Section: Pharmacology

Research

A SYSTEMATIC REVIEW OF THE PROSPECTIVE STUDIES ON ADVERSE DRUG REACTIONS REPORTED WITH ANTI-MICROBIALS AMONG INDIAN PATIENTS

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Abstract

Background: Adverse Drug Reactions (ADRs) are an added economic burden on the healthcare system and thus a well-recognized public health problem affecting the quality of life of patients. Evidence-based systematic reviews on ADRs from India are sparse. A comprehensive systematic review and meta-analysis was undertaken from the literature with prospective monitoring for identifying ADRs related to anti-microbial drugs in Indian patients according to the PRISMA guidelines. **Materials and Methods:** MEDLINE and EMBASE databases from January 2001 until July 2018 were searched for identification of literature and information pertaining to the characteristics of pharmacovigilance studies such as occurrence, class of drug, age, gender, structure of hospital was collated. ADR occurrence was calculated using random-effects model meta-analysis with their 95% confidence intervals and heterogeneity evaluation. **Result:** For systematic review and meta-analysis, 115 and 61 prospective studies respectively were included. There is a substantial difference observed among the types of reported ADRs, seriousness and types of medicines due to variations in study methodology. The pooled ADR incidence was 4.92% [CI 95% 2.77 – 7.63] among the included 61 studies published over 18-year period, however, the results should be considered cautiously owing to high heterogeneity (I2 = 99.97% [95% CI: 99.96 – 99.98]). The most frequently associated ADRs against antimicrobial drugs were attributed to skin and sub-cutaneous tissue disorders (30.33%), followed by gastrointestinal disorders (22.83%). Most of the ADRs are attributed to the beta-lactam antibiotics (including penicillin and cephalosporins) followed by aminoglycosides. **Conclusion:** The incidence for anti-microbials observed was lower in comparison to the global studies. The study highlights variations among the studies and the need to standardize the reporting criteria among the reported studies across country.

INTRODUCTION

Medicines are critical for the treatment of the patients regardless of the risk of the adverse drug reactions. World Health Organization defines 'Adverse Drug Reactions' (ADRs) as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".[1] One of the most important steps would be to maintain the balance of the risk versus benefits and prevent the occurrence of an ADR.[2] ADRs negatively impact the quality of life, are among the leading causes of mortality and also lead to an increase in healthcare costs.[3,4,5] ADR incidence varies from 0.15% to 30% globally and account for 2-6% hospital admissions. This also among the top ten causes of mortality.[6,7] To safe-guard the public health and to reduce harm it is essential that we detect the ADRs early.

The post-marketing surveillance is an essential tool to establish the safety of the medicines in market and studies published from the country are an important evidence to evaluate the same apart from the data from the national pharmacovigilance centre, however underreporting is the major hinderance for true incidence of ADRs.[8]

An evidence-based study of adverse drug reactions in India are sparsely reported. In the present work,

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systematic review and meta-analysis will be presented on the data in pharmacovigilance from India from the anti-microbial class of drugs. The evidence from such studies not only help in collating the evidence for known ADRs in the population bit is also able to identify the unknown threats related to the unknown ADRs or rare ADRs to help safeguard the population against the unwanted burden of ADRs as well as provide information to healthcare professionals related to the ADRs.

MATERIALS AND METHODS

The current study was performed as systematic review and meta-analysis for estimation of incidence of adverse drug reactions in Indian patients according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.[9]

Search Strategy for Identification of Studies

The meta-analysis performed here followed the guidelines of PRISMA. Electronic search on databases like PubMed, IndMed/MedInd, Google Scholar, and the Cochrane Database of Systematic Reviews databases, in between 2001 and 2018 used the terms 'pharmacovigilance', 'adverse drug reactions', 'adverse drug event', 'adverse drug effect', 'severe ADRs', 'prescription event monitoring', 'drug side-effect', 'incidence of ADRs', 'prevalence of ADRs' The Boolean search code used were "adverse drug reactions AND pharmacovigilance", "drug side effect AND reporting", and "incidence OR prevalence of adverse drug reactions". We also performed bibliographic search using title, abstract and if required full articles as per inclusion and exclusion criteria.

Inclusion Criteria

Studies were included if they were prospective studies related to ADRs with anti-microbial drugs among Indian population and published between 2001 and June 2018. The drugs included in the anti-microbials include beta-lactam antibiotics, quinolones and floroquinolones, macrolides, aminoglycosides, tetracyclines, glycopeptide antibiotics, sulfonamides, anti-mycobacterials, anti-lepra drugs, nitroimidazole antibiotics, antifungals, anti-malarials, anti-virals. Those studies that reported ADRs in hospitalized patients from all age groups and clinical settings (outpatient and/or inpatient) were included. The individual studies clearly mentioned the definition of ADR which they strictly followed.

Exclusion Criteria

Studies published earlier than 2001 and after 2018 and not related to Indian population were excluded. Retrospective studies, case reports, non-research letters, editorials, review articles, meta-analysis on ADRs and animal studies were also excluded from the study. Research articles with primary objective not ADR identification or related to medication errors and drug interactions that reported doubtful, unlikely, and/or unclassified type of reactions were excluded. Those studies with only abstracts without available full text were excluded, as it restricted meaningful evaluation.

Data Extraction

A general guideline based on the principles of pharmacological research to analyse the articles systematically was developed as part of the protocol.[10] Primary screening involved screening of articles on the basis of the title, followed by the abstract of the article and irrelevant articles were excluded for the secondary screening. The titles and abstracts that fulfilled inclusion criteria were assessed critically per eligibility criteria of the present study. The full text assessed articles were further excluded based on the insufficient information regarding the ADR.

The data was extracted for following characteristics: publication year, geographical location, duration of study, setting, data collection methodology, demography, total number of patients, number of patients developed ADR, age and gender, causality, reported causative drugs- class of drug-ATC code, events reported as per the preferred terms and System Organ Classification as per MedDRA. Extracted data was entered into excel sheet for descriptive data analysis.

Classification of reported ADRs: From the included articles, reported ADRs were classified according to MedDRA (Medicinal Dictionary for Regulatory Activities) terminology as per the preferred terms and primary System Organ Class (SOC).[11] MedDRA helps to standardize the safety data for analysis per international standards.

Classification of therapeutic groups: Anatomical Therapeutic Chemical (ATC) classification system was used to categorize the reported medications on ATC level 1 (anatomical main group).[12]

Outcome Measure

Primary outcome variable was occurrence of ADRs and pooled incidence done by meta-analysis from the prospective studies. ADR prevalence was calculated as the number of total ADRs reported, divided by total number of study population.

Statistical Method

The cumulative ADR incidence was investigated by meta-analysis. Data analysis was carried out using R version 4.0.5 2021(©The R Foundation for Statistical Computing). A random-effects model was used to calculate the pooled incidence as well as their 95% confidence intervals (CIs) and are represented using forest plot. The method used for meta-analysis was inverse variance with double arcsine transformation. Presence of heterogeneity

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was assessed by the Cochran's Q-statistic and I2 statistics (with 95% confidence intervals) assessed the proportion of variability. Egger's test assessed publication bias and is represented by funnel plot.

The variables used for the meta-analysis were 'Author Year', 'No. of ADRs' and 'Total number of patients'. Datasheet was imported in the R software (version 4.0.5 2021). A structured R code was used to calculate individual effect size and pooled effect size, measure heterogeneity, identify outlier studies, test publication bias and generate forest plots and funnel plots. To evaluate the robustness of the meta-analysis outliers were removed and sensitivity analysis was performed.

RESULTS

Literature Search and Data Extraction

A systematic search based on the search criteria to identify Indian studies reporting adverse drug reaction published from January 2001 to June 2018 was carried out. The drugs included in the anti-microbials include beta-lactam antibiotics, quinolones and floroquinolones, macrolides, aminoglycosides, tetracyclines, glycopeptides, sulfonamides, anti-mycobacterials, anti-lepra drugs, nitroimidazole antibiotics, anti-fungals, anti-malarials and anti-virals. A total of 115 studies were included as per the selection criteria for the systematic review of prospective studies related to anti-microbial class of drugs. Out of the 115 studies, 61 are included for meta-analysis, as represented in PRISMA Flow chart in [Figure 1].

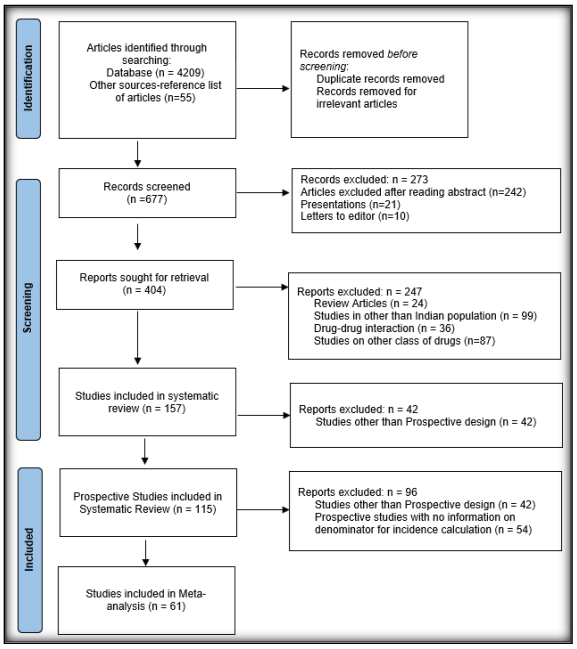

Figure 1: PRISMA Chart Antimicrobials

Year-wise distribution: Most of the studies for prospective studies (16.5%) were conducted in the year 2018. In the years, 2003-2005 demonstrated lowest number of studies representing only 0.9% [Table 1].

Geographical Distribution

Based on the geographical distribution, the selected studies have been classified based on different zones such as Central, East, North, South and West Zones of India. Among the 115 prospective studies included the majority of the studies i.e. 54 (46.9%) were conducted in Southern part of India, followed by Western and Northern part of India, which represents 28 (24.35%) and 15 (13.04%), followed by Centre part i.e. 7 (6.1%) [Figure 2].

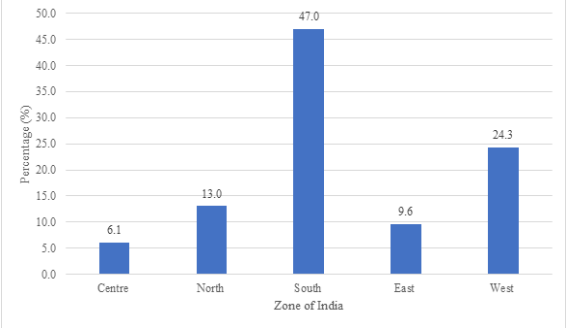

Figure 2: Percentage of Geographical location of Prospective studies for Anti-microbials with ADRs

Hospital Structure

Based on the hospital structure type, out of 115 prospective studies included, the majority (66.1%) of the studies were conducted in tertiary care hospitals whereas 27.8% of the studies did not report the type of hospital followed by studies conducted in secondary care hospitals (6.09%).

Methods for Identifying ADRs

The ADR data collection method shows that among the included 115 prospective studies, the majority of the studies (59.13%) did not report the method of ADR detection whereas 30.4% reported identification by clinical records and 10.4% reported interview of the healthcare professional as the detection technique.

Most of the ADRs were identified using direct interview (39.2%) with patients or through referring the clinical records after getting prior consent from patients or family members (27.6%). Healthcare professionals were part of the largest group of reporters (9.5%). About 23.7% of the studies did not report the method for the identification of ADR.

Causality Assessment

Among the included 115 prospective studies, the majority of the studies i.e. 87 (75.65%) used WHO Probability scale followed by 11 (9.57%) studies not reporting causality assessment, 10 (8.7%) studies reporting assessment by both WHO Probability & Naranjo causality assessment scale followed by 7 (6.1%) studies reporting assessment done by Naranjo's scale only [Figure 3].

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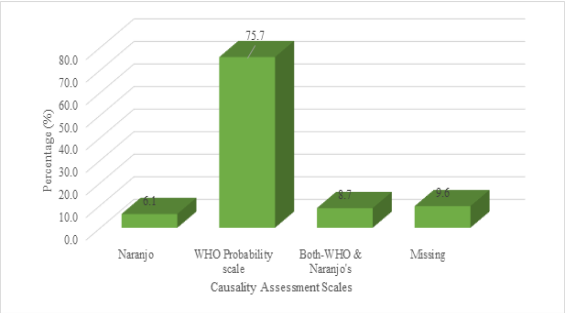

Figure 3: Percentage of Causality assessment

Sample size and Gender distribution: About 81,952 patients of all age group were included in the study. The ADR was found to be high among patients between the age group of 21-40 (56.05%) towards antimicrobial drugs. Male preponderance towards ADRs was reported in 57.7% of studies.

From the included prospective studies, minimum and maximum sample size in which the ADRs were reported was 18 and 4357, respectively. The minimum number of male and female patients represents 9 each and the maximum number represents each 2517 and 1840, respectively [Table 2].

Incidence of ADR against antimicrobial drugs

Suspected therapeutic class of drugs reported: Table 3 describes ADRs by therapeutic groups (ATC level 1) among the included prospective studies in ADR incidence of antimicrobial drugs demonstrated that the beta-lactam antibiotics class of drugs involved in 21.59% of the incidence of ADR, followed by sulfones, aminogylcosides and, non-nucleoside reverse transcriptase inhibitors (NNRTIs), which represents 10.38% 10.09%, and 9.68%, respectively. The drug classes other antivirals and tetracycline antibiotics account for the low number of ADR events, which represents, 0.16% and 1.58%, respectively [Table 3].

Adverse drug reactions and causative drugs reported: The reported ADRs are segregated based on the MedDRA's System Organ Classification (SOC), in order of highest to lowest frequency among the included studies against the drugs segregated based on ATC code. [Table 4] shows the top three reported ADRs from each SOC under each class of drugs. The most frequently associated ADRs against antimicrobial drugs were attributed to skin and sub-cutaneous tissue disorders (30.33%), followed by gastrointestinal disorders (22.83%).

Table 1: Year-wise Distribution of Prospective studies for Anti-microbials with ADRs

Year	Frequency (n)	Percentage (%)
2001	2	1.74
2003	1	0.87
2004	1	0.87
2005	1	0.87
2006	3	2.61
2007	5	4.35
2008	2	1.74
2009	3	2.61
2010	5	4.35
2011	11	9.57
2012	8	6.96
2013	12	10.43
2014	7	6.09
2015	9	7.83
2016	16	13.91
2017	10	8.70
2018	19	16.52
Total	115	100.00

Table 2: Prospective Study: Sample size and gender of Prospective studies for Anti-microbials with ADRs

	Mean	Maximum	Minimum	Standard Deviation
Sample size	256.9	4357	18	596.1
Male	136.3	2517	9	43.7
Female	124.9	1840	9	272.2

Table 3: Incidence of ADRs against Drugs for antimicrobials

Class of the Drug	ATC Code	ADR Incidence (percentage)
Beta-lactam Antibiotics	J01CR02	21.59
Penicillin derivatives	J01CA	14.19
Cephalosporins	J01DC	7.40
Sulfones	D10AX05	10.38
Aminoglycoside antibiotics	J01G	10.09
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	J05AG	9.68
Antitubercular agents	J04A	7.66
Quinolones & Fluoroquinolones	J01MA01	7.56
Antimalarials	P01B	6.52
Azole antifungals	J02AC01	6.17
Nucleoside reverse transcriptase inhibitors (NRTIs)	J05AF	5.21
Anti-mycobacterials	J04	4.74

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Sulfonamides	J01E	4.71
Glycopeptide antibiotics	J01XA	3.77
Macrolide	J01FA03	2.26
Nitroimidazole antibiotics	J05AF	1.92
Tetracycline antibiotics	J01AA07	1.58
Other Antivirals	J05	0.16

Table 4: ADR terms reported with each drug from each sub-class of anti-microbial drugs

Name of the Drug	ATC Code	ADR Terminology	ADR Incidence (%)
Fluoroquinolones and Quinolones			
Ciprofloxacin	J01RA10	Skin and subcutaneous tissue disorders	
		Acneiform eruption	9.27
		Fixed drug eruption	7.79
		Rashes	6.78
		Gastrointestinal Disorders	
		Vomiting	2.22
		Immune system disorders	
		Angioedema	1.33
		Psychiatric disorders	
		Hallucination	1.24
		Acute psychosis	0.94
		Nervous System Disorders	
		Seizures	1.00
		Giddiness	0.83
		Surgical Medical Procedures	
		Chest compression	0.83
Ofloxacin	J01MA01	Gastrointestinal Disorders	
		GI discomfort	8.89
		Dry mouth	1.00
		Skin & Sub-cutaneous Tissue Disorders	
		Maculopapular rash	8.69
		Fixed drug reaction	6.67
		Urticaria	3.34
		Nervous System Disorders	
		Severe Headache	3.33
		Seizure	2.14
		Vascular Disorders	
		Hypertension	1.18
		Psychiatric Disorders	
		Insomnia	1.00
		Immune System Disorders	
		Angioedema	1.00
Moxifloxacin	J01MA16	Rash	37.50
		Anaemia	8.00
Sparfloxacin	J01MA09	Gastrointestinal Disorders	
		Diarrhoea	18.52
		Skin & Sub-cutaneous Tissue Disorders	
		Pustular rash	16.67
		Fixed drug eruption	12.74
		Erythema multiforme	5.55
Antimalarials			
Chloroquine	P01BA01	Skin and subcutaneous tissue disorders	
		Pustular rash	23.62
		Erythema multiforme	11.82
		Toxic epidermal necrolysis (TEN)	10.00
		Gastrointestinal Disorders	
		Gastritis	7.35
		Diarrhoea	5.42
		Vomiting	4.0
		General Disorders and Administration Site Conditions	
		Fever	3.94
		Reproductive System and Breast Disorders	
		Menstrual irregularity	0.89
Sulfones			
Dapsone	J04BA02	Skin rashes	10.23
		Low Body Mass Index	8.52
Anti-mycobacterials			
Rifampicin	J04AM05	Flu like syndrome	12.5
		GIT disturbances	6.25
		Hypersensitivity	6.25
Pyrazinamide	J04AK01	Skin and Sub-cutaneous tissue disorders	
		Itchy rashes	5.61
		Itchy lesions	2.61

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		Gastrointestinal Disorders	
		Diarrhoea	5.35
		Abdominal pain	2.13
		Reduced appetite	1.13
Beta-lactam antibiotics			
Penicillin	J01CA	Skin and Sub-cutaneous Tissue Disorders	
		Rash	27.83
		Urticaria	18.52
		Fever	8.26
Cephalosporins	J01DC	Skin and Sub-cutaneous Tissue Disorders	
		Rash	9.26
		Fixed skin eruptions	7.41
		Urticaria	5.56
		Gastrointestinal Disorders	
		GI discomfort	5.00
		Diarrhoea	4.55
		Abdominal pain	4.55
		Immune System Disorders	
		Angioedema	4.00
		General disorders and administration site conditions	
		Fever	3.00
		Psychiatric Disorders	
		Hallucinations	2.00
Penicillin			
Piperacillin	J01CR05	Skin and Sub-cutaneous Tissue Disorders	
		Skin rashes	13.33
		Fixed drug eruptions	10.0
		Blood and Lymphatic Tissue Disorders	
		Anaemia	6.33
		Gastrointestinal Disorders	
		Diarrhoea	10.91
		Vomiting	4.55
		Abdominal pain	4.55
Amoxicillin	J01CA04	Skin and Sub-cutaneous Tissue Disorders	
		Skin rashes	39.42
		Erythema multiforme	8.33
		Morbilliform rash	7.50
		Blood and Lymphatic Tissue Disorders	
		Thrombocytopenia	6.67
		Psychiatric Disorders	
		Insomnia	9.34
		Metabolism Disorders	
		Weight gain	9.34
		Nervous System Disorders	
		Headache	5.21
		Seizure	3.33
		Dizziness	1.53
		Gastrointestinal Disorders	
		GI discomfort	14.86
		Vomiting	6.59
		Dryness of mouth	4.17
		Hepatobiliary disorders	
		Moderate rise in ALT	2.00
		Musculoskeletal and connective tissue disorders	
		Acute dystonia	1.83
		General disorders and administration site conditions	
		Fever	4.59
		Induration at the forearm	3.33
		Itching	1.24
		Shivering	0.39
Ampicillin	J01CR01	Gastrointestinal disorders	
		Diarrhoea	5.50
		GI discomfort	3.09
		Respiratory, thoracic and mediastinal disorders	
		Bronchopneumonia	4.79
		Emphysema	0.59
		Pneumonia	0.49
		Skin and subcutaneous tissue disorders	
		Urticaria	4.54
		Erythema	3.78
		Rashes	3.33
		Nervous system disorders	
		Giddiness	2.00

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Cephalosporins			
Ceftriaxone	J01DD04	Skin and subcutaneous tissue disorders	
		Rashes	6.39
		Erythema multiforme	5.21
		Skin reactions	4.17
		Gastrointestinal disorders	
		Abdominal pain	5.95
		GI discomfort	4.01
		Nausea	3.58
		Blood and lymphatic system disorders	
		Anaemia	5.56
		Ear and labyrinth disorders	
		Vertigo	5.56
		Nervous system disorders	
		Headache	5.21
		Psychiatric Disorders	
		Insomnia	4.17
Cefixime	J01DD08	Skin and subcutaneous tissue disorders	
		Rashes	9.10
		Gastrointestinal disorders	
		Diarrhoea	10.91
		Abdominal pain	4.55
		Vomiting	3.22
		Immune system disorders	
		Swelling of lips	8.69
		Swelling	2.22
		Nervous system disorders	
		Headache	1.91
		Metabolic Disorders	
		Height gain	1.04
Aminoglycoside antibiotics			
Amikacin	S01AA21	Gastrointestinal Disorders	
		Abdominal pain	13.63
		GI disorder	11.82
		Vomiting	10.00
		Renal Disorders	
		Fluid and electrolytes imbalance	5.45
		Skin and Subcutaneous Tissue Disorders	
		Rash	4.90
Gentamicin	S01AA11	Skin and Sub-cutaneous Tissue Disorders	
		Urticaria	36.44
		Erythema multiforme	20.00
		Erythematous skin lesion	13.33
		Renal Disorders	
		Increased blood urea	6.00
		Respiratory Tract Disorders	
		Bronchopneumonia	5.00
		Chest tightness	4.44
		Pneumonia	4.01
		Ear and Labyrinth Disorders	
		Ototoxicity	3.00
		Immune System Disorders	
		Facial oedema	2.22
		Lip oedema	2.22
		Hypotension	2.00
		General disorders and administration site conditions	
		Rigor	2.22
Antitubercular agents			
Ethambutol	J04AM03	Gastrointestinal Disorders	
		GI discomfort	9.43
		Skin and Sub-cutaneous Tissue Disorders	
		Skin rashes	5.67
		Eczematous drug eruption	4.35
		Renal Disorders	
		Hyperuricemia	2.80
Isoniazid	J04AC01	Immune System Disorders	
		Drug hypersensitivity	9.34
		Angioedema	9.34
		Skin and Sub-cutaneous Tissue Disorders	
		Rashes	9.00
		SJS	7.50
		Fixed drug eruption	7.00

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		Gastrointestinal Disorders	
		Abdominal pain	8.33
		Reduced appetite	2.00
		Diarrhoea	0.60
Macrolides			
Erythromycin	J01FA01	Skin and Sub-cutaneous Tissue Disorders	
		Vesicular eruption	4.35
		Nervous System Disorders	
		Seizures	3.00
		Gastrointestinal Disorders	
		Vomiting	0.17
Azithromycin	S01AA26	Skin and Sub-cutaneous Tissue Disorders	
		Fixed drug eruptions	7.69
		Hyperpigmentation	4.55
		Itching	3.84
		Gastrointestinal Disorders	
		Gastritis	2.41
		Abdominal pain	2.00
		Diarrhoea	1.20
Sulfonamide			
Sulfadiazine	D06BA01	Gastrointestinal Disorders	
		Appendages disorder	2.11
		Vomiting	1.00
		Nausea	0.40
		Infections and Infestations	
		Urinary tract infection	1.05
		Skin and Sub-cutaneous Tissue Disorders	
		TEN	1.14
		Urticaria	1.00
		Morbilliform rash	1.00
Sulfonamides	J01E	Skin and Sub-cutaneous Tissue Disorders	
		SJS	20.00
		TEN	15.00
		Skin rashes	13.15
		Nervous System Disorders	
		Headache	15.00
		Renal Disorders	
		Metabolic acidosis	15.00
		Crystalluria	12.00
		Gastrointestinal Disorders	
		GI discomfort	7.89
		Blood and Lymphatic System Disorders	
		Megaloblastic anaemia	7.00
Co-trimoxazole (Trimethoprim / Sulfamethoxazole)	J01MA09	Skin and Sub-cutaneous Tissue Disorders	
		Fixed Drug Eruption	9.93
		Urticaria	9.90
		Acneiform eruption	4.34
		Nervous System Disorders	
		Headache	0.09
		Gastrointestinal Disorders	
		Nausea	0.39
		Vomiting	0.30
		Constipation	0.28
		Blood and Lymphatic System Disorders	
		Leucopenia	0.17
		General disorders and administration site conditions	
		Tenderness	0.09
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz	J05AG03	Nervous System Disorders	
		Giddiness/ Dizziness	6.73
		Skin and Subcutaneous Tissue Disorders	
		Fixed drug reactions	3.33
		Urticaria	3.00
		Morbilliform rash	2.67
		Metabolic Disorders	
		Weight loss	2.20
		Cardiac Disorders	
		Cardiomyopathy	1.33
Nevirapine	J05AG01	Skin and Sub-cutaneous Tissue Disorders	
		Skin rashes	11.10
		SJS	8.75
		TEN	3.21
		Nervous System Disorders	

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		Headache	15.5
		Encephalitis	3.45
		Hepatic Disorders	
		Hepatotoxicity	11.63
		Gastrointestinal disorders	
		GI discomfort	7.70
		Nausea	1.80
		Vomiting	1.96
		Metabolic disorders	
		Weight Loss	3.10
		Respiratory, thoracic and mediastinal Disorders	
		Respiratory infection	2.90
		General Disorders	
		Fever	2.00
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Didanosine/zidovudine	J05AF02	Nervous System Disorders	
		Peripheral Neuropathy	21.00
		Headache	1.09
		Dizziness	0.25
		General Disorders	
		Fatigue	0.66
		Malaise	1.96
		Myalgia	0.66
		Gastrointestinal Disorders	
		Abdominal pain	12.63
		Vomiting	9.27
		Nausea	4.65
		Psychiatric Disorders	
		Insomnia	0.10
		Skin and Sub-cutaneous Tissue Disorders	
		Rashes	4.56
		Hyperpigmentation	2.92
		Blood and Lymphatic Tissue Disorders	
		Anaemia	7.79
		Neutropenia	0.02
		Thrombocytopenia	8.76
		Hepato-biliary Disorders	
		Dyslipidaemia	7.3
		Hyperbilirubinemia	2.48
		Pancreatitis	1.92
Stavudine	J05AF04	Angioedema	6.98
		Hepatic steatosis	6.98
		Herpes zoster	11.00
		GI discomfort	8.50
		Enlarged lymph nodes	7.75
Tenofovir	J05AF03	Gastrointestinal disorders	
		Nausea	30.30
		Vomiting	10.45
		diarrhoea	9.50
		Nervous system disorders	
		Headache	16.85
		General disorders and administration site conditions	
		Fatigue	12.2%
		Musculoskeletal and connective tissue disorders	
		Myopathy	6.74%
		Metabolism and nutrition disorders	
		Hyperphosphatemia	5.60%
		Hypokalemia	2.85%
Nitroimidazole antibiotics			
Metronidazole	J01XD01	Gastrointestinal Disorders	
		Vomiting	4.53%
		Diarrhoea	1.24%
		GI discomfort	2.22%
		Skin and Sub-cutaneous Tissue Disorders	
		Rashes	3.46%
		Itching	1.18%
		Fixed drug reaction	2.22%
Azole antifungals			
Flucanozole	J02AC01	Skin and Sub-cutaneous Tissue Disorders	
		Urticaria	9.26%
		Toxic Epidermal Necrolysis	9.26%
		Maculopapular rash	8.70%
Other Anti-virals			

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Ganciclovir	J05AB06	Blood and Lymphatic Tissue Disorders	
		Thrombocytopenia	0.08%
		Neutropenia	0.08%
Tetracycline antibiotics			
Doxycycline	J01AA02	Gastrointestinal Disorders	
		Diarrhoea	3.7%
		Abdominal discomfort	2.73%
		Nausea	1.19%
		Skin and sub-cutaneous tissue disorders	
		Rashes	3.48%
		Itching	3.28%
		Photosensitivity reaction	3.09%
		Nervous System Disorders	
		Headache	5.27%
		Ear and Labyrinth Disorders	
		Vertigo	1.26%
Glycopeptide antibiotics			
Vancomycin	J01XA01	Immune System Disorders	
		Drug hypersensitivity	7.08%
		Skin & Sub-cutaneous Tissue Disorders	
		Erythema multiforme	7.87%
		Pustular rash	4.37%
		Exfoliative dermatitis	3.94%
		Gastrointestinal Disorders	
		Diarrhoea	1.76%
		Vomiting	1.97%
		General Disorders	
		Fatigue	2.65%

3.9 ADRs Incidence reported using Forest Plot

The pooled incidence of adverse drug reaction reported from 61 studies due to antimicrobial drugs was 4.92% [CI 95% 2.77 – 7.63]. The distribution of incidence is presented in the forest plot [Figure 4].

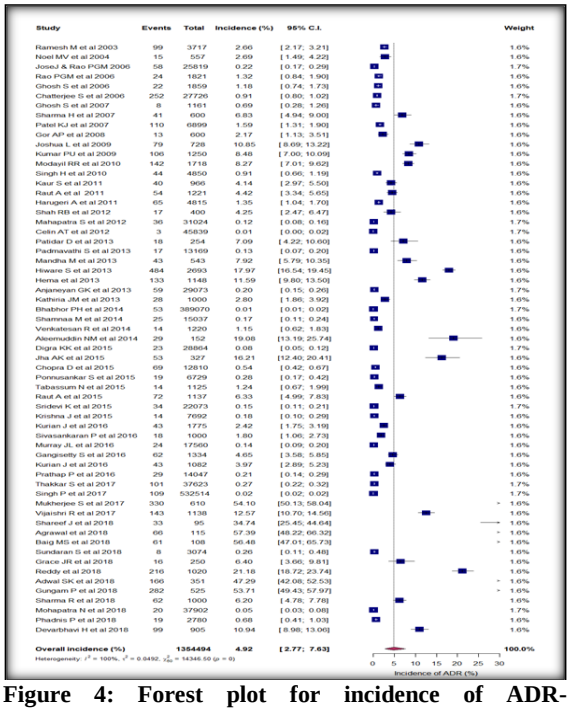

Figure 4: Forest plot for incidence of ADR-antimicrobial drugs

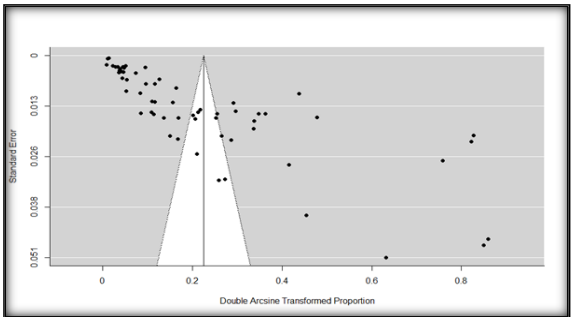

Figure 5: Funnel plot to assess publication bias-antimicrobial drugs

Publication Bias reported using Funnel Plot

The level of heterogeneity was high between studies (I2 = 99.97% [95% CI: 99.96 – 99.98]). Egger's test is used to assess the publication bias for incidence estimates (Egger's test: z = 9.5233, p < 0.0001) and is represented in funnel plot [Figure 5].

Outlier studies

The statistically identified outlier studies include Mukherjee S et al 2017, Agrawal et al 2018, Baig MS et al 2018, Adwal SK et al 2018, Gungam P et al 2018. After removing the outlier studies heterogeneity was re-calculated and was found to be high (I^2 = 99.93% [95% CI: 99.901 – 99.95]. The test for heterogeneity showed a value of Q (df =60) = 10108.115, p < 0.0001.

DISCUSSION

A total of 115 prospective studies have been identified for systematic review and 61 among those studies were included for meta-analysis to analyse the pooled ADR incidence of anti-microbial drugs in Indian population over a period of 18 years. This is

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one of the few such studies from India and is a step in the direction to collate the incidence of ADRs, assess various characteristics assessed over the years since the inception of pharmacovigilance in India.

The incidence and prevalence among the anti-microbials have been reported higher among the studies carried after 2011 specifically in 2018 focusing on the anti-microbials compared to the initial studies as well as the studies from spontaneously reported data with less information on ADRs from one class of drugs.

India has Pharmacovigilance Programme of India since 2005 and, in a better structured programmatic approach since 2010, as National Coordinating Centre. Currently more than 500 ADR Monitoring Centres (AMCs) are part of PVPI with more than 90 percent of AMCs in tertiary care hospitals. This is also evident from the fact that most of the studies on pharmacovigilance are after 2011, hence pointing towards the need of awareness, trainings and dedicated resources required in the area of pharmacovigilance. The data from our study shows that most of the studies have been conducted in tertiary care hospitals and intra- study variability owing to the non-structured data collection and methodology.

Lower incidence has been observed in western region than southern and northern region of India. The inception of pharmacovigilance was in core institutes in South & North region could be the confounding factors. The hard to reach areas and difficult terrains in terms of availability of the healthcare infrastructure per say in the east zone might have been the reason for least studies being reported from that region. The west and centre region despite no such hardships have surprisingly reported smaller number of studies. There seems to be a dire need of intensive monitoring and rigorous training at the grass root level in these zones.

The ADRs were observed more in males (57.7%) than females as reported from our study as opposed to the data observed from literature. In accordance with the literature, the female gender was associated with higher risk of ADRs than male by 50 to 75% owing to lower lean body mass, more body fat, different gastric motility, a reduced hepatic clearance, and lower glomerular filtration rate.[13,14]

Our study reveals the ADRs were reported more among the age group of 21-40 (56.05%) for anti-microbials. This might be due to the fact that the anti-microbials are used more in the ICU settings and younger population is also prescribed antibiotics. However, as per the literature, two- fold higher incidence of ADRs have been observed in the elderly age group. The pharmacokinetics and pharmacodynamics among the elderly predisposes them to the ADRs due to polypharmacy, chronic diseases, severity of illness, and drug interactions.[13,14]

Our ADR incidence for anti-microbial drugs are lower than earlier reviews from India and globally. This observation, however, needs to be interpreted cautiously in the context of - presentation of high heterogeneity. The ADR incidence from our study is lower in comparison to the earlier systematic reviews reported globally.[15,16,17,18,19,20] Literature reports lower ADR incidence from Asian studies compared to the European and American studies reporting high ADR incidence.[17] Patel TK & Patel PB 2016 estimated the incidence of ADRs in Indian population and reported low incidence.[21]

It has been observed in many studies such as systematic review across the different age-groups that anti-microbial class of drugs elicit the most ADRs as much as 60.4%.[15,16,17,18,19,20,21] Anti-infectives were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital and children in hospital and in outpatient children.[20] Skin and sub-cutaneous tissue reactions (maculopapular rash, fixed drug eruptions, urticaria and Stevens-Johnson syndrome/toxic epidermal necrolysis) accounted for 49.0% of all reported ADRs from our study. A similar finding has been observed from global reviews.[15,16,17,18,19,20,21]

The heterogeneity between studies in our review was high (I2 = 99.97% [CI 95%: 99.96 – 99.98]). High heterogeneity was observed from the studies globally as well as India 21 After working through meta-analysis, to identify outlier studies contributing to heterogeneity and influencing the pooled estimate, a few outlier studies were identified, however, even after removal of these studies the heterogeneity remains high (I2>95%).[15,16,17,18,19,20] The studies with the highest incidence are the ones that most contributed to heterogeneity and were Mukherjee S et al, 2017 with 54.10 (CI95%: 50.13, 58.04), Agrawal et al, 2018 with 57.39 (CI95%: 48.22, 66.32), Baig MS et al, 2018 with 56.48 (CI95%: 47.01, 65.73), Adwal SK et al, 2018 with 47.29 (CI95%: 42.08, 52.53), Gungam P et al, 2018 with 53.71 (CI95%: 49.43, 57.97). These studies were focused ADR monitoring studies for anti-microbial drugs. Studies with the lowest incidences were Celin AT et al, 2012 with 0.01 (CI95%: 0.00; 0.02), Babhor PH et al, 2014 with 0.01 (0.01, 0.02), Digra KK et al, 2015 with 0.08 (CI95%: 0.05; 0.12), Singh P et al, 2017 with 0.02 (CI95%: 0.02, 0.02), and Mohapatra N et al, 2018 with 0.05 (CI95%: 0.03, 0.08). These studies were spontaneous ADR reporting studies hence the lower incidence for one particular class of drugs.

Among the prospective studies one of the main challenges when comparing ADR incidence rates is the variation in methodology with respect to the place of conduct of study, duration of study and characteristics of study population. Pooled estimate of the incidence rate of ADRs has been provided owing to the large amount of heterogeneity. Incidence rate of ADRs is affected by many characteristics of the pharmacovigilance studies such as identification of ADRs by definition; taking the ADR numerator with inclusion of ADRs at emergency units as well as clinical department visits

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and admission; studies with focus on ADRs on particular drugs from class of drug, variation in studies with focus on one particular age group and taking all age groups in one study, focus on adverse drug events without assigning causality in the earlier systematic reviews. This explains variation in the incidence rates reported and also highlights absolute importance of creating standardized methodologies based on the specific quality criteria about reporting of ADRs.

The results from our study might be underestimation of the true ADR prevalence from India. Under reporting has been a huge challenge in India, to get better evidence on the ADRs from the country the primary requirement is to improve the reporting. The low incidence of ADRs despite a huge population with good reach of medicines owing to India's strength in generic drug manufacturing points towards the need of intensive monitoring, multidisciplinary teams with standardized methodologies to monitor ADRs. There are systematic review studies that provide evidence globally on the under-reporting.[22]

Strengths and Limitations of the Study

The strengths of this systematic review include a meticulous literature search; objective selection criteria with good level of evidence; steps to identify heterogeneity factors from the included studies over the last 18 years i.e. since 2001 (inception of pharmacovigilance in India) till 2018 June (i.e. the start of the study), unlike previous systematic reviews.

The study focuses on collation of evidence on ADR incidence from India which is lacking from Indian scenario so far. Retrospective, cross-sectional, case studies were excluded to improve the quality of analysis. For meta-analysis of prospective studies, only those studies with both numerator and denominator values for calculation of ADR incidence have been included.

There are several limitations of this systematic review and meta-analysis. The studies reporting data from clinical records usually underestimate the incidence as the data accuracy and completeness. Similarly, spontaneous reporting studies underestimate the incidence, however they have been included as India is a country where majority of the studies are taking data from the spontaneous post-marketing surveillance.

Among the studies published since 2001 analysing ADRs the studies conducted over a period of approximately 18 years across the country, have a great deal of inconsistency in reporting the characteristics of ADRs such as defining the ADRs, occurrence of ADRs, reported ADRs as per standardized terminologies, seriousness, severity, causality and preventability assessments. There is a need to conduct large observational studies related to ADRs across Indian population, age -stratified and setting specific thus also evaluating the differences in prescribing patterns and practices. The present review although has broad parameters but significant common elements between all studies included and hence the limitation of generalizability may arise.

Meta-analytic summary for the incidence in our study shows high heterogeneity which is in-line with other systematic reviews of ADRs globally thus warranting attention towards the lack of standard methodology in the pharmacovigilance studies globally.[13,14,15,16,17,18,19,20,21] When the heterogeneity is high, the summary effect measure (overall incidence in our case) carries less value. One possible source of heterogeneity is the fact that dataset for each drug class is a mix of studies. First type, where studies have shown the overall incidence of ADR in all populations out of which we have extracted the data on specific ADR for that class (drug specific ADR/all patients irrespective of what drugs they are taking). Second type, studies that have shown incidence of ADR for that drug class only (ADR due to specific class of drugs/number of patients actually taking that class of drugs). The first type results in a large denominator with few ADR and the second type results in a small denominator and large number of ADR. Ideally, to find out the incidence of ADR due to specific drugs there is a need to include studies of the second type.

CONCLUSION

The study showed that the incidence of ADRs reported with anti-microbial class of drugs is less as compared to the global studies. The literature is extensive, with highly diversified objectives and methodology. Data requires cautious interpretation since there is a variation in the estimates of frequency thus demand additional effort for in-depth and critical analysis.

The results also identify the need to address the issue of underreporting and increase the ADRs reporting, even if the events are minor and known so as to create a database for robust pharmacovigilance analysis. It is evident that since there is a huge variation in studies a standardized approach on methodology and study protocols for ADRs would help assess the magnitude of the ADRs in the country and there can pooled data for better interpretation. There is a need for systematic analyses of data on ADRs reported to national database as well as to monitor the ADRs ad-hoc basis for post marketing surveillance by Marketing Authorization Holders (MAHs) and regulatory agencies to study the incidence of the drugs in market.

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