Drug-related events in an emergency department of a tertiary health care facility in South- South Nigeria.

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Abstract

Background: Drug-related adverse events refer to any injury from a medical intervention relating to a drug. This study identified suspected drug-related events presenting to the accident and emergency (A&E) unit of a teaching hospital.
Methods: The adult admission registers of the A&E unit of the University of Benin Teaching Hospital, Benin-City, Nigeria were retrospectively reviewed over a four-year period (January 2015 –December 2018). Patients with diagnosis that may indicate a drug-related event were included in the study.
Results: A total of 24510 new patients were seen over the 4-year period, with 648(2.6%) presenting with a drug-related event (DRE). There were 353 (54.5%) males, and the mean age (SD) was 48.9(20.4) years. Main DRE identified were adverse drug reactions (n=465, 71.8%) and of these, Non-steroidal anti-inflammatory drugs (NSAIDs)-induced upper gastrointestinal bleeding (n=145, 31.2%), drug-induced hypoglycaemia (n=79, 21.5%), herbal medicines related events(n=27, 4.2%), were the commonest. Other DREs were substance abuse/misuse (n=105, 16.2 %), causing substance (notably cannabis) - induced mental and behavioural disorders (n=60, 9.3%), and lastly poisoning (n=78, 12%) which were mostly intentional poisoning (notably organophosphates) (n=43, 6.6%).
Conclusions: Drug-related events constitute a significant burden on the emergency system. Upper gastrointestinal bleeding following use of NSAIDs, drug induced hypoglycaemia, organophosphate poisoning were found to be notable life threatening causes of emergency admissions. These and other drug-related events pose significant public health burden and hence require multifaceted public health interventional strategies to mitigate the burden.

Keywords: drug-related medical emergencies; adverse drug reactions; poisoning; anti-inflammatory agents non-steroidal; Nigeria

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Introduction

Drug-related adverse events refer to any injury from a medical intervention relating to a drug. It encompasses adverse drug reactions, medication errors, overdose as well as poisoning[1,2]. Drug-related events constitute a significant health burden seen in emergency departments of health care facilities. About 1.2-40% of emergency ward admissions attributed to drug-related events[3-5], with age and increasing number of medications increasing the risk of developing an adverse drug reactions (ADR)[5]. The cost attributed to managing ADRs has also been demonstrated to be considerable especially in a resource-constrained setting[6,7].

The emergency room is a very important point of provision of immediate care for many ill patients[8] and the recognition of adverse drug-related events in the emergency department may determine the outcome and severity of most diseases and also improve the survival rates of such patients[5]. Studies have however shown that drug-related problems are usually not documented in the case records, also only 0.2% of recognized ADRs were appropriately coded in the hospital information systems and none reported to the regulatory agency[9,10].

Most of the studies on ADR in Nigeria have focused on patients admitted to the wards[6,11,12] , and this suggests that there may be an under-quantification of the burden of drug related events (DRE) in our setting as some patients who present to the emergency unit may get discharged in less than 24 hours. The burden of drug-related adverse events presenting to the A&E has not been properly estimated. Our objective therefore was to determine if diagnosis of suspected drug-related adverse events were being documented in the emergency admission registers and also to characterize the profile of identified drug-related events presenting to the medical emergency (MER) unit of a teaching hospital in South –South zone of Nigeria.

Methods

Design and setting: A four-year (January 2015 –December 2018) retrospective evaluation of the medical emergency (MER) unit nurses' admission register at the University of Benin Teaching Hospital, an 850-bed teaching hospital in South-South Nigeria was conducted.

An emergency ward admission was considered drug-related in the register and included in the study if the diagnosis included words such as adverse drug

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reaction, drug-induced, adverse drug event, iatrogenic, drug- intoxication, overdose, toxicity or poisoning, attempted suicide due to a drug. Others were adverse events related to herbal drug use, as well as cases of substance misuse and drug abuse including alcohol intoxication. All the admitting diagnoses of patients who had presented to the MER unit during the period were as stated in the nurses' register culled from physician case records. The preference for the register was due to the comprehensiveness of this record with additional information obtained.

The presentation was registered as an adverse drug event (defined as harm caused by drug and includes adverse drug reactions and overdose)[2]. An adverse drug reaction was defined as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or treatment for the modification of physiological function[13].

Diagnosis suggestive of therapeutic ineffectiveness, non-adherence to therapy, and drug interactions were however excluded from the study due to the definitions of adverse drug events chosen for the study[2]. Children's emergency registers were also excluded from this study.

For all included cases, a data collection form was used to abstract the data which included age, gender, admitting diagnosis, duration of stay, suspected drug, and outcome. The outcome was classified as death, discharged, discharged self against medical advice, or admitted.

Ethical approval was obtained from the University of Benin Teaching Hospital Ethics and research committee, protocol number: ADM/E 22/A/VOL. VII/14573.

Data analysis: All diagnoses retrieved from the admission register were documented and categorized into adverse drug reactions, poisoning and substance abuse, and drug misuse. The suspected medicines (where applicable) were classified using the Anatomic Therapeutic Chemical (ATC) Classification level II (2018 version)[14]. The affected systems of the drug-related adverse events were coded using the Medical Dictionary for Drug Regulatory Activity (MedDRA) coding dictionary (version 20 for English) and described using the system organ classification method when applicable[15].

Statistical analysis: Suspected drug-related events were analyzed descriptively using frequencies, mean, and Standard Deviation *(SD)*. Proportions of the types of adverse drug-related events were compared using chi-square. P-value of <0.05 was considered significant. The analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 21 for Windows (IBM Corps Armonk N.Y USA).

Results

Over the four year period, a total of 24510 new patients were seen at the A&E. A total of 648 (2.6%) presented with an adverse DRE, with a male-female ratio of 1.3:1, and the mean age (SD) was 48.9(20.4) years. The trend in yearly admission of adverse DRE ranged from 2.1% in 2015 to 3.1% in 2018. (Figure 1)

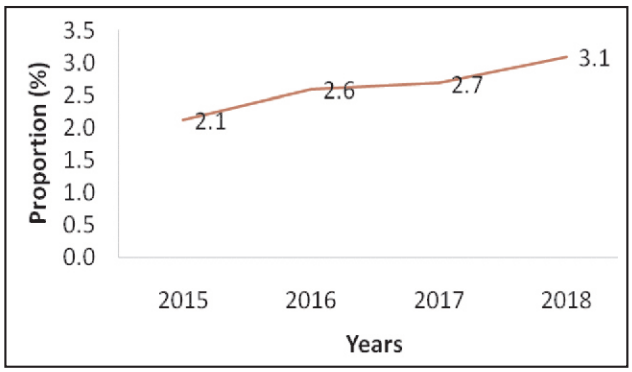

Figure 1: Yearly Trend of Drug-related events seen at the UBTH over the four year period. (2015-2018)

Types of Drug-related adverse events

The majority of the DRE found in the admission register suggested an adverse drug reaction 465 (71.8%), substance abuse/drug misuse 105(16.2), poisoning 78(12%) (Table 1). Older patients (aged 60 and above) had the highest proportion of diagnosis of ADR 204(45.3%), while younger patients (aged 40 and below) had more diagnosis of substance abuse/drug misuse 83 (79.8%).This was statistically significant, p=<0.001. Furthermore, substance abuse/drug misuse was more in males 88(83.8%) than females (Table 1).

Table 1: Characteristics of the types of adverse drug-related events diagnosed in the admission registers of UBTH over a 4 year period; 2015-2018

Characteristics	ADR n=465(%)	Poisoning n =78(%)	Substance abuse/drug misuse n=105(%)	P value
Sex				
Male	242(52.0)	37(47.4)	88(83.8)	<0.001
Female	223(48.0)	41(52.6)	17(16.2)	
Age group				
Young (16-40)	125(27.8)	42(54.5)	83(79.8)	<0.001
41-59	121(26.9)	13(16.9)	17(16.3)	
60 and above	204(45.3)	22(28.6)	4(3.8)	

ADR: Adverse Drug Reaction, UBTH; University of Benin Teaching Hospital.

Adverse drug reactions related diagnoses

Of the 648 patients with DREs, there were 465(71.8%) recorded cases of ADR related diagnosis in the registers.

Table 2: Some Notable adverse drug reactions in the admission register of UBTH from 2014-2018 using the MedDRA® System Organ Classification

System Organ Class	Diagnosed Event	Suspected agents
Gastrointestinal disorders 198(30.6)	Upper gastrointestinal bleeding (152)	NSAIDS(142),NSAIDS and corticosteroids(4), Herbal medications(3) Anticoagulants(3)
	Gastritis (37)	NSAIDS 34(90%), NSAIDS and herbal mixture1 (2.5%) corticosteroids2 (5%),
	Emesis(2)	HAARTS, antimalarial
	Nausea(1)	Tramadol
	Difficult swallowing(1)	Artemether/Lumenfantrine
	Gastroenteritis (2)	Herbal medicines,(1), laxatives, antimalarial Oral glucose lowering agents-64(83.5%), Insulin 2(7.6%), OGLA-Insulin Combination 1, Antimalaria1s 2(1.3%) antihypertensive 1(1.3%), herbal medicines1 (1.3%), unspecified 1(5.1%)
Metabolism and nutritional disorders 79(12.2)	Drug induced hypoglycemia(69)	
	Steroid related disorders-hyperglycemia, ischiorectal abscess, iatrogenic Cushing syndrome(10)	Corticosteroids (50%) Prednisolone (50%)
Nervous system disorders 66(10.2)	Hypoglycemic coma(32)	Oral glucose lowering agents 28(80.6%), Insulin-3(9.7%) OGLA-Insulin Combination1 (3.2%), unspecified 2(6.5%)
	Dystonic reaction(17)	Metoclopramide 4(23.5%), Psycholeptic 3(17.6%), Antimalarial 1(5.9%), Phenothiazine 1(5.9%), unspecified(4), Antimalarial 2(11.7%), benzodiazepine 1
	Seizures (5)	Chlorpromazine, fluroquinolone, unspecified.
	Dizziness (4)	Psycholeptics(2), herbal mixtures(1), unspecified(1)
Renal and urinary disorders 32(4.9)	Toxic nephropathy (13)	Herbal mixtures(14)
	Analgesic nephropathy(12)	NSAIDS, Analgesic
	Acute Kidney Injury due to contrast induced nephropathy(1)	Contrast media
	Hematuria(2)	Herbal medicine
Skin and subcutaneous disorders 24(3.7)	Exfoliative dermatitis(6)	Antimalarial(2),Unspecified (5),
	Erythema multiforme (Stephen Johnson syndrome, toxic epidermal necrolysis)-6	Sulphonamide3(50%), cotrimoxazole 1(16.7%) Unspecified 2(33.3%)
	Urticaria rash(1)	Herbal medicines
	Fixed drug eruption(2)	Carbamazepine, Sulphadoxine-pyrimethamine
	Generalized rash(2)	Purified protein derivative, Unspecified
Vascular disorders 6(1.0)	Drug induced hypotension(4)	Antihypertensive 4(100%)
	Syncopal attack(1)	Isosorbide dinitrate
Psychiatric disorders 8(1.2)	Restlessness (3)	Multiple medicines 3(100%)-
	Acute confusional state (1)	Erythropoietin
	Steroid induced dementia(1)	Corticosteroids
Hepatobiliary disorders 5(0.8)	Drug induced liver diseases -5	Nevirapine, Antituberculous medicines, NSAIDs and Herbs, unspecified(1)
Reproductive system and breast disorders-	Menorrhagia(1)	Herbal medicines

UBTH-University of Benin Teaching Hospital,,ADR-Adverse Drug Reaction, NSAIDS-Non Steroidal Anti Inflammatory Drugs, OGLA-Oral Glucose Lowering Agents. MedDRA: Medical Dictionary for Drug Regulatory Activity

Of which, upper gastrointestinal bleeding from Non-Steroidal Anti Inflammatory Drug (NSAID) induced gastropathy [145(31.2%)] was the commonest. Others were drug induced hypoglycaemia [79 (21.5%)], NSAID induced gastritis [35 (7.5%)]. Other notable ADRs are as shown in (Table 2).

The medication class most commonly implicated include anti-inflammatory and antirheumatic products [193(41.5%)] and the products documented were piroxicam, diclofenac, ibuprofen, and in most cases multiple NSAIDs were used. Four patients used NSAIDs with prednisolone. Also, 24(12.4%) patients had chronic use of NSAIDS documented. Other commonly implicated medication classes include drugs used in diabetes [94(20.2%)],herbal medications [27(5.8%)] (Table 3).

Table 3: Anatomic Therapeutic Chemical Classification (Therapeutic group) of the suspected medicines causing the adverse drug-related events at the UBTH

ATC Therapeutic class (Therapeutic group)	ATC code	Frequency n=465(%)
AntiinflammatoryAnti-inflammatory and antirheumatic products	M01	193(41.5)
Drugs used in diabetes	A10	95(20.4)
Antiprotozoal medicines	P01	19(4.1)
Corticosteroids for systemic use	H02	15(3.2)
Psycholeptics	N05	12(2.6)
Analgesics	N02	7(1.5)
Antivirals for systemic use	J05	6(1.3)
Antibacterials for systemic use	J01	6(1.3)
Antiemetics and antinauseants	A04	6(1.3)
Antihypertensive	C02	5(1.0)
Herbs**		27(5.8)
Others		20(4.4)

Other medicine classes include: antianaemics, antiparkinsons, bacterial vaccine, cardiac therapy, acid related disorders, drugs for constipation, drugs for obstructive airway diseases, skin lightening agents, yellow fever vaccine, and agents acting on the rennin-angiotensin system, antimycobacterials, and contrast media. ATC: Anatomic Therapeutic Chemical ** Herbal medicines do not have an ATC code. UBTH: University of Benin Teaching Hospital

Substance abuse and drug misuse

There were 105(16.2%) patients diagnosed with substance abuse and drug misuse; cannabis [38(36.2%)], was the most implicated agent. Others were multiple substances [38(36.2%)], alcohol intoxication [21(20.0%)], analgesics (opioid abuse of tramadol and pentazocine) [7(6.7%)] and bromocriptine [1(1.0%)]. Psychiatric disorders [81(77.1%)] manifesting as substance induced mental and behavioural disorders [60/81(74.1%)] was the commonest organ system presentation seen, followed by nervous system disorders [16(15.2%)] presenting as decreased sensorium in over [8(50%)].Others were seizure disorder, acute dystonic reactions, hypoglycemia and codeine ingestion and a case of syncopal attack following bromocriptine drug abuse [1(1.6%)].

Poisoning

There were 78(12.0%) cases of poisoning, of which intentional poisoning was observed in 43(55.1%) cases with the following agents- pharmaceuticals including prescription medicines (paracetamol, psycholeptics, antibiotics, multiple medicines) [12(15.4%)], organophophates [12 (15.4%)], hydrocarbon [6(7.7%)]. Other suspected agents include chemicals, cosmetic agent, cement, rodenticide, paraquat, alkaline battery, hydrogen peroxide [8(10.2%)] and unidentifiable agents [5 (6.4%) cases].

Of the 35(44.9%) cases of accidental poisoning, 11(31.4) were due to carbon monoxide poisoning from the use of generating sets in enclosed spaces and 15(60.0%) cases of overdoses of oral glucose lowering agents. Psychoanaleptics (chlorpromazine, amitriptyline as well as olanzapine) were suspected in 3(13.0%). Others include enteritis following laxative overdose, gastroenteritis following carbamazepine overdose, hypotension from antihypertensive overdose [1(4.3%)] and a case of anticoagulant overdose. In 2 instances no medicine was specified. There was also a case of accidental organophosphate poisoning.

Outcome

A greater proportion of the patients were discharged [295(45.5%)], 26(4.0%) patients discharged self against medical advice and while 61(20.7%) were admitted into the wards, and 51(8.2%) died. Of the 51 deaths, 23(45.1%) had a diagnosis of upper gastrointestinal bleeding due to NSAID gastropathy, 9 (17.6%) had drug induced hypoglycaemia, 2 (3.9%) were completed suicides from organophosphate poisoning, and 1 (1.8%) from psychoanaleptics. Other causes of death include Steven Johnson syndrome following antimalarial use [2 (3.9%)], toxic nephropathy [2(3.9%)], chronic steroid use with is chiorectal abscess, carbon monoxide poisoning [2(3.9%)], drug induced liver injury from anti-tuberculosis medicines use [1(1.8%)] and ADR to promethazine (3.9%). Majority [43(84.3%)] died within the first 24-48 hours of admission. The admission register did not specify the outcome in 216(33.3%) patients.

Discussion

This study on DRE using the adult emergency registers revealed that the prevalence of DRE was considerable,

similar to a study in Nigeria which showed an ADR incidence rate of 10.7 per 100 patients admitted into the medical wards[11]. Recognition of DREs requires a high index of suspicion, a proper drug history which is hindered by the dynamics of the emergency room[8]. There is need for physicians to have a high index of suspicion and records staff to appropriately code and document DREs.

Furthermore, while insufficient documentation and poor record keeping have hampered appropriate quantification of morbidity in this setting[16], the study confirms that the nurses' admission register facilitates documentation of DRE data when compared to the routine admission records due to the documentary processes applied by nurses in A&E[17].

This study showed that younger persons were more likely to present with substance abuse and poisoning to the A&E as seen in another study[18]. This may be due to peer pressure to use psychoactive substances and development of depressive illness[19]. Older persons presented more with ADRs and accidental poisoning from drug overdoses, their multiple morbidities including impaired cognition, poor vision, consequent high pill burden and increased risk of drug interactions[20] may be responsible for this finding.

Upper gastrointestinal bleeding following the use of NSAIDs was the commonest ADR suspected at the A&E in this study. This was also observed in a study conducted two decades ago in the same center[21]. This constitutes a notable burden in the A&E with consequent socioeconomic implications[22]. This further underscores the modalities of obtaining drugs in the setting as well as inappropriate prescriptions[23,24] .

Hypoglycaemia resulting from accidental drug overdose was observed in this study. This may be attributed to inappropriate use, poor understanding of the administration, dosing issues and their relation to food intake amongst others. A case in point is the inappropriate use of oral hypoglycaemics for the treatment of lower urinary tract symptoms[25].

In Nigeria, herbal medications are generally regarded as safe[26] and this may explain the number of herbal remedy - related adverse event presenting to the A&E. The use of herbal products should always be sought in patients. Although the limited provision for toxicological screening in the facility makes it difficult to confirm the use of herbs, the diagnosis of herbal induced injuries must be considered.

Organophosphates were the commonest agents utilized for intentional poisoning in this study as seen previously[27]. A stringent regulation for the use of organophosphate and other agents found in this study is required. Increased sensitization will also be needed to prevent harm from accidental poisoning resulting from carbon monoxide fumes related to the use of generating sets in closed spaces.

From the deaths recorded, most occurred in the first 24hours. The mortalities observed may be attributed to resource challenges, insufficient infrastructure for emergency care amongst others.

Limitations

Though the nurses' admission register provided elaborate information on DRE seen on admission, the follow up details including causality assessments and outcomes were not documented.

Conclusion

Drug-related events constitute a significant burden on the emergency system. Upper gastrointestinal bleeding following use of NSAIDs, drug induced hypoglyceamia, organophosphate poisoning were found to be notable life threatening causes of emergency admissions. These and other drug-related events pose significant public health burden and hence require multifaceted public health interventional strategies to mitigate the burden.

Furthermore, it is therefore imperative to plan health education with a focus on drug use and public health strategies to address the possible contributors that increase mortality of DREs and reduce the burden of these diseases.

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