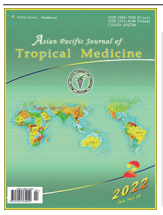

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Patterns of adverse drug reaction reporting in Ethiopia: A database analysis of spontaneous reports from 2013 to 2018

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ABSTRACT

Objective: To examine the frequency and profile of spontaneous reports of adverse drug reactions (ADRs) sent to Ethiopia's pharmacovigilance (PV) database system.

Methods: The descriptive and retrospective study analysed spontaneous ADR complaints reported to the PV database by healthcare professionals between 2013 and 2018. Spontaneous ADR reports that reached the PV center and met the minimum reporting criteria were identified and assessed in terms of reporting rate, patient characteristics, type of ADRs, suspected drugs, report sources, and reporters' profession.

Results: A total of 657 spontaneous ADR reports were filed to the PV center between 2013 and 2018. During the study period, the reporting pattern of ADRs changed dramatically. The number of reports increased from 2013 (n=12) and peaked in 2015 (n=205), and then declined from 2016 to 2018 (n=144, 142 and 65 in 2016, 2017 and 2018, respectively). Females had a higher percentage of reported cases (56.3%) than males (43.7%). The highest number of ADRs was reported in the age categories of 15-64 years (475, 72.3%), followed by 0-14 years (154, 23.4%), and 65 years and above (21, 3.2%). Pharmacists reported the majority of ADRs (81.7%), followed by health officers (7.2%), nurses (5.8%), and physicians (5.2%). Skin and subcutaneous tissue abnormalities were the most commonly reported ADRs. The anatomical therapeutic chemicals code class "anti-infective for systemic use" was the most usually suspected medication. Trimethoprim with sulfamethoxazole as a combination ADRs was the most commonly reported drug that cause ADRs (14.2%).

Conclusions: The number of ADRs reported in Ethiopia was small and unpredictable compared to developed countries, indicating the performance of PV system and level of awareness of health care professionals towards ADR reporting was not satisfactory. In order to increase the frequency of spontaneous reports, more efficient PV methods and public policies must be implemented.

KEYWORDS: Pharmacovigilance; Adverse drug reactions; Spontaneous report

1. Introduction

Adverse drug reactions (ADRs), which are one of the top causes of morbidity and mortality globally, will continue to be a public health issue if medicines are used to treat a variety of conditions[1].

Significance

In Ethiopia, increased availability to complex treatment of concomitant infectious and non-communicable diseases has led to an increase in drug-related problems. This study indicated that ADRs reported by female patients were substantially higher than those reported by male patients during the study period. The highest percentage of reports came from pharmacists, followed by reports from other health care providers.

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According to the World Health Organization, adverse drug reactions (ADRs) is "any unpleasant and unanticipated reaction to a drug that could occur at levels utilized for prevention, diagnosis, or therapy"[2].

In Ethiopia, only a few studies have been undertaken to analyze health care professionals' knowledge, attitude, and practice regarding ADRs reporting. These findings revealed that health care professionals have a good attitude toward ADRs reporting but insufficient knowledge and practice[3,4]. Ermias *et al*.[3] found that the degree of ADRs case reporting in Ethiopia is relatively low, based on a review of case reports from 2002 to 2007. In Ethiopia, there is a scarcity of data on healthcare personnel's knowledge, attitudes, and practices concerning ADRs reporting at the health facility level[4]. As a result, the goal of this study was to examine the national ADR reports that were filed to the pharmacovigilance (PV) center during 2013-2018.

2. Materials and methods

2.1. Data source

Between 2013 and 2018, the national ADRs data reports trends for all marketed drugs reported to the PV database center were evaluated. Spontaneous ADR reports that reached the PV center and met the minimum reporting criteria were identified and assessed in terms of reporting rate, patient characteristics, type of ADRs, suspected drugs, report sources, and reporters' profession according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A criteria used in VigiBase[6]. Patient support program ADR reports, research cases, case reports, and follow-up reports were all eliminated. Furthermore, more than one suspect drug and/or ADR could be included in a single report.

The database was used to extract information about the patient's characteristics (age and sex), the reporter's qualifications, suspected drugs, ADRs, and the severity of the ADRs for each ADR report. Healthcare professionals, such as physicians, pharmacists, nurses, health officers, and midwives, were classed as reporters of ADRs.

There were three age groups included in this study. Patients were split into pediatric (0-14 years old), adults (15-64 years old), and geriatric (65 and above years old)[7]. The anatomical ttherapeutic chemical (ATC) cclassification system one level was used to classify suspected drugs[8].

The Medical Dictionary for Regulatory Activities was used to code ADRs, which were extracted from source data using system organ classifications and preferred terms[9].

2.2. Statistical analysis

Descriptive statistics were performed based on ADRs as counts and percentages. ADR reports were analyzed based on demographic characteristics (age and gender), geographical area or location from which they were reported, involved body system as defined by the system organ classifications, time of occurrence, health professional who reported cases, drug implicated, and ADR manifestations.

3. Results

The study examined all of the marketed drugs' spontaneous ADRs reports that were reported to the PV center between 2013 and 2018. During the study period, 657 spontaneous reports met the reporting minimum criteria and were thus included in the analysis.

3.1. Trends in ADR reporting

The number of reports in 2013 was 12, which peaked in 2015 (n=205), and then began to decline between 2016 and 2018 (144, 142 and 65, respectively) (Figure 1).

Figure 1. The annual numbers of spontaneous adverse drug reactions reports submitted to Ethiopia's pharmacovigilance center between 2013 and 2018.

3.2. ADRs by sex

In terms of patient gender, females were reported in 370 (56.3%) of reports, while men were reported in 287 (43.7%) of reports. Females reported a higher percentage of incidents than males.

Table 1. The pattern of spontaneous adverse drug reactions reporting by health care professionals in Ethiopia from 2013-2018.

Qualification reporters	2013	2014	2015	2016	2017	2018	Total
Pharmacist	10 (83.3)	69 (77.5)	168 (82.0)	114 (79.2)	119 (83.8)	57 (87.7)	537 (81.7)
Physician	1 (8.3)	9 (10.1)	8 (3.9)	5 (3.5)	10 (7.0)	1 (1.5)	34 (5.2)
Nurse	1 (8.3)	6 (6.7)	16 (7.8)	5 (3.5)	7 (4.9)	3 (4.6)	38 (5.8)
Health officer	0	5 (5.6)	12 (5.9)	20 (13.9)	6 (4.2)	4 (6.2)	47 (7.2)
Midwifery	0	0	1 (0.5)	0	0	0	1 (0.2)
Total	12 (100)	89 (100)	205 (100)	144 (100)	142 (100)	65 (100)	657 (100)

0 indicates no report.

Table 2. Top 10 drug lists and their respective therapeutic classes related to the adverse drug reactions rreports by health care professionals during 2013-2018 (n=657).

No.	Therapeutic classes (ATC code)	Suspected drug (s)	Reports [(n, (%)]
1	Anti-infective for systemic use (J)	Trimethoprim and sulfamethoxazole	93 (14.2)
2	Anti-infective for systemic use (J)	Amoxicillin	69 (10.5)
3	Anti-infective for systemic use (J)	Zidovudine, lamivudine and nevirapine	44 (6.7)
4	Anti-infective for systemic use (J)	Ciprofloxacin	36 (5.5)
5	Anti-infective for systemic use (J)	Zidovudine	25 (3.8)
6	Antiparasitic products, insecticides and repellents (P)	Praziquantel	21 (3.2)
7	Anti-infective for systemic use (J)	Rifampicin, isoniazid, pyrazinamide, ethambutol	15 (2.3)
8	Anti-infective for systemic use (J)	Efavirenz	12 (1.8)
9	Anti-infective for systemic use (J)	Nevirapine	10 (1.5)
10	Anti-infective for systemic use (J)	Lamivudine, tenofovir disoproxil and efavirenz	9 (1.4)

3.3. ADRs by age

To observe the trend of reporting with respect to age groupings, ADRs by age were estimated in three categorical age groups. The highest number of ADRs were reported in the age category of 15-64 years (475, 72.3%), followed by 0-14 years (154, 23.4%), and 65 years and above (21, 3.2%). A tiny percentage of reports (7, 1.0%) neglected to mention the age category.

3.4. Qualification of reporters

During 2013 and 2018, pharmacists reported the majority of ADRs (81.7%), followed by health officers (7.2%), nurses (5.8%), nurses (5.8%) and physicians (5.2%). Midwifery (0.2%) reported a small proportion of reports (Table 1).

3.5. ADRs for different therapeutic groups

The first ATC code levels were used to analyze suspected drugs mentioned in ADRs reports. The ATC level classes "anti-infective for systemic use" (78.6%), "antiparasitic products, insecticides, and repellants" (4.8%), "alimentary tract and metabolism" (3.6%), and "nervous system" (3.6%) are the most commonly reported ATC classes of drugs. These ATC classes were the most commonly reported drug groups throughout all years studied. "Antibacterial for systemic use" and "antivirals for systemic use" are the two main product groups implicated in "ant infective for systemic use" (Figure 2).

Trimethoprim and sulfamethoxazole have the highest number of ADRs (14.2%), followed by amoxicillin (10.5%), zidovudine, lamivudine, and nevirapine (6.7%), and ciprofloxacin (5.5%) (Table 2).

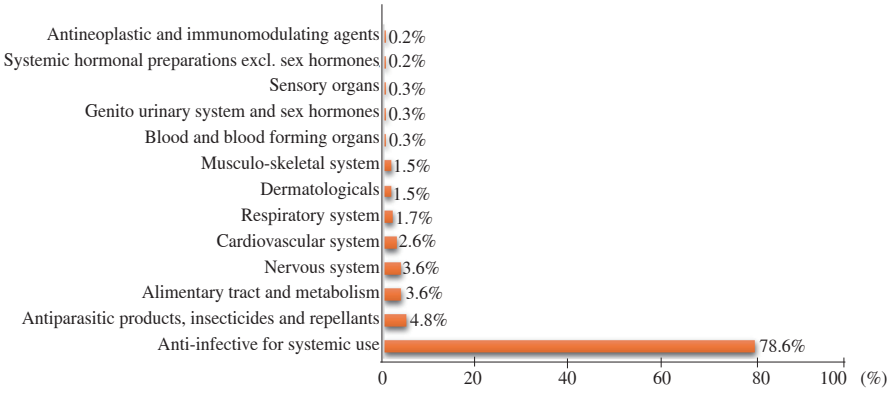

Figure 2. Percentage distribution of adverse drug reactions reports by anatomical therapeutic chemical class (first level) of suspected drugs between 2013-2018.

3.6. ADRs by system organ classification

The most commonly reported ADR system organ classification in the database are skin and subcutaneous tissue disorders (437, 66.5%), gastrointestinal disorders (47, 7.2%), blood and lymphatic system problems (40, 6.1%), and nervous system illness (28, 4.3%). Figure 3 depicts the most often reported terms during the study period. Rashes (220, 33.5%), itching (76, 11.6%), anemia (51, 7.8%), allergy (47, 7.2%), and vomiting (30, 4.6%) were the most commonly reported phrases by healthcare professionals.

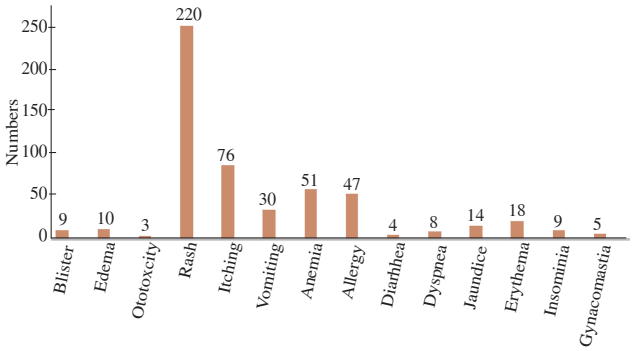

Figure 3. The most frequent preferred terms in adverse drug reactions reports by healthcare professionals.

3.7. ADR report by location

The capital Addis Ababa reported 353 (53.7%) of the ADR reports, followed by the Amhara area 142 (21.6%), Oromia 59 (9.0%), Snnpr 46 (7.0%), Tigray 40 (6.1%), Afar 14 (2.1%), Dire Dawa 2 (0.3%), and Harar 1 (0.2%). During the data collection period for this study, no reports were recorded in the remaining regions (Figure 4).

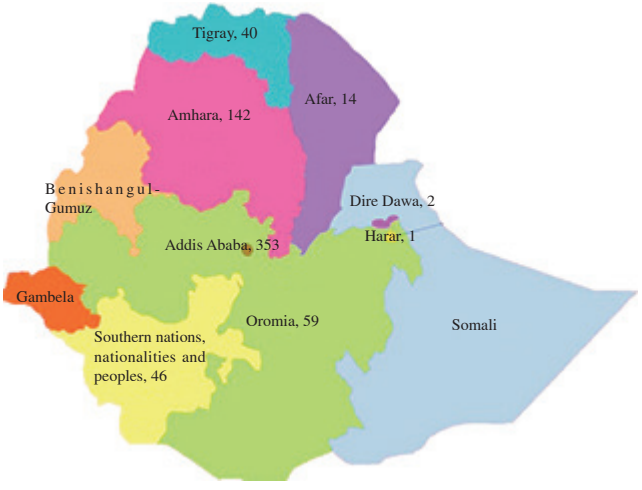

Figure 4. The number of cases of adverse drug reactions reports from different regions in Ethiopia 2013 to 2018.

3.8. ADR out come at the time of reporting

At the time of reporting, the majority of patients (430, 65.4%) had recovered without sequela. However, 18 (2.7%) cases were found with sequela, 58 (8.8%) had not yet been recovered, and 8 (1.2%) died (drug may be contributory) and 143 (21.8%) were unknown outcome.

4. Discussion

The goal of this study was to examine the trends of spontaneous ADR reporting in Ethiopia's national PV database. During the study period, the ADRs profile in the country revealed a fluctuating pattern. Between 2013 and 2015, there was the greatest increase, however, between 2016 and 2018, there was a considerable reduction. Despite the fact that the number of ADRs reported in Ethiopia was low and fluctuating in comparison to that in industrialized countries, it nevertheless shows an increased tendency, indicating that the health care professionals are becoming more aware of PV system in Ethiopia which was established under Food, Medicines and Healthcare Administration and Control Authority in 2002. In 2008, Ethiopia became an official member of the World Health Organization Program for International Drug Monitoring[10] and voluntary reporting has been effective as in 2010[11]. Since the establishment of the PV system, the number of ADR reports received from health care professionals is limited in numbers[12]. The low level of ADRs reporting in this study can be linked to a variety of reasons, including insufficient HCP training, a lack of reporting tools, limited utilization and poor feedback on ADRs surveillance reports, and low coverage/poor integration at health facilities[3].

During 2013 and 2018, ADRs reported in female patients (56.3%) were substantially higher than those reported in male patients (43.7%). This is in line with earlier research that have found that females are more likely than males to develop ADRs[10–12]. Males, on the other hand, had a higher risk of ADR than females, according to studies by Sriram *et al*., and Richa *et al*[13,14]. The higher prevalence of reporting among females could be due to a variety of factors. ADR occurrence is affected by a variety of factors such as patient age, gender, number of drugs taken, length of hospital stay, genetic factors, ethnicity, dietary, and environmental factors[13]. Female patients may have a higher frequency of ADRs, and they may also consult health care practitioners about ADRs more

frequently[14].

Most number of ADRs reported was in the 15-64 year old age group (72.3%) which was much higher than those for the other age groups of pediatric and geriatric populations. Multi-drug therapy or other disorders such as hypertension, diabetes, asthma, or other chronic diseases may be the cause of excessive morbidity in the adult population. Our findings are similar with the finding of Adimasu *et al*[12,15].

Only a few (3.2%) reports were received from those aged 65 and above. This is supported by other studies. Geriatric ADR was reported at a rate of 4.3% in a study by Amin *et al*[20] also, similar results indicated by Sriram *et al*[16]. Despite the fact that patients in the geriatric age group are particularly prone to adverse drug reactions, the minimal number of ADRs reports received indicates that this group has gotten inadequate attention[17].

For the years 2013-2018, it was observed that pharmacists reported more ADRs than physicians, health officers, and nurses. This rise in ADR reports among pharmacists could be explained by Ethiopia's recent shift in pharmacy practice from product-oriented to patient-focused clinical pharmacy practice[18].

Gurmesa and Dedefo[19] compared health care preofessionals' understanding of ADR reporting, finding that physicians and pharmacists were more aware of ADR than health care officers and nurses. Another study found that nurses, health care officials, and physicians were 93.1% less likely than pharmacy professionals to have adequate knowledge of ADR reporting.

Skin and subcutaneous tissue diseases (66.5%), gastrointestinal disorders (7.2%), blood and lymphatic system disorders (6.1%), and nervous system disorders (4.3%) were the most frequently reported ADRs among SOCs for ADRs. This pattern differs from the global pattern of ADRs from 2000 to 2009, when the most often reported SOCs for ADRs were general disorders and administrative site problems, skin and subcutaneous tissue disorders, and GIT disorders[20]. On the other hand this study is consistent with other studies by Coelho *et al*[24] Tripathy *et al*[25] and Patidar *et al*[17] but it differs from reports of Asiama *et al*[26] where gastrointestinal manifestations had the highest rate, which was second highest in our study (7.2%).

Suspect drugs mentioned in ADR reports were investigated at the ATC level 1. The drugs suspected of being linked to an ADR most frequently reported by health care professionals belong to the classes "anti-infective for systemic use" (78.6%), "antiphrastic products, insecticides and repellants" (4.8%), "aalimentary tract and metabolism" (3.6%), and "nervous system" (3.6%) at the first ATC level. This is similar to the patterns of ADRs observed by Aagaard *et al*[20] in upper middle-income countries, where drugs from the ATC class of anti-infective for systemic (24.5%) showed high rates of reporting. However, antineoplastic and immune modulating medicines accounted for 26.5% of all ATC drugs reported in Turkey[14]; although it was the eight most common ATC groups in the upper middle-income countries[20]. "Antibacterial for systemic use" and "antivirals for systemic use (dominated by antiretroviral)" are the main therapy groups implicated in "anti-infective for systemic use" in this study. The domination of antiretroviral products in African ADRs is perhaps not surprising considering the high burden of HIV/AIDS on the continent. With well-funded programmes providing access to antiretroviral, it is expected that there would be more ADRs on these products since healthcare workers in these programmes tend to be trained about PV system. Indeed, most published PV studies from Africa tend to be on the safety of antiretroviral[22].

Drugs from the "anti-infective for systemic use", "gastrointestinal tract and metabolism", and "nervous system" classes are among the most widely used in Ethiopia, therefore it's no surprise that they were among the most commonly reported drugs at the first ATC level. Our findings resemble another study on this topic by Aagaard *et al*[23].

Trimethoprim plus sulfamethoxazole (14.2%) is the most prevalent drug that causes ADR, followed by amoxicillin (10.5%) and zidovudine, lamivudine, and nevirapine (6.7%). It's possible that the high reporting rate for these therapeutic groups is due to higher drug consumption. Furthermore, most of these agents cause immediate and easily observable reactions that are classified as skin and subcutaneous tissue disorders, general disorders, and administration site conditions, for which causality between the drug and the reaction can be established quickly. This result is inconsistent with other studies in Turkey where adalimumab was the most commonly reported active substances by Fattinger *et al*[14], and Rivaroxaban by Graan *et al*[24] respectively.

This study examined only at spontaneous reports received to a national database between 2013 and 2018, which is similar to study by Aaagard *et al*[20] who analyzed spontaneous reports submitted to VigiBase from 2000 to 2009. Antiretroviral and antibiotics are the main product classes implicated in ADRs, according to Ampadu *et al*[22], who examined spontaneous ADRs characteristics between Africa and the rest of the world using Vigibase data.

The drug classes associated in ADRs from Africa differ from those from the rest of the globe. Disparities in disease patterns

and prescriptions, variances in PV systems and ADR reporting, and differences in health systems and health literacy, to name a few, could all have a role[22]. Rajesh *et al*[12], Desai *et al*[17], Leone *et al*[26], reported that antibiotics are the most common classes causing ADRs which is similar in our study patients on anti-infective for systemic use had maximum ADRs. Trimethoprim and sulfamethoxazole were the most common drugs to cause ADRs (14.2%), followed by amoxicillin (10.5%), zidovudine, lamivudine, and nevirapine (3.8%), and ciprofloxacin (5.5%). It is because of increased consumption of anti-infective for systemic use for long duration as compared to other classes of drugs.

Despite the fact that the number of ADRs recorded in Ethiopia were few and unpredictable in comparison to that in developed nations, it nevertheless shows an upward trend, indicating that health care providers are becoming more aware of PV system. This study showed that more effective pharmacovigilance methods and public policies must be established in order to improve the number of spontaneous reports. To summarize, increasing the number of spontaneous reports and improving the quality of notifications, promoting active surveillance in hospitals, and conducting healthcare professional training are all important.

Data limitations in this study need to be addressed in the future to allow for more rigorous analysis and findings. Many ADR reports collected were excluded due to incomplete information. Nonetheless, our findings could help researchers develop hypotheses for future drug-event interactions research.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

ZG collected and analyzed the data. NA provided technical assistance and oversaw the research. The final manuscript was read and approved by both authors.

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