

## PRESCRIBING PATTERNS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN OUTPATIENT CLINICS AT ROYAL REHABILITATION CENTER IN KING HUSSEIN MEDICAL CENTER

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### ABSTRACT

**Objective:** The purpose of this paper is to analyze the prescribing patterns for both conventional and non-conventional non-steroidal anti-inflammatory drugs (NSAIDs) with concomitant gastro-protective agents, at the outpatient clinic at Royal Rehabilitation Center (RRC) in King Hussein Medical Center (KHMC) in Jordan.

**Methods:** A retrospective study was conducted at the outpatient clinic pharmacy in RRC. A total of 25,692 prescriptions were reviewed. Collected data includes: percentage of each type of NSAIDs, dosage form, percentage share for each selective and non-selective NSAID, and concomitant therapy with gastroprotective agent.

**Results:** 52% of the collected prescriptions contain NSAIDs. 76% of the prescriptions are for women and 24% are for men. Age of patients included in the prescription ranges between 16 and 80 years, with a mean of  $59.3 \pm 15.8$  years. Indications for NSAIDs are 58.3% for osteoarthritis, 12.1% for rheumatoid arthritis, and 20.1% for orthopedics pain. Additionally, 96.4% of prescriptions are for conventional NSAIDs, while only 3.6% prescriptions are for the selective COX-2 inhibitors. Furthermore, diclofenac topped the list with 83.74% of prescriptions of NSAIDs. Concomitant therapy with gastroprotective agents was reported in 71.2% of prescriptions. Famotidine is the most prescribed gastroprotective agents followed by antacid and omeprazole.

**Conclusions:** In summary, Diclofenac was the most prescribed NSAIDs as a result of its low price and availability in different dosage forms. Conventional NSAIDs combined with a gastroprotective agent is the most appropriate first-line NSAIDs therapy for many patients. To minimize the occurrence of gastrointestinal toxicity, the study suggests adopting the National Institute of Clinical Excellence (NICE) guidance or the American College of Gastroenterology recommendations.

**KEYWORDS:** conventional NSAIDs, non-conventional (selective COX-2 inhibitors) Non-steroidal anti-inflammatory drugs; gastro-protective agents,

### INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered as one of the largest groups of pharmaceutical agents. Worldwide, over 30 million people use NSAIDs every day (1, 2). In the USA alone, the annual number of prescriptions exceeds 111 million. Additionally, NSAIDs account for more than 60% of over-the-counter (OTC) analgesic market (3). Unfortunately, Jordan and other Arab countries lack any published official information in relation to the volume of NSAIDs use (4).

NSAIDs are utilized widely for a variety of disorders, which are related to pain and inflammation including musculoskeletal disorders (5). However, clinical and epidemiological studies have shown that the use of NSAIDs causes adverse reactions in the gastrointestinal system. In particular, NSAIDs have both bleeding and dyspepsia effects (6, 7). These adverse effects are a consequence of NSAIDs ability to inhibit cyclooxygenase-1 (COX-1) in the gastrointestinal tract (8). The selective COX-2 inhibitors emerged as potentially gastro-friendly NSAIDs (9, 10). Recent studies revealed cardiovascular adverse effects with the use of COX-2 selective inhibitors, which raised

concerns among both prescribers and consumers (11).

The British National Formulary (BNF) lists more than 20 NSAIDs that are available in at least 40 different formulations. Patients' response to NSAIDs is highly variable (12). There are several factors that contribute to patients' preference for one drug over another such as treatment efficacy, time and chance to benefit, potential side effects, ease of administration, cost, physician and patient beliefs drug interaction, severity of disease, and health status (13, 14, 15).

The purpose of this study is to analyze the prescribing patterns of conventional NSAIDs, non-conventional (selective COX-2 inhibitors) and concomitant gastro-protective agents. Data for this research project were collected from the out-patient pharmacy of the Royal Rehabilitation Center (RRC) at King Hussein Medical Center (KHMC) in Jordan. The results of the study provide valuable information to scholars, practitioners, and policy makers.

### METHODS

A retrospective study was conducted at the outpatient pharmacy in RRC during the last quarter of 2012. The study was approved by the Ethical

Committee at the Royal Medical Services (RMS). For the period of the study, the researchers reviewed all prescriptions, which totaled 25,692 prescriptions. Prescriptions surveys are regarded as effective means to provide insights into the underlying prescription patterns.

The collected data includes information as follows: age, sex, indication for use, average number of drugs per prescription, percentage of each type of selective and non-selective NSAIDs, dosage form, and concomitant therapy with gastroprotective agents. Prior to conducting the study, the researchers' obtained the approval of the Ethical Committee at the Royal Medical Services (RMS).

## RESULTS AND ANALYSIS

The total number of prescriptions in RRC during the period of study totaled 25,692 prescriptions. 52% of these prescriptions include NSAIDs. Out of the total number of NSAIDs prescriptions, 76% are for women, while the remaining 24% are for men. Age of patients ranges between 16 and 80 years, with a mean of  $59.3 \pm 15.8$  years. The average number of drugs per prescription is 3.76 with a range of 1-8 drugs. About 72% of the patients use 3 or more medications. Table 1 shows descriptive statistics for the collected data in relation to age and indication for use. As shown in Table 1, 58.3% of NSAIDs are used for osteoarthritis, 20.1% for orthopedic pain, 12.1% for rheumatoid arthritis, and 9.5% for other musculoskeletal disorders.

**Table 1: Descriptive statistics for age and indication for use**

Age (years)	Percentage
16-39	19.4
40-59	40.0
60-80	40.6
Indication for use	
Osteoarthritis	58.3
Orthopedic pain	20.1
Rheumatoid Arthritis	12.1
Other musculoskeletal disorders	9.5

Figure 1 shows the percentage for each NSAID. 96.42% prescriptions are for conventional NSAIDs, while only 3.58% prescriptions are for the newer selective COX-2 inhibitors. The majority of NSAIDs is prescribed in oral dosage form (73.42 %) followed by topical (18.24%) and rectal (7.33 %). The injectable dosage form is the least prescribed with only (1 %) of all prescribed NSAIDs.

Figure 1 reveals that Diclofenac tops the list and is the most frequently prescribed NSAIDs with 83.74%. Dosage forms include tablet (58.72%), gel (18.24%), and suppository (5.78%). Ibuprofen tablets and Indomethacin capsule are prescribed 5.63% and 3.84% respectively. COX-2 inhibitor that is available in RRC is meloxicam in both tablet and suppository dosage forms. These two forms were prescribed 2.85 % and 0.75 % respectively.

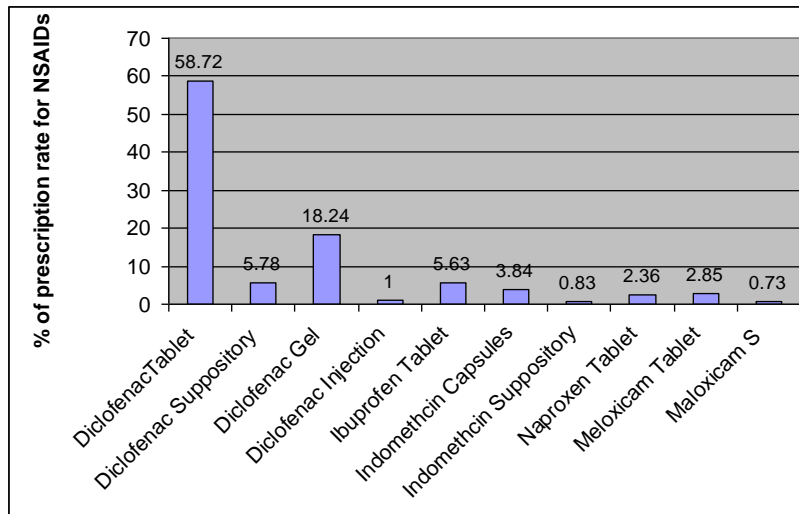


Figure 1: Average prescription rates for individual NSAIDs

Concomitant therapy with gastroprotective agents were reported in 71.16% of prescriptions. Figure 2 shows gastroprotective agents prescribed. Famotidine is the most commonly prescribed one (86.30%), followed by antacid (10.85 %) and omeprazole (2.85 %).

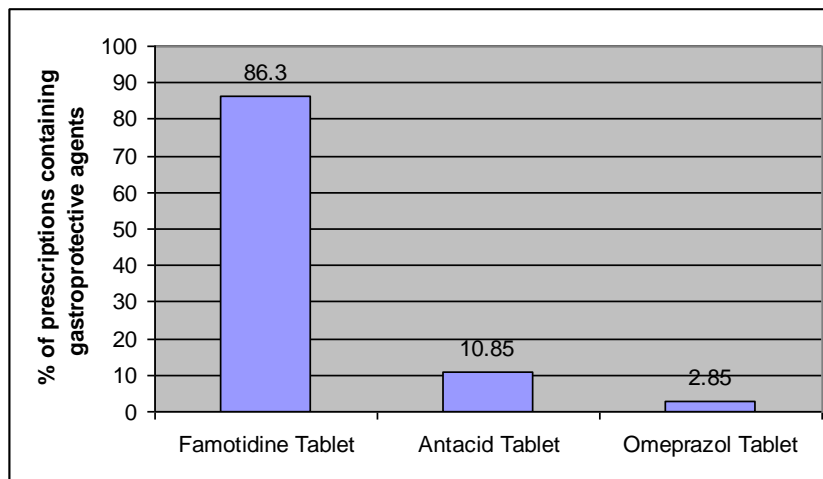


Figure 2: Gastroprotective agents prescribed

**DISCUSSION**

The result from this study shows that the use of selective COX-2 at RRC was limited to a mere 3.58% of prescriptions. These results are consistent with Zandman and Langville study, which reported that only 4% of patients were treated with COX-2 inhibitors (16). To the contrary, Thompson et al. study indicated that 24% of prescriptions are COX-2 inhibitors (17).

The conventional and the selective NSAIDs are broadly prescribed for indications including osteoarthritis, rheumatoid arthritis, and acute pain. Both drugs have identical clinical efficacy (18, 19, 20). COX-2 inhibitors are more costly compared to

nonselective NSAIDs, which results in lower COX-2 prescriptions compared to nonselective NSAIDs prescriptions (21, 22).

Even though that COX-2 selective inhibitors were developed to achieve safer renal and gastrointestinal profile compared to non-selective NSAIDs, but these former drugs have a pattern of nephrotoxicity and drug interactions similar to those of conventional NSAIDs (23, 24). Rostom et al. conducted a Cochrane meta-analysis that compared gastrointestinal safety of coxibs and NSAIDs (25). The study advocated that coxibs are significantly associated with fewer gastroduodenal ulcers and ulcer complications. Yet, a previous study showed

no evidence that coxibs are less toxic to the gastrointestinal tract than conventional NSAIDs combined with a gastro protective agent such as a proton pump inhibitor (PPI), especially in patients with high risk of developing gastrointestinal adverse events (26,27).

Additionally, clinical, experimental, and reviews suggest that the use of selective COX-2 inhibitors is associated with the increase in systolic blood pressure and cardiovascular morbidity due to myocardial infarction (MI) and cardio vascular system (CVS) toxicity (28, 29, 30, 31,32,33 ). Convincingly, studies by Lamarque and Bannwarth support reversing the trend back to the use of conventional NSAIDs (34,35). More recently, Olsen et al. indicated that both selective and conventional NSAIDs have potential cardiovascular risk. The authors argued that both drugs appear to increase the risk of subsequent cardiac events following MI (36).

Table 1 shows that NSAIDs use was significantly higher in female (76%) compared with male (24%). The dominant indication for prescription of NSAIDs is osteoarthritis with (58.3%) of prescriptions. This is followed by orthopedic pain (20.1%), rheumatoid arthritis (12.1 %), and musculoskeletal disorders (9.5%). These results are consistent with the argument of Bannwarth , who concluded that these conventional NSAIDs combined with a gastroprotective agent would be the most appropriate first-line NSAID therapy in many patients with osteoarthritis (37) . Kean suggested re-establishing the conventional NSAIDs as the preferred choice in the management of arthritis and musculoskeletal disorder (38).

Figure 1 shows that (83.74%) of the prescriptions were for diclofenac, followed by (5.63%) for ibuprofen. These results are similar to Fosbøl et al. study, which investigated the pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs). Fosbøl et al. concluded that Ibuprofen and diclofenac were the most frequently used conventional NSAIDs (39). While IMS Health reports that diclofenac is more common prescribed in the UK . However, in the USA, ibuprofen and naxprofen are the most commonly prescribed NSAIDs (40). Another study by Al-bsoul et al. showed that the diclofenac is the preferred NSAID among the Jordanian patients. According to the authors, this preference is attributed to availability in different dosage forms and low price (4).

The use of Diclofenac is distributed as

follows: tablet (58.72%), gel (18.24%), suppository (5.78%), and injection (1%). The increased utilization of gel is due to the fact that this topical compound offers the advantage of relieving symptoms of osteoarthritis with lower incidence of systemic adverse effect (20). Injectable dosage form was the least prescribed with only (1%). According to Drug and Therapeutic Bulletin the use of injection is seldom preferred route for musculoskeletal disorders(41).

This study showed that there is a high prescription rate of gastro protective agent concomitantly with NSAIDs. Among the total (8720) prescriptions of conventional systemic NSAIDs, (71.16%) are co-prescribed with gastroprotective agents. Figure 2 shows that Histamine type 2 receptor antagonist (H<sub>2</sub>RA), available at RRC as Famotidine 40 mg tablet, was prescribed in (86.30%) of prescriptions, representing the most frequent gastroprotective agent prescribed. This is followed by antacids and proton pump inhibitor ( PPI ), available at RRC as omeprazole, that represented (10.85%) and (2.85%) of prescriptions respectively. These results are consistent with recent recommendations by Lanza et al. and Brown et al. which suggested that the use of co-therapy with misoprostol, histamine type-2 receptor antagonists (H<sub>2</sub>RAs), or PPIs with non-steroidal anti-inflammatory and/or the use of cyclooxygenase-2 selective inhibitors decrease gastrointestinal toxicity (42, 37).

In RRC, H<sub>2</sub>RA is prescribed in standard dose (famotidine 40 mg). Rostom et al. ( conducted Cochrane review and Koch et al. conducted meta-analysis. They found that standard doses (40 mg tablet) of H<sub>2</sub>RAs were effective at reducing the risk of duodenal but not gastric NSAID associated ulcers (43,44). Rostom et al. concluded that high dose H<sub>2</sub>RAs is effective at preventing chronic NSAIDs related duodenal and gastric ulcer (43).

A study that was conducted in Italy found that 35% of the chronic NSAIDs users, who reported gastrointestinal symptoms, prescribed a drug for acid-related disorders, while only 14% used daily a PPI (45). Additionally, another study from France found that the proportion of prescriptions combining NSAIDs and gastroprotective agents was 29.5%, with omeprazole accounted for 58% of the co-prescriptions and misoprostol for 29.5% (5). Furthermore, Lazzaroni and Porro indicated that PPI are efficient in the treatment as well as prophylaxis

of non-steroidal anti-inflammatory drug related mucosal lesions of gastrointestinal tract (46).

Figure 2 shows that (10.85%) of the prescriptions are NSAIDs-antacid combination, which is much lower than the percentage (87.3%) reported by Liu et al. (47).

The sample of this study consists of (40.6%) of elderly patients. The risk of NSAID-related gastrointestinal toxicity is increased in this group of patients by more than 2 folds (48). As a result, this group of patients should be prescribed appropriate gastroprotective agents and/or COX-2 inhibitor.

#### CONCLUSION AND RECOMMENDATION

The study concludes that the traditional NSAIDs combined with a gastroprotective agents are the most appropriate first-line NSAID therapy for many patients. To minimize the occurrence of gastrointestinal toxicity, it is advised to use the National Institute of Clinical Excellence (NICE) guidance or the American College of Gastroenterology recommendations.

Future research should incorporate patient related factors such as the concurrent low dose aspirin use, prior upper GI events, concomitant use of anticoagulation, or corticosteroid therapy and use of multiple NSAIDs or high dose NSAIDs.

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