

ORIGINAL RESEARCH

Evaluation of Adult Outpatient Antibiotics Use at Jimma Medical Center (with Defined Daily Doses for Usage Metrics)

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Introduction: Inappropriate antibiotic use is a major public health concern and driver of antibiotic resistance. Excessive exposure to antibiotics results in the emergence and spread of drug-resistant microorganisms. This study aimed to measure the volume of antibiotic consumption at the outpatient settings in a tertiary-care teaching hospital in Ethiopia.

Methods: A cross-sectional study was undertaken from February 01, 2019 to March 31, 2019 at Jimma Medical Center in southwest Ethiopia. Antibiotics use was analyzed using Anatomical Therapeutic Chemical Classification and Defined Daily Dose (DDD) system. Antibiotic use was calculated as DDD per 100 outpatients per day. Antibiotics were classified based on World Health Organization "AWaRe" classification scheme as "Access", "Watch" and "Reserve" group antibiotics and measured their consumption intensity.

Results: A total of 496 adult patients were included in the study. The mean (SD) age of participants was 33.07 (14.05) years. The total amount of antibiotics consumed was 5.31 DDD/100 outpatients per day. Ciprofloxacin was the most commonly [122 (21.12%)] prescribed antibiotics with DDD/100 outpatients per day value of 1.13, followed by amoxicillin [68 (11.76%)] with DDD/100 outpatients per day value of 0.44, and azithromycin [61 (10.55%)] with DDD/100 outpatients per day value of 0.51. On antibiotic consumption index, antibiotics in the "Watch" group had 2.10 DDD/100 outpatients per day.

Conclusion: There was high consumption of antibiotics in the study setting. Based on the use control criteria, half of the antibiotics used were in the "Watch" group. The high level of consumptions of antibiotics, such as ciprofloxacin, norfloxacin, and azithromycin, in particular, requires further scrutiny and calls for an urgent implementation of an antibiotic stewardship program at the hospital.

Keywords: antibiotics, antibiotics consumption, antibiotic resistance, defined daily dose, Ethiopia

Introduction

Antibiotics resistance (AMR) is a major threat to health and human development, affecting the ability to treat a range of infections. Treatments for a growing number of infections have become less effective in many parts of the world due to AMR.¹ When antibiotics stop working against microorganisms, standard antibiotics treatments become ineffective and hence, infections with antibiotic resistant pathogens increase the risk of death.² Hundreds of thousands of deaths per year are estimated to be attributable to AMR and that number is likely to rise to many millions per year by 2050.² The misuse and overuse of antibiotics is a key contributor to this problem.³ Excessive exposures to antibiotics result in the emergence and spread of drug-resistant bacteria, potentially avoidable adverse drug reactions, and increased healthcare utilization and cost.⁴

Antibiotics are indispensable part of modern medicines and the cornerstone for treating bacterial infections. They are now one of the most common medicines prescribed in hospitals and across sectors^{5,6} to reduce morbidity and mortality.⁷ Improving antibiotic prescribing based on necessity in all healthcare settings is critical in combating antibiotic resistant bacteria.8 The link between AMR and their use is well documented. 9-11 However, little information is available on appropriate antibiotics use in lowincome countries. Previous studies from low resource settings showed a high prevalence of inpatient and outpatient antibiotic use. 12,13 Among 18 hospitals in Egypt, the prevalence of antibiotic use was 59%; 14 and in Nigeria, 55.9% of the patients were prescribed with antibiotics.⁷ Similarly, in a recent study from China, the prevalence of antibiotic use was 56%. 15 Nearly two-thirds of United States (U.S.) antibiotic expenditures are catering the outpatient settings. 16,17 Similarly, in other developed countries, about 80% to 90% of antibiotic use occurs among outpatients. 18 Therefore, drug use studies using aggregate data from different settings indicate that there is over consumption of antibiotics.

Data on utilization may provide useful information for promoting appropriate use of medicines. 19 The Defined Daily Dose (DDD) can be used as a unit for measurement of drug consumption. It is the assumed average maintenance dose for the medication's main indication in adults. The DDD method converts and standardizes readily available product quantity data into estimates of clinical exposure to medicines. The method was developed in Scandinavian countries in the late 1970s and is now internationally adopted and supported by World Health Organization (WHO).²⁰ It should be emphasized that the DDD is a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose. Drug utilization figures should ideally be presented as numbers of DDDs per 100 patients per day or, when drug use by inpatients is considered, as DDDs per 100 inpatient days.²¹ For anti-infective and other drugs normally used for short periods, it is often considered to be the most appropriate to present the figures as numbers of DDDs per 100 inpatient days. Thus, DDDs of antibiotics prescribed per 100 patients per day or 100 inpatient days are a good measure of antibiotics consumption.²⁰

There are limited studies in Ethiopia that have published DDDs of antibiotic consumption. ^{22–24} In this report, we presented the 2019 data on the consumption of systemic antibiotics at Jimma Medical Center in Ethiopia with the aim to assess variations in consumption and to assist monitoring of the rise of resistance. The ultimate goal is to guide development of rational-use policies and to provide a baseline data for future assessment.

Methods

Study Design and Settings

A hospital-based cross-sectional study was conducted at Jimma Medical Centre (JMC). JMC is the only teaching and referral hospital in the southwest of Ethiopia with a bed capacity of 660 and a catchment population of over 20 million. Jimma Medical Center (JMC) is one of the oldest public hospitals in the country. Geographically, it is located about 350 km southwest of Addis Ababa, the capital. It provides services for approximately 15,000 inpatient, 11,000 emergency cases and 4500 deliveries per year. The overall catchment population for the outpatients reaches 160,000 attendants including the pediatrics and those patients on ambulatory follow-up for chronic diseases, human immunodeficiency virus (HIV) and tuberculosis per year. The hospital gives services both for patients from the community presenting directly to the outpatient department and those referred after attending some other healthcare facility or primary hospitals. However, as the hospital is the tertiary teaching hospital in the country, more than 75% of outpatient attendants are referred to hospital from lower-level health institution.

Study Population

Adult patients (with age ≥18 years) who were treated at the outpatient department for acute presentations were included in the study. The inclusion criteria were patient who prescribed with at least one systemic antibiotic for the suspected or confirmed infections during the study period. Patients who prescribed with topical antimicrobial, antifungal, antiviral, anthelmintic and antiprotozoal and antituberculosis were excluded. A total of adult 930 patients visited the outpatient clinics of the hospital; from these 496 patients received systemic antibiotics, and were included in the study.

Data Collection Procedure

Pharmacists and general practitioners were trained to collect data following pre-designed and pre-tested data

1650 h

collection formats. Antibiotics which were classified as J01 category (antibiotics for systemic use) under the Anatomical Therapeutic Chemical classification (ATC) classification system were included in this study. Amount of antibiotics prescribed and dispensed during 60 consecutive days (from February 01 to March 31, 2019) were included and data were extracted from patients prescriptions and pharmacy dispensing records. Data about the antibiotics' dosage regimen, age of patients, number of antibiotics prescribed per prescription, duration of antibiotics use, and prescriber's information were collected from the prescription of the patient. Medical record of the patient was used to extract data on the primary diagnosis and comorbid conditions. Pharmacy dispensing records were used to confirm the amount and/or the number of the antibiotics, which were actually dispensed for the patient. Data collection was supervised by the investigators frequently in order to monitor the process and to assist in case of queries. The WHO in 2017 suggested that antibiotics be classified into three groups; "Access", "Watch" or "Reserve" (AWaRe) groups, to emphasize the importance of their optimal use and potential for development of AMR and we used the 2019 database to classify them accordingly.^{25,26} The "Access" antibiotics are firstand second-choice options for common infections; they should be available in all countries and all facilities. The "Watch" group includes antibiotic classes that should be prescribed only for specific indications, since they are at higher risk of bacterial resistance. Some "Access" antibiotics, such as ceftriaxone or azithromycin, are also part of the "Watch" group and the "Reserve" group is made up of last-resort options, such as colistin or IV fosfomycin. 25-27

Consumption Measurement Metrics

The DDD is a standard globally accepted unit of measuring drug consumption of different strengths, pack sizes or combinations. It can be used to compare rates between regions, countries, hospitals and wards. ^{28,29} The number of DDDs was calculated by first converting the total amount of antibiotics prescribed and dispensed in a given time into grams. This was then divided by the standard WHO DDD value given in grams by multiplying by the number of days in the study. When measuring antibiotic consumption in an outpatient setting, DDD per 100 outpatients per day is the recommended method. ³⁰ DDDs = Calculation of consumption of antibiotics as DDD per 100 patients is calculated from the following formula

DDD per 100 outpatients per day

Total number of dosage strength of each antibiotic prescribed

 $= \frac{\times \text{ Dosage unit}}{\text{WHO assigned DDD X Duration of}} x100 \text{ outpatients}$ $\text{study} \times \text{Total number of outpatients}$ during study period

Statistical Analysis

All data were coded and entered into a Microsoft Excel file. The spreadsheet was used for the calculation of DDDs based on the strength of each antibiotic, the number of dose units and the DDD values allocated by the World Health Organization. The statistical analyses were done using SPSS version 22.0 (IBM Corp, Armonk, NY, USA) software package for windows. Continuous variables were presented as means, standard deviations, and sums. Categorical variables were presented as frequencies and percentages. Measures of relative consumption, expressed as a percentage of total consumption of groups of antibiotics, were derived for each antibiotic and DDD for "Watch" and "Access" category of antibiotics was calculated.

Results

Background Characteristics of Study Participants

From a total of adult 930 patients visited the outpatient clinics, 496 patients received systemic antibiotics and included to the final analysis. The mean \pm SD age of the patients was 33.07 \pm 14.05 years. Majority (68.21%) of them were in the age range of 18-35 years. Patients prescribed with combination antibiotics were 16.53%. The majority (85.7%) of the patients received drug/s prescriptions for seven or less days. In more than three-fourths of the cases, antibiotic prescriptions were ordered by medical interns (Table 1).

Primary Infectious Condition and Comorbidities

From a total of 556 primary infectious conditions for which an antibiotic were prescribed, 120 (21.58%) accounted for urinary tract infections and 94 (16.91%) for lower respiratory tract infections. About 13.49% of study participants used antibiotics for the treatment of upper respiratory tract infection (Table 2).

Table I Study Participants' Baseline Characteristics and Other Related Information

Variables	Frequency	Percentage		
Age (years)	Mean ± SD	33.07 ± 14.05		
	18–35 36–50 51-65 ≥66	338 103 25 30	68.21 20.81 5.04 6.04	
Number of antibiotics prescribed	Monotherapy Dual antibiotics Three antibiotics	414 79 3	83.47 15.93 0.60	
Duration on	Mean ± SD	5.86± 3.23		
antibiotics(days)	≤7 >7	425 71	85.7 14.3	
Prescriber	Medical intern Resident Senior General practitioner	380 84 11 21	76.61 16.94 2.22 4.23	

With regard to co-morbidities, which did not require antibiotic treatment as defined within this study as primary management, dyspepsia/peptic ulcer disease was present in 4.03%, and pulmonary tuberculosis in 11 (2.22%) of study participants. Seven (1.41%) participants had a diagnosis of arterial hypertension (Figure 1).

Antibiotics Consumption Metrics

From a total of seventeen types of antibiotics prescribed, ten were in the "access" category, seven in the "watch" category and none were in the "reserve" category. The total antibiotic consumption was 5.31 DDD/100 outpatients per day. Based on the consumption volume of

antibiotics, doxycycline accounted for 1.59 DDD/100 outpatients per day followed by ciprofloxacin for 1.13 DDD/100 outpatients per day, azithromycin for 0.51 DDD/100 outpatients per day, and amoxicillin for 0.44 DDD/100 outpatients per day (Table 3).

The most commonly prescribed antibiotic was ciprofloxacin (21.12%) followed by amoxicillin (11.76%), and azithromycin (10.55%) (Table 4).

AWaRe Classification of Antibiotics

A total of 578 antibiotics was prescribed for a total of 496 adult patients with an average of 1.2 antibiotics per prescription. Based on AWaRe classification scheme, 293 (50.69%) prescriptions contained antibiotics classified under "Watch" group and the rest under the "Access" group. From the "Watch" group of antibiotics, more than one–fifth of prescriptions accounted for ciprofloxacin and about 10.55% for azithromycin. The total volume of consumption for "Watch" group was1172 DDDs, with 2.10 DDD/100 outpatients per day (Table 5).

Discussion

Surveillance of antibiotic consumption is important in improving the quality of antibiotic use. It plays a key role in establishing the rationale for the use of antibiotics. Countries with the highest per capita antibiotic consumption have the highest AMR rates.³¹ This problem is seen globally and drug utilization studies have always been useful in emphasizing the problem and the pitfalls of daily prescribing of different antibiotics. Many organizations have recommended that antibacterial drug use at institution and national levels should be monitored to

Table 2 Primary Infectious Condition for Which Antibiotics Were Prescribed

S.No.	Disease/Disorder Type	Frequency	Percentage
1.	Urinary tract infection	120	21.58
2.	Lower respiratory tract infection	94	16.91
3.	Gastro intestinal infection (including acute gastroenteritis, PUD [£])	76	14.21
4.	Upper respiratory tract infection (AOM, pharyngitis, tonsillitis)	75	13.49
5.	Acute febrile illness	54	9.71
6.	Skin & soft tissue infection (non- occult abscess)	45	8.10
7.	Trauma (soft tissue injury, animal bite)	44	7.91
8.	Eye infection (conjunctivitis, blepharitis, etc.)	15	2.69
9.	Sexually transmitted disease/infection	6	1.10
10.	Medical prophylaxis (eg Ols in HIV)	4	0.72
11.	Unknown	23	4.14

Note: [£]Triple therapy regimen. Percentage given as per total number of infections (n = 556).

Abbreviations: HIV, human immune deficiency virus; OI, opportunistic infections; AOM, acute otitis media.

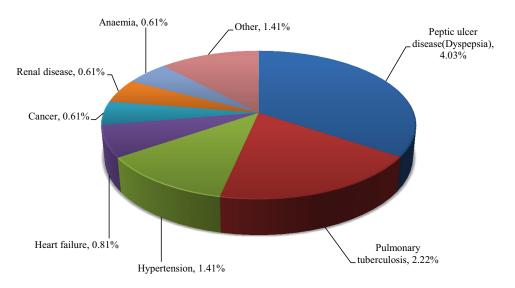


Figure 1 Comorbidity profile among study participants. Other includes retroviral infection, benign prostatic hyperplasia, irritable bowel syndrome, interstitial lung disease, and glaucoma; percentage given as per total number of patients (n = 496).

have a better understanding of the relationship between the uses of antibacterial drugs and emerging bacterial resistance.³²

The use of an ATC/DDD system in hospitals would provide internationally valid data in the evaluation of antibiotics use. The efficient utilization of antibiotics by infectious diseases experts in hospitals, as well as creating guidelines for antibiotic use specific to every hospital and more efficient use of the microbiological laboratories may be of benefit in resolving such existing problems. Until today, no data were available on the status of antibiotics consumption in JMC. This is the first study to report the antibiotic consumption in the hospital, using the WHO metrics of drug consumption methodology.

In this study, a total of 496 patients treated at JMC were included. The average antibiotics prescribed per prescription was 1.2. This finding was comparable with the other data reported from India (1.49),³³ Iran (1.27),³⁴ Saudi Arabia (1.26),³⁵ and Cameroon (1.14).³⁶ It is advised that the number of medications per prescription be kept as low as possible in order to reduce the likelihood of medication error, occurrence of AMR and costs to patients and health facilities. Antibiotics are widely known to be overused, but it is difficult at the population level to determine which antibiotic prescriptions are actually needed. Thus, monitoring the cumulative use of antibiotics allows one to consider the effects of antibiotic treatment efforts and to recognize areas for change. A reduction in excessive use would be mirrored in a drop in total antibiotic use, given that infection rates remain stable over time. Monotherapy was more frequently used with respect to dual or triple therapy. This might be the fact that our study populations were from the outpatient setting, where most of the patients come with acute self-limited condition.

The overall antibiotic consumption volume was 5.31 DDD/100 outpatients per day. This was lower than reports from other countries, such as Tanzania (4.99 DDD/1000 inhabitants per day), 37 Montenegro (39.05 DDD/1000 inhabitants/day). 38 Slovenia (59.8 DDD/1000 inhabitants per day),³⁹ and Syria (20.13 DDD/1000 inhabitants per day). 40 However, nearly approachable result with study from Croatia (3.29 DDD/1000 inhabitants per day).41 Unlike the study from Tanzania,37 and Montenegro³⁸ where the penicillins, quinolones and tetracycline were consumed most frequently, in the current study tetracycline (doxycycline) was consumed most frequently (1.59 DDD/100 outpatients per day) followed by fluoroquinolones (1.48 DDD/100 outpatients per day) and penicillins (1.13 DDD/100 outpatients per day). This difference in volume of consumption may be related to short data collection period (two months) in the current study. The other reason might be due to the difference in seasonality of infections, infection prevention strategy, and antibiotic use policy between our country and the aforementioned countries.

In this study, the most frequently used antibiotics were ciprofloxacin (J01MA02) [23.65%] followed by cloxacillin (J01CF02) [17.71%], and amoxicillin (J01CA04) [13.85%]. These antibiotics also have a higher

Table 3 Defined Daily Doses (DDDs) per 100 Outpatients per Day of Antibiotics Subgroups and Substances (in Accordance with the Anatomic Therapeutic Chemical (ATC) Coding System)

S. No.	ATC Code	Antibiotic Chemical Subgroup	DDD/100 Outpatients per Day	Antibiotic Type	DDD	DDD/100 Outpatients per Day
1.	J01MA	Fluoroquinolones	1.48	Ciprofloxacin	627	1.13
				Norfloxacin	196	0.35
2.	J01FA	Macrolides	0.624	Azithromycin	280	0.51
				Erythromycin	8	0.014
				Clarithromycin	53	0.10
3.	JOIDB	First-generation cephalosporins	0.35	Cephalexin	197	0.35
4.	J01DD	Third generation cephalosporins	0.0146	Ceftriaxone	7	0.013
				Ceftazidime	0.9	0.0016
5.	J01XD	Imidazole derivatives	0.13	Metronidazole	69.6	0.13
6.	JOICE	Beta-lactamase sensitive penicillins	0.0314	Crystalline Penicillin	0.8	0.0014
				Benzanthine penicillin	15	0.03
7.	J01CA	Penicillins with extended spectrum	0.44	Amoxicillin	245	0.44
8.	J01CF	Beta-lactamase resistant penicillins	0.42	Cloxacillin	234	0.42
9.	J01CR	Combinations of penicillins	0.24	Amoxicillin-clavulanic acid	131	0.24
10.	JOIEE	Combinations of sulfonamides and trimethoprim	0.008	Sulfamethoxazole- trimethoprim	4.5	0.008
11.	JOIAA	Tetracycline	1.59	Doxycycline	883	1.59
12.	JOIBA	Amphenicols	0.02	Chloramphenicol	12	0.02
	Total				2964	5.31

Table 4 Top Ten Frequently Prescribed Antibiotics in the Setting

S. No.	Antibiotics	AWaRe Class	Frequency (Percentage) [£]
1.	Ciprofloxacin	Wa	122 (21.12)
2.	Amoxicillin	Α	68 (11.76)
3.	Azithromycin	Wa	61 (10.55)
4.	Doxycycline	Α	56 (9.69)
5.	Cephalexin	Α	49 (8.48)
6.	Cloxacillin	Α	48 (8.30)
7.	Norfloxacin	Wa	44 (7.61)
8.	Amoxicillin-clavulanic acid	Α	37 (6.40)
9.	Metronidazole	Α	37 (6.40)
10.	Benzathine penicillin	Α	35 (6.06)

Note: [£]Number of patients prescribed. Abbreviations: A, Access; Wa, Watch. consumption index in the current study. This is similar to reports from Turkey, 42 Libya 43 and Tanzania. 37 Out of the seventeen most commonly used antibiotics, ciprofloxacin is the one that is of particular concern. The main indication is for urinary tract infections (UTI) which is reported to be one of the prevalent diseases in the study setting. This is related to the prevalent infections and related conditions in the setting for which these antibiotics are routinely recommended on the current national and international standard treatment guidelines for infectious diseases.

Interestingly, the consumption index of beta-lactamase sensitive penicillins like Crystalline penicillin (J01CE01) was relatively low [0.0014/100 outpatients per day] in the

Table 5 Percentage and Total DDD of Antibiotic Consumption Based on AWaRe Classification

AWaRe	Specific Antibiotics	Antibiotic Prescribed	Percentage*	Total	DDD/100 Outpatients per
Class		(n=578)		DDD	Day
Watch group	Azithromycin	61 (10.55)	50.69	1172	2.10
	Ceftazidime	I (0.17)			
	Ceftriaxone	6 (1.04)			
	Ciprofloxacin	122 (21.12)			
	Clarithromycin	5 (0.86)			
	Erythromycin	5 (0.86)			
	Norfloxacin	44 (7.61)			
Access group	Amoxicillin	68 (11.76)	49.31	1792	3.21
	Amoxicillin -clavulanic acid	37 (6.40)			
	Benzathine Penicillin	35 (6.06)			
	Crystalline Penicillin	I (0.17)			
	Cephalexin	49 (8.48)			
	Chloramphenicol	I (0.17)			
	Cloxacillin	48 (8.30)			
	Sulfamethoxazole/Trimethoprim	2 (0.35)			
	Doxycycline	56 (9.69)			
	Metronidazole	37 (6.40)			

Note: *Calculated from the percentage prescription (293 prescription had antibiotics within "watch" group).

setting. This is in line with a study from Mongolia⁴⁴ which reported dramatic decline in the use of these antibiotics from 11.4 DDD/100 bed days per day to no consumption. However, study from Norway⁴⁵ showed the frequent use (up to 34%) of this antibiotic in the setting. This may be related to the size, type and geographical location of the hospital. Small size hospital may frequently use the common antibiotics such as penicillins. The different use of drugs across different countries may be also due to differences in the types of infections that are prevalent. Literature indicates that resistance of local bacterial strains to these agents and treatment failures were the main reasons to stop procuring and using these antibiotics.⁴⁶ There is also only a weak recommendation in the guidelines to use these drugs for adults with infectious disease(s).⁴⁷

In the current study, the use of antibiotics in "Watch" group (50.69%) and "Access" group (49.31%) was nearly in equal proportions. This is similar to studies from Eritrea, 48 Tanzania 37 and Libya. 43 Antibiotics in the "Reserve" category were not available and prescribed in the study setting. The WHO AWaRe system recommends at least 60% of prescribed antibiotics in the "Access" list, instead of the "Watch and Reserve" list, to cope with the problem of antibiotic resistance. 49 Thus, the use of "Watch" group antibiotics at the study indicated relative over consumption, which warrants further investigation. However, clinicians should focus on the evidence to use

those very crucial antibiotics found in the "Watch" group. In terms of consumption volume, "Access" group relatively showed higher outpatient antibiotic dispensing patterns (3.21 DDD/100 outpatients per day). This is in contrast to study from Syria, 40 where higher percentage accounted for "Watch" group (13.26 DDD/1000 inhabitants per day).

Strength and Limitations of the Study

The main limitation of our study is that it was conducted during a single, limited period of time and in a single center. It is also not known whether the antibiotics that were sold were actually consumed, although this can be assumed most of the time. There were limited literatures for comparison of the current study, based on the WHO recommended defined daily dose consumption metrics. Nevertheless, the results of this study could serve as a starting point for future studies that will yield a greater understanding of the prescriptions and uses of antibiotics in our hospital. The limited possibilities of aggregating or accessing data on antibiotics usage in Ethiopia, specifically in the study area is a major challenge in conducting a study that aims to be representative of the entire population. This study represents a pioneering step toward the complete picture of antibiotic dispensing in the setting. Repetition of the study (by applying the same ATC/DDD methodology) in different seasons and in consecutive years could reveal highly relevant data on antibacterial consumption trends, which, especially if correlated to data on antibacterial resistance, could be of help in the control of infectious diseases. It would also be an important tool flanking the introduction of educative measures and antibiotic stewardship initiatives.

Conclusion

Our study has revealed that there is a high level of antibiotic consumption at the hospital. This is the first of its kind study in JMC after the framing of antibiotics stewardship program initiatives at a country level, looking into the consumption data of antibiotics. The study provides the baseline data for comparison later, in order to assess the trend in their use. It has also identified that drugs like ciprofloxacin, norfloxacin and azithromycin are overused. This requires further investigation to assess their appropriateness in different clinical settings. The use also needs to be correlated with local pathogens and antibiotics susceptibility patterns.

Abbreviations

AWaRe, Access, Watch and Reserve; ATC, Anatomical Therapeutic Chemical classification; DDD, Defined Daily Dose; JMC, Jimma Medical Center; WHO, World Health Organization.

Data Sharing Statement

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

Ethical clearance and approval was obtained from the Institutional Review Board (IRB) of Jimma University. It was based on the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All study participants provided written informed consent. We kept the participant's information confidential.

Consent

Not applicable. No person's details, images, or videos were used in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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