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# Comparative Profile of Adverse Drug Reactions with Antimicrobials: Women Vs Men

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**Abstract**

The current retrospective cross sectional study was undertaken using suspected ADR data collection form used under Pharmacovigiliance Programme of India (PvPI). A total of 2586 ADR events were recorded in 3years out of which 392(15.15%) were because of antimicrobials. males constituted 253 patients (64.54%) and females constituted 139 patients (35.45%) with male: female ratio as 1.8:1. Adults were more commonly affected followed by geriatric and pediatric population in both the groups. I.V route followed by oral route of drug administration accounted maximum ADR in similar way in both the genders. Monotherapy was responsible for 81.81% for males and 82.01% for females. Among combinations 78.26% in males and 64% in females were irrational as per latest WHO13$^{th}$ essential drug list. Majority of ADR, 88.14% and 92.80% were of moderate severity among males and females respectively. Maximum ADR were latent, type-A, probable in nature as per Naranjo and WHO-UMC scale. Inj.ceftriaxone followed by tab. azithromycin, tab.ofloxacin-ornidazole were the commonest antimicrobials responsible for ADRs in both the genders. The most common system involved was dermatological followed by GI in both males and females. On statistical comparison, no significant differences were observed among both the genders in any of the parameters except causality assessment scale ($P<0.5$). The current study suggests the ADRs due to antimicrobials are a significant health problem. No major gender related differences were observed in ADR profile of our study cohort.

**Key Words**

Adverse Drug Reaction, Pharmacovigiliance, Gender Differences, Antimicrobials

## Introduction

Female gender, advancing age, paediatric age, multiple drug usage, smoking, alcohol, inappropriate drug usage and irrational drug combination have been documented as important risk factors for adverse drug reactions (ADRs). (1-4) Women experience more adverse reactions with therapeutic drugs than men and often they are more serious than men. (5) However, there are contrary reports also which suggest that no major gender-related differences exist for ADR patterns. (6, 7)

Due to high prevalence of infectious diseases in developing countries antibiotic are commonly prescribed group of drugs. Antimicrobials have also the potential for being misused both by patients and doctors which can result into increase prevalence of adverse drug events among users. Though, the data on gender related differences in ADR's profile exists in volumes for other group of drugs. (5-7) To best of our knowledge, there exist no study exclusively analyzing the gender related differences in ADR's trends and patterns related to antibiotics in Indian population. Hence to best of our knowledge, the current study is the first study of its kind conducted to evaluate gender related differences in ADR profile of antimicrobials.

## Material and Methods

A three year retrospective observational cross-sectional analysis was carried out to evaluate the profile of adverse drug events related to antimicrobials in ADRM Centre, working under PvPI in a tertiary care teaching hospital from north India using suspected drug reactions monitoring data collection form used under PvPI.

Information about patient, suspected ADR, suspected medication, reporter, date of reaction, date of recovery and presentation of problem were recorded. Under suspected medication, name of drug, brand of

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manufacturer, generic name of manufacturer (if known), expiry date, dose used, route, frequency and therapy dates as well as reason for prescribing suspected drug were also assessed. The information about de-challenge and re-challenge, concomitant medical treatment record, the relevant laboratory biochemical abnormality were recorded separately. Other relevant history including pre-existing medical conditions like allergy, pregnancy, smoking and alcohol used and any organ dysfunction was noted. The ADRs were defined and categorized as per the definition of Edwards & Arsonson, 2000. (8) The severity and seriousness of reaction, mode of onset, nature of ADRs, type of reaction, the outcome of reaction and onset time was recorded for every suspected ADR. Severity of reaction was classified as mild (bothersome but requires no change in therapy); moderate (requires change in therapy, additional treatment, hospitalization); severe (disabling or life-threatening). Serious reactions were defined as any event leading to death, life threatening, prolonged hospitalization, disability, required intervention to prevent permanent impairment/damage or congenital anomaly. Onset of event was categorized as acute (within 60 minutes); sub-acute (1 to 24 hours) and latent (> 2 days). Where as nature and Type of reaction was classified as Type A (Augmented ); Type-B ( Bizarre); Type-C ( continues Use); Type-D (Delayed ) and Type -E (End of Use). Outcome was described as Fatal, recovering, recovered, unknown, continuing or other) as per recommended SOP of PvPI.

The suspected ADRs were classified in term of causality using WHO-UMC scale and (8) Naranjo scale. (9)Detail subgroup analysis of ADRs detected and various socio-epidemiological, drug related parameters like combination antibiotics, route of drug administration, rational/irrational antibiotics were also analyzed in the current study. The details were collected by an independent observer with consultation of doctors which was finally validated and confirmed by the In-charge ADRM Centre, as an expert. The identity of reporter was kept confidential.

*Inclusion:* Any ADR from OPD or inpatient of any severity, duration and any type of reaction were included pertaining to antimicrobials. Exclusion: Whereas, any case of poisoning, medication error, over dosage, over/ non-compliance, natural products/alternate medicines and unidentified drugs, anti tubercular, antileprotic and antimalarial were excluded.

**Statistical Analysis**

Analysis was carried out with the help of computer software SPSS Version 15 for windows. The data was categorized as per male and female for evaluation of all the variables. The data was expressed in n (%).Chi-square test was applied to prove their statistical significance. P value < 0.05 was considered significant.

**Results**

A total of 2586 ADR events were recorded in 3years out of which 392(15.15%) were because of antimicrobials. males constituted 253 patients (64.54%) and females constituted 139 patients (35.45%) with male: female ratio as 1.8:1. Adults were more commonly affected followed by geriatric and pediatric population in both the groups. intravenous route followed by oral route of drug administration accounted maximum ADR in similar way in both the genders. Monotherapy was responsible for 81.81% of ADRs for males and 82.01% for females. Among combinations 78.26% in males and 64% in females were irrational as per latest WHO essential drug list. Majority of ADR, 88.14% and 92.80% were of moderate severity among males and females respectively. No fatal reaction was observed in any of the group. Maximum ADR were latent, type-A, probable in nature as per Naranjo and WHO UMC scale. Whereas, 6.71% male and 10.06% female required active medical intervention for the ADRs and 64.03% of male and 52.51% of female recovered from ADR. (*Table-1, 2*) On statistical comparison, no significant differences were observed among both the genders in any of the parameters except causality assessment scale (P<0.5).

Injection ceftriaxone followed by tablet azithromycin, oflox-ornidazole were the commonest antimicrobials responsible for ADRs in both the genders. The most common system involved was dermatological followed by gastrointestinal in both the genders. (*Table-3, 4*)

**Discussion**

On statistical comparison, no significant differences were observed among both the genders in any of the parameters while comparing ADR profile of antimicrobial except causality assessment scale. The reasons for predominance of male and adult patients in the current study may be due to the fact that this population is a working class and more exposed to communicable diseases hence, more likely to be prescribed antibiotics which can increase their risk towards ADRs.

The results of the current study are in agreement with the studies of Kunnoor NS *et al* (6) , Admassie E *et al* (7) & Rashed AN. (10) No major gender-related differences were observed in the prescription, drug utilisation and ADR patterns (P>0.05) of cardiovascular and non-cardiovascular drugs in the study of Kunnoor NS *et al* (6) In the study of Admassie E *et al* (7), numbers of drugs per prescription as well as older age were found to be predisposing factors for the occurrence of potential

*Table 1. Gender Wise Comparative Demographical Profile of ADRs due to Antimicrobials*

| Parameters | Male | Female | Statistical Analysis |
|---|---|---|---|
| **Total number of Antibiotics related ADRs-** 2586 ADR events were recorded in 3years out of which 392 (15.15%) were due to antibiotics | n=253 | n=139 | |
| **ADR rate due to Antibiotics** | 64.54% | 35.45% | |
| **Age wise classification-** Adult/ Geriatric/ Pediatric | 158(62.45%)/45(17.78%)/ 50(19.76%) | 89(64.02%)/20(14.38 %)/30(21.58%) | $\pi^2$= 0.8058 , DF=2, P=0.6684 NS |
| **Specialty**: Dermatology/GI/CNS/ Cardiology/Hepatobiliary/Vascular /Renal/Haematology/Metabolic/ Multisystemic/Non specific | 119(47.03%)/104(41.10%) /13(5.14%)/0/7(2.76%)/1(0 .39%)/1(0.39%)/4(1.58%)/ 1(0.39%)/1(0.39%)/1(0.39 %)/1(0.39%) | 69(49.64%)/54(38.84 %)/5(3.59%)/1(0.71 %)/3(2.15%)/1(0.71 %)/3(2.15%)/3(2.15 %)/0/0/0/0 | $\pi^2$= 2.026 , DF=4, P=0.7310 NS |
| Route of Drug Administration- Oral/I.V/IM/SC | 113(44.66%)/135(53.35%) /5(1.97%)/0/ | 65(46.76%)/74(53.23 %)/0/0 | $\pi^2$= 2.834 , DF=2, P=0.2424 NS |

*Table-2. Gender Wise Comparative Parameters of ADRs due to Antimicrobials*

| Parameters | Male | Female | Statistical Analysis |
|---|---|---|---|
| Monotherapy Vs Combination Therapy | 207(81.81%)/46(18.18 %) | 114(82.01%)/25(17.98 %) | $\pi^2$= 0.002329 , DF=1, P=0.9615 NS |
| Rational Vs Irrational Combination | 10(21.73%)/36(78.26% ) | 9(36%)/16(64%) | $\pi^2$= 1.681 , DF=1, P=0.1951 NS |
| **Severity of ADRS –** Mild/ Moderate/ Severe/ Fatal | 10(3.95%)/223(88.14% )/20(7.90%) | 3(2.15%)/129(92.80%) /7(5.03%) | $\pi^2$=2.16 , DF=2, P=0.3395 NS |
| **Mode of onset –** Sub acute/ Acute/ Latent | 64(25.29%)/62(24.50% )/127(50.19%) | 35(25.17%)/43(30.93% )/61(43.88%) | $\pi^2$= 2.13 , DF=2, P=0.3447 NS |
| **Type of reactions** - A,B,C,D,E & Unclassified | 166(65.61%)/86(33.99 %)/0/0/0/1(0.39%) | 89(64.02%)/50(35.97% )/0/0/0/0 | $\pi^2$= 0.6853 , DF=2, P=7099 NS |
| **Causality as per Naranjo's Scale** - Probable/Possible | 172(67.98%)/81(32.01 %) | 113(81.29%)/26(18.70 %) | $\pi^2$=8.009, DF=1, P=0.004654 S |
| **Causality as per WHO - UMC scale** – Probable/Possible | 179(70.75%)/74(29.24 %) | 114(82.01%)/25(17.98 %) | $\pi^2$= 6.029 , DF=1, P=0.01407 S |
| **Outcome of the ADRs** - Recovered/Recovering/ Continuing | 162(64.03%)/88(34.78 %)/3(1.18%) | 73(52.51%)/65(47.79% )/1(0.71%) | $\pi^2$= 5.474 , DF=2, P=0.064 NS |
| **Management of ADRs** - Intervention required Vs No Intervention Required | 17(6.71%)/236(93.28% ) | 14(10.06%)/125(89.92 %) | $\pi^2$=1.406 , DF=1, P=0.495 NS |

ADRs while sex was not a risk factor for ADR. Use of five or more low-risk drugs per patient or three or more high-risk drugs was a strong predictor for ADRs ($p < 0.001$). Gender was not significantly found associated for ADRs in the study of Rashed AN (10)

The results of the current study are contrary to the findings of various studies. (5, 11-17)

Women experience more adverse reactions to treatment with therapeutic drugs than men. (5) Women have a nearly 2-fold greater risk for developing ADRs

***Table 3. Detail of ADRs due to Antimicrobials by Injectable Route***

| Drugs | Male | Female |
|---|---|---|
| Inj. Ceftriaxone (140) (35.71%) | Rash (29), Gastritis (14), Diarrhoea (14), Hypotension(10), Pain epigastrium (10), Nausea (6), vomiting (2), Oral candiaisis (2), Nephrotoxicity (2), Epigastric discomfort (2), Anxiety (2), Stomach cramps (2), restlessness (2),vomiting (2), Glossitis (2), Toothache (1), Tacharythmias (1), Abnormal movement of limb (1), Shivering/chills (1), Breathlessness(1) | Rash (5), Gastritis (4), Diarrhoea (3), Epigastric discomfort (2), Allergic reaction (2), Pain abdomen (2), Itching and allergic reaction (1), Drowsiness (1), Oral thrush (1), Palpitations (1), Nausea vomiting (1), Anaphylaxis (1), Thrombophlebitis (1) |
| Inj. Ciprofloxacin (9) (2.29%) | Diarhhoea (3), Allergic reaction (1), Drowsiness (1), Abdominal pain (1), Abdominal discomfort (1) | Diarhhoea (1), Urticaria (1) |
| Inj. Linezolid (8) (2.04%) | Shivering and chills (1) | Diarrhea (1), dizziness (1), Constipation (2), Swelling lower limbs (1), Renal dysfunction (1), Liver and renal dysfunction (1) |
| Inj. Amikacin (7) (1.78%) | Mild rash (1), Pain abdomen (1), Hypotension/anaphylaxis (1), Dizziness (1), Increased frequency of micturition (1) | Nephrotoxicity(1), Itching and Pruritis (1) |
| Inj. Ampicillin (7) (1.78%) | Rash (4) | Rash (2), Gastritis (1) |
| Inj. Tazobactam (7) (1.78%) | Allergic reaction (2), Severe gastritis (1), vomiting (1), Oral candidiasis (1) | Allergic reaction (2) |
| Inj. Cloxacillin (6) (1.53%) | Diarrhoea (2), Rash (2), Thrombophlebitis (1) | Purities (1) |
| Inj. Metronidazole (4) (1.02%) | Rigors and chills (1) | Rigors and chills(1)diarrhea(1)nausea/metallic taste(1) |
| Inj. Lincomycin (3) (0.76%) | Diarrhea (2), Urticaria and rash all over body (1) | - |
| Inj. Vancomycin (3) (0.76%) | Rash(1) | Rash(1), Allergic reaction(1) |
| Inj. Tinidazole (3) (0.76%) | - | Rash (1), Pain epigastrium (1), Constipation(1) |
| Inj. Ceftriaxone+ sulbactum (2) (0.51%) | Rash (1), Diarrhea(1) | - |
| Inj. Tazobactam+ Piperacillin (3) (0.51%) | Diarrhoea (1), Hypoglycemia (1) | Severe allergic reaction (1) |
| Inj. Teicoplanin (2) (0.51%) | Severe allergic reactions (2) | - |
| Inj. Amoxicillin+dicloxacillin (2) (0.51%) | Diarrhoea(1), Epigastric discomfort (1) | - |
| Inj. Aztreonam (1) (0.25%) | Severe diarrhea (1) | - |
| Inj. Cefoperazone (1) (0.25%) | Severe persistent vomiting (1) | - |
| Inj. Ampicillin+ Cloxacillin (1) (0.25%) | Severe allergic reaction (1) | - |
| Inj. Benzathine Penicillin (1) (0.25%) | Petechial haemorrage (1) | |
| Inj. Levofloxacin (1) (0.25%) | - | Diarrhoea (1) |
| Inj. Ceftazidime (1) (0.25%) | Rash (1) | |

than men, and they are more likely to be hospitalized secondary to an ADR. (11) Further, those ADRs reported for women are usually more serious in nature. (5)

Harugeri A *et al* (12) reported female gender as the influential risk factor for ADRs among elderly age group. Hofer-Dueckelmann C *et al* (13) recorded older age and female gender to be significantly associated with ADR related hospital admissions. Analyzing separately by age groups, the gender difference was shown to become significant at an age of 81 years. The most common ADRs reported were electrolyte imbalances and over-anticoagulation. Diuretics and vitamin K antagonists were significantly correlated with ADRs.

In the study of Rodenburg EM *et al.* (14) the most pronounced sex differences in ADRs were seen in women users of low-ceiling diuretics, cardiotonic glycosides, high-ceiling diuretics and coronary vasodilators. Clear sex differences exist in ADRs requiring hospital admission for different cardiovascular drug groups.Whereas our study pointed towards a high percentage of patients presenting with in adult group (62.45% vs 64.02%) then geriatric age group (17.78% vs 14.33%) in men and women respectively. However, the current study focused only on evaluating gender related differences in ADR profile of antimicrobial.

In a prospective analysis from German university hospitals, female sex were also shown independent predictors for ADRs. (15)

Unlike current study results which depicted no major gender related differences in ADR profile due to antimicrobials, Rodenburg EM (16) recorded differences between the sexes in risk for ADR-related hospitalization for antineoplastic and immunosuppressive drugs, antirheumatics, anticoagulants and salicylates, cardiovascular and neurological drugs, steroids and antibiotics. In a multivariate regression analysis adjusting

***Table 4. Detail of ADRs Due to Antimicrobials by Oral Route***

| | | |
|---|---|---|
| Tab. Azithromycin (29) (7.39%) | Diarrhoea (8), Gastritis (4), Epigastric pain (2), TEN(2), Urticaria (1), Oral thrush (1), Gastritis leading to headache (1), Headache (1), Epigastric pain (1) | Diarrhea(5), Maculopapular rash (1), Urticaria (1), Epigastric pain |
| Tab. Ofloxacin+ Ornidazole (21) (5.35%) | Severe allergic reactions (4), Rash(4), Rash and urticaria (2), urticaria (1), Fixed drug eruptions (3), Vertigo (1), Papules, erythema, purpura, deep seated vesicles over upper limbs (1) | Severe allergic reactions (2), Anaphylaxis (1), Rash (1), Maculopapular rash (1) |
| Tab. Ofloxacin (14) (3.57%) | Glossitis (1), Jaundice (1), Allergic reactions (4), Rash (2) | Gastritis (2), Palpitations (2), Anxiety (1), allergic reaction (1) |
| Tab. Amoxicillin (10) (2.55%) | Rash (3), diarrhea, (2), TEN(1), Diarrhoea with severe dehydration(1) | Diarrhoea (3) |
| Tab. Cefixime (9) (2.29%) | Allergic reactions (2), Rash (2), Erythema multiforme (1) | Diarrhoea (2), rash (1), Erythema multiforme (1) |
| Tab. Ornidazole (7) (1.78%) | Fixed drug eruption (1), Skin rash (1), Severe allergic reaction (1) | Severe allergic reaction (2), Anaphylaxis (1), Angioedema and anaphylaxis (1) |
| Tab. Ceftriaxone (4) (1.02%) | Tachycardia (1), hypotension (1), acute urticaria (1) | Hypotension (1) |
| Tab. Cefpodoxime (6) (1.53%) | Diarrhoea (1), Maculopapular rash of upper limb (1) | Macules,papules, erythema over upper and lower limb (1), Severe allergic reaction(1) |
| Tab. Trimethoprim sulfamethaxazole (6) (1.53%) | Rash(2), Bullous pemphigoid (1) | Rash(2), Vasculitis (1) |
| Tab. Clavulanate+ Amoxicillin (10) (2.55%) | Rash(3), Diarrhea(2), Gastroenteritis(1) | Diarrhea (2), Rash all over body (1), Maculopapular rash (1) |
| Tab. Tinidazole (5) (1.27%) | Rash(1) | Fixed drug eruption (2), shivering and fever (1), Skin itching pruritis and rash (1) |
| Tab. Clarithromycin (4) (1.02%) | Nausea and vomiting (1), Vertigo (1), Epigastric pain (1), Anxiety (1) | - |
| Tab. Ciprofloxacin (4) (1.02%) | Diarrhoea (2), Rash (1) | Allergic reaction(1) |
| Tab. Metronidazole (4) (1.02%) | Fixed drug eruption (2), Glossitis (1) | Rash(1) |
| Tab. Linezolid (4) (1.02%) | Severe diarrhea (1), Allergic reaction (1), Oral candidiasis (1) | Diarrhoea (1) |
| Tab. Cefixime+ Clavulinic acid (4) (1.02%) | Rash (2) | Glossitis(1), Maculopapular rash(1) |
| Tab. Levofloxacin (4) (1.02%) | Rash (1), Gastritis(1) | Diarrhoea(1), Vasculitis(1) |
| Tab. Norfloxacin+ tinidazole (3) (0.76%) | Allergic reactions (2) | Macules, erosions, erythema and bulaae at upper limbs (1) |
| Tab. Cefodoxime+ clavulinic acid (3) (0.76%) | Rash(1), Severe diarrhea (1) | Super-infection and Oral thrush (1), Allergic reaction (1) |
| Syp. Amoxicillin+ Clavulanate (2)(0.51%) | Diarrhoea (1) | Fixed Drug Reaction (1) |
| Tab. Cefuroxime (2) (0.51%) | Rash(1), Macules, papules, erythema and erosions (1) | - |
| Tab. Amoxicillin+ dicloxacillin (2) (0.51%) | Rash(1) | Breathlessness (1) |
| Tab. Ampicillin (2) (0.51%) | Rash(1), Abdominal distension (1) | |
| Tab. Rifamycin (2) (0.51%) | - | Diarrhoea (1), Aggravation of diarrhea (1) |
| Tab. Cloxacillin (1) (0.25%) | Cellulites (1) | - |
| Tab. Levofloxacin+ Ornidazole (1) (0.25%) | | Rash(1) |
| Tab. Ciprofloxacin+ Tinidazole (1) (0.25%) | Maculopapular rash on face and upper limbs (1) | - |
| Syp. Ofloxacin+ ornidazole (1) (0.25%) | Severe allergic reaction(1) | - |
| Tab. Rifampcin (1) (0.25%) | Petechial rash on face abdomen and feet (1) | - |
| Syp. Lincomycin (1) (0.25%) | Diarrhoea (1) | - |
| Tab. Cefixime+ Ornidazole (1) (0.25%) | Severe allergic reaction (1) | - |
| Tab. Cefadroxil (1) (0.25%) | - | Vomiting (1) |
| Tab. Novaclox (1) (0.25%) | - | Severe allergic reaction and gastritis (1) |
| Tab. Moxifloxacin | - | Severe anaphylaxis (1) |

for age, body mass index (BMI) and number of prescribed drugs showed a significant influence of female gender on the risk of encountering ADRs ( $p < 0.0001$). Dose-related ADRs were the dominant type in female subjects. Comparing system organ classes of the World Health Organisation, cardiovascular (CV) ADRs were particularly

frequent in female subjects (p = 0.012). Thereby, confirming the higher risk of ADRs among female subjects compared with a male cohort. (17) In another study older age and female gender are significantly associated with adverse bleeding events of antithrombotic treatment related hospital admissions. (18) Differences at pharmacokinetics & pharmacodynamics level may predispose women at risk for developing adverse drug reactions (ADRs). (19) In women, absorption, protein binding, volume of distribution, clearance and metabolism of drugs may differ due to hormonal influences. Sex-related differences exist for phase I (cytochrome P450) as well as phase II (especially glucuronidation) reactions. (20) A sex difference in pharmacodynamics, as aptly elucidated by occurrence of drug-induced torsade de pointes, to occur more frequent in women. (20)

On statistical comparison, significant differences were observed among male and female in causality assessment scale (P<0.5) using both the scales, with male showing less percentage being probable type of ADR. Causality assessment is the evaluation of likelihood that a particular adverse event has occurred due to any particular drug.

Its assessment is basically based on temporal relationship, de-challenge, re-challenge, confounding factors and outcome of the adverse event. (21) Thus, the possible explanation of this gender based difference can be higher occurrence of confounding factors among male in the current study. However, this interesting finding need to be studied in future research.

## Conclusion

ADRs due to antimicrobials are a significant health problem. No major gender related differences were observed in ADR patterns of our study cohort.

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