

## Original Research Article

# Prescription pattern of non-steroidal anti-inflammatory drugs (NSAIDs) among community patients with musculoskeletal and co-morbid conditions: A cross-sectional study from an Iraqi province

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### Abstract

**Purpose:** To determine the pattern of prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) co-prescription with NSAIDs in a sample of patients suffering from musculoskeletal disorders with and without co-morbid cardiovascular (CV) disease conditions in Baghdad Province, Iraq.

**Methods:** A descriptive, cross-sectional study was conducted using a structured questionnaire to assess the clinical characteristics of patients that used NSAIDs alone or with PPIs for the treatment of different musculoskeletal disorders with and without co-morbid cardiovascular (CV) disease conditions.

**Results:** A total of 102 participants were enrolled in the study. More than half of the participants had co-morbid disease conditions (53.9 %), particularly hypertension (47.1 %). Nearly a quarter of the participants with CV disease conditions used non-selective NSAIDs (25.5 %). The majority of NSAIDs intake were orally administered for more than one month (79.4 %). Physicians were the major source for patient education about the risk of NSAIDs-associated complications according to 59.6 % of the participants. The majority of participants reported non-adherence to the prescribed PPIs (86.5 %). There was a statistically significant difference between the participants that used NSAIDs alone, and those with PPI co-prescription within the age group of 31 - 60 years ( $p < 0.0001$ ) and for a duration of more than one month for NSAIDs administration ( $p < 0.0001$ ).

**Conclusion:** There is improper use of NSAIDs, particularly the non-selective agents, among patients with co-morbid cardiovascular disease conditions, as well as poor medication adherence and improper co-prescription of PPIs. This requires periodic revision for long-term intake of NSAIDs, while applying more care to high-risk patients regarding co-prescription of NSAIDs with PPIs.

**Keywords:** Cardiovascular, Co-morbidity, Gastrointestinal complications, NSAIDs, Proton-pump inhibitors

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## INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are the most common anti-inflammatory and analgesic agents used for the treatment of a wide range of musculoskeletal disease conditions [1]. They act through inhibition of COX-1 and COX-2 enzymes. The inhibition of COX-1 isoform enzyme is associated with the incidence of NSAIDs side effects, whereas inhibition of COX-2 isoform enzyme is associated with their pharmacological effects, including analgesic and anti-inflammatory effects [2].

Therefore, extensive use of NSAIDs in prescriptions or short-term, low doses of over-the-counter administration has been frequently associated with many gastrointestinal tract (GIT) complications, such as dyspepsia, gut inflammation, mucosal erosions, gastric and duodenal ulcers and bleeding [3]. The mechanism of NSAIDs-induced mucosal injury involves endothelial and epithelial erosions, and direct toxicity through ion trapping and ulceration. Besides GIT adverse effects, the use of NSAIDs is associated with a range of serious complications, including cardiovascular (CV) events, renal failure and hypersensitivity reactions [4,5].

Earlier studies reported that patients who use NSAIDs are four times more likely to develop uncomplicated peptic ulcer (PU) compared with non-users and 25% of chronic NSAID users. For arthritis, may develop signs of endoscopic ulcers [6,7]. Therefore, NSAIDs are associated with a high incidence of morbidity, particularly in elderly patients with co-morbid disease conditions, making their adverse effects a challenge in the optimized treatment of musculoskeletal disorders [8,9].

Proton pump inhibitors (PPIs), through their effective role in suppression of gastric acid secretion, are one of the most important drugs used in the treatment and prophylaxis of PU disease, severe reflux oesophagitis, Zollinger–Ellison syndrome, stress ulceration and prevention of NSAIDs-associated gastric ulcers. They have a central role in the eradication regimen of *Helicobacter pylori*, in combination with antibiotics, a treatment of PU disease [7,10]. The NSAIDs and PPIs are among the most frequently co-prescribed medications. Although there are no comprehensive and standard guidelines for the prescription of PPIs in NSAID-associated ulcers, these drugs are highly effective in the prevention and treatment of NSAID-associated ulcerative complications [11]. The aim of this present study was to evaluate the

pattern of prescription of NSAIDs alone, or with co-prescription of PPIs in a real-life setting in a sample of patients suffering from musculoskeletal conditions with and without CV events in Baghdad Province, Iraq.

## METHODS

### Study design and population settings

This was a descriptive, observational, and cross-sectional study involving patients enrolled from December 2018 to February 2019. A convenient sample of participants of different age groups was selected. Patients above the age of 18 years, and those who used NSAIDs alone or with co-prescription of PPIs for treatment of different musculoskeletal disease conditions with and without CV events were included in the study. Patients with a current or history of PU disease, GIT bleeding, renal disorders and those on concomitant intake of corticosteroids were excluded. The sample size calculation was based on Cochran's sample size formula for a large population whose degree of variability is not known, and taking 95% confidence level with  $\pm 5\%$  precision. Therefore, the required sample size with 0.35 effect size, 0.80 powers and alpha 0.05 was 105 participants.

Approval of the study was granted by the Ethical Committee of Human Research of the Pharmacy Department, Osol Aldeen University College, Baghdad Province, Iraq (03. 15.11.2018), based on the ethical standards of the Institutional Research Committee and the 1964 Helsinki Declaration and its later amendments [11]. There was no up-to-date list of community pharmacies around the time this study was performed. Therefore, a four-step sampling approach was implemented to ensure generalizability and minimize selection bias as following: the two main parts (divisions) of Baghdad Province were selected (Al-Karkh and Al-Rusafa) and each of these two parts was divided into four locations. Then, two of the most populous districts from each location were randomly selected. Finally, a convenience sample of community pharmacies was selected within each of these districts. The participants who expressed an agreement to take part in the study were fully informed about the objective of the study, and received written informed consent introduced by the researchers in the community pharmacy setting.

### Study outcomes

As aforementioned, all data were collected from the community pharmacies in Baghdad Province,

Iraq. The information was gathered via a structured, self-administered questionnaire developed for the present study, were distributed and filled by direct interview with the participants. The questionnaire was developed after a thorough and comprehensive literature search in well-known databases, and customized to suit the study purpose. The questionnaire consisted of 15 items in the data collected about the demographic and clinical characteristics of the participants, such as age, gender, educational level, cigarette smoking, the presence of co-morbid disease conditions, and information about use of NSAIDs alone or with co-prescription of PPIs for treatment of different musculoskeletal disease conditions, with and without CV events.

Medication adherence to the prescribed PPIs was assessed based on 4-item Morisky Medication Adherence Scale-MMAS which comprises of four questions. The scores of this scale are based on patient responses to four questions, and patients were considered adherent when they had a maximum score of four points if they answered "no" (No = 1). While, they were considered non-adherent when they had three points or less if they answered "yes" to any question (Yes = 0) [12].

### Statistical analysis

Data were analysed using Statistical Package for Social Science (SPSS) version 23.0 and Microsoft Office Excel 2013. Descriptive analysis was used to analyse the study population, and the findings for each of the study variables and characteristics are expressed in numbers, percentages, means, and standard deviations. Chi-Square Test was used to study the association between groups. Significant results were considered at  $p < 0.05$  and highly significant at  $p < 0.01$ .

## RESULTS

In this study, 102 participants were enrolled with a mean age of  $44.1 \pm 17.5$  y. The socio-demographic characteristics of the study participants are as presented in Table 1. The majority of the study participants were females (53.9 %), and possessed university-level qualification (43.2 %) and within the group of 31 – 60 y (59.8 %).

The clinical characteristics of the study participants prescribed NSAIDs are as presented in Table 2. The majority of the study participants had simultaneous occurrences of musculoskeletal and CV conditions (53.9 %).

Hypertension (HT) and diabetes mellitus (DM) were the most common co-morbid medical conditions observed (47.1, 27 %), respectively. Moreover, the findings of this study showed that 25.5 % of the participants with CV conditions used non-selective NSAIDs, aside from low-dose aspirin.

**Table 1:** Demographic characteristics of the study participants

Variables	Number (n)	Percentage (%)
<i>Gender</i>		
Males	47	46.1
Females	55	53.9
<i>Age range (years)</i>		
18-30	15	14.7
31-60	61	59.8
>60	26	25.5
<i>Educational level</i>		
No formal education	24	23.5
Primary	15	14.7
Secondary	19	18.6
University	44	43.2
<i>Cigarette smoking</i>		
Yes	45	44.1
No	57	55.9

Data presented in number and percentage: n, %

Table 2 shows the types and routes of administration of the prescribed NSAIDs among the study participants. The findings of the present study showed that more than three-quarter of the study participants used different oral NSAIDs, including aspirin (17 %), ibuprofen (12.3 %) followed by 9.4 % as a similar proportion for the other agents. Majority of the prescribed NSAIDs were orally administered (79.2 %) with duration of more than one month (79.4 %).

More than half of the study participants recorded having proper education about the risk of NSAIDs-associated complications. Consequently, 59.6 % of those participants stated that physicians were the major source for patient education about the risk of NSAIDs-associated complications.

The present study revealed that 36.3 % of the study participants prescribed PPI. Meanwhile, omeprazole was the most common PPI medication co-prescribed with NSAIDs, followed by pantoprazole (27.9 %). The majority of the study participants reported non-adherence to the prescribed PPIs medication (86.5 %), as shown in Table 3.

**Table 2:** Clinical characteristics of the study participants prescribed NSAIDs

Variables	Number (n)	Percentage (%)
<i>Presence of co-morbid disease conditions</i>		
Yes (musculoskeletal and CV)	55	53.9
No (musculoskeletal alone)	47	46.1
<i>Common types of co-morbid disease conditions</i>		
Diabetes Mellitus	23	27
Hypertension	40	47.1
Hyperlipidaemia	8	9.4
Other CV	14	16.5
<i>Use of non-selective NSAIDs in patients with CV conditions (aside from low-dose aspirin)</i>	26	25.5
<i>Types of the prescribed NSAIDs (n=106)</i>		
Naproxen	10	9.4
	13	12.3
Ibuprofen	18	17
Aspirin	10	9.4
Diclofenac	10	9.4
Mefenamic acid	25	23.6
Paracetamol	10	9.4
Meloxicam	10	9.4
Piroxicam		
<i>Route of administration of the prescribed NSAIDs (n=106)</i>		
Oral	84	79.2
	7	6.6
Parenteral	15	14.2
Rectal		
<i>Duration of therapy of the prescribed NSAIDs</i>		
< 1-month duration	21	20.6
> 1-month duration	81	79.4
<i>Provision of proper education about the risk of NSAIDs-associated complications</i>		
Yes	57	55.9
	45	44.1
No		
<i>Source for the previous education about the risk of NSAIDs-associated complications</i>		
Physician advice	34	59.6
Pharmacist advice	23	40.4

CV: Cardiovascular; NSAIDs: Non-steroidal anti-inflammatory drugs; Data presented in number and percentage: n, %

**Table 3:** Clinical characteristics of the study participants prescribed NSAIDs plus PPIs

Variable	Number (n)	Percentage (%)
<i>Provision of PPI therapy</i>		
Yes	37	36.3
No	65	63.7
<i>Types of PPI medications prescribed based on the current medical condition</i>		
Omeprazole	26	70.3
Pantoprazole	11	29.7
<i>Medication adherence to PPI therapy</i>		
Yes	5	13.5
No	32	86.5

PPIs: Proton pump inhibitors. Data presented in number and percentage: n, %

The present study also revealed that there was a statistically significant difference between the participants using NSAIDs alone and those with co-prescription of a PPI regarding age group of 31-60 years (62.3 %;  $p < 0.0001$ ), university

education level (72.7 %;  $p < 0.0001$ ), and duration for the administration of NSAIDs of more than one month of treatment (66.7 %;  $p < 0.0001$ ), as shown in Table 4.

**Table 4:** Association between participants' characteristics and use of NSAIDs alone and NSAIDs plus PPIs

Variables		Use of NSAIDs plus PPIs N=37 n (%)	Use of NSAIDs Alone N=65 n (%)	*P-value
<i>Gender</i>	Males	17 (36.2)	30 (63.8)	0.52
	Females	20 (36.4)	35 (63.6)	
<i>Age range (years)</i>	18-30	4 (26.7)	11(73.3)	<0.0001
	31-60	23 (37.7)	38 (62.3)	
	>60	10 (38.5)	16 (61.5)	
<i>Educational level</i>	No formal education	11 (45.8)	13 (54.2)	<0.001
	Primary	6 (40)	9 (60)	
	Secondary	8 (42.1)	11 (57.9)	
	University	12 (27.3)	32 (72.7)	
<i>Smoking</i>	Yes	12 (32.4)	30 (46.2)	0.52
	No	25 (67.6)	35 (53.8)	
<i>Presence of co-morbid medical conditions</i>	Yes (musculoskeletal and CV)	28 (51)	27 (49)	0.17
	No (musculoskeletal alone)	9 (19.1)	38 (80.9)	
<i>Duration of therapy of the prescribed NSAIDs</i>	< 1-month duration	10 (47.6)	11 (52.4)	<0.0001
	> 1-month duration	27 (33.3)	54 (66.7)	

Data presented in number and percentage: n, %; highly significant at  $P \leq 0.01$ , \*Chi square test

## DISCUSSION

The NSAIDs are the most frequently prescribed drugs, and their use requires careful consideration among high-risk patients. The present study shows that the majority of the participants using NSAIDs had chronic co-morbid disease conditions, particularly HT and DM. An earlier study reported that the short or long-term use of selective and non-selective NSAIDs, excluding low-dose aspirin, is associated with increased CV risk. The use of non-selective NSAIDs in patients with pre-existing co-morbid disease conditions particularly HT could elevate systolic blood pressure by an average value of 2-3 mmHg. Therefore, BP should be regularly monitored in hypertensive patients particularly during long-term treatment. Furthermore, these drugs may double the risk of hospital admission due to heart failure (HF) in individuals with no history of CV disease conditions and 10-fold increase in patients with HF. On the other side, inhibition of platelet aggregation by the activity of selective COX-2 NSAIDs results in thrombosis and other CV events such as myocardial infarction (MI) [3,13,14].

A cohort study by Schjerning Olsen *et al* [15] conducted on patients with a history of MI found that the short-term use of NSAIDs increased the risk of MI recurrence or death by 1.45 times, particularly during the first week of therapy, and this risk could be continued throughout the course of treatment. Many drug interactions are also reported with the use of NSAIDs in CV disease conditions, such as antagonizing the effect of antihypertensive drugs and decreasing the efficacy of diuretics. On the other hand, patients with type 2 DM should avoid NSAIDs where possible since the preservation of renal function is an essential part in the management of patients with type 2 DM, in order to prevent the development of micro- and macro-vascular complications [16].

The findings in this study reveal that the majority of the participants used different oral non-selective NSAIDs with their recommended daily dose to achieve the required analgesic and anti-inflammatory response. Moreover, a quarter of the study participants with simultaneous musculoskeletal and CV disease conditions used non-selective NSAIDs. An earlier study reported that patients with CV conditions are at increased risk even after the use of selective NSAIDs, or

after few doses of non-selective NSAIDs particularly diclofenac, which could increase the risk of MI and/or death by 3.26 times within the first week of treatment [15]. Based on this evidence, 1 g daily dose of naproxen does not appear to be associated with increased CV risk. This is related to its relatively prolonged and intense inhibition of COX-1, effective platelets blocking and its ability to offset the prothrombotic effect of COX-2 inhibition [2,15]. Therefore, longer half-life NSAIDs, such as naproxen, or NSAIDs with long-acting dosage forms with once or twice daily administration are more appropriate for the treatment of chronic musculoskeletal disorders in patients with co-morbid disease conditions [17].

In the present study, the majority of the prescribed non-selective NSAIDs were orally administered with their recommended daily dose for a duration of more than one month to achieve the required analgesic and anti-inflammatory response. This could increase the risk of GIT complications by 2-4 folds in a dose dependent manner, particularly in co-morbid elderly patients [17]. Therefore, topical use of NSAIDs is considered a safe alternative for treatment of musculoskeletal disorders in patients with co-morbid disease conditions or NSAIDs-associated GIT complications. Alternatively, the use of relatively less gastrototoxic NSAID, such as diclofenac may be preferred in place of a more potent gastrototoxic NSAID, such as ibuprofen, indomethacin, piroxicam and naproxen [18]. However; this could go contrary to the preferred use of naproxen and the avoidance of diclofenac in patients with CV disease conditions. Therefore, the alternative use of selective COX-2 inhibitors, such as celecoxib, nabumatone, and etodolac is recommended for long-term NSAIDs treatment, as they have fewer gastrototoxic effects by 4-fold than non-selective NSAIDs. However, their use is also limited by the increased risk of poor CV outcomes [2,16].

In the present study, a high proportion of the study participants stated having proper education about the risk of NSAIDs-associated complications majorly provided by the physicians. However, considering that the majority of patients were seen in the community pharmacies, this highlights the responsibility of pharmacists to the provision of patient education for disease conditions, rational intake of drugs, enhance medication adherence, identification of drug-related problems and optimization of pharmacotherapy [19-21]. Regarding the co-prescription of NSAID with PPI, the majority of the participants were non-adherent to PPI intake. Accordingly, physicians have to consider the high-risk features for GIT adverse effects while

prescribing NSAIDs, including a history of a GI event, age above 45 years, history of CV disease conditions and simultaneous use of other medicines particularly anticoagulants, corticosteroids, aspirin, previous adverse reaction to NSAIDs and renal diseases [5].

The findings of this study showed a statistically significant difference between the participants using NSAIDs alone, and those with co-prescription with a PPI regarding age group of 31-60 years, education level and duration of NSAIDs administration after more than one month of treatment. A survey study by Duong *et al* [22] found a clinically underutilized knowledge regarding the use of gastro-protective drugs with NSAIDs among internal medicine residents in several major teaching hospitals. An earlier study reported that NSAID-related GIT lesions tend to persist even after drug discontinuation, and use of alternative agent may not help in ulcers healing [23].

Therefore, less gastrototoxic NSAID can be used in patients with low GIT risk; selective COX-2 NSAID can be used in patients with a high-risk development of GIT complications or co-prescribed with PPI for long-term use in treatment of musculoskeletal conditions [1,24]. PPIs should be taken on a regular daily basis, rather than on need use, in order to achieve maximum inhibition of gastric acid secretion and produce the required therapeutic effect of these drugs [25]. However, as the long-term use of PPIs is associated with severe adverse effects, their prescriptions should be supported by evidence-based medicine, with the lowest effective dose and for the shortest possible duration [26].

### Limitations of the study

The present study has some limitations that should be taken into account. Firstly, the study was conducted with a reduced sample size of participants. Secondly, a number of exclusion criteria such as patients with current or history of PU, GIT bleeding, renal disorders and those on concomitant intake of corticosteroids led to a reduction in the number of participants. Thirdly, the study did not include the assessment of disease duration concerning musculoskeletal conditions and medications used in patients with co-morbid disease conditions. Finally, further studies could be carried out on a large sample size to determine the impact of a pattern of NSAIDs use in patients suffering from musculoskeletal conditions with different co-morbid diseases.

## CONCLUSION

The findings of the present study reveal improper use of NSAIDs, particularly the non-selective agents, and under-recognised risk of NSAIDs-related complications among patients with comorbid cardiovascular disease conditions. The study also indicates poor medication adherence and improper co-prescription of PPIs among the patients. This requires determining true needs based on individual basis, and a periodic revision for long-term intake of NSAIDs while applying more care to high-risk patients regarding the co-prescription of NSAIDs with PPIs.

## DECLARATIONS

### Conflict of interest

No conflict of interest is associated with this work.

### Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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