

# Utilization Pattern of Non-steroidal Anti-inflammatory Drugs at a Primary Health Care in Malaysia

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## ABSTRACT

**Introduction:** Non-steroidal anti-inflammatory drugs (NSAIDs) are among medications most commonly prescribed and used world wide mainly in the developed countries. Variation in terms of drug utilization pattern and adverse events may exist in different population and healthcare centres. The objective of the study was to determine consumption pattern of NSAIDs at the Klang health district primary healthcare clinics in Malaysia. **Methods:** A retrospective cohort study of medical records of patients prescribed with NSAIDs over a period of 12 months (January to December, 2013) was conducted at Klinik Kesihatan Anika, Bukit Kuda and Pandamaran, Klang Health district primary healthcare clinics, Malaysia. **Results:** Records of 852 eligible patients were included for the study. Based on the WHO Defined Daily Dose (DDD), the most commonly used NSAIDs were Diclofenac (1.5725), Mefenamic Acid (1.4108), Ibuprofen (0.0166) and Meloxicam (0.0016). Up to 17.6% of the NSAIDs users, had chronic diseases such as diabetes mellitus hypertension and other cardiovascular diseases. 1.8% to 22.9% of NSAIDs users were concurrently taking antihypertensive, whereas, 8.6% experienced potential drug-drug interaction with NSAIDs. **Conclusion:** The NSAIDs utilization pattern among the patients at the primary healthcare clinics is appropriate based on the symptoms presented. However, concomitant administration with other drugs and use in patient with chronic disease poses risks of adverse drug reactions and drug-drug interaction.

**Key words:** NSAIDs, Malaysia, Utilization Pattern, Defined Daily Dosing.

Submission Date: 12-09-2016;

Revision Date: 17-11-2016;

Accepted Date: 23-11-2016

DOI: 10.5530/ijper.51.1.21

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the classes of drugs most commonly utilized in clinical settings. They are one of the readily available and widely used medications in the world particularly in the developed countries.<sup>1</sup> NSAIDs are broadly used medications in the management of both acute and chronic pain and inflammatory disorders such as rheumatoid arthritis and osteoarthritis.<sup>2,3</sup>

In Malaysia, NSAIDs were ranked as the 8<sup>th</sup> most frequently utilized drugs according to Anatomical Therapeutic Chemical (ATC)-system curative groups in 2007

(12.311 DDD/1000 inhabitants/day) with an anticipated 1.23% of the population utilizing them. Despite the widespread utilization and effectiveness, the use of NSAIDs is associated with adverse drug reactions (ADR) such as gastro-intestinal (GI) complications, leading to hospitalization and deterioration of disease conditions.<sup>4,5</sup> A report has shown that, Diclofenac Sodium, a sub-class of NSAIDs was among the top three drugs most commonly implicated in ADR based on the Malaysian Adverse Drug reaction Advisory Committee (MADRAC) report in 2008.r. Another study has indi-



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cated that the risk of serious GI complications in NSAID's users is almost four times higher than non-users. This risk and the severity however differs among the different sub-classes of the NSAIDs.<sup>2,3</sup>

NSAIDs are mostly inexpensive, commonly available in retail pharmacies as over the counter medications (OTC) and among most frequently prescribed medications in clinical settings. These made NSAIDs to be more accessible by patients, more likely to be abuse, misuse, involve in self-medication and most often leading to adverse drug reactions and complications of disease condition.<sup>6</sup> In Malaysia, NSAIDs have been reported to be among the drugs frequently implicated in ADR and consequent increase in healthcost and lost of quality of life<sup>3,4</sup>. The rampant abuse, misuse and frequent implication of NSAIDs in severe ADR necessitated the need to determine the pattern of utilization of this group of drug at a most commonly accessible healthcare setting in the rural community (primary healthcare clinic). This is similar to previous study in India<sup>7</sup> The findings of the current study will inform and assist the policy makers in preventing NSAIDs-related morbidity, mortality and extra healthcare spendings.

The study was aimed to determine the utilization pattern of NSAIDs at Klang Health District primary healthcare clinics in Malaysia. Other study objectives include the estimating of Define Daily Dose (DDD) for each NSAIDs prescribed at each centre, and to identify the potential NSAIDs-related problems at the three primary healthcare centres.

## MATERIALS AND METHODS

### Study Design/Settings

This is a retrospective cohort study design of medical records of adult patients at government primary healthcare clinics of Klang Health District, Malaysia. The Klang Health District consisted of three primary healthcare clinics; Klinik Kesihatan Klang (Anika), Klinik Kesihatan Pandamaran and Klinik Kesihatan Bukit Kuda. All the three clinics were using the Tele Primary Care (TPC) prescribing method since 2009, and were classified as type 3 clinics with 300-500 patient attendances per day and have at least one Family Medicine Specialist (FMS).

### Inclusion Criteria

- Patient who was prescribed with any class of oral NSAIDs in the Klang Health District's drug Formulary
- Patients aged 18 years and above
- Patient with complete patient's medical record (according to Data Collection Form in Appendix 1)

### Exclusion Criteria

- Patients prescribed with NSAIDs in an injectable dosage form
- Patient with presenting complaints related to dental disorder, pregnancy and disabilities
- Patient who was prescribed with Acetylsalicylic Acid (Aspirin) as an antiplatelet medication

### Data collection

The records of all patients that met the study eligibility criteria between January and December 2013 were retrieved from the TPC-online system. TPC is an online healthcare applications for patient's record from registration to collection of medications, it is also known as Electronic Clinic Management System (e-CMS). The patient's records were sorted out according to their identification (ID) number by in ascending order. Data was collected using NSAIDs usage estimation form as in Appendix 1.

### Outcome Parameter

To determine the consumption of NSAIDs in the primary care clinics, the defined daily dose (DDD) methodology described as DDD per 1,000 populations per day and the anatomical therapeutic chemical (ATC) system of classification of drug were used. Analysis and association with the WHO classification of ATC/DDD data using the ATC/DD Index 2011.

No.	Generic NSAIDs name	ATC Code
1.	Acetylsalicylic Acid	B01AC06
2.	Diclofenac Sodium 50mg Tablet	M01A B05
3.	Ibuprofen 200mg Tablet	M01A E01
4.	Mefenamic Acid 250mg Capsule	M01A G01
5.	Meloxicam 7.5mg Tablet	M01A C06
6.	Naproxen 250mg Tablet	M01A E02

Calculations are as follows:

$$DDD/1000\text{inhabitants}/\text{day} = T * 1000 / (DDD * P * 365)$$

Where:

- T is an estimate of the total quantity of the drug (mg) utilized in the year 2013
- DDD is the DDD assigned for the drug according to the ATC/DDD system
- P is the population of patients in primary care clinics studied.
- 365 refers to the 365 days in a year

### Statistical Analysis and Interpretation

The data collected was analysed using Statistical Package for Social Science (SPSS) software version 22.0 and Microsoft Excel version 2010 Kolmogrov-Smirnov test

and descriptive analysis were used to analyse the socio-demographic characteristics of the patients and the patient's prescribing confirmation and demographic data. Data were presented as mean (standard deviation) for numerical variables and frequency (percentage) for categorical variable. *P* value was considered significance at 0.005

### **Ethical Considerations**

The study was approved by the UiTM's ethics committee and the clinical research centre, iMinistry of health before commencement of the study. The data of the patients and medical records collected from the e-CMS were kept confidential by the investigators.

## **RESULTS**

### **Demographic and Patients Characteristics**

A total of 11,931 records of patients prescribed with NSAIDs were retrieved from the e-CMS of the three clinics, out of which 852 records of patients were included for the study. The mean age (standard deviation) was 45.5 years old (SD 1.63). The racial distribution of the patients were majority Indian patients (n=365, 42.8%), followed by Malay (n=313, 36.7%), Chinese (n=130, 15.3%) and others which included Bumiputera Sabah, Indonesian, Pakistani, Bangladeshi and European (n=44, 5.2%) for all the three clinics. Table 1 demonstrated the result of socio-demographic characteristics of the included patients

### **Most prescribed NSAIDs according to clinics**

**Table 2** shows the most prescribed NSAIDs, according to clinics. Only 4 out of 6 NSAIDs available in Klang health district drug formulary were prescribed in the 3 clinics.

Diclofenac was more prescribed among male (45.2%) compared to female patients (34.1%), followed by Mefenamic acid; female (13.8%) and male (12.6%) (Table 3).

### **Defined Daily Dose ( DDD) in/1000 inhabitants/day of NSAIDs**

**Table 4** shows the results of DDD/1000 inhabitants/day of NSAIDs at the 3 clinics. Diclofenac and mefenamic acid were found to be the most prescribed NSAIDs based on the DDD index calculated.

### **Prevalence rate of chronic diseases among patients prescribed with NSAIDs at the 3 clinics**

The KK Bukit Kuda had the highest number of patients with chronic diseases (32.4%), followed by KK

Pandamaran (17.6%) and KK Anika (3.2%). The KK Bukit Kuda has the highest percentage of patients with hypertension (14.1%) being followed by KK Pandamaran (9.5%) and KK Anika (1.1%) (table 5).

Potential drug-drug interaction with NSAIDs

## **DISCUSSION**

### **Drug utilization pattern of NSAIDs**

The drug utilization pattern of sub-classes of NSAIDs in the current study varies among the three clinics and also in comparison with the Ministry of Health National medicines use survey of 2006 and 2007. Which was aimed at providing data on common drugs (including NSAIDs) prescribed in both public and private facilities based on the distribution, procurement, utilization and pattern of use. In the current study, the DDD/1000 inhabitants/day of diclofenac was higher in Bukit Kuda and the lowest in Anika primary healthcare clinic. The overall was higher than that of the survey of the Ministry of Health (1.1058) in the public sector. Similarly, Mefenamic acid was also higher in Bukit Kuda and lowest in Anika clinic and in the overall was lower than that of the national survey by the Ministry of health (1.4147). In contrast, Ibuprofen was higher at Anika clinic and lowest at Pandamaran clinic, and the average value was lower than that of the national survey (0.1111). The discrepancies may be because the previous survey by the Ministry of health Malaysia included data from both hospital and health clinics while the data in the current study was limited to only primary healthcare clinics. Another reason may be due to the fact that not all sub-classes of NSAIDs were listed in the hospital formulary of the three clinics used in the current study, example; there are only six NSAIDs listed in the approved formulary of Klang primary healthcare clinic out of the 12 approved NSAIDs in the MOH Drug formulary. Moreover, the use Acetylsalicylic acid in the Klang health district formulary is restricted only as anti-platelet.

Majority of the patients in the current study were prescribed with NSAIDs for a duration of less than 28 days. Moreover, some patients with chronic musculoskeletal disorders were placed on a long term treatment of NSAIDs. However, the reason may be because, it has been established that continuous therapy for a long time more than 28 days, may put the patient at a higher risk of ADR, drug-interaction and medication non-adherence.<sup>5,8</sup> In many reported cases, the gastrointestinal (GI) complications related to NSAIDs use was four times higher when compared to non-users.<sup>9,10</sup> Furthermore, findings of the current study has also

indicated that patients on medications for management of chronic underlying illness are among the frequent users of NSAIDs. Up to 22.9% of the NSAIDs users were on antihypertensive medications, even though, the figure is less than the previously reported estimate of 61%.<sup>11</sup> The concomitant administration of NSAIDs with antihypertension will lead to increase likelihood of drug-drug interaction and drug-disease interaction resulting in deterioration and complication of disease condition. A study among ambulatory patients in Mexico has shown a high proportion of drug-drug interaction involving NSAIDs and antihypertensive medications.<sup>12,13</sup> Another findings by Jerry H. *et al.*, (1994) also found NSAIDs as one of the risk factors among elderly newly prescribed with antihypertensive medications.<sup>14</sup> The present study showed the occurrence of drug-NSAIDs interaction of up to 15.5%, a value that is higher than a study conducted by Dhabali *et al.*, (2012) at University Sains Malaysia, primary care clinic (6.6%).<sup>15</sup> The reason

may be due to variation in the utilization pattern and hospital formulary between the centres.

The disease-drug interaction and ADR involving NSAIDs may be related to its pharmacologic effects of the drug. NSAIDs' effect on prostaglandins causing reduction in renal blood flow, may interfere with the pharmacologic activity of some diuretics.<sup>16</sup> Similarly, the vasoconstriction of renal arteriole caused by NSAIDs may also decrease the actions of Angiotensin Converting Enzymes Inhibitors (ACE-Inhibitors), leading to reduced antihypertensive effects and consequent renal injury. A study by Loboz et. Al (2011) at a Medical ward shown that patients who were on concomitant medications involving one or more ACE Inhibitors or angiotensin receptor antagonists, diuretics or NSAIDs were found to have some form of renal injury.<sup>17</sup>

This study highlights some potential drug-drug interactions of NSAIDs that needs further evaluations. Thus it is crucial that NSAIDs patterns and consumption needs to be re-examined so as to improve its therapeutic utili-

**Table 1: Demographic Characteristics of the Patients Stratified by Clinics (n=852, 284 each clinic)**

Demographic Variables	ALL		KK ANIKA		KK BUKIT KUDA		KK PANDAMARAN		p value	
	n	%	n	%	n	%	n	%		
AGE	<45 years	418	49.1	142	50.0	115	40.5	161	56.7	0.022
	45 to 49 years	80	9.4	27	9.5	23	8.1	30	10.6	0.63
	50 to 54 years	84	9.9	24	8.5	36	12.7	24	8.5	0.180
	55 to 59 years	86	10.1	31	10.9	32	11.3	23	8.1	0.428
	60 to 64 years	63	7.4	23	8.1	25	8.8	15	5.3	0.264
	>65 years	121	14.2	37	13.0	53	18.7	31		
	10.9	0.040								
Mean Age (SD)		45.54 (1.63)		45.13 (1.70)	48.45 (1.60)		43.05 (1.54)			0.000
GENDER	Male	374	43.9	119	41.9	131	46.1	123	43.3	0.701
	Female	478	56.1	165	58.1	152	53.5	161	56.7	0.757
RACE	Malay	313	36.7	79	27.8	93	32.7	141	49.6	0.000
	Chinese	130	15.3	25	8.8	72	25.4	33	11.6	0.000
	Indian	365	42.8	163	57.4	101	35.6	101	35.6	0.000
	Others	44	5.2	17	6.0	18	6.3	9	3.2	0.190



zation effects and prevent any untoward side-effects especially on high-risked patients

The current study is limited to only three primary healthcare clinics in Malaysia, thus, the findings will not be generalized to larger population in Malaysia. The other challenge included technical difficulties in extracting complete information on patient's history and laboratory results from the e-CMS system.

## CONCLUSION

The utilization pattern of NSAIDs among the three primary healthcare centres in Malaysia is appropriate based on the presenting complaints. However, the dose of NSAIDs prescribed was not in accordance with WHO Defined Daily Dose. NSAIDs were found to interact with antihypertensive medications and were responsible for ADRs, thus, preventive interventions should be put in place to ameliorate future occurrence and drug-related morbidity and healthcare

## ACKNOWLEDGEMENT

The authors would like to thank the staff of the KK Anika, KK Bukit Kuda and KK Pandamaran for their assistance in the data collection

## CONFLICT OF INTEREST

The authors have declared no conflict of competing interest.

## ABBREVIATIONS USED

ADR: Adverse Drug Reaction; ATC: Anatomical Therapeutic Chemical; CI: Confidence Interval; COX: Cyclooxygenase; CVD: Cardiovascular Disease; DDD: Defined Daily Dose; DM: Diabetes Mellitus; DUR: Drug Utilization Review; DUS: Drug Utilization Study; E-CMS: Electronic Clinic Management System; FDA: Food and Drug Administration; GI: Gastrointestinal; HPT: Hypertension; ID: Identification; IHD: Ischemic Heart Disease; KK: Klinik Kesihatan; MADRAC: Malaysian Adverse Drug Reaction Committee; MNMP: Malaysian National Medicines Policy; MOH: Ministry of Health; NPCB: National Pharmaceutical Control Bureau; NSAIDs: Non-Steroidal Anti Inflammatory Drugs; PKD: Pejabat Kesihatan Daerah; PRP: Prescription-related Problems; RA: Rheumatoid Arthritis; RR: Relative Risk; SD: Standard Deviation; SPSS: Statistical Package for Social Science; TPC: Tele Primary Care; WHO: World Health Organization.

## Fund

This work was supported by Academic and Research Assimilation grants: 600-IRMI/DANA 5/3/ARAS (0035/2016; 0036/2016). The authors would like to express their gratitude to Ministry of Higher Education and Universiti Teknologi MARA (UiTM), Malaysia for financial support for this research

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**Cite this article:** Khairudin KA, Jatau AI, Manan MM, Tiong CS, Chitneni M, Abdullah AH, et al. Utilization Pattern of Non-steroidal Anti-inflammatory Drugs at a Primary Health Care in Malaysia. Indian J of Pharmaceutical Education and Research. 2017;51(1):156-161.