.4 Limitations of the study .....	45
5.5 Delimitation of the study.....	46
<b>CONCLUSIONS.....</b>	<b>48</b>
6.1 Conclusions .....	48
<b>RECOMMENDATIONS.....</b>	<b>51</b>
<b>REFERENCES.....</b>	<b>59</b>
<b>APPENDICES .....</b>	<b>66</b>
9.1 Appendix 1: Ethical Clearance Certificate .....	66
9.2 Appendix 2: Research Permission Letter .....	67
9.3 Appendix 3: List of key terms .....	68
9.4 Appendix 4: Data Abstraction tool .....	69
9.5 Appendix 5: Consent Form.....	70
9.6 Appendix 6: Survey .....	73

## LIST OF TABLES

Table 1 WHO ATC and DDD for Benzodiazepines and Z-drugs. ....	18
Table 2 Determined variables and study measurements .....	19
Table 3 Characteristics of medicine dispensing encounters (n=867 168).....	24
Table 4 Duration of use of benzodiazepines and Z-drugs by product name and ATC class .....	26
Table 5 Key-informant survey on drivers of use of benzodiazepines and Z-drugs in Namibia .....	33
Table 6 Key-informant survey on control of use of benzodiazepines and Z-drugs in Namibia .....	35
Table 7. Cost per pack of benzodiazepines and Z-drugs. ....	36

## LIST OF FIGURES

Figure 1: Patterns of consumption of benzodiazepines and Z-drugs (DDD per 1000) ..	29
Figure 2: Trends of consumption of benzodiazepines and Z-drugs ( BDZs Vs Z-Drugs) .....	31
Figure 3: Trends of use of benzodiazepines and Z-drugs over 6 years period .....	32

## **LIST OF ABBREVIATIONS AND ACRONYMS**

<b>ATC</b>	Anatomical Therapeutic Chemical
<b>BDZs</b>	Benzodiazepines
<b>DDD</b>	Drug Daily Dose
<b>HOD</b>	Head of Department
<b>HREC</b>	Institutional Research and Ethical Committees
<b>MoHSS</b>	Ministry of Health and Social Services
<b>PV</b>	Pharmacovigilance
<b>SD</b>	Standard Deviation
<b>SPSS</b>	Statistical Package for Social Sciences
<b>UNAM</b>	University of Namibia
<b>USA</b>	United States of America
<b>WHO</b>	World Health Organization

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## **DEDICATION**

I dedicate this work to Mr. Herobiam Heita, an outstanding BI developer who assisted me in the data analysis of this research. I equally dedicate this work to community pharmacies that participated in the study. May we continue to work together and support one another to improve the literature on benzodiazepines and Z-drugs in Namibia and globally resulting in the appropriate management of patients on benzodiazepines and Z-drugs.

**DECLARATIONS**

I, Taimi Iipinge, hereby declare that this study is my own work and is a true reflection of my research and that this work, or any part thereof has not been submitted for a degree at any other institution.

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Taimi N Iipinge		October 2024
<b>Name of Student</b>	<b>Signature</b>	<b>Date</b>

## INTRODUCTION

### 1.1 Background

The rising burden of mental illnesses globally has escalated the use of benzodiazepines and Z-drugs, for treatment of anxiety and/or sleep related disorders (5–7). Benzodiazepines are employed for managing anxiety and insomnia by binding to the GABA receptor subtypes alpha 1 (benzodiazepines and Z-drugs) and alpha 2 (anxiolytic). Although structurally distinct from BDZs, Z-drugs exhibit similar pharmacology, and as a result, they are utilized for the treatment of insomnia(1). According to the Medicines Management Programme guideline produced in Ireland, there are twelve benzodiazepines and Z-drugs (1). The benzodiazepines are alprazolam, bromazepam, chlordiazepoxide, clobazam, diazepam, flurazepam, lorazepam, lormetazepam, nitrazepam, prazepam, temazepam, and triazolam, and the Z-drugs are zolpidem, zopiclone (1), esozopiclone and zaleplon. BDZs were the first to be introduced to treat anxiety in the early 1960's and were shown to be more effective and safer options compared to barbiturates and meprobamate(5,8). BZDs consumption reached an unusual level in 1970s and due to side effects, there was a reduction of use in the 1980's(9,10). During the same period, Z-drugs namely zopiclone, zolpidem, and zaleplon were introduced and they were widely preferred over BZDs which led to a drastic increase in the use of Z-drugs in the 1990's (11) despite little to no evidence of difference in efficacy and safety between the BZDs and Z-drugs (12). Due to side effects such as long term tolerance, dependency, abuse, withdrawal syndrome, high risks of falls, and hip fractures in the elderly from the benzodiazepines and Z-drugs, the recommended treatment duration is 4 weeks up to 3 months based on the indication (13).

Despite recommendations on the use of benzodiazepines and Z-drugs, studies reported a high duration of treatment (8) due to various reasons such as patient's chronic stress, sleeping problems, fear of symptoms re-occurrence, lack of knowledge regarding management of psychological changes, and available alternatives, lack of contributions from other healthcare teams such as pharmacists in terms evaluating the appropriateness, effectiveness, safety, and compliance of such medicines; in addition to nurses who often lack the responsibility of ensuring proper medical process especially when managing elderly patients (14).

This is a public health concern, given that the chronic use of BZDs and Z-drugs is associated with poor safety outcomes, especially drug dependence (8,15)(16). However, despite the serious patient safety concerns related to the long-term use of BZDs and Z-drugs, little is known about their utilization in resource-limited settings such as Namibia, where the greatest irrational use of medicines is estimated at over 50% by the World Health Organization (8,17). The available BZDs for this study are alprazolam, bromazepam, clobazam, diazepam, lorazepam, midazolam, nitrazepam, oxazepam and triazolam while the Z-drugs are zolpidem and zopiclone. Meanwhile, other countries have additional BZDs such as triazolam, temazepam, flunitrazepam and Z-drugs namely zaleplon and eszopiclone.

A research study conducted in the United States of America (USA) has yielded compelling evidence suggesting that in addition to the well-documented side effects of benzodiazepines and Z-drugs, there exists a significant association between the use of these medications and various adverse health outcomes. Specifically, the study findings have revealed a noteworthy link between benzodiazepines and Z-drugs use and an

increased risk of infections, cancers, falls, automobile accidents, as well as overdoses leading to emergency hospital admissions and heightened mortality rates (18).

In Namibia, despite recent concerns with the use of illicit medicines such as cannabis and codeine, amongst others, there is limited data on the use of benzodiazepines and Z-drugs in the private setting, where treatment can vary widely between practices and prescribers(19). Healthcare professionals, especially clinical pharmacists who possess specialized knowledge in medication management, can assume a pivotal role in the promotion of the rational use of benzodiazepines and Z-drugs. This can be achieved by implementing comprehensive medicine use audits, which involve meticulous assessments and evaluations of medication utilization patterns, aiming to identify potential areas for improvement and facilitate enforcing strict compliance to prescribing guidelines, thus ensuring optimal and safe patient care(17). Consequently, the primary objective of this study is to comprehensively investigate and analyze the various patterns, trends, and underlying factors that drive the utilization of benzodiazepines and Z-drugs within the context of private pharmacy outlets situated in Namibia. By conducting an in-depth examination, this research aims to shed light on the intricate dynamics surrounding the prescription and consumption practices of these medications, ultimately contributing to a deeper understanding of their usage patterns and facilitating the development of informed interventions and strategies for improved patient outcomes.

## **1.2 Problem statement**

The increasing global burden of illicit use of benzodiazepines and Z-drugs for mental and sleep disorders amongst the elderly population is a major public health concern, predisposing patients to dependence, among other patient safety concerns (15). The

excessive use of these drugs is uncertain, however reported to be due to a lack of clinical guidelines implementation and underestimation of the chronic use of these medicines by patients and prescribers. Some of the consequences of long-term use of these drugs are tolerance, dependence, abuse withdrawal syndrome, and life-threatening side effects such as increased risks of falls and motor vehicle accidents among the elderly population(20–22).

Several studies done in developed countries reported mostly a rise in use the of benzodiazepines and Z-drugs, the safety profile associated with the long-term use of these drugs, and sociodemographic factors that lead to the increased utilization of benzodiazepines and Z-drugs(14,23). The unnecessary use of benzodiazepines and Z-drugs, that is for over 2–4 weeks for insomnia and over 3 months for anxiety is common, attributable to poor compliance to treatment guidelines, and demand from patients, particularly in Namibia which suffer from a high prevalence of alcohol and drug abuse, where BZDs are used to treat the withdrawal symptoms.

In Namibia, there is an established framework of standard treatment guidelines that have been put in place to provide comprehensive guidance for the accurate diagnosis and effective treatment of insomnia and anxiety disorders. However, it is currently observed that these guidelines are not readily accessible to healthcare providers, and even if they are, the lack of updated versions also poses an additional challenge. This situation presents a significant gap in the healthcare system, particularly in the private sector where the risk of irrational use of benzodiazepines and Z-drugs is more pronounced.

Compounding the issue, Namibia also faces a dearth of comprehensive data on consumption patterns, prevailing trends, and underlying determinants of benzodiazepines and Z-drugs usage within the private healthcare sector. This lack of information hampers

the ability to develop evidence-based interventions and policies that effectively address the potential risks associated with the irrational use of these medications. It is crucial to acknowledge that if these existing gaps and deficiencies in the system remain unresolved, they could potentially contribute to adverse scenarios and compromise the overall healthcare landscape in the country.

In light of these challenges, the findings derived from this study will play a pivotal role in informing and influencing policy development and implementation, with a specific focus on optimizing the appropriate and rational utilization of benzodiazepines and Z-drugs. By leveraging these research-driven insights, policymakers will be equipped and able to establish guidelines and protocols that prioritize optimal treatment outcomes and patient safety. Consequently, these evidence-based policies will contribute to bridging the existing gaps, ensuring improved access to up-to-date treatment guidelines, and promoting the responsible and informed use of benzodiazepines and Z-drugs within the Namibian healthcare system.

### **1.3 Study objectives**

#### **Main objective**

To evaluate the utilization of benzodiazepines and Z-drugs in the selected community pharmacies of Namibia between 2017-2022 period.

#### **Specific objective**

- i. To determine the patterns of use of benzodiazepines and Z-drugs in community pharmacies in Namibia, (i.e., consumption rates by Anatomical Therapeutic Chemical (ATC) classes, Defined Daily Dose (DDD) per 1 000 population and duration of use)

- ii. To determine trends of use of benzodiazepines and Z-drugs medicines by DDDs per 1 000 population community pharmacies in Namibia
- iii. To identify drivers of the use of new classes of benzodiazepines and Z-drugs (Z-drugs) compared to BZDs in community pharmacies in Namibia

#### **1.4 Justification of the Study**

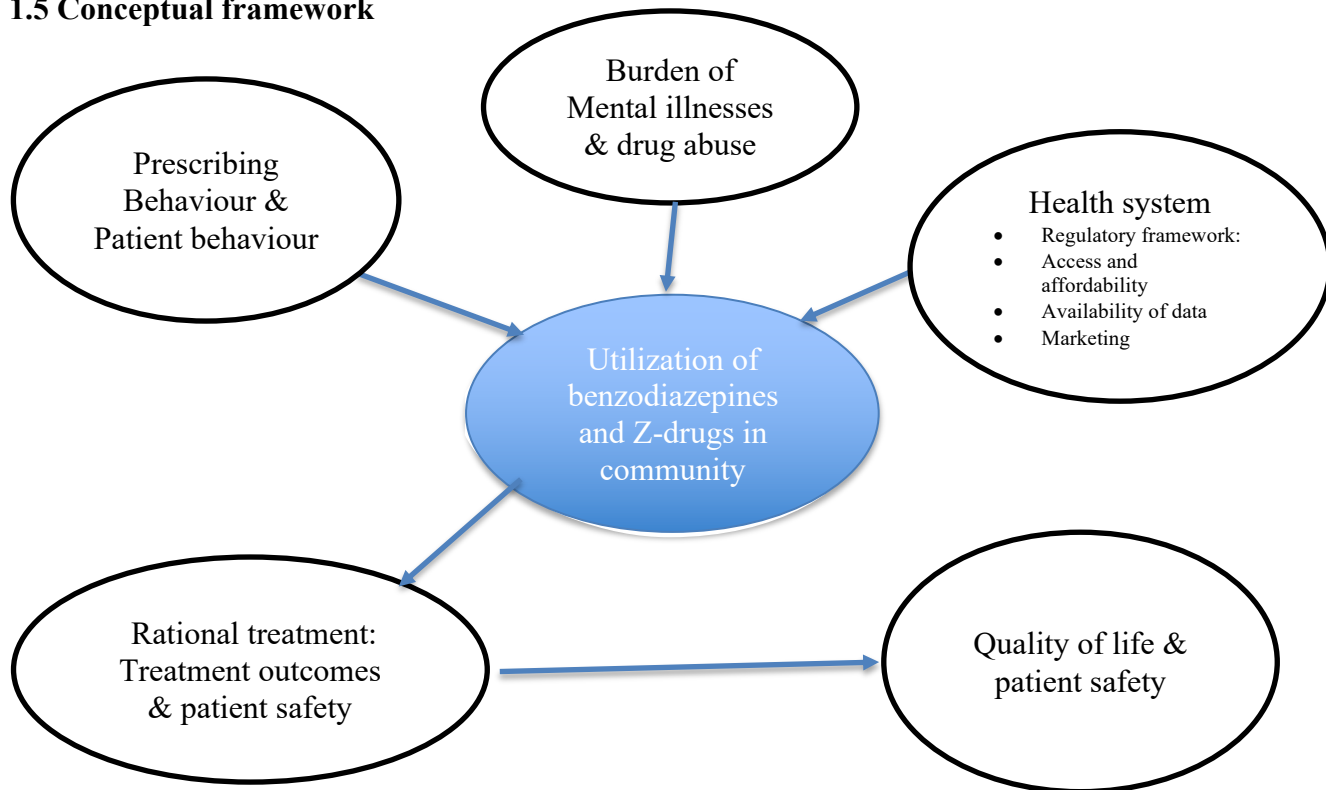
The overuse of benzodiazepines and Z-drugs is associated with poor patient outcomes particularly dependence and addiction. This has a negative impact on the productivity of a population given that abuse of drug is more common in the young and productive age groups. Also overuse of benzodiazepines and Z-drugs is associate with high health costs given that management and rehabilitation of patients is of chronic basis. This has a social impact on the family including stigma impose by the community. This preliminary data will inform current practices on the use of benzodiazepines and Z-drugs in practice.

#### **1.4 Significance of the Study**

The exploration and examination of various research findings pertaining to the consumption rates, prevailing trends, and underlying factors influencing the use of benzodiazepines and Z-drugs within the geographical context of Namibia will provide crucial insights and valuable knowledge that can be utilized to inform the development and implementation of effective policies and guidelines, as well as to enhance clinical practices in the rational utilization of these medications. Consequently, these insightful and evidence-based discoveries may serve as a powerful catalyst, stimulating the need for potential revisions and amendments to the prevailing policies and regulations, thereby contributing to the establishment of benzodiazepines and Z-drugs of a more robust

framework aimed at curtailing and restricting the accessibility of benzodiazepines and Z-drugs. The comprehensive and insightful findings derived from this research endeavor will play a pivotal role in informing and guiding the development, implementation, and enhancement of various public health and mental health programs within the Namibian context. By serving as valuable baseline indicators, these findings will facilitate future monitoring and evaluation efforts, ensuring a systematic and evidence-based approach to assessing the utilization patterns of benzodiazepines and Z-drugs. Additionally, the knowledge garnered from this research will significantly contribute to informing and influencing health outcomes, enabling policymakers and healthcare professionals to make informed decisions and implement targeted interventions aimed at promoting improved health and well-being within the Namibian population. Moreover, the comprehensive findings obtained through this research will serve as a valuable source of information and insight, offering a deeper understanding of the consumption patterns and practices associated with these medicines. These findings will not only shed light on the cost burden borne by patients, but they will also provide crucial guidance to pharmacists and healthcare professionals regarding potential interventions aimed at optimizing the utilization of benzodiazepines and Z-drugs and effectively minimizing the risk of abuse within the private sector. By integrating these research-derived insights into their practice, pharmacists will be empowered to develop and implement targeted strategies and interventions that prioritize patient safety, enhance cost-effectiveness, and ensure the rational use of benzodiazepines and Z-drugs, thereby contributing to improved health outcomes and overall well-being within the private healthcare setting.

## 1.5 Conceptual framework



**Figure 1: conceptual framework on factors influencing utilization of benzodiazepines and Z-drugs** (source: original figure)

Figure 1 Indicates several factors including, patient, prescriber, and health system that can influence the utilization of benzodiazepines and Z-drugs. The overuse of benzodiazepines and Z-drugs may influence treatment outcomes and patient safety.

## LITERATURE REVIEW

### 2.1 Search strategy

A search strategy consisted of search and/or MESH terms including, (benzodiazepines and Z-drugs\* OR \* OR benzodiazepine OR Z-drugs) AND “use OR utilization OR dispensing OR patterns OR trends) were applied in Scopus and PubMed as primary and Google Scholar as secondary search engines. English language articles were selectively retrieved and a manual search of bibliographies of selected articles was done to identify other related research papers from reference lists.

### 2.2. Patterns of use of benzodiazepines and Z-drugs

A study by Torres-Bondia (15) estimated the prevalence of the use of benzodiazepines and Z-drugs in people over 65 years of age in four countries at ; 30% in France (24), >20% in Spain and Canada , 15% in Australia (25–27) and 9-12% in USA (28,29). The same study also indicated that the long term use of these drugs in Spain is 10% in the age group between 25-44 years and 22% between 45-64 years (15). Furthermore, the study reported a total of 14.2 % use prevalence of benzodiazepines and Z-drugs which was higher in women (18.8%) than in men (9.6%) (15). The Irish Medicines Management Programme (1) indicated that 42% of patients consumed Z-drugs and 27% consumed benzodiazepines over 6-12 months duration, regardless of the maximum licensed period of four weeks in the treatment of insomnia and anxiety. Studies showed the duration of treatment to be higher mainly due to a lack of updated and readily available guidelines that are implemented(8,15).

The above reviews suggested a notable shift in the prevailing pattern of benzodiazepines and Z-drugs usage, particularly among the elderly population, with a majority being

females. The studies consequently revealed a clear shortage of resources contributing to the prolonged use of benzodiazepines and Z-drugs, where Z-drugs are more frequently consumed than benzodiazepines. The identified gaps warranted the need for a study to be conducted in Namibia to ascertain the patterns and factors associated with the use of benzodiazepines and Z-drugs.

### **2.3 Trends in utilization of benzodiazepines and Z-drugs**

A study in Israel affirmed a continuous increase in the prevalence of the use of benzodiazepines and Z-drugs from 2005-2013 (30). Parsons (16) stated that from 1991 to 2009 the dispensing trends were suggestive of a switch from benzodiazepine to Z-drug prescribing. A study by Booker *et al.* (31) based on the New Zealand pharmaceutical dispensing tool showed that the rate of consumption of zopiclone in 2013/14 was equivalent to the use of any benzodiazepines. Furthermore, zopiclone was reported to be the 14th highest medicine dispensed in 2013/14, accounting for 120.2 dispensed scripts per 1000 registered patients compared to lorazepam with 30.8 dispensed scripts and diazepam with 25.6 dispensed scripts per 1000 registered patients (31).

The aforementioned findings indicated a consistent global pattern of escalating use of benzodiazepines and Z-drugs across various countries, with Z-drugs, especially zopiclone, being the most prescribed among various benzodiazepines and Z-drugs. This observation underscores the necessity of conducting a similar study to discern the trends specific to Namibia.

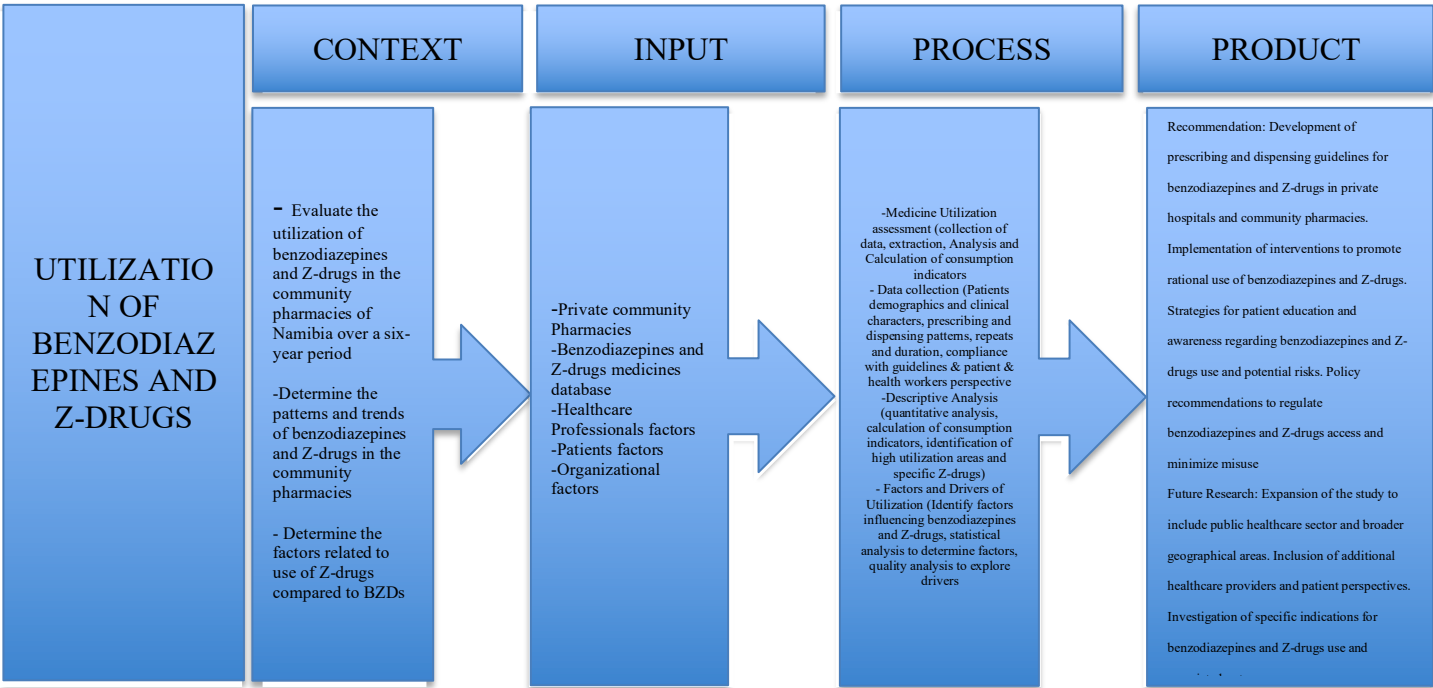
## **2.4 Drivers of utilization of newer versus older benzodiazepines and Z-drugs**

Several studies report that the unfavorable side effect profile related to the likelihood of dependence and abuse is an important factor of the use of benzodiazepines and Z-drugs (5,17,32). Olfson *et al.* (33) article reported high rates of long-term use of benzodiazepine in older adults due to treatment of ongoing anxiety disorders, lack of specialized knowledge about benzodiazepine prescribing risks in geriatric care, reduced access to alternative effective evidence-based treatments, some older people refuse to reduce or discontinue benzodiazepines, and challenging clinical demands on physician's time associated with the other physical health needs of their patients. Also, a study by Olfson *et al.* (28) indicated the use of benzodiazepines was approximately 3 times more common in the elderly than in younger adults while the use of benzodiazepines was significantly higher amongst women than men and it increased with age. The same study reported a high usage of long-acting agents particularly in men for anxiety, while women consumed more of short-acting agents for insomnia. A study on dispensing rates in 2011-2012 indicated that on average 1 out of 10 people over 65 years and 1 out of 5 people aged 85 years and above, receive a benzodiazepine in any quarter during that time period (31). In this same study, the inappropriate use of benzodiazepines and Z-drugs was associated with long-term prescribing of benzodiazepines, high doses or use of long-acting agents.

The above findings have highlighted that various factors, including dependence, ongoing anxiety disorders, limited awareness of the risks associated with the use of benzodiazepines and Z-drugs in the elderly, restricted access to alternatives, physician-patient demands, patients' refusal to discontinue treatment, and the high consumption of long-acting agents, have collectively contributed negatively to favoring newer benzodiazepines and Z-drugs over their older counterparts.

Additionally, the findings have revealed an increase in the prolonged prescribing of high doses and long-acting benzodiazepines and Z-drugs with advancing age. The results have raised significant concerns regarding irrational practices among healthcare providers and inappropriate use, particularly within the geriatric population, potentially impacting the quality of life for these individuals. Based on these observations, there is a compelling need to conduct a study aimed at identifying the factors influencing the utilization of both old and newer benzodiazepines and Z-drugs, as well as determining the specific types of benzodiazepines and Z-drugs being consumed in the Namibian population.

**2.5 Conceptual framework**



## **2.6 Summary of gaps in current literature**

When considering the overall body of research regarding the utilization of benzodiazepines and Z-drugs, it becomes apparent that the majority of studies have been predominantly conducted within developed countries. This disparity is quite evident, demonstrated by the findings of a particular study conducted by Kafula (19) . This study shed light on the limited nature of research specifically addressing the patterns, trends, and factors that influence the utilization of benzodiazepines and Z-drugs in resource-limited settings, such as Namibia. These settings face substantial challenges related to the burden of mental illnesses and the prevailing issue of irrational use of medicines, exacerbating the need for comprehensive investigations into this critical area of healthcare. By recognizing this research gap and acknowledging the significant burden faced by such resource-limited settings, this study highlighted the pressing need for further exploration and understanding of the unique dynamics that shape the utilization patterns of benzodiazepines and Z-drugs in contexts where the burden of mental illnesses and irrational medicine use is most pronounced, such as Namibia.

## **METHODOLOGY**

### **3.1 Research design and setting**

The study employed a mixed-method approach. A quantitative longitudinal descriptive method to capture and analyze the patterns and trends in the use of benzodiazepines and Z-drugs, retrospective data extraction was performed using the Unisolv® dispensing software. This enabled a comprehensive examination of the utilization patterns over time. Additionally, the study applied a qualitative purposive analysis to capture qualitative data from key informants associated with community pharmacies in Namibia. Through in-depth interviews and discussions, these key informants provided valuable insights into the drivers that influence the utilization of benzodiazepines and Z-drugs within these healthcare settings. By incorporating both quantitative and qualitative data collection methods, the study aimed to provide a holistic understanding of the utilization patterns and underlying factors associated with benzodiazepines and Z-drugs in Namibia's community pharmacies.

### **3.2 Population**

The study focused on the individual patients' dispensing records of benzodiazepines and Z-drugs obtained from private pharmacy outlets, spanning a six-year timeframe from 2017 to 2022. These patients' records constituted the target population for analysis. The accessible population, on the other hand, encompassed the individual patient dispensing records of benzodiazepines and Z-drugs contained within the Unisolv® database utilized by all private pharmacies operating in Namibia throughout the specified period. This database provided a comprehensive and representative source of data for the study.

Furthermore, the study involved the participation of 10 key informants who were specifically identified and selected. These informants played a crucial role in a survey conducted to gather insights into the utilization of benzodiazepines and Z-drugs within the private sector. Their expertise and perspectives added valuable qualitative data to complement the quantitative analysis based on the dispensing records.

### **3.3 Selection criteria**

The study purposively selected 10 pharmacies that utilize the Unisolv® database, that have been in operation for the past six years, 2017-2022 and have given consent to participate in the study. The research encompassed data from all Unisolv® database containing information on dispensed benzodiazepines and Z-drugs obtained from 10 pharmacies. The study excluded pharmacies that do not use the Unisolv® database, pharmacies that were not in operation during the study period, and pharmacies that did not give consent. The selection bias is minimized by good exclusion and inclusion criteria as stated above. Data points with missing data will be excluded during the analysis of trends.

### **3.4 Sample Size Estimation and Sampling Technique**

The study aimed to obtain a comprehensive data set covering a substantial and recent period to examine consumption patterns and trends over time. With over 350 private pharmacies utilizing the database, 10 pharmacies from Erongo, Khomas, Oshikoto, and Omusati regions that met the predefined inclusion criteria were included in the study sample. This approach ensures a broad representation of private pharmacies in the analysis. Additionally, 10 pharmacists from diverse sectors namely public hospital

pharmacies, community pharmacies, Central medical stores, private hospital pharmacies, Namibia Medicines Regulatory Council, and local pharmaceutical wholesales were identified as key informants and actively participated in the study. Their valuable insights and perspectives contributed to a more comprehensive understanding of the subject matter.

### **3.5 Research Instrument**

To collect data from the Unisolv® database, an abstraction tool specified in Appendix 1 was employed. The primary investigator utilized this tool to extract the necessary information and subsequently merged the various data sets, consolidating them into a single dataset for analysis. Before implementation, the abstraction tool underwent a pilot phase, involving 10% of the pharmacies, to ensure its effectiveness and reliability. The research supervisor provided validation and oversight during this process.

In addition to the data collected from the Unisolv® database, a Google Form was created and included as Appendix 3. This form served as a means to gather data from the identified 10 key informants who participated in the study. The Google Form was carefully designed to elicit specific information and insights from the informants, complementing the quantitative data obtained from the database.

### **3.6 Research Procedure**

The data collection process involved the abstraction of various types of information from the Unisolv® database, which is extensively utilized by private pharmacies. Specifically, consumption data relating to benzodiazepines and Z-drugs was extracted from the database, providing insights into the patterns and trends of medication use. Additionally,

the data abstraction encompassed patient socio-demographic and clinical characteristics, allowing for a comprehensive understanding of the population utilizing these medications. Furthermore, information related to prescriber and pharmacy characteristics was also collected, shedding light on the factors that may influence prescribing and dispensing practices.

In order to capture a broader range of data, a complementary approach was implemented through the utilization of a Google Form. This form, designed to gather information on demographic characteristics, perceived factors, and recommendations, served as an additional source of valuable insights. The Google Form allowed for the collection of qualitative data from respondents, providing a deeper understanding of the various factors influencing the utilization of benzodiazepines and Z-drugs. By combining data from both the Unisolv® database and the Google Form, the study aimed to provide a comprehensive and multi-dimensional analysis of the consumption patterns and influential factors related to benzodiazepines and Z-drugs.

### **3.7 Data Analysis and Management**

All quantitative data collected during the study was entered into the SPSS software version 25 for subsequent analysis. The drug utilization data was analyzed to identify patterns in benzodiazepines and Z-drugs usage. Descriptive statistics were applied, specifically utilizing the Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) per 1,000 patients methodology. The World Health Organization (WHO) employs the ATC classification system to categorize drugs based on their organ or system of action, considering their chemical, therapeutic, and pharmacological properties (34). Benzodiazepines and Z-drugs fall into three distinct

groups: N05BA (anxiolytics, benzodiazepine derivatives), N05CD (Z, benzodiazepine derivatives), and N05CF (Z and benzodiazepines and Z-drugs, benzodiazepine-related drugs, also called Z-drugs)(35,36).

Additionally, the WHO defines the Defined Daily Dose (DDD) as the assumed average maintenance dose per day for a drug when used for its primary indication in adults (34). Each benzodiazepine (BZD) and Z-drugs in this study has an ATC class code and DDD according to World Health Organization Collaborating Centre for Drug Statistics Methodology(34) as indicated in table 1. below:

**Table 1 WHO ATC and DDD for Benzodiazepines and Z-drugs.**

Drug	ATC code	DDD
Alprazolam	N05BA12	1mg
Bromazepam	N05BA08	10mg
Clobazam	N05BA02	20mg
Diazepam	N05BA01	10mg
Loprazolam	N05CD11	1mg
Lorazepam	N05BA06	2.5mg
Midazolam	N05CD08	5mg
Nitrazepam	N05CD02	5mg
Oxazepam	N05BA04	50mg
Triazolam	N05CD05	0.25mg
Zolpidem	N05CF02	10mg

Zopiclone	N04CF01	7.5mg
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The calculation of the DDD involved the following formula: Prescription per drug × Mass × Quantity × 1000 / DDD assigned × Population × Time. This formula considered the number of prescriptions dispensed containing either BZDs or Z- drugs, dose of the medicine in milligrams, the quantity prescribed in pack sizes, the DDD assigned to the specific medication as per WHO, population is the total sample size of prescriptions containing BZDs and Z- drugs, and the duration of the study period in days.

By utilizing this calculation, the study aimed to accurately assess and quantify the utilization of benzodiazepines and Z-drugs in relation to the defined DDD, providing a standardized measure for comparison and analysis. The perceived drivers and recommendations for limiting the accessibility of benzodiazepines and Z-drugs were identified by key informants and categorized into themes.

**Table 2 Determined variables and study measurements**

<b>Objective/dependent variable</b>	<b>Independent variable</b>	<b>Measurement</b>
i.To determine the patterns of use of benzodiazepines and Z-drugs	<ul style="list-style-type: none"> <li>• ATC class</li> <li>• Dosage schedule</li> <li>• BZD vs Z-drugs</li> </ul>	DDDs/ 1 000 ATC class Duration of treatment
ii.To determine the trends of use of benzodiazepines and Z-drugs in Namibia	<ul style="list-style-type: none"> <li>• Year</li> <li>• Pharmacy characteristics</li> </ul>	Change in slope between the years (2017-2022)
iii.To determine drivers of use of newer benzodiazepines and Z-drugs	<ul style="list-style-type: none"> <li>• Use of BZDs vs Z-drugs</li> </ul>	Identify the factors related to the use

### **3.8 Reliability and validity**

To ensure the effectiveness and suitability of the data collection tool, a pilot test was conducted in October 2021 utilizing the Unisolv® database. The purpose of this pilot test was to confirm that the tool could successfully extract the relevant data necessary to answer the research question and address the study objectives. However, it was discovered that the records used during the pilot exercise were incomplete and therefore excluded from the final study analysis. Prior to accessing the database, permission to obtain the records was obtained from the Ministry of Health and Social Services, ensuring compliance with ethical considerations.

To further enhance the quality and reliability of the collected data, the data collection tool was shared with experts in data analysis for thorough scrutiny. Their valuable insights and feedback were incorporated to refine and improve the tool. Additionally, a face validation exercise was conducted in collaboration with the research supervisor and an expert in data analysis. This exercise involved carefully reviewing and verifying the collected data to ensure accuracy and reliability. Through these rigorous validation processes, the study aimed to enhance the credibility and robustness of the collected data, thereby strengthening the overall validity of the research findings. Experts in medicine utilization independently validated each of the questions in the google form.

### **3.9 Research Ethics**

Considering that the focus of the current study revolved around the analysis of secondary records of patients rather than direct patient involvement, a waiver was obtained from the Ministry of Health and Social Services. The permission letter, dated 22 October 2021 and

referenced as Ref: 17/3/3 TI, was obtained from the Ministry of Health and Social Services, and it has been included as Appendix 4 for reference.

Furthermore, ethical clearance was obtained from the University of Namibia Decentralized Ethics Committee to conduct this study. The ethical clearance, dated 17 August 2021, has been granted and bears the reference number H-G /616/2021. This clearance confirms that the study adheres to ethical guidelines and safeguards the rights and welfare of participants. The official documentation of the ethical clearance has been included as Appendix 5 for transparency and reference purposes. Prior to the data collection, permission from individual pharmacies was obtained and a written agreement between Unisolv manager, pharmacies and UNAM was acquired before extracting data from Unisolv® database.

### 3.9.1 Autonomy

Consent was obtained from the individual private pharmacies to utilize the database. The study used secondary data in the Unisolv® database and waiver for need of patient consent was sought from the MOHSS and UNAM ethics committee.

### 3.9.2 Private and confidentiality

Permission was sought from Head of Department (HOD) to ensure all data collected will be kept confidential and protected using a passcode and kept anonymous using serial numbers and will be exercised only in this study. Participant specific identity will not be acknowledged however serial number recognized by the researcher will be used. The data integrity will be ensured using password protection and only accessible to the researcher.

### 3.9.3 Do no harm. Increase benefit

The study is a non-interventional study using secondary data and causes no direct or significant harm to the participants. In addition, the results of the study will be beneficial to both the researcher and the data providers as it will provide trends of use at patient level.

#### 3.9.4 Fairness

All pharmacies in the private sector that met the criteria were included. The results of the study will be communicated back to the pharmacies.

## RESULTS

### 4.1 Characteristics of the study population

Table 3 shows the characteristics of the study population, that is private pharmacies and benzodiazepines and Z-drugs. A total of ten Unisolv® dispensing databases from the respective community pharmacies were included in the analysis. In the six-year study duration from 2017 to 2022, a cumulative of 867,168 items were dispensed. Among the dispensed items, the predominant demographic was male, comprising 53.6%. Furthermore, the majority of these recipients obtained their prescriptions from community pharmacies located in the Khomas and Erongo regions, accounting for 88.7% of the total **(Table 3)**. Of the total, 17,840 drugs, constituting 2%, belonged to the N05 (BDZs and Z-drugs) therapeutic group **(Table 3)**.

Of the ten key informants that completed an exploratory survey on the drivers of the utilization of benzodiazepines and Z-drugs in Namibia, 70% were female, 70% worked in private hospital or pharmacy sector and 60% had more than five years work experience **(Table 3)**.

**Table 3 Characteristics of medicine dispensing encounters (n=867 168)**

<b>Characteristic</b>	<b>Total medicines dispensed (%)</b>
<b>Geographic location of pharmacy</b>	
Erongo region	380 518(43.9%)
Khomas region	388 911(44.8%)
Omusati region	350 96(4.0%)
Oshikoto region	62 643(7.2%)
<b>Patient's gender</b>	
Female	71 773 (46.4%)
Male	84 022 (53.6%)
<b>Benzodiazepines and Z-drugs dispensed</b>	
Benzodiazepines (BZDs)	9993 (1%)
Z-drugs	7847 (1%)
Other medicines (not benzodiazepines and Z-drugs)	849 328 (98%)
<b>Private Pharmacy</b>	
PP01	224 630 (25.9%)
PP02	28 586(3.3%)
PP03	31 962(3.7%)
PP04	125 037(14.4%)
PP05	35 096 (4.0%)
PP06	11 958(1.4%)
PP07	155 888(18.0%)
PP08	165 868(19.1%)
PP09	50 685(5.8%)
PP10	37 458(4.3%)
<b>Survey: Amongst key-informants on drivers of the utilization of benzodiazepines and Z-drugs</b>	
<b>Key-informants gender</b>	
Female	7 (70%)
Male	3 (30%)
<b>Pharmacy work experience (years)</b>	
1-5 years	4 (40%)
6-10 years	6(60%)
Private Hospital and Retail Pharmacy	4(40%)
Community Pharmacy	2(20%)
Namibia Medicine Regulatory Council	2(20%)
Central Medical Stores	1(10%)
Wholesale pharmacy	1(10%)

#### 4.2 Patterns of utilization of benzodiazepines and Z-drugs in private pharmacies

Table 4 shows the patterns of utilization of benzodiazepines and Z-drugs in the private pharmacies. A total of 17 840 benzodiazepines and Z-drugs were dispensed in private pharmacies over the six-year study period, 2017-2022; the majority of the drugs were BZDs (N05BA+ N05CD) comprising of 56%, n=9993/17840 compared to the Z-drugs (N05CF) (**Table 3**). The proportion of N05BA, N05CD, and N05CF dispensed out of the total items was ~1%, and was not significantly different between the two groups (**Table 3**). This indicates that both benzodiazepines and Z-drugs were equally dispensed during the study period. The number of encounters with benzodiazepines and Z-drugs was 56% and 44% respectively.

A total of 26 products of benzodiazepines and Z-drugs were dispensed in 17 840 encounters, 53% (n=9454/17840) of these were repeat prescriptions. Repeat prescriptions were highest among Z-drugs at 54% (n=5105/9454) compared to BZDs at 46% (n=4349/9454) (Table 4). Overall, the Z-drug with the highest repeats was zolpidem 10mg (Adco-zolpidem®, n=4 519). Repeats of benzodiazepines were high among alprazolam (Zopax®, n=1 007), alprazolam (Adco-alzam®, n=804), and clobazam (Urbanol®, n=787) (**Table 4**). The benzodiazepines and Z-drugs with the least number of repeat prescriptions were diazepam (Betapam ®, n=11), midazolam (Dormicum®, n=15), and oxazepam (Purata®, n=14). The brands of zolpidem (Noxidem ®) and diazepam (Valium®) had no repeat prescriptions dispensed (**Table 4**). In general, zolpidem, alprazolam, diazepam, and lorazepam demonstrated a notable presence of various generic equivalents. Zolpidem featured seven branded generics, alprazolam had four generic versions, while both diazepam and lorazepam had three generic alternatives each. (**Table 4**).

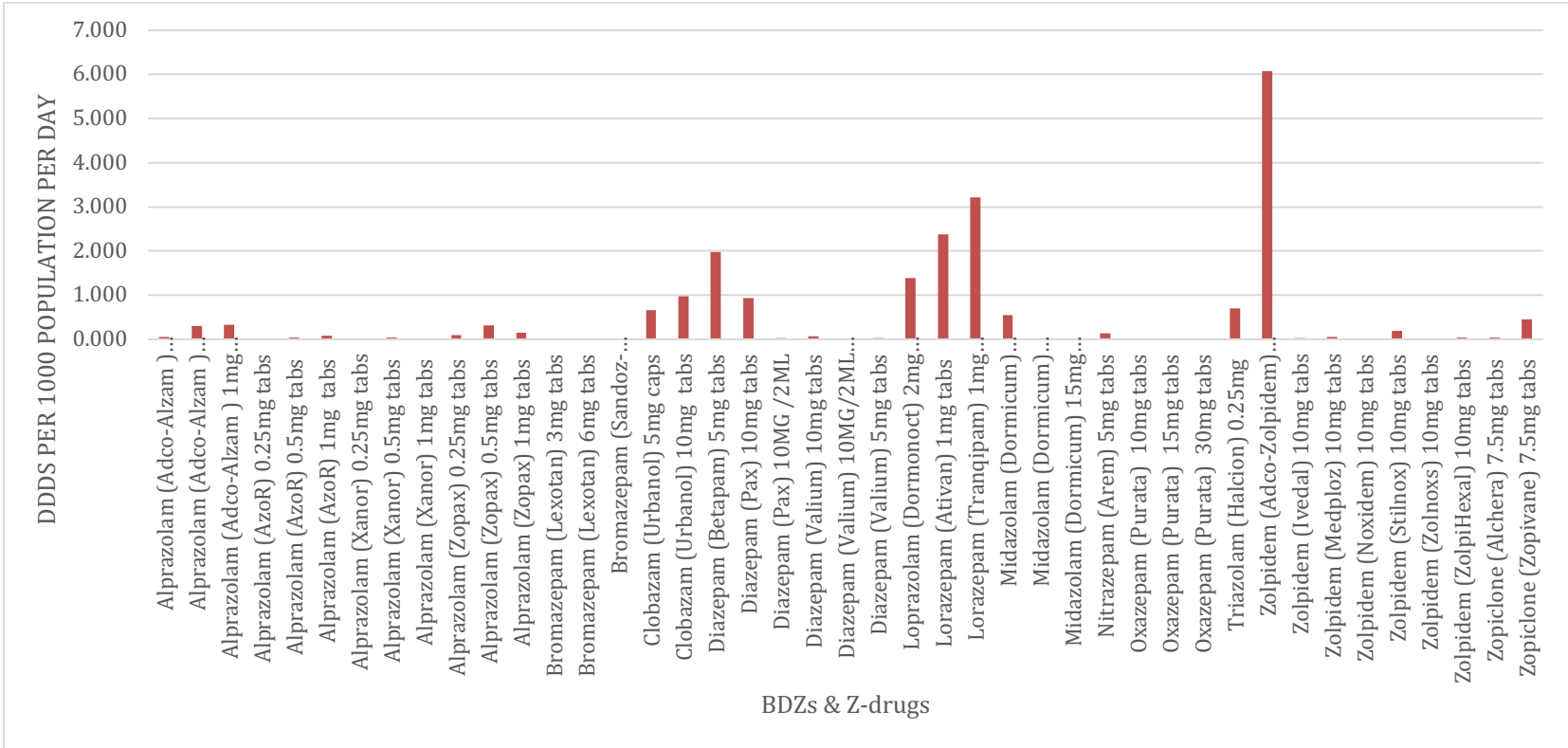
In terms of duration, repeat periods of prescriptions of benzodiazepines and Z-drugs varied widely with a mean of 5±1 (month± standard deviation, SD) (Table 4). Of the 26 benzodiazepines and Z-drugs products dispensed, 1 item was prescribed for an average of 7 months, and eight items were prescribed for an average duration of 6 months (Table 4). For the average repeat prescriptions issued, about 50% of the specified months were effectively dispensed for the majority of benzodiazepines and Z-drugs. (Table 4).

**Table 4 Duration of use of benzodiazepines and Z-drugs by product name and ATC class**

Product (Generic)	Dispensing encounters	Repeat dispensing (%)	Duration of use of benzodiazepines and Z-drugs-			ATC classification
			Average repeats prescribed	Average repeats filled	DDD/1000 Dispensed/day	
<b>Z-drugs (n= 7847)</b>						
Zolpidem 10mg tablets (Adco-zolpidem®)	6913	4519 (58.2)	6.0	2.9	6.07	N05CF02
Zolpidem 10mg tablets (Ivedal®)	31	16	5.3	2.1	0.03	N05CF02
Zolpidem 10mg tablets (Medploz®)	66	38	6.5	3.3	0.06	N05CF02
Zolpidem 10mg tablets (Noxidem®)	3	-	-	-	0.003	N05CF02
Zolpidem 10mg tablets (Stilnox®)	211	130	5.5	2.9	0.19	N05CF02
Zolpidem 10mg tablets (Zolnox®)	17	11	2.9	1.3	0.01	N05CF02
Zolpidem 10mg tablets	44	37	6.3	3.3	0.04	N05CF02

(Zolpihexal®)						
Zopiclone 7.5mg tablets (Alchera®)	40	25	7.08	2.32	0.04	N05CF01
Zopiclone 7.5mg tablets (Zopivane®)	522	329	6.2	2.9	0.46	N05CF01
<b>Benzodiazepines -BZDs (n= 9993)</b>						
Alprazolam (Adco- Alzam®) 0.25mg tablets 0.5mg tablets 1mg tablets	1412	804 (57.5) 128 422 254	6.2 6.5 5.9 5.9	3.0 3.3 3.0 3.0	 0.05 0.30 0.33	N05BA12
Alprazolam (Azor®) 0.25mg tablets 0.5mg tablets 1mg tablets	246	122 20 55 47	5.3 6.25 4.7 5.6	2.7 2.2 2.5 3.0	 0.01 0.05 0.08	N05BA12
Alprazolam (Xanor®) 0.25mg tablets 5mg tablets 1mg tablets	126	79 3 64 12	5.4 4.3 5.3 5.9	2.6 1.7 2.7 2.6	 0.002 0.04 0.01	N05BA12
Alprazolam (Zopax®) 0.25mg tablets 0.5mg tablets 1mg tablets	1536	1007 337 541 129	5.5 5.7 5.3 5.2	2.5 2.5 2.6 2.5	 0.09 0.32 0.14	N05BA12
Bromazepam (Lexotan®) 3mg tablets 6mg tablets	65	45 19 26	5.5 5.1 5.8	2.9 2.5 3.2	 0.01 0.01	N05BA08
Bromazepam 3mg tablets (Sandoz- Bromazepam ®)	38	26	6.4	3	0.01	N05BA08
Clobazam (Urbanol®) 5mg caps	1817	787 286 501	5.5 5.6 5.2	2.1 2.3 1.8	 0.67 0.98	N05BA09

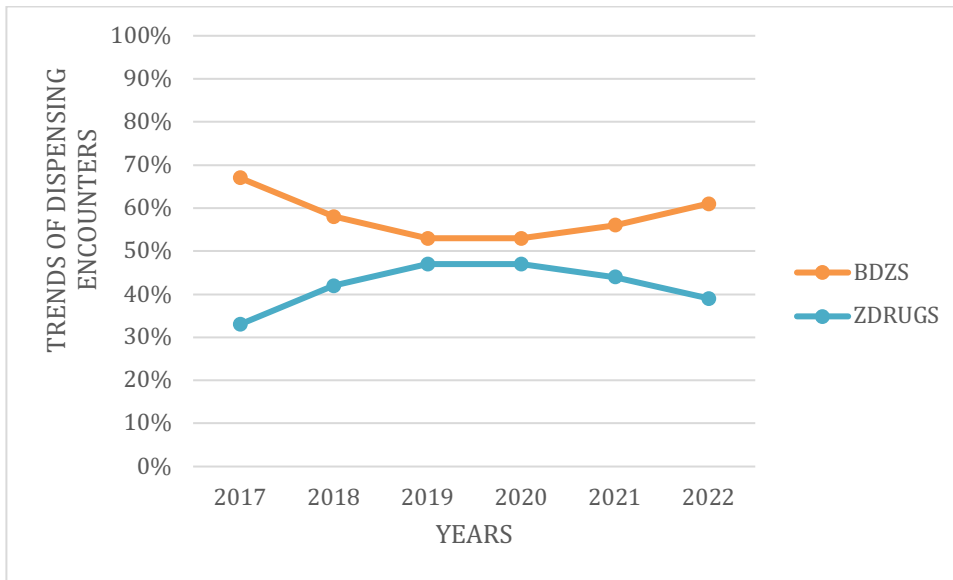
10mg tablets						
Diazepam Betapam® 5mg tablets	144	11	4.5	2.8	0.21	N05BA01
Diazepam (Pax®) 10 mg tablets 10mg/2ml inj	1171	158 150 8	4.4 4.3 5.1	1.6 1.6 1.6	0.93 0.03	N05BA01
Diazepam (Valium®) 5mg tablets 10mg tablets 10mg/2ml amps	93	-	-	-	0.08 0.02 0.06 0.001	N05BA01
Loprazolam 2mg tablet (Dormonoc ®)	315	129	6.2	2.1	1.38	N05CD11
Lorazepam 1mg tablet (Ativan®)	901	189	5.5	2.1	2.37	N05BA06
Lorazepam 1mg tablets (Tranqipam® )	914	299	5.2	2.7	0.80	N05BA06
Nitrazepam 5mg tablet (Arem®)	74	33	5.3	2.7	0.13	N05CD02
Midazolam (Dormicum® ) 15mg tablets 5 mg/5ml inj 15 mg/3ml inj	304	152 133 4 15	4.9 4.9 4.0 5.3	3.4 2.4 2.3 1.8	0.55 0.001 0.001	N05CD08
Oxazepam (Purata®) 10mg tablets 15mg tablets 30mg tablets	36	14 1 12 1	4.9 2.0 5.3 4.0	1.6 1.6 1.6 1.6	0.0002 0.01 0.01	N05BA04
Triazolam (Halcion®) 0.25mg tablets	801	494	6.8	2.8	0.70	N05CD05



**Figure 1: Patterns of consumption of benzodiazepines and Z-drugs (DDD per 1000)**

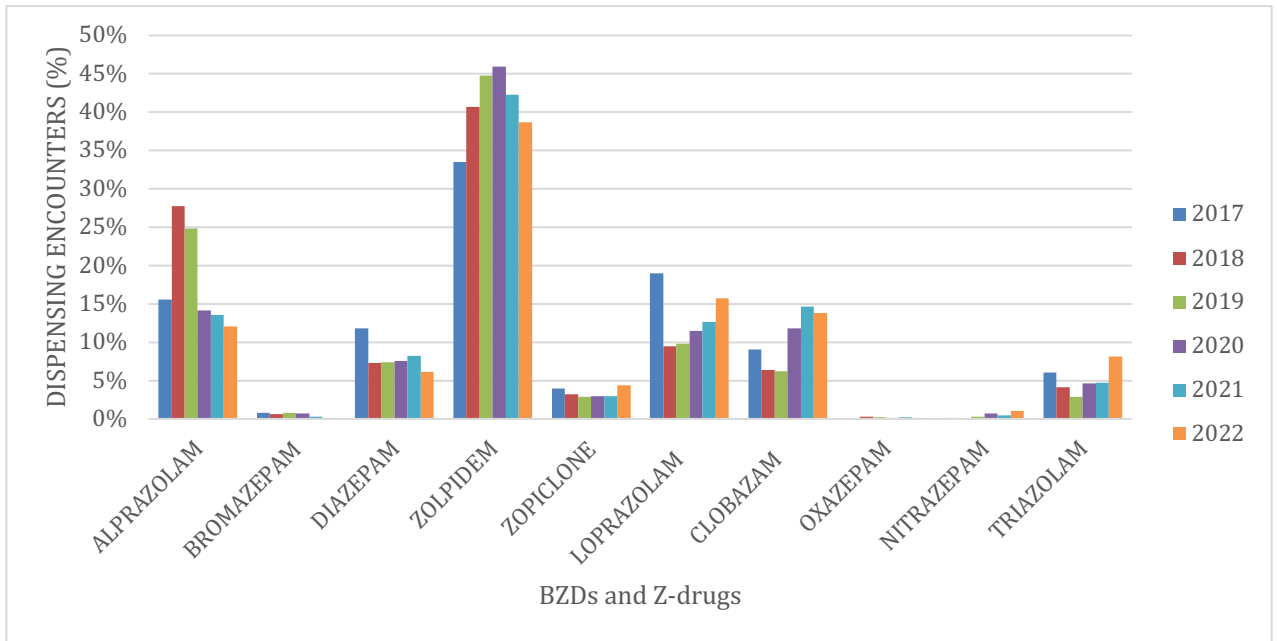
The overall DDD for benzodiazepines and Z-drugs is 2.14 with the most consumed benzodiazepines and Z-drugs brands per DDDs per 1000 population/day being zolpidem 10mg (adco-zolpidem®, 6.07 DDDs/1000 population/day), lorazepam 1mg (tranqipam®, 3.21 DDDs/1000 population/day), and lorazepam 1mg (Ativan®, 2.37 DDDs/1000 population/day). In terms of brand names, the least consumed benzodiazepines and Z-drugs were alprazolam 0.25mg (xanor®), diazepam 10mg/2ml (valium®), Midazolam (Dormicum®) 5 mg/5ml inj and 15 mg/3ml inj and oxazepam (purata®) (**Figure 1**).

### 4.3 Trends of consumption of benzodiazepines and Z-drugs



**Figure 2: Trends of consumption of benzodiazepines and Z-drugs over the six-year period.**

The graph depicts an increasing trend in the consumption of Z-drugs from 2017 to 2020 with a decline in consumption of BDZs over the same period. The consumption of BDZs and Z-drugs was steady between 2019 & 2020 and thereafter there was an incline and decline by 20% in both BDZs and Z-drugs respectively.



**Figure 3: Trends of use of benzodiazepines and Z-drugs over 6 years period**

Figure 3 indicates the trend in consumption of benzodiazepines and Z-drugs by generic names over the study period. This figure indicates an increasing trend of use of zolpidem with the highest consumption being 2020 and the least being 2017. In addition, there was a noticeably increased consumption of alprazolam between 2018 and 2019 and the highest consumption of lorazepam in 2017 compared to other benzodiazepines and Z-drugs (**Figure 3**). Oxazepam was the lowest consumed benzodiazepines and Z-drugs over the 6-year study period.

#### 4.4 Factors associated with the use of new classes of benzodiazepines and Z-drugs in Namibia

##### 4.4.1 Perceived consumption of benzodiazepines and Z-drugs in Namibia

**Table 5** indicates the responses of the key informant pharmacists included in the survey. Of the pharmacists that completed the google form, equally; indicated that BZDs (50%) or Z-drugs as the most used benzodiazepines and Z-drugs in Namibia. Zolpidem was identified as the most used Z-drug, diazepam, lorazepam, and alprazolam as the most prescribed BDZs (**Table 5**).

##### 4.4.2 Perceived drivers of consumption of benzodiazepines and Z-drugs in Namibia

The main thematic areas perceived to drive the use of benzodiazepines and Z-drugs in Namibia were high incidences of depression, irrational prescribing, product marketing and drug dependency (**Table 5**). Key informants recommend the need for developing educational strategies for patients and prescribers on the use of benzodiazepines and Z-drugs and developing medicine formularies to guide practice. As well as regulatory policies such as up-scheduling of benzodiazepines and Z-drugs to control access and use (**Table 6**).

**Table 5 Key-informant survey on drivers of use of benzodiazepines and Z-drugs in Namibia**

Theme	subtheme	Quotation
<b>Mental health: Depressive illness</b>	Poverty <i>Dependence and over prescription Insomnia due to depression</i>	<i>“Poverty leading to depression” “Social and economic factors such as income, education and community safety (Gender Based Violence)” (KI07) “Depression and anxiety; addiction; negative consequences of COVID which leads to drug dependence”(KI01,06 &amp; 08)</i>

<b>Irrational prescribing</b>	Overprescribing	<i>Misdiagnosis or inappropriate diagnosis and prescribing by prescribers (KI04,07)</i>
<b>Regulatory limitations</b>	<i>Lack of restrictions Marketing of products  Access</i>	<i>Physicians are given incentives from medical reps to prescribe these products (KI03,09)  Easily accessible, easy solution to stress, HCP do not look for root cause but treat symptoms, medication is very cost effective (KI02,10)</i>

<b>Table 6 Key-informant survey on control of use of benzodiazepines and Z-drugs in Namibia</b>		
<b>Theme</b>	<b>subtheme</b>	<b>Quote</b>
<b>Improve livelihoods</b>	<i>Tackle socioeconomic issues</i>	<i>Better the lives of people (KI01) Extensive and continuous psychotherapy required for patients who are addicted is a long-term solution from the patient's perspective (KI07)</i>
<b>Promote prescribing</b>	<i>Promote rational prescribing</i>	<i>More control, Drs should stop prescribing these for 3 months. Diagnosis of ailments requiring benzodiazepines and Z-drugs should be stricter in terms of ICD 10/11. (KI04)  Prescription they provide their patients with Benzodiazepines - short term usage, RX should not be written/dispensed for longer than 5 days. If repeated-needs psychiatric support (KI10)</i>
<b>Regulatory</b>	<i>There is a need to implement formularies based on available evidence based information on what should be used as a first line.  Stricter control of distribution by categorizing these drugs as specified schedule  Ask physicians to motivate for the use of these drugs with each new prescription</i>	<i>Educate patients and prescribers (KI06) Reduce access to Benzodiazepines and Z-drugs by regulating prescribing (KI03,05) Up scheduling of benzodiazepines and Z-drugs is an option; develop and implement more restrictive measures in terms of access and control of the drugs (KI08,09)</i>

Table 7 displays cost per brand as a contributing factor in the use of benzodiazepines and Z-drugs. With the conversion of Namibian Dollar (N\$) to US Dollar (\$) being N\$1=\$0.05 The cheapest BDZs brand was betapam® 5mg 30's (\$ 0.43) followed by purata® (\$1.27) and sandoz-bromazepam® (\$1.90). The most expensive BZDs is xanor® 1mg 60's (\$43.22) followed by dormonoct® 2mg 30's (\$33.97). Stilnox® 10mg 30's (\$24.10) is

the most expensive Z-drug while medploz® 10mg 30's (\$ 8.35) and Adco-zolpidem 10mg 30's (\$9.84) is the most cost-effective amongst Z-drugs.

**Table 7. Cost per pack of benzodiazepines and Z-drugs.**

<b>BZDs</b>	<b>Cost</b>
<b>Adco-Alzam® 30's</b>	
0.25mg	2.19
0.5mg	3.22
1mg	5.66
<b>Arem® 30's</b>	
5mg	2.33
<b>Ativan® 30's</b>	
1mg	9.55
<b>Azor® 30's</b>	
0.25mg	2.23
0.5mg	3.48
1mg	6.48
<b>Betapam® 30's</b>	
5mg	0.43
<b>Dormonoct® 30's</b>	
2mg	33.97
<b>Halcion® 30's</b>	
0.25mg	10.94
<b>Lexotan® 30's</b>	
3mg	7.84
6mg	16.54
<b>Pax®</b>	
10mg 30's	2.36
10mg/ml 10's	13.77
<b>Purata® 30's</b>	
15mg	1.27
<b>Sandoz-Bromazepam® 30's</b>	
3mg	1.90
<b>Tranqipam® 30's</b>	
1mg	4.56
<b>Urbanol® 30's</b>	
5mg	7.10
10mg	10.17
<b>Valium®</b>	
5mg 30's	10.67
10mg 30's	16.96
10mg/2ml 5's	13.72
<b>Xanor®</b>	
0.25mg	4.14

<i>0.5mg 30's</i>	7.03
<i>1mg sr 60's</i>	43.22
<b>Dormicum®</b>	
<i>5mg/5ml 5's</i>	10.78
<i>15mg/3ml 5's</i>	16.43
<b>Zopax®</b>	
<i>0.25mg 30's</i>	2.08
<i>0.5mg 30's</i>	2.85
<i>1mg 30's</i>	4.92

<b><u>Z-drugs</u></b>	<b><u>Cost</u></b>
<b>Adco-zolpidem® 30's</b>	
<i>10mg</i>	9.84
<b>Ivedal® 30's</b>	
<i>10mg</i>	10.21
<b>Medploz® 30's</b>	
<i>10mg</i>	8.35
<b>Noxidem® 30's</b>	
<i>10mg</i>	9.99
<b>Stilnox® 30's</b>	
<i>10mg</i>	24.10
<b>Zolnoxs® 30's</b>	
<i>10mg</i>	9.16
<b>Zolpihexal® 30's</b>	
<i>10mg</i>	9.11
<b>Alchera® 30's</b>	
<i>7.5mg</i>	4.25
<b>Zopivane® 30's</b>	
<i>7.5mg</i>	4.47

## DISCUSSION

The overall aim of this study was to evaluate the utilization of benzodiazepines and Z-drugs in the private hospitals and community pharmacies of Namibia over 6 years 2017-2022. The use of benzodiazepines and Z-drugs was assessed by determining the patterns, trends and the factors contributing to the use of benzodiazepines and Z-drugs in 10 selected community pharmacies. A total of 867 168 prescriptions were dispensed during the study period; two percent contained benzodiazepines and Z-drugs of which most consumed were BDZs (56%) compared to Z-drugs. While the consumption of BDZs in Namibia is comparable to that of other countries (37), the usage rate of these medications in Namibia (2%) remains significantly lower in comparison to other nations. It was evident that a higher proportion of prescriptions were utilized by males (53.6%) compared to females. This aligns with a study conducted in a military health system, where 79.2% of benzodiazepines and Z-drugs were dispensed to males. This study suggesting elevated consumption of benzodiazepines and Z-drugs in male may not accurately reflect the overall consumption pattern in males, given that the study was conducted within a military health system where the majority of the population is male. These results are contrary to other studies that reported higher consumption of benzodiazepines and Z-drugs among females.(13,35,38,39). While this study lacked specific data regarding the age group with the highest consumption of benzodiazepines and Z-drugs, other research studies have identified an increase in the use of benzodiazepines and Z-drugs with advancing age (6,32,40).

## **5.1 Patterns of utilization of benzodiazepines and Z-drugs**

The research revealed that the Khomas and Erongo regions exhibited the highest frequency of dispensing encounters. This observation could be attributed to the comparatively higher development of medical centers and pharmacies in these regions compared to others. Additionally, the elevated population density in the Khomas and Erongo regions may contribute to increased awareness of the accessibility of benzodiazepines and Z-drugs in these areas. Among the pharmacists who participated in the survey, constituting key informants, seventy percent are actively employed within the pharmacy sector. These respondents highlighted that factors such as mental health considerations, regulatory constraints, and instances of irrational prescribing significantly contribute to the utilization of drugs in the N05 group.

The research findings indicated that the population-wide consumption of all benzodiazepines and Z-drugs is 2.14 (DDD) per 1000 population per day. This implies that, on average, approximately 2% of the population may receive one of these drugs daily. This consumption rate is notably low when compared to developed countries like Argentina (77.6 DDD), Spain (89.3 DDD), and Portugal (96 DDD) (13,41,42).

Furthermore, zolpidem (N05CF) was reported to be the most consumed benzodiazepines and Z-drugs with 6.4 DDDs per 1000 population per day which indicates that approximately 1% of the population on average may receive zolpidem per day. The other highly consumed benzodiazepines and Z-drugs is lorazepam (4.6 DDD per 1000 population). The elevated usage of both these medications is linked to the accessibility of diverse branded generics. Zolpidem, for instance, has seven branded generics, while lorazepam has three. Furthermore, the increased utilization of zolpidem and lorazepam may be associated with the treatment of insomnia, particularly sleep-onset insomnia, given

that these two drugs are short-acting agents with zolpidem being favored over zopiclone due to the absence of noticeable hangover effects the next day(1). On the other hand, the heightened consumption of lorazepam in managing anxiety may result from misconceptions regarding the use of BDZs as a primary treatment, public perceptions, and concerns about the potential for abuse and dependence with prolonged use(1). Comparable research conducted in Belgium and South Africa revealed that zolpidem ranked as the most dispensed drug within the N05 group (43,44). In contrast, a study conducted in Morocco identified alprazolam as the highest-consumed drug (0.98 DDD), followed by bromazepam, nordazepam, and zolpidem (37). The findings of this study suggest that while there is a rise in the consumption of benzodiazepines and Z-drugs in other countries, it is not as pronounced in Namibia as in other countries. However, there is a discernible need for intervention to prevent the situation from deteriorating further.

Out of the 26 dispensed benzodiazepines and Z-drugs, the majority (53%) consisted of repeat prescriptions, with zolpidem (n=4651) and alprazolam (n=2012) being the primary medications receiving repeat prescriptions. This implies that out of every 10 patients, five individuals have been prescribed benzodiazepines and Z-drugs consistently for several months to address issues related to insomnia or anxiety. These repeat prescriptions exhibited a mean duration of five months, ranging from four to six months. Zopiclone (achera®) emerged as an outlier with the highest average duration of repeats of 7 months. This prolonged usage might be attributed to its extended duration of action compared to zolpidem, making it a viable choice for addressing persistent sleep disturbance insomnia. This suggests that medications within the N05 group are being prescribed for durations exceeding the recommended guidelines, which may lead to undesirable side effects.

Amongst the drugs in N05 group that are issued as repeat prescriptions, a successful dispensation for two months was observed. This implies that patients were able to consistently consume these drugs for an average duration of two months for insomnia and anxiety. This suggests that the N05 group of drugs is being used beyond the recommended duration of 2-4 weeks. Prolonged treatment for insomnia and anxiety is associated with the development of tolerance, dependence, and withdrawal symptoms. A study in Norway indicated a high percentage (82%) of repeat prescriptions with more than 75% of consumers being prescribed these drugs beyond 6 months while in another study in Ireland, up to 49% of patients were taking benzodiazepines and Z-drugs for 3 months with about 10% of patients prescribed those drugs for 12 months (17).

Despite the low overall consumption, the research highlights evident instances of overprescribing and over-dispensing of N05 group drugs in the private sectors of Namibia. This suggests a deficiency in comprehensive guidelines within the country to aid healthcare professionals in treating and managing patients with insomnia and anxiety. This situation raises concerns about the potential risks of undesirable effects associated with the current healthcare practices. Established countries developed prescribing guidelines for benzodiazepines and Z-drugs. In the UK, the committee on the safety of medicines recommended short term duration of benzodiazepines and Z-drugs to be 2-4 weeks while in Canada, the standard of practice for prescribing BDZs and Z-drugs indicated 3 months (17,45). Similar guidelines have been developed in Denmark, Norway, the USA, Australia & New Zealand indicating how to prescribe for short term duration with possible therapeutic doses and long term cases where benzodiazepines and Z-drugs are considered the drug of choice and where benefits outweigh risks (46–48). The findings imply the need

for the development of a comprehensive standard of practice in the management of insomnia and anxiety.

## **5.2 Trends of consumption of benzodiazepines and Z-drugs**

There was an increased trend of Z-drugs in 2017 and 2020 while BDZs showed a decreased trend over the same period. Similar studies from the UK indicated that BDZs prescribing was subsiding and Z-drugs were taking over as they were perceived to be more effective and safer than BDZs in the treatment of sleep disorders despite sufficient proof to support the claim (17,43). The consumption of both BZDs and Z-drugs was reported to be steady between 2019 and 2020 and thereafter there was an incline and decline by 20% in both BDZs and Z-drugs respectively. A study in Morocco indicated a high to low trend in N05 group of drugs over the years (37) while other studies reported that the consumption of drugs in N05 group remains high but stable (15,39). The study findings suggest that the utilization of BDZs for the treatment of insomnia and anxiety remains consistently high when compared to Z-drugs, even though there were fluctuations in consumption observed during the study period.

While BDZs are indicated as the most consumed class, zolpidem emerged as the predominant individual medication, reaching its highest consumption peak in 2020 and the lowest in 2017. This pattern could be associated with social issues related to the COVID-19 pandemic amongst other reasons. Furthermore, there was a noticeable increase in the consumption of alprazolam (2018 and 2019) and lorazepam (2017) compared to other N05 drugs. The elevated consumption of alprazolam and lorazepam may be attributed to alprazolam belonging to the N05BA group of drugs, primarily prescribed for

anxiety, while lorazepam can be used for insomnia associated with anxiety (1). Findings in Belgium indicated that the most frequently used was zolpidem followed by lormetazepam and lorazepam in the treatment of insomnia (49) while studies in Spain reported lorazepam and alprazolam to be the most consumed used for similar indication(50). There was a declining trend of use of individual drugs in N05 group after 2021 with 2022 being the lowest. The data in 2022 was insufficient to validate the data hence the declining trend cannot be concluded with 2022 data. Oxazepam was the lowest consumed benzodiazepines and Z-drugs over the 6-year study period which was similar to a study done in South Africa(51).

### **5.3 Factors associated with the use of new classes of benzodiazepines and Z-drugs-**

The pharmacists who partook in the study indicated that both BDZs and Z-Drugs are equally the most used benzodiazepines and Z-drugs in Namibia. In this study, short to intermediate-acting benzodiazepines and Z-drugs were found to be the most consumed due to numerous aspects such as poverty, education, COVID-19 disease consequences, irrational prescribing, product marketing, and drug dependency. Similar results have been reported in studies from France, Canada, and Australia where low-income people, population with mental illness, and addicts were most likely to consume these drugs(8,52,53). Based on the perceived drivers, the pharmacists suggested that there is a necessity to educate patients and prescribers on the use of benzodiazepines and Z-drugs, develop medicine formularies to guide the current practice and implement regulatory strategies to control access and use of benzodiazepines and Z-drugs.

A study by Van der Linden on the impact of pharmacists led interventions in discontinuing BDZs one month after discharge was effective and safely reduced

benzodiazepines and Z-drugs in elderly patients a month after discharge without loss of sleep(54). Mixed interventions including tapering by doctors and pharmacists, patient education, psychological support, and short-term pharmacological substitution were used to measure the rate of reductions in the use of benzodiazepines and Z-drugs (55). It was indicated that pharmacological substitution with and without psychological support had the highest rate (56–58) followed by tapering of N05 drugs which showed favorable results in a reduction rate from 65% to 80% withdrawal rates (59,60). Patient directed education intervention yielded the lowest reduction rates of BDZs and Z-drugs (61,62). In Ireland, benzodiazepines and Z-drugs are classified as controlled under Misuse of Drug Act (17) which is similar to The UK, including a ban on repeat prescriptions which may provide some control over access to these drugs (63). A policy change in Hong Kong including BDZ as a risky drug resulted in a 50% and 10% reduction mean annual number of BDZs prescriptions in the general and psychiatric population, respectively between a period of 1991-1994 respectively(64). Other policies involved insurance companies excluding BDZs from reimbursement (65) and providing necessary incentives to the pharmacist to engage in interventions to reduce unnecessary drug use (66). Implementation of policies on N05 drugs should be done with caution as unwarranted policies may results in increased prescribing of more harmful drugs such as barbiturates for the treatment of anxiety and insomnia (67).

The recent cost per brand was analyzed as a factor contributing to the use of N05 drugs in this study and it was reported that the cheapest N05BA drugs were diazepam (Betapam®) followed by oxazepam (Purata®) and Bromazepam (Sandoz-Bromazepam®) while the most expensive BZDs were alprazolam (xanor®) and loprazolam (dormonoct®). In terms

of cost and consumption, alprazolam is expensive, yet its usage remains high compared to more affordable BDZs, given its short-acting nature. It has been reported that among BDZ prescriptions, preference is more likely given to drugs that have a short duration of action (19,68).

The most economical N05CF drugs reported were zolpiclone (Alchera® and Zolpivane®), while zolpidem (Stilnox® and Ivedal®) was identified as the most expensive. Similarly, in line with BDZs, the findings indicate that zolpidem has been the most widely consumed, despite not being the most cost-effective option. Nevertheless, the results reveal a significant repeat prescription of zopiclone (Alchera®), possibly attributed to its longer duration of action and cost-effectiveness compared to zolpidem. Based on the outcomes, it can be concluded that cost did not have a substantial impact on the selection of N05 drugs prescribed or dispensed for anxiety or insomnia.

#### **5.4 Limitations of the study**

The study presented several limitations. First, the study adopted a retrospective longitudinal design and used a patient dispensing record database in Unisolv® software, which had incomplete data on benzodiazepines and Z-drugs, diagnoses, age & socioeconomic status of patients, prescriber, and other covariates and this limited the researcher to provide adequate results. In addition, there are other databases not included in the study therefore there is an underestimation of the use of benzodiazepines and Z-drugs in the private sector. Secondly, there could be errors in some data entered into the Unisolv® database. Third, the use of a dispensing data makes the assumption that medications were indeed dispensed and consumed by the patients, which may not be the case. Therefore, this may provide an overestimation of use. Fourth, the study only covered

private sector which may not provide actual consumption of benzodiazepines and Z-drugs in Namibia. Fifth, the DDD indicator is a limitation on its own as it only indicates the crude estimate of the doses, and it does not indicate that patients are using benzodiazepines and Z-drugs in other patterns not recommended. Sixth, As the study period concluded in March 2022, the data collected does not represent the consumption for the entire year, which could lead to an inaccurate reflection of actual consumption. Seventh, there was insufficient data on pricing of benzodiazepines and Z-drugs which limited the in-depth analysis of the use of benzodiazepines and Z-drugs in relation to cost. Lastly, retrospective studies also require large sample sizes and tend to be time-consuming.

### **5.5 Delimitation of the study**

The focus of the study was to analyze the utilization data of benzodiazepines and Z-drugs obtained from the Unisolv database. Specifically, the study concentrated on pharmacies that utilize the Unisolv system. During the analysis process, the researchers utilized SPSS software to filter out invalid and incomplete data, ensuring that only reliable and complete data were included in the final analysis.

It is important to note that the unit of measure employed in the study was primarily for the purpose of making comparisons between the consumption of benzodiazepines and Z-drugs in Namibia and other countries. This comparison aimed to provide valuable insights into the utilization patterns and trends within a broader context.

The study aimed to examine various aspects, including trends, patterns, and drivers of benzodiazepines and Z-drugs use, as well as perceived factors associated with their

consumption. By investigating these factors, the study sought to gain a comprehensive understanding of the utilization patterns and identify potential areas for improvement in the rational use of these medications. Based on the findings obtained from the analysis, the study will be able to provide recommendations to promote the rational use of benzodiazepines and Z-drugs, ensuring better healthcare outcomes and patient safety.

## CONCLUSIONS

### 6.1 Conclusions

The primary objectives of the study were to investigate the patterns, trends, and factors associated with the utilization of these benzodiazepines and Z-drugs under ATC classification. By exploring these factors, the study sought to gain insights into the various aspects influencing their use, such as prescribing practices, patient demographics, and other related factors. These outcomes contribute to a deeper understanding of the utilization patterns of drugs in N05 group in the context of private community settings in Namibia.

#### 6.1.1 Patterns of utilization of benzodiazepines and Z-drugs

Drawing from the research findings, the study revealed that the overall consumption of N05 group of drugs was observed to be lower compared to findings from other studies. With low consumption figures, it suggests that Namibia is not extensively using these medications, portraying a positive scenario. Furthermore, the study concludes that both benzodiazepines (BDZs) and Z-drugs have comparable utility, lorazepam and zolpidem are the prevailing choices for treating anxiety and insomnia, respectively, in community pharmacies in Namibia.

Interestingly, a majority of the identified N05 drugs were repeatable prescriptions with durations exceeding three months. This prescribing pattern implies a non-compliant approach to established guidelines, which advocate for selective serotonin reuptake inhibitors (SSRIs) as the first line for the treatment of anxiety(69) and BDZs and Z-drugs

are recommended to treat anxiety and/or insomnia respectively for shorter durations during crises characterized by disabling and severe events(1).

### **6.1.2 Trends of consumption of benzodiazepines and Z-drugs**

An analysis of the utilization trends over the studied period indicated a contrasting pattern between Z-drugs and BDZs. While there was an increase in the utilization of Z-drugs, there was a concurrent decrease in the utilization of BDZs and vice versa. This observation highlights the dynamic nature of N05 group utilization and suggests a shifting preference among prescribers and patients.

### **6.2.3 Factors associated with the use of new classes of benzodiazepines and Z-drugs-**

The study also explored the perceived drivers behind the use of benzodiazepines and Z-drugs. Mental health emerged as a predominant factor influencing their consumption, suggesting a significant role of benzodiazepines and Z-drugs in managing mental health conditions. Furthermore, irrational prescribing practices and limited regulations were identified as additional drivers contributing to the use of benzodiazepines and Z-drugs. These findings underscore the need for targeted interventions to prevent an overuse of benzodiazepines and Z-drugs, promote rational prescribing practices, development of treatment guidelines, and ensure adherence to regulatory guidelines.

In summary, the study findings shed light on the consumption patterns of benzodiazepines and Z-drugs, with zolpidem being the most prevalent. The long durations of repeatable prescriptions indicate non-compliance with existing guidelines or lack of guidelines. The trends indicate changes in the utilization of Z-drugs and BDZs over the studied period. Mental health, irrational prescribing, and limited regulations were identified as key drivers of benzodiazepines and Z-drugs use, emphasizing the importance of implementing

interventions to address these factors and promote responsible utilization of benzodiazepines and Z-drugs.

This study represents the initial endeavor of its kind conducted in Namibia, making it a pioneering pilot study contributing to the methodology of medicine utilization in Sub-Saharan Africa. Additionally, it serves as a benchmark for future studies in Sub-Saharan Africa.

## RECOMMENDATIONS

### **7.1 Educational Interventions on safe prescription of benzodiazepines and Z-drugs**

The study reveals a generally low consumption of benzodiazepines and Z-drugs, accompanied by a persistent pattern of repeat prescriptions extending beyond the recommended period. The prolonged consumption raises concerns about the potential for misuse, dependency, and associated economic burdens. Patients may resort to increased out-of-pocket expenses to acquire these drugs to address their anxiety or insomnia. Therefore, it becomes imperative to prioritize patient education regarding the appropriate use of benzodiazepines and Z-drugs and to create awareness about the potential consequences such as tolerance, dependency, withdrawal symptoms, and high risks of falls associated with long-term utilization of these drugs.

The Ministry of Health and Social Services alongside the Namibia Medicine Regulatory Council should train Healthcare workers through educational programs to disseminate information discouraging the use of benzodiazepines and Z-drugs. This includes providing educational materials to enhance patients' awareness of the risks associated with the misuse of these medications. Additionally, organizing educational visits to old age homes can be beneficial in offering appropriate information on the long-term use of benzodiazepines and Z-drugs in the elderly population.

Development of strong relations amongst healthcare professionals, allowing easy implementation of continuous professional development programs to facilitate open discussions and knowledge exchange on managing patients who are prescribed

benzodiazepines and Z-drugs. Such collaborations can be instrumental in devising effective strategies to limit access to these medications and prevent unnecessary overuse. Moreover, it is crucial to broaden educational initiatives to encompass health insurance providers. By actively engaging with insurance companies, strategies such as endorsing the dispensing of more cost-effective brands and necessitating a motivation letter for approving claims related to benzodiazepines and Z-drugs after a recommended period can be implemented. These measures by insurance providers can help restrict access to N05 group beyond a specified period, such as three months. This approach aims to strike a balance between patient needs and responsible medication use, thereby promoting patient safety and reducing the potential for long-term dependence, ultimately ensuring better patient outcomes and cost-effectiveness in healthcare delivery.

## **7.2 Guidelines Implementations to ensure safe use of benzodiazepines and Z-drugs**

The study uncovered a significant gap in the existing healthcare system concerning the absence of local guidelines for prescribing and dispensing benzodiazepines and Z-drugs. This notable finding highlights the need for proactive measures to address this issue and ensure the safe and appropriate management of these medications.

To address this concern, a crucial recommendation is the establishment of a dedicated benzodiazepine and Z-drugs committee at the Ministry of Health and Social Services. This committee would play a pivotal role in developing comprehensive guidelines specifically tailored to guide healthcare professionals in prescribing and dispensing of benzodiazepines and Z-drugs. By leveraging the collective expertise of professionals from various relevant fields, including pharmacology, psychiatry, and general medicine, the committee can ensure the guidelines are evidence-based and in line with international best practices.

The primary objective of this committee would be to create a set of guidelines that encompass essential aspects such as appropriate dosing, first drug of choice in anxiety and insomnia, duration of therapy, tapering down or change from benzodiazepines and Z-drugs to diazepam, monitoring parameters, and considerations for special patient populations. These guidelines would serve as a valuable resource for healthcare professionals, providing them with clear and standardized protocols to follow when prescribing and dispensing benzodiazepines and Z-drugs.

Implementation of the guidelines would require a comprehensive approach involving collaboration between healthcare professionals, regulatory bodies, and relevant stakeholders. This collaborative effort would be essential to ensure the guidelines are widely disseminated and effectively integrated into routine clinical practice.

Furthermore, ongoing monitoring and evaluation of the implementation of the guidelines would be critical. Regular assessments of healthcare professionals' adherence to the guidelines, as well as monitoring patient outcomes and trends in benzodiazepines and Z-drugs utilization, can provide valuable insights into the effectiveness and impact of the guidelines. This feedback loop would enable timely adjustments and updates to the guidelines as needed, fostering continuous improvement in the management of benzodiazepines and Z-drugs. By implementing these guidelines, healthcare providers can ensure the rational and responsible use of benzodiazepines and Z-drugs, leading to improved patient care and safety.

### **7.3 Policy Development to regulate use of benzodiazepines and Z-drugs**

The study findings shed light on a critical issue in Namibia's healthcare system, namely the absence of legislation aimed at restricting access to benzodiazepines and Z-drugs. This

gap in regulatory control underscores the need for immediate action to address the situation and ensure the safe and responsible use of these medications.

To address this concern, it is strongly recommended that the Namibia Medicine Regulatory Council (NMRC) take proactive measures to revise and update the existing legislation. Specifically, the council should consider implementing new policies that encompass benzodiazepines and Z-drugs within the regulatory framework. This can be achieved through revisiting the gazette of schedule 4 medicine, which currently does not include drugs belonging to N05 group, and subsequently up scheduling these medications to schedule 4.

Up-scheduling benzodiazepines and Z-drugs from schedule 3 to schedule 4 would have significant implications in terms of regulatory oversight and control. Schedule 4 is typically reserved for medications with a higher potential for misuse, abuse, and dependence. By including benzodiazepines and Z-drugs in this schedule, the NMRC would be able to apply stringent measures and regulations that are already in place for other medications classified as schedule 4. This would help ensure that all benzodiazepines and Z-drugs are subjected to the same rigorous standards and safeguards, promoting patient safety and reducing the risk of misuse or improper access.

The implementation of these policies would require close collaboration between the NMRC, healthcare professionals, and relevant stakeholders. It is crucial to engage in comprehensive consultations and discussions to gather expert opinions and perspectives to inform the development and implementation of the revised legislation. Additionally, public awareness campaigns should be initiated to educate the general population about the rationale behind these regulatory changes and to foster a better understanding of the responsible use of benzodiazepines and Z-drugs.

#### **7.4 Further Research on the clinical drivers of use and outcomes**

The study findings have illuminated the need for further research to expand our understanding of the patterns, trends, and factors of benzodiazepines and Z-drugs use in Namibia. To enhance the generalizability of the findings, future research endeavors should encompass not only the private healthcare sector but also the public healthcare sector. This would enable a more comprehensive analysis of benzodiazepines and Z-drugs utilization across different healthcare settings, providing a more holistic view of the overall landscape.

Furthermore, it is crucial for future research to cover a broader geographical scope, including multiple regions within Namibia. By including a diverse range of regions, researchers can capture any regional variations or unique factors that may influence the patterns and trends of benzodiazepines and Z-drugs use. This broader perspective would contribute to a more robust understanding of the national landscape and facilitate the development of targeted interventions and policies.

Expanding the scope of future research to include statistical comparisons between sex groups and a wider range of age groups is also essential. Benzodiazepines and Z-drugs use can vary across different age cohorts, and it is important to examine these variations to better understand the specific needs and challenges faced by different population segments. By including a comprehensive age range, from adolescents to the elderly, researchers can identify any age-specific trends or factors that may impact benzodiazepines and Z-drugs utilization.

In addition, future research should aim to incorporate perspectives from various healthcare providers, including doctors and patients. By gathering insights from these stakeholders, researchers can gain a deeper understanding of the factors influencing benzodiazepines

and Z-drugs use, such as the decision-making processes of doctors and the experiences and perspectives of patients. This comprehensive approach would contribute to a more nuanced understanding of benzodiazepines and Z-drugs utilization and inform the development of tailored interventions and strategies.

Lastly, future research should endeavor to capture the specific indications or medical conditions that warrant the use of benzodiazepines and Z-drugs. Understanding the clinical contexts in which these medications are prescribed can provide valuable insights into the appropriateness of their use and help identify areas where alternative approaches or interventions may be more suitable.

By expanding the research parameters in these ways, we can attain a more comprehensive and nuanced understanding of the patterns, trends, and factors of benzodiazepines and Z-drugs use in Namibia, ultimately facilitating the development of evidence-based interventions and policies to promote the rational and responsible use of these medications.

### **7.5 Pharmacist led Interventions to improve safe use of benzodiazepines and Z-drugs**

The study's findings underscore the essential role of pharmacists in the monitoring and management of patients using benzodiazepines and Z-drugs. As custodians of medicines, pharmacists possess a wealth of knowledge and expertise that can greatly contribute to the safe and effective use of these medications. It is imperative for pharmacists to actively engage in providing ethical, legal, and pharmaceutical guidance to patients who are prescribed benzodiazepines and Z-drugs.

Given their unique position within the healthcare system, pharmacists have the opportunity to implement various interventions aimed at optimizing medication management for patients on benzodiazepines and Z-drugs. These interventions can

encompass a range of strategies, including patient counseling, medication reviews, adherence monitoring, and collaborating with other healthcare professionals to ensure comprehensive care. Pharmacists can play a crucial role in educating patients about the risks and benefits of benzodiazepines and Z-drugs, assisting in enrolling patients on benzodiazepines and Z-drugs step down programs, promoting adherence to prescribed regimens, and addressing any concerns or questions that patients may have.

Furthermore, pharmacists can contribute to limiting access to benzodiazepines and Z-drugs through appropriate dispensing practices, and adherence to regulatory guidelines aimed at reducing the misuse of these medicines as indicated above. They can implement measures to prevent overuse or misuse of these medications by conducting thorough assessments of patients' medication histories, considering potential drug interactions or contraindications, computerized alert systems on the usage of benzodiazepines and Z-drugs, and employing appropriate monitoring protocols. By actively engaging in these activities, pharmacists can help mitigate the risks associated with benzodiazepines and Z-drugs use and promote the responsible and rational utilization of these drugs.

In addition, pharmacists can collaborate with other healthcare professionals, including physicians, to implement a multidisciplinary approach to the management of patients on benzodiazepines and Z-drugs. Pharmacists can spearhead monthly meetings to review benzodiazepines and Z-drugs usage, conduct benzodiazepines and Z-drugs medicine use evaluations and provide feedback to doctors and nurses on the use, and conduct monthly meetings with psychiatrists to discuss high doses and duration of use of these benzodiazepines and Z-drugs. This collaboration allows for shared knowledge, expertise, and perspectives, leading to more comprehensive patient care. By actively participating in professional development activities and staying abreast of the latest research and

guidelines, pharmacists can enhance their role in providing evidence-based recommendations and interventions for patients using benzodiazepines and Z-drugs. By embracing their role as medication experts, pharmacists can play a pivotal role in optimizing patient outcomes and contributing to the overall quality of healthcare delivery.

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## APPENDICES

### 9.1 Appendix 1: Ethical Clearance Certificate



#### ETHICAL CLEARANCE CERTIFICATE

**Ethical Clearance Reference Number:** HG-/ 616/ 2021    **Date:** 17 August, 2021

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

**Title of Project:** A medicine utilization evaluation of Sedative-Hypnotics in private hospital and community pharmacies in Namibia.

**Student:** TAIMI IIPINGE

**Student Number:** 201208311

**Supervisor(s):** *Dr. D. Kibuule (Main) Ms. E. Hango (Co)*




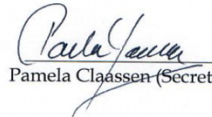
**Hage Geingob Campus**

Take note of the following:


1. Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the HREC-H. An application to make amendments may be necessary.
2. Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the HREC-H
3. The Principal Researcher must report issues of ethical compliance to the HREC-H (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by HREC-H
4. The HREC-H retains the right to:
  - i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,
  - ii) Request for an ethical compliance report at any point during the course of the research.

HREC-H wishes you the best in your research.

  
Prof. C Wilders (Chairperson)

  
Pamela Claassen (Secretary)

## 9.2 Appendix 2: Research Permission Letter

  
REPUBLIC OF NAMIBIA

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**MINISTRY OF HEALTH AND SOCIAL SERVICES**

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Ministerial Building  
Harvey Street  
Private Bag 13198, Windhoek

**OFFICE OF THE EXECUTIVE DIRECTOR**

Tel: No: 061 -203 2507  
Fax No: 061-222 558  
Andreas.Shipanga@mhss.gov.na

**Ref:** 17/3/3/TI  
**Enquiries:** Mr. A. Shipanga

**Date:** 22 October 2021

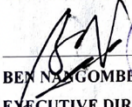
**Ms. Taimi lipinge**  
**Private Bag 31283**  
**Pioneerspark**  
**Windhoek**


Dear Ms. lipinge


**Re: A medicine utilization evaluation of Sedative-Hypnotics in private hospital and community pharmacies in Namibia.**

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**
  - 3.1 The data to be collected must only be used for academic purpose;
  - 3.2 No other data should be collected other than the data stated in the proposal;
  - 3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
  - 3.4 A quarterly report to be submitted to the Ministry's Research Unit;
  - 3.5 Preliminary findings to be submitted upon completion of the study;
  - 3.6 Final report to be submitted upon completion of the study;
  - 3.7 Separate permission should be sought from the Ministry for the publication of the findings.
4. All the cost implications that will result from this study will be the responsibility of the applicant and not of the MoHSS.

Yours sincerely,

  
**BEN NSO GOMBE**  
**EXECUTIVE DIRECTOR**





All official correspondence must be addressed to the Executive Director.

16/17/618

### 9.3 Appendix 3: List of key terms

**Anxiety:** Unpleasant emotional state characterized by feelings of fear and frequently involving distressing physical/somatic symptoms(1)

**Drivers:** Includes factors related to user, prescriber, and drug that influence the use of benzodiazepines and Z-drugs

**Drug Daily Dose-** The average maintenance dose of the drug when used for its major indication in adults (2).

**Drug utilization-** Defined as consumption / the use of benzodiazepines and Z-drugs in the study with special emphasis on the resulting medical, social, and economic consequences (2)

**Insomnia:** Insomnia is a disturbance of normal sleep patterns commonly characterized by difficulty in initiating sleep (sleep onset insomnia) and/or difficulty maintaining sleep (sleep maintenance)(1)

**Key informants:** Selected pharmacists who took part in the survey

**Long-term use:** Defined in a study as the use of more than 3 months of benzodiazepines and Z-drugs

**N05C:** Refers to benzodiazepines and Z-drugs in the study

**Patterns:** Consumption of benzodiazepines and Z-drugs using DDD

**Benzodiazepines and Z-drugs:** They are medicines used to reduce excitement and calm patients. (3)

**Z-drugs:** They are medicines used to treat insomnia (1)

**Short-term use:** Defined as 4 weeks when treating insomnia and a minimum of 3 months when treating when treating anxiety (4).

**Trends:** Use of benzodiazepines and Z-drugs over a set period



## **9.5 Appendix 5: Consent Form**

**RESEARCH: A MEDICINE UTILIZATION EVALUATION OF BENZODIAZEPINES AND Z-DRUGS IN THE PRIVATE HOSPITALS AND COMMUNITY PHARMACIES IN NAMIBIA.**

**Primary investigator: Ms. Taimi Iipinge**

**CONSENT (AGREEMENT) FROM PHARMACIES TO USE DATA IN THIS STUDY.**

### **PURPOSE OF STUDY:**

My name is Taimi Iipinge, a third-year master student at the School of Pharmacy, University of Namibia. The main objective of this research is to evaluate the utilization of benzodiazepines and Z-drugs in the private hospitals and community pharmacies of Namibia.

Your involvement in this study will aid identify the patterns, trends and factors of utilization of benzodiazepines and Z-drugs benzodiazepines and Z-drugs in private pharmacies of Namibia.

### **STUDY PROCEDURE**

I agree to take part in the study as a study unit, giving permission for the researcher to access data available on the usage of benzodiazepines and Z-drugs medicine from the UNISOLV database. I understand that my records will be used confidentially for this study.

### **BENEFITS**

Obtaining information back from the researcher will be of great benefit to improve the usage of benzodiazepines and Z-drugs in Namibia.

### **RISKS**

My data will not be utilized for any other purposes other than this study. My data will be kept confidential and in a professional manner.

**REIMBURSEMENT**

I will not be rewarded/paid for participating in this research.

**RIGHT TO REFUSE OR WITHDRAW**

The use of my data is voluntary, and I have the right to withdraw at any state of the study.

**CONFIDENTIALITY**

The record will be kept anonymous by omitting the use of names and rather use serial numbers for identification. Data will be stored in password protected files and only accessible to researcher and the supervisors.

**STATEMENT OF CONSENT**

..... has explained to me the research process, the risks and benefits involved during the research. I know my involvement in the study is voluntary and my data will be kept confidential. In addition, I understand by signing this consent form. I do not relinquish any of my legal rights but simply specify that I have been informed about the research in which I agreed to participate voluntarily.

A copy of this form will be provided to me.

Signature of pharmacist..... Date .....

Signature of witness.....Date.....

Research results will be made available to you on request. Should you have any questions regarding this project, feel free to contact me at:

Cell number 0812320428

Thanking you in advance.

Yours faithfully

.....

Taimi Iipinge

## 9.6 Appendix 6: Survey

### **A MEDICINE UTILIZATION EVALUATION OF BENZODIAZEPINES AND Z-DRUGS IN THE PRIVATE HOSPITALS AND COMMUNITY PHARMACIES IN NAMIBIA.**

I am Taimi Iipinge a final year MPharm student at the University of Namibia. I am carrying a study on benzodiazepines and Z-drugs in private Hospitals and pharmacies in Namibia.

The Objectives of the study is as follow:

- To determine the patterns of use of benzodiazepines and Z-drugs in private hospitals and community pharmacies in Namibia, (i.e., consumption rates by ATC classes, DDDs per 1 000 population and duration of use)
- To determine trends of use of benzodiazepines and Z-drugs medicines by DDDs per 1 000 population in private hospitals and community pharmacies in Namibia
- To determine factors of use of new classes of benzodiazepines and Z-drugs compared to BZDs in private hospitals and community pharmacies in Namibia

Due to limitations of the obtained data, I was unable to obtain qualitative data to determine the factors of use of the new classes of benzodiazepines and Z-drugs. Therefore, I am

humbly asking you to take 3 minutes of your time to fill in this survey to help provide qualitative data for the study.

\* Indicates required question

1. Indicate Sector you are currently working \*

*Mark only one oval.*

- Public Hospital Pharmacy
- Community Pharmacy
- Central Medical Stores
- Private Hospital Pharmacy
- Private Local Distributor
- NMRC

Other:

2. Based on your experience, which of the benzodiazepines and Z-drugs is mostly used

\*

*Mark only one oval.*

- Benzodiazepine
- Z-drugs (Zolpidem, Zopiclone & Zaleplon)

3. Specify which of the follow benzodiazepines and Z-drugs are mostly used. \*

*Mark only one oval.*

- Alprazolam (Xanor, Adcoalzam, Azo, Zopax)
- Bromazepam (Lexotan, Sandoz-Bromazepam)
- Diazepam (Valium, Pax, Betapam)
- Zolpidem (Dormicum, Stilnox, AdcoZolpidem  
, Ivedan, Noxidem, Zolnox, ZolpiHexal, Medploz)
- Flunitrazepam (Alchera, Zopivane)
- Loprazolam (Ativan, Tranqipam, Dormonoct)
- Clobazam (Urbanol)
- Oxazepam (Pureta)
- Nitrazepam (Arem)
- Triazolam (Halcion)

4. Based on quantitative data obtained from community pharmacies, it shows an  
\* increased use of both benzodiazepines and Z-drugs in 2019 & 2021 by 10% and  
3% respectively. In your opinion, what are the drivers of the increase in consumption  
In Namibia.

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5. What can be done to further regulate the use? \*

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6. Years of experience \*

*Mark only one oval.*

- < 1 Year
- 1 - 5 Years
- 5 - 10 Years
- > 10 Years

7. Gender \*

*Mark only one oval.*

Male

Female