

## AGE AND GENDER VARIATION IN BURDEN OF NON-STEROIDAL ANTI-INFLAMMATORY MEDICATION INDUCED ADVERSE DRUG REACTIONS

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### ABSTRACT

**Background:** Non-steroidal anti-inflammatory medications (NSAIM) shall produce mild to severe adverse reactions resulting in morbidity and mortality. The reversible or irreversible disability need to be measured to understand the burden due to the ADRs. Age and gender are important variables in NSAIM induced ADRs.

**Methods:** Our objective of the study includes evaluating the age and gender variables in the NSAIM induced peptic ulcer and cutaneous allergy. We use to calculate only Years Lost due to Disability (YLD) and not the Years of Life Lost (YLL) in Disability Adjusted Life Years (DALY). And YLD is calculated only in the NSAIM induced peptic ulcer and cutaneous allergy.

**Results & Discussion:** In this prospective study, adult and old group, male and female group were evaluated for the Quality Of Life (QOL) reduction and YLD. Female patients have shown 4% lesser QOL in NSAIM induced peptic ulcer disease (PUD) and 6% lesser QOL in NSAIM induced cutaneous allergy. The average duration of disease was significantly higher in female than men with a P-value 0.046 with  $SD \pm 5.87$ . The burden of NSAID induces PUD was 0.14 YLD in men and 0.22 YLD in women. The average duration of NSAIM induced skin reactions were significantly higher in females with a P-value 0.000 with  $SD \pm 2.49$ . The burden of NSAIM induced skin reactions were 0.12 YLD in men and 0.208 YLD in women. The old patients (on or above 65 years old) had 63% QOL and adult group had 72% QOL in NSAIM induced PUD. In adverse skin reactions the old age group had shown 74% QOL and the adult group shown 74% QOL. The duration of illness was higher in old group as supported by the literature.

**Conclusion:** Many studies suggest that the NSAIM induced PUD or skin reaction is higher in men than female. But the disease burden was seen to be higher in female group. The QOL was lower and duration of disease was higher. Bigger difference was seen in duration of disease making the YLD significantly higher in females. As predictable the severity and burden of the ADR is higher in old age group. Duration of ADR was pretty higher the as of the severity. Healing in old age is slower as predicted.

**Key words:** NSAIM, ADR, Peptic Ulcer, YLD, burden

## INTRODUCTION

Non-steroidal anti-inflammatory medication or drugs (NSAIM or NSAID) are some of the widely used medicines in India or around the world.<sup>1</sup> There are many mild, moderate and severe adverse reactions reported to the NSAIDs. Cyclooxygenase –II enzyme specific NSAIDs (s-NSAIDs) came to market with the evidence of lesser adverse effects compared to the non-specific NSAIDs. But further evidences suggested the serious adverse drug reactions (ADRs) of s-NSAIDs were higher than ns-NSAIDs. Even in ns-NSAIDs the highly safe NSAID is yet to be discovered.<sup>2</sup>

Out of the ADRs caused due to medications, NSAIDs may cause 21-25% of the total reactions.<sup>3</sup> ADRs increases or creates disabilities in patients. Cutaneous adverse drug reactions are very common among the ADRs. Adverse drug reactions produce morbidity and mortality depending on multiple factors. There are no medicines free of ADRs. But many of the times it is possible to avoid or manage ADRs checking the risk benefit assessment.<sup>4-5</sup>

The adverse drug profiles of the NSAIDs include cardiovascular, renal, hepatic, gastrointestinal, cutaneous reactions. Cutaneous and gastrointestinal ADRs are most commonly occurring compared to other ADRs.<sup>6</sup>

Age and gender are considered as one of the important variables in medication effectiveness and safety. Most of the studies state that the ADRs are more in pediatric (Children below 12 years of age) or geriatric (Old people of 65 & above years of age) compared to adults (18 to 64 years of age). Also more ADRs are reported in females compared to males.<sup>7</sup>

The Global Burden of Diseases (GBD) study was conducted by the Harvard School of Public Health, World Bank and World Health Organization (WHO) in 1990. The study was repeated in 2002 and 2004.<sup>8</sup>

The new Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2005 Study), started on 2007 by WHO in collaboration with Harvard University, University of Washington, Johns Hopkins University and University of Queensland. The project was expected to produce the final set of reports by the end of 2010.<sup>9</sup>

Disability Adjusted Life Years (DALY) is used to quantify the burden of disease.<sup>10</sup> The average disability weight of peptic ulcer is counted as 0.024 - 0.092 (GBD 2004).<sup>11</sup> DALYs for a disease, health condition or ADR are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the equivalent healthy Years Lost due to Disability (YLD).<sup>8</sup>

Using age weighing was one of the most debated parts of the GBD study. There were strong criticisms on the rationality of age weighing. The GBD study used 3% time discounting and non-uniform age weighing in 1990 study, 3% time discounting but uniform age weighing in 2002 study and 3% time discounting & non-uniform age weighing in 2004 study.<sup>8</sup>

In measuring the future stream of healthy YLL due to each incident cases of disease and injury, the time discounting reduces the error. But it is criticized widely that these weights do not represent the state equivalent to death. Also these weights are not considering any societal value of the person in illness.<sup>12</sup> In the global, countrywide, or statewide study calculating YLL is more useful and easier compared to YLD. Calculating YLD is time consuming and need high level expertise. The incidence, severity, age of onset, duration and the categorization of disease are required to calculate YLD.<sup>13-14</sup>

## METHODS

DALY is used to calculate the burden or ill health due to disease or other health condition including any injury.<sup>13</sup> We use DALY calculation to find out the burden of disability due to ADR injuries. Our aim of the study is not to find out the national burden of adverse drug reactions or to predict DALY. Therefore we are not using time discounting. Also our objective is to find the differences in age and gender groups in disability and the disability weights are calculated in individual cases and averages are used for adult, geriatric patients, male and female groups. This type of grouping is used in NSAID induced peptic ulcer and cutaneous allergy. We focus only to calculate YLD and not YLL.<sup>15</sup>

We evaluated the age and gender variable in YLD for NSAID induced peptic ulcer disease and skin reactions. NSAIDs studied include tablet and injection preparations of Aceclofenac, Diclofenac, Ibuprofen, Nimesulide and Mefenamic acid. The selected 5 medications were the most commonly prescribed NSAIDs in the study area.<sup>16</sup> Skin reactions include urticaria and rashes. The study was done on the patients attending the community pharmacy at Kasaragod district, South India. The patients were enquired about their ADRs due to

NSAIMs. Central Drugs Standard Control Organization (CDSCO), New Delhi, ADR reporting form was used along with Narijo Scale for causality assessment.<sup>17</sup>

Patients with age between 18-64 Years were grouped in to adult and from 65 years of age were grouped in to old people. Another way the patients were grouped was based on their gender. For comparison between groups two adverse reaction categories were selected including peptic ulcer and skin rashes as discussed above.

The formula for calculating YLD with uniform age weight and no discounting is:

$$YLD = I \times DW \times L$$

I is the number of incidences of disease or injury

DW is the disability weight and

L is the average duration of disease or injury in years up to clinical recovery or death.

DW could be calculated in an analogue scale from 0-1. Zero represents complete health with no illness and 1 represent death. The disability weight value is the reverse of quality of life values.

The Quality Of Life (QOL) in the study groups are also measured using the Karnofsky rating scale.<sup>18</sup> Data collected was entered to the Microsoft Excel format and processed to estimate the averages. The calculation for YLD was done by using the GBD equation with no discounting. Statistical analysis was performed using SPSS version 12.0 to find the significance of the results using paired samples T – test.

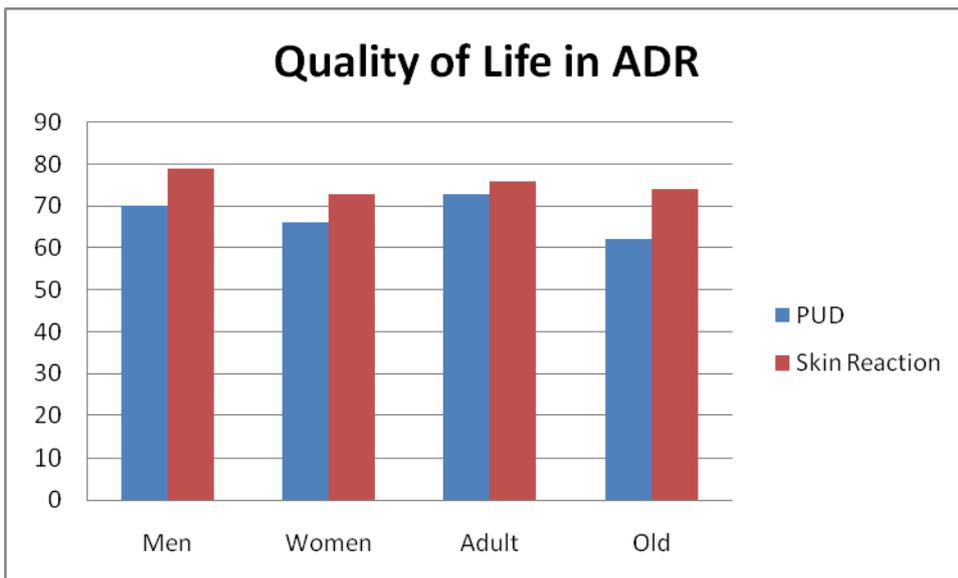
## RESULTS

The patient interview and data collection were done from august 2009 to may 2010. Severely ill patients or end stage disease patients were less attending the pharmacy. Many recovering and patients with past history of ADRs were interviewed. In case of NSAID induced peptic ulcer disease (PUD) men were selected who do not smoke for the past 6 months prior to the occurrence of the ADR. Still there were more males than females with the incidence of PUD. For the comparison of YLD between groups we collected equal number of patients in both the groups. Out of 29 patients in each group, males have shown 70% and females have shown 66% QOL with 0.3 and 0.34 DW. The average duration of ADR was significantly high (P-value 0.046 with SD± 5.87) in females than men. Females suffered on an average 8.1 days with a DW of 0.34, while men suffered 5.8 days with a DW of 0.3. The burden of NSAID induces PUD was 0.14 YLD in men and 0.22 YLD in women.

**Table 1:** QOL in NSAID induced ADRs

QOL	PUD	Skin Reaction
Men	70	79
Women	66	73
Adult	73	76
Old	62	74

**Graph 1:** QOL in NSAIM induced ADRs

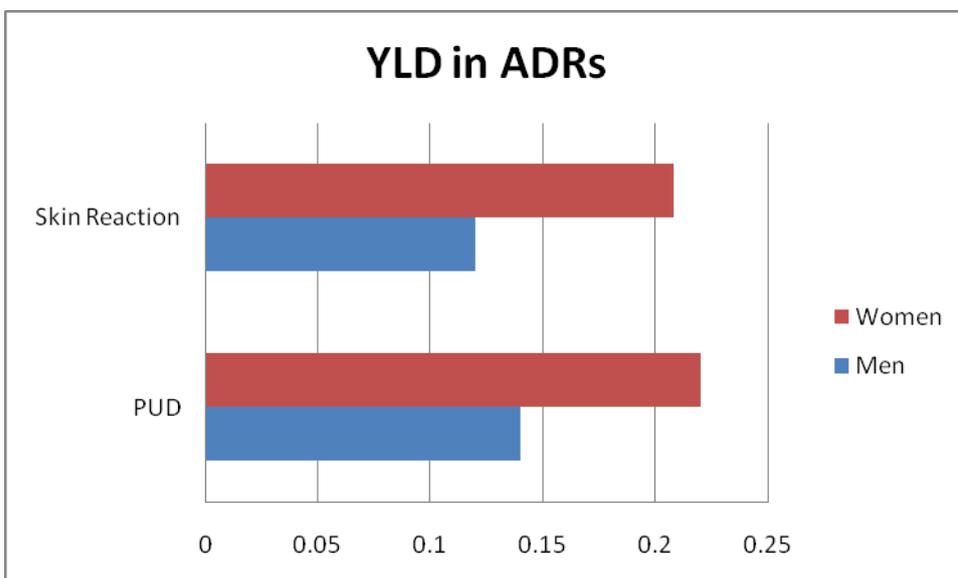


For evaluating adverse skin reactions 63 patients were selected in male & female groups each. Patients were randomly selected to avoid the influence of other variables than NSAIM induces skin reaction and gender. Males have shown 79% and females have shown 73% QOL with 0.21 and 0.27 DW respectively. The average duration of disease was significantly higher (P-value 0.001 with  $SD \pm 2.49$ ) in females on an average 4.5 days compared to 3.2 days in men. The burden of NSAIM induced skin reactions were 0.12 YLD in men and 0.208 YLD in women. This again states generally that the disease burden due to ADRs is higher in women than men.

**Table 2:** Gender variation in burden of NSAIM ADRs

YLD	PUD	Skin Reaction
Men	0.14	0.12
Women	0.22	0.208

**Graph 2:** Gender variation in burden of NSAIM ADRs

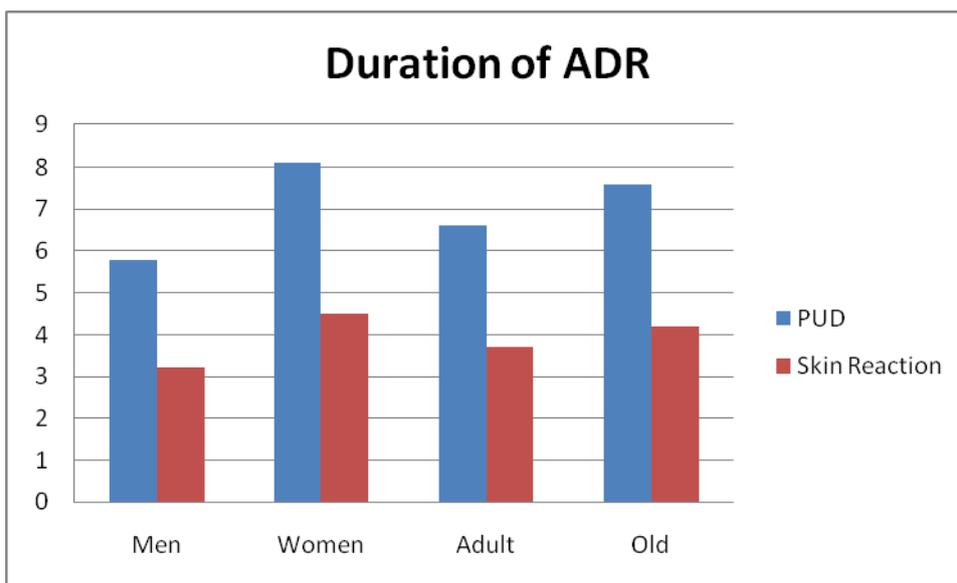


Age is an important variable in ADRs. Generally ADRs and its severity are higher in geriatric population (on or above 65 years old) than adults. In our study, we had 24 old patients and 34 adult who suffered from NSAID induced PUD. Average age of the old patient group was 70 years and they had 62% QOL with 0.38 DW. The average age of the adult group was 45 years and they had 73% QOL with 0.27 DW. There is significant variation in the disability caused due to ADRs. Naturally the old group was affected the worst. For the recovery the old group took on an average 7.6 days but the adult group was faster with an average 6.6 days. We are not comparing YLD because the sample size was not the same in both the groups.

**Table 3:** ADR duration for age & gender groups

ADR Duration	PUD	Skin Reaction
Men	5.8	3.2
Women	8.1	4.5
Adult	6.6	3.7
Old	7.6	4.2

**Graph 3:** ADR duration for age & gender groups



In case of adverse skin reactions 23 old patients and 103 adult were the causalities. The sample size is not the true representation of the occurrence of ADRs. The old group had an average 74% QOL with 0.25 DW. The adult group had 76% QOL with 0.24 DW. The average duration of skin ADR was 4.17 days in old and 3.75 days in adult. The QOL was calculated by considering the effect of other age related health issues and un-employment.

## DISCUSSION

The importance of health problem including the ADRs could be represented by DALY. Burden of Disease (BOD) gives an in depth information about the severity in morbidity and mortality of the health problem. And these outcomes are valuable tools in the management of the health related issue effectively.<sup>19</sup>

Global or nationwide studies focus more on YLL than YLD in calculating the DALY. In our study we focus only on YLD with the objective of studying the effect of gender and age in the burden of ADRs. Peptic ulcer and the skin rashes were selected for the comparison between groups. Peptic ulcer was found to be double or more for men compared to female.<sup>20</sup> There are regional variations for peptic ulcer sometimes the ratio of men: women is 4:1. But the YLD was found to be higher in men than women.

Smoking is an important variable in the development PUD. Also smoking decrease the rate of healing of the ulcers. There are many study results suggesting that the ADRs are more in women compared to men.

Even though occurrence of PUD was seen more in men, the disability due to it was found to be more in women. The study excludes children. PUD and skin reactions due to NSAIDs were found to cause higher burden on health in women than men. Literature suggests the occurrence of PUD is higher in the old age group. The study reveals the disease burden is also higher in the old group. The QOL and DW were taken in the old group considering the reduction in health due to age factor. The number of study population is not representative of the real occurrence of the condition. The incidence rate might be higher and severe, but the patients attending the pharmacy might be lesser. The study was designed mainly to evaluate the disease burden due to ADRs

There was no significant difference in the burden of adverse skin reactions found for adult and old groups. But the NSAID induced PUD was affecting badly in the old age compared to the adult age groups.

## CONCLUSION

YLD is a valuable tool in assessing the severity and duration of the disease happened to a patient until death (if the casualty dies, then it will be counted under YLL) or survival with no disabilities. It could be used effectively to evaluate the disability happened due to ADRs or adverse drug events. Generally adverse drug reactions are more common (or more frequent) in females than men and more in old age than adults. NSAID induced PUD which has regional variations. Studies in different population suggest the rate is higher in males than females. Our study aims at the burden of the ADR and females were found to be higher in YLD, especially in the duration of PUD or skin reactions. Old age also show a longer duration of ADRs as expected.

## ACKNOWLEDGMENT

We are expressing our gratitude to the Karpagam University research wing, Coimbatore, South India. Dr. P. Lakshmanaperumalsamy, Dr. S. Ravi and Dr. T. Subburaju, were keen on proceedings of the research work on adverse drug profiles of non-steroidal anti-inflammatory drugs.

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