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Adverse Drug Reactions and Hypersensitivity: The Sulfonamide Story

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ABSTRACT:
The knowledge and station of healthcare professionals toward robotic ADR reporting were low. There was also under reporting of ADR by healthcare professionals. The knowledge and attitude of healthcare professionals toward spontaneous ADR reporting were low. There was also underreporting of ADR by healthcare professionals. Conducting awareness and educational training can fill the observed gap in knowledge and attitude. Simplification of the ADR reporting process, improving access to ADR reporting form, and implementation of electronic reporting combined with other methods for ADR reporting can improve the efficiency of the ADR reporting practice. An overview of sulfonamide development from its beginnings to today: Early Discovery (1930s): In 1932, Domagk discovered the antibacterial properties of Prontosil, the first sulfonamide drug, while working for the Bayer pharmaceutical company. Prontosil, a derivative of azo dyes, was found to be effective against streptococcal infections in mice Clinical Application (1930s1940s): Following the discovery of Prontosil, researchers worldwide began synthesizing and testing various sulfonamide derivatives. Discovery of sulfanilamide in 1937 and other derivatives like sulphapyridine and sulfadiazine shortly thereafter. Sulfonamides were quickly adopted for clinical use and became the first effective treatment for bacterial infections before the discovery of penicillin. They are used in the treatment of conditions such as inflammatory bowel disease, rheumatoid arthritis, and certain types of cancer. However, the overuse and misuse of sulfonamides have led to the emergence of antibiotic-resistant bacteria, posing challenges to their continued effectiveness in clinical practice.

KEYWORDS: Adverse medicine response, ADRs, Sulfonamides, Inflammatory, Clinical practice.

1. INTRODUCTION

The knowledge and practices related to the discovery, assessment, understanding, and prevention of adverse effects or any other drug-related problems are essential components of Pharmacovigilance. ADR stands for Adverse Drug Reaction defined as any unwanted, harmful, and unintended effect of a drug that occurs at doses normally used in humans for prophylaxis, diagnosis, or treatment of disease. An ADR may result from the drug itself or one of its metabolites. ADRs are primarily identified through premarketing studies and post-marketing surveillance. According to the World Health Organization (WHO), an ADR is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

Any undesirable change that occurs with drugs used at standard therapeutic doses and is suspected to be drug-related may require discontinuation, dosage adjustment, or caution in future use of the same medication. As per the WHO guidelines (2000), the main role of Pharmacovigilance is the detection, assessment, understanding, and prevention of adverse drug reactions. (1)

Adverse Drug Event (ADE): An Adverse Drug Event refers to any undesirable medical occurrence that may arise during treatment with a drug, regardless of whether there is a confirmed causal relationship with the medication. In other words, ADEs may or may not be directly related to the drug itself. They can occur due to the drug or its metabolites being present in the body and producing harmful effects, or they may be coincidental and not caused by the suspected medication.

Adverse Effect: An adverse effect is any unwanted or unintended outcome following the administration of a medication. These effects may appear immediately, after prolonged use, or even after discontinuation of the drug. Adverse effects can be classified into two types:

- **Predictable (Type A):** These are related to the known pharmacological properties of the drug and are usually dose-dependent.
- **Unpredictable (Type B):** These are not related to the drug's known pharmacological effects and often depend on individual patient factors, such as immune response or genetic makeup.

Prevention of Adverse Effects:
While adverse effects cannot be completely eliminated, they can be significantly minimized through the following measures:

- Careful patient history and assessment before prescribing
- Appropriate drug selection and dosing
- Monitoring for drug interactions
- Educating patients about possible side effects and when to seek medical help
- Regular follow-up and adjustment of therapy as needed

Prevention of Adverse effect of medicine –
Adverse effect can be minimized but not altogether excluded by observing the following.

- Avoid all unhappy use of medicines in the environment of case's clinical condition.
- Use applicable cure, route and frequence of medicine administration grounded on case specific variables.
- Prescriber have to prescribed and tell everything to patients

1.1 Classification of Adverse Drug Reaction:
Based on onset of event:

1. Acute: less than 60min.
2. Sub-acute: 1-24 hour
3. Latent: more than 2days

Based on type of reaction:
Type A (Augmented): This type of ADR is acute in nature, and it is dose dependent i.e., If the dose of any drug is given in higher amount, then it shows Adverse Drug Reaction. This type of ADR normally occurs when the drug concentration in plasma cross. The MSC (maximum safe concentration) and due to which the more action of drug occurs. In body which results in toxic effect. It can be predicted by pharmacology of drug. **Example:** Hypoglycemia by antidiabetics.

Type B (Bizarre): This type of ADR is unforeseen and unpredictable response of any drug on patient. This ADR occurs due to specific drug by its immune system so, it is called as immunological mechanism related ADR. This type of reactions is less common. and not depend on dose of drug. If reaction is more serious immediate withdrawal of drug should be required. **Example:** Methyldopa induced hemolytic anemia.
Type B further Classified as: 1. Predictable 2. Unpredictable
Predictable: Those type of ADR which can be predictable by the pharmacology of drug and are associated with high morbidity and low mortality.

- **Unpredictable:** Those type of ADR which cannot be predictable by the pharmacology of drug and are associated with low morbidity and High mortality. .[4]
- **Type C (Chronic):** This type of ADR is Irreversible, unexpected, unpredictable in nature. It is dose related and time related. Arises because of continuous or long-term. use of drug or due to accumulation of drug. This type of ADR is managed by reducing the dose of drug or stops the drug administration. Example: Steroid induced Osteoporosis, dementia by anticholinergic drugs.
- **Type D (Delayed):** This type of ADR is Delayed Occurrence ADR. These are Generally uncommon reactions in nature. Usually, dose related which may occur or become appear after some time use of medicine or even after the cessation of treatment. Example: Antipsychotic induced tardive dyskinesia's.[4]
- **Type E (End of Treatment):** it is withdrawal reactions. Occurs during a withdrawal especially when Drug is stopped abruptly. Occurs typically with the depressant drugs.

Example: Seizures on alcohol or benzodiazepines withdrawal.

- **Type F (Familial):** it is occurring when unexpected failure of therapy. Results from the ineffective treatment or when the expected response to treatment is not achieved it is dose related. It also may observe due to cause of drug interactions. Example: Failure of oral contraceptive in presence of enzyme inducer.
- **Type G (Genotoxicity): T**he Irreversible genetic damage caused by type G ADR. Drug may lead to cause genetic variation. Example: Teratogenic agent like Thalidomide causes genetic damage to developing foetus.

Adverse drug reaction (ADR) monitoring involves following steps:

1) Identifying adverse drug reaction (ADR)
2) Assessing causality between drug and suspected reaction
3) Documentation of ADR in patient's medical records
4) Reporting serious ADRs to pharmacovigilance center's ADR regulating authorities.

Advantage of Adverse Drug Reactions monitoring:

1. It provides data regarding the safety and quality of pharmaceutical items.
2. It starts the preparations for risk management.
3. It helps measure adherence to ADRs and prevents predictable adverse effects.
4. It raises awareness of adverse drug reactions (ADRs) and provides patients, chemists, and nurses in the health care team with information about these effects.

ADR monitoring aims to detect the risk variables that may lead to adverse responses and to reveal the frequency and quality of ADRs.[14]

2. Drug Profile

2.1 Sulfonamide:

Sulfonamide - chrysotile (Prontosil Red) was one of the colorings included by Domagk to treat experimental streptococcal infection in mice and set up to be largely effective. (5) By, 1937 it came clear that prontosil was broken down in the body to release sulfonamide which was the active antibacterial agent. (6) Sulfonamide is first antimicrobial medicine that are pharmacologically used for treatment of bacterial infection and eventually for fungal infection. Amino Benzoic Acid) containing sulfonamide group (So2NH2) in their chemical structure. (6,7) Sulfonamides have bacteriostatic action against gram-positive and gram-negative bacteria. It is competitive inhibitor of PABA in the folic acid metabolism cycle in the organism. Sulfanilamide is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase. (8)

Table No. 1 Sulfonamide classification:

A.	Orally Absorbable		
	1.	Short Acting (4-8 hrs)	• Sulfadiazine • Sulfacytine • Sulfamethizole • Sulfisoxazole
	2.	Intermediate Acting (8-12hrs)	• Sulfamethoxazole • Sulfamoxole
	3.	Long Acting (~7 days)	• Sulfadoxine • Sulfamethopyrazine
B.	Orally Non- Absorbable		• Sulfasalazine • Olsalazine • Balsalazine
C.	Topical Agents		• Silver sulfadiazine • Mafenide • Sulfacetamide sodium

Numerous sulfonamides were developed and extensively used in posterior times, but due to the rapid-fire development of antibacterial exertion and the vacuity of important safer antibiotics, these are presently used only in combination with trimethoprim (as cotrimoxazole) or pyrimethamine (for malaria). (9)

Sulfonamide Mechanism of Action -

Numerous bacteria synthesize their own folic acid(FA) of which is absorbed from the media and of which p-aminobenzoic acid(PABA) is a part.(30) In 1940, the thesis that sulfonamides, being structural analogues of PABA, inhibit bacterial folate synthase, so that FA is n't formed, and a number of essential metabolic responses suffer.(3) Sulfonamide competitively inhibit the union of PABA with pethidine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydromorin acid. also, being chemically analogous to PABA, the sulfonamide may itself get incorporated to form an altered folate which is metabolically pernicious. (10) Host cell also bear FA, but they use preformed FA supplied in diet and are innocent by sulfonamide are PABA, in small quantities, antagonizes the antibacterial action of sulfonamides.

(a) PABA, in small amounts, antagonizes the antibacterial action of sulfonamides.

(b) Only those microbes which synthesize their own FA and cannot take it from the medium are susceptible to sulfonamides.

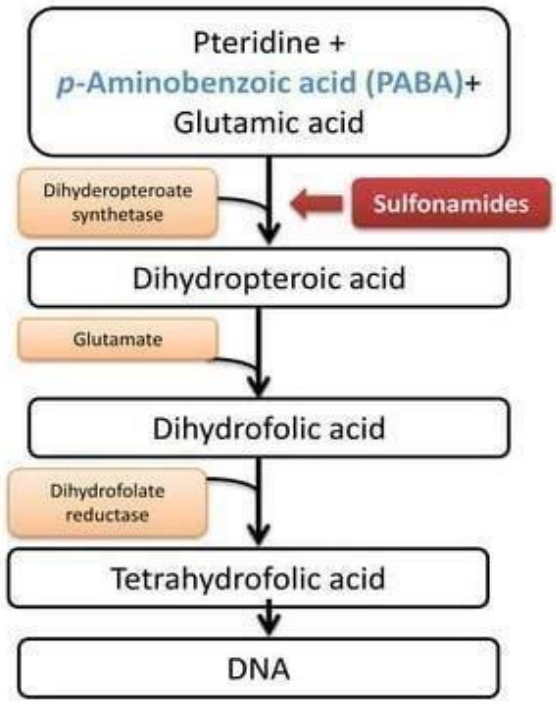

Fig. 1 Mechanism of action

Sulfonamide medicine in gestation -
The main suggestion to use these agents during gestation in the history was to treat urinary tract infections caused by gram positive cocci or gram-negative rods. (11)
Two hours after medicine administration, a balance between motherly and fetal blood attention is reached. Sulfonamide can contend with bilirubin for binding spots of plasmatic albumin when administered right before the birth, causing a high attention of free bilirubin in the fetal blood, which is called kernicterus.

Toxicological effect - The toxicological effect of SN medicines includes duration and lozenge of the medicine, actuality of the heterocyclic ring in N1 replaced SN, the case's age, nutritive status, order condition, and solubility in blood and other natural fluids. (12) A exploration report explain SNs are kindly poisonous for blood cells, with sulphadiazine outgrowth being more poisonous in comparison to other drugs in the SN class [5,6].

Sulfonamide tragedy: when Sulfanilamide (Prontosil), already in use since 1932 for treatment of streptococcal infections, was launched as a syrup, containing Diethylene glycol as a solvent. Although it was tested regarding pharmacokinetic aspect, taste, and odor, but its safety was not evaluated. [5,6]

Contraindications of sulfonamide:
Hypersensitivity: Individuals who have a known hypersensitivity or allergic reaction to sulfonamides or any of its components should avoid using sulfonamide antibiotics [13]
Severe renal impairment: Sulfonamides are primarily eliminated from the body through the kidneys. Patients with severe renal impairment may have difficulty excreting sulfonamides properly, leading to increased drug levels in the body and potential toxicity. [9,5]
Hepatic impairment: Patients with severe hepatic impairment may also experience difficulties metabolizing and excreting sulfonamide antibiotics, which can lead to increased drug levels and potential toxicity.[10]. G6PD deficiency: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited condition that can cause haemolytic anemia in response to certain medications, including sulfonamides. Sulfonamides can trigger hemolysis (destruction of red blood cells) in individuals with G6PD deficiency. [15,12]

Objectives of the Study:
1. Identify the risk factors of Adverse Drug Reaction.
2. Highlight the ADR monitoring.
3. Promote drug safety and safely use of sulfonamides and their derivatives.
4. Increase awareness among pregnant individuals about antibiotic risks.
5. Provide guidance for selecting safe antibacterial non antibacterial drugs.
6. Prevent adverse effects outcomes by avoiding contraindicated antibiotics.

7. Optimize maternal and neonatal health through judicious antibiotic use.
8. Contribute to ongoing research for informed clinical and public health decisions.

3. Methodology

The development of sulfonamides marked a vital moment in drug, offering a targeted approach to combatting contagious conditions and reducing mortality rates worldwide. Despite their early success, the wide use of sulfonamides led to the emergence of resistance, egging the continual disquisition of new derivations and combination curatives to enhance efficacy and overcome resistance mechanisms.

Continued exploration sweats have concentrated on optimizing sulfonamide structures to ameliorate pharmacokinetic parcels, broaden diapason of exertion, and minimize adverse goods. also, strategies similar as combination remedy and rational medicine design have been employed to combat resistance and enhance remedial issues. Recent advancements in molecular modeling and high- outturn webbing ways have eased the identification of new sulfonamide derivations with enhanced energy and selectivity against resistant bacterial strains. Despite ongoing challenges, sulfonamides remain necessary in the treatment of colorful bacterial infections and continue to inspire invention in antibiotic development.

Sulfonamides and trimethoprim:

Sulfonamides and trimethoprim are linked to kernicterus, a severe form of brain damage in babe, due to their impact on bilirubin metabolism. Bilirubin, an unheroic color formed during the breakdown of red blood cells, is generally reused by the liver and excluded from the body. still, in babe, particularly unseasonable babies, the liver may not be completely developed, leading to reduced bilirubin metabolism and elevated situations of unconjugated bilirubin in the blood.

This can overwhelm the immature liver's capacity to reuse bilirubin, performing in hyperbilirubinemia (high blood situations of bilirubin) and potentially driving kernicterus if left undressed. Kernicterus occurs when inordinate situations of unconjugated bilirubin crosses the blood- brain hedge, leading to neurotoxicity and endless brain damage. This damage can manifest as severe neurological impairments, including experimental detainments, movement diseases, and hail loss.

Adverse drug reactions: causing adverse medicine responses among medical convalescents.
Types of study: Descriptive, Prospective study.
Place of study -Cases admitted into internal wards of UBTH, Benin City, Edo State, South
Nigeria.
Duration of study 9-month period from December 2013 to August 2014.
Age of Cases Grown-ups> 17 times. 507 Cases. 269(53.1) manly, 238(46.9) ladies.
Addition Criteria- All Cases admitted to Cases wards after commencing the study handed they granted their informed concurrence to share in study.
Rejection Criteria - Those Cases formerly on admission before commencing study, those Cases admitted from other wards, those Cases who did n't grant their informed concurrence.

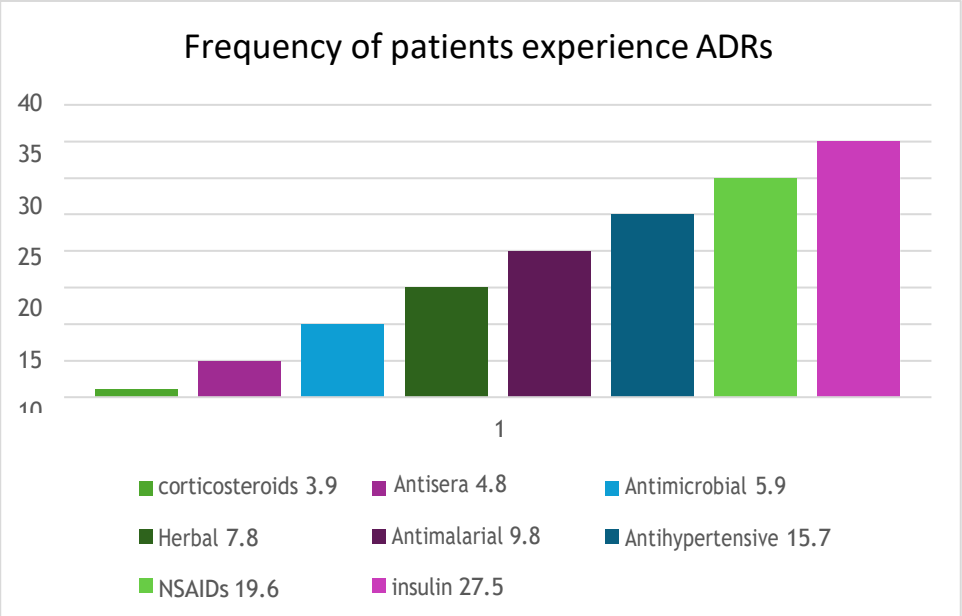

Fig. 2 Frequency distribution for patients experience ADRs

Results
The ADR causality describes the mortality rate and case fatality rate fir ADRs were significantly high among this medical inpatient.

Sulfonamides Antibiotics and Non-Antibiotics Drugs:
Sulfonamides are generally classified into 2 groups: antibiotics and no antibiotics. Recent studies showed that patients allergic to sulfonamide antibiotics do not have a specific risk for an allergy to sulfonamide non-antibiotic. Key determinant feature of allergic response involve substitution at N4 aryl amine group position they are antibiotics other sulfonamide drug tends not to increase all allergic response so, safe to taken as non-antibiotics.

Antibacterial sulfonamide	Uses
Sulfamethoxazole with trimethoprim	To treat UTI, RTI, diarrhea
Sulfadiazine with pyrimethamine	Treat parasitic infection toxoplasmosis.
Sulfisoxazole with erythromycin	Treat UTI infection, ear infections
Sulfacetamide with prednisolone	Treat mainly bacterial eye infections.
Sulfadoxine with pyrimethamine	In Treatment of malaria caused by p. falciparum.

Non-antibacterial sulfonamide	Uses
Sulfasalazine	Treat inflammatory bowel diseases
Mafenide	As Topical agent prevent or treat bacterial infections in burn wounds.
Acetazolamide	An Carbonic anhydrase inhibitor used to treat glaucoma.
Celecoxib	An NSAID used to relive pain an inflammation condition
Dapsone	Used in treatment of leprosy

Table No. 2 Examples of antibacterial Sulfonamides and Non-Antibacterial Sulfonamides

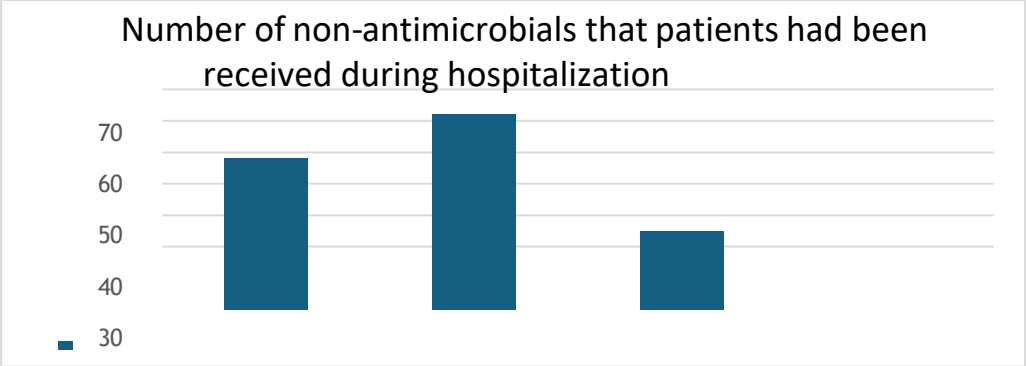

Fig. 3 Number of non-antimicrobials that patients had been received during hospitalization

Type of study: Retrospective cohort study using General practice research database in UK. Examine the risk of allergy reaction within 30 days after receipt of non-antibiotics Sulfonamide.

Duration of study: Database from 1987 through March 1999.

Inclusion: They had received a systemic Sulfonamide antibiotic and had subsequently at least 60 days later received a prescription for Sulfonamide non antibiotic. Overall, 4.8% of patients (969 of 20,226) had an apparent allergic reaction within 30 days after receiving Sulfonamide antibiotics. Overall, 2.0% of patients (1) had an apparent allergic reaction after subsequently receiving the Sulfonamide non antibiotics. A total 9.7% of allergic reactions after the Sulfonamide non antibiotics were serious require to hospitalization.
Causality assessment rating of adverse drug reactions observed among medical inpatients in a Nigerian Teaching Hospital using the World Health Organization and the Naranjo Algorithms.

Table No. 3 Causality assessment (WHO v/s Naranjo algorithm)

WHO Rating	(%)	**Naranjo algorithm**	(%)
Certain	10 (19.6)	Definite	9 (17.6)
Probable	17 (33.3)	Probable	19 (37.3)
Possible	24 (47.1)	Possible	24 (45.1)
Unlikely	0 (0)	Doubtful	0 (0)
Unconditional	0 (0)		
Unlikely	0 (0)		

Result: The indeed patients, with a history of Hypersensitivity to Sulfonamide antibiotics are at even greater risk for subsequent reactions to penicillin, then to non-antibiotics Sulfonamide. Prescribers should understand that patients with history of allergic reactions to the drug may at increased risk for all drugs induced adverse events that appear to be allergic in nature. ADRs mild (41.2%) and moderate (47.1%).
Incidence and assessment of ADR:

Objective: To determine the prevalence of an ADR in a hospital. Over the period of 12 months, a total of ADRs 374 was reported in 600 patients. The ADR observed higher in female patients. The predominance of gastrointestinal reactions 18.7% was observed.

Inclusion: All in patients of both genders who experienced an ADRs were enrolled for the study.

Exclusion: Patients admitted to hospital due to an ADR.

The antimicrobial drugs are shown high risk of ADR in which vancomycin, Trimethoprim/ Sulfamethoxazole, Amoxicillin are having high chances of causing ADR.

Result: The PVAs PI was suffering from the problem of under reporting to overcome this wide spread awareness programmed targeting health care personnel at each and every level is warranted.

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