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Original article

# Nonsteroidal Anti-inflammatory Drugs Utilization Patterns and Risk of Adverse Events due to Drug-Drug Interactions among Elderly Patients: A Study from Jordan

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## ABSTRACT

**Background:** Worldwide, the prescribing pattern of the Nonsteroidal Anti-inflammatory Drugs (NSAIDs) has increased. They are considered highly effective medications in controlling various conditions including inflammatory diseases. They are associated with various adverse effects including gastrointestinal bleeding and ulcer and renal toxicity though. These adverse effects are generally potentiated when NSAIDs are co-prescribed with other drugs that share similar adverse effects and toxicities. Developing severe side effects from NSAIDs is more prone among elderly patients. Hence, it is crucial to evaluate prescribing pattern of these agents to prevent/decrease the number of unwanted side effects caused by NSAIDs.

**Aim:** The aim of this study is to assess the prescribing pattern of NSAIDs among elderly and the co-prescribing of NSAIDs and different interacting drugs, which could lead to more incidences of NSAIDs-induced toxicities among Jordanian elderly patients.

**Settings and Methodology:** A multicenter retrospective study was performed during a three months period in Jordan. The study involves a total number of (n = 5916) elderly patient's records obtained from Four governmental hospitals in Jordan.

**Results:** A total number of (n = 20450) drugs were prescribed and dispensed for patient. NSAIDs drugs prescribing percentage was 10.3% of total medications number. Aspirin was the most commonly prescribed NSAIDs among patients (70.4%), followed by Diclofenac sodium in all dosage forms (25.1%) and oral Ibuprofen (3.1%. In addition, Aspirin was the highest NSAIDs co-prescribed with ACEI (e.g., Enalapril), ARBs (e.g. Candesartan and Losartan), Diuretics (Furosemide, Indapamide, Hydrochlorothiazide, Amiloride, and Spironolactone), Warfarin and antiplatelets (Clopidogrel and Ticagrelor) followed by Diclofenac and other NSAIDs.

**Conclusion:** NSAIDs prescribing rate among elderly patients was high. Additionally the co-prescribing of NSAIDs especially Aspirin with other agents, which contributes to NSAIDs nephrotoxicity and gastrointestinal toxicity, were high. Strict measurements and action plans should be taken by prescribers to optimize the medical treatment in elderly through maximizing the benefits and decreasing the unwanted side effects.

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**Abbreviations:** NSAIDs, Nonsteroidal Anti-inflammatory Drugs; ACEI, Angiotensin converting enzyme inhibitors; ARBS, Angiotensin II Receptor Blockers; GIT, Gastrointestinal; COX-1&2, Cyclooxygenase enzyme 1&2; AKI, Acute Kidney Injury; CKD, Chronic Kidney Disease.

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## 1. Introduction

Over the last few years, the clinical and experimental evidence of the use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) including aspirin for the treatment and relief of various inflammatory conditions has increased. NSAIDs are drugs of choice for the management of many inflammatory disorders, such as arthritis (rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and reactive arthritis), ankylosing spondylitis, and muscle and joint injuries. Moreover, they are widely prescribed to relief symptomatic post-operative pain, muscle stiffness, acute gout, dysmenorrhea, headache, and migraine (Wongrakpanich et al., 2018). Low dose Aspirin is a commonly prescribed antiplatelet to inhibit thrombus formation, thus, primary and secondary prophylaxis against cardiovascular events and ischemic stroke (Capodanno et al., 2019).

NSAIDs are pharmacologically classified into two main classes, (i) the selective COX-2 inhibitors like Celecoxib and (ii) the non-selective COX inhibitors like Aspirin, Ibuprofen and Diclofenac sodium/potassium. NSAIDs work through inhibiting the activity of cyclooxygenase enzymes-1 and 2 (COX-1 and COX-2), therefore inhibiting the formation of prostaglandins from arachidonic acids, which are involved in various physiological and pathological conditions including inflammation, platelets aggregation, and body temperature elevation (Vitale et al., 2016).

Indeed, several previous studies and reports have confirmed that NSAIDs are associated with unwanted adverse effects, some of which exert a serious health impact (Wongrakpanich et al., 2018). Utilization of NSAIDs may cause liver and renal toxicity, gastrointestinal (GIT) bleeding and ulcer. Furthermore, all NSAIDs except aspirin can increase the risk of major cardiovascular (CVS) events such as edema, stroke, myocardial infarction and congestive heart failure (Harirforoosh et al., 2013, Huang et al., 2019).

Furthermore, a number of reports have revealed that NSAIDs could alter kidney function leading to renal impairment particularly, when co-utilized / prescribed with other nephrotoxic agents including angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs) and diuretics (Bucsa et al., 2015, Dorks et al., 2016). Inhibition of COX-1 and COX-2 enzymes at renal level could lead to changes in the renal hemodynamic process, decrease in the glomerular filtration rate (GFR), and hyperkalemia (Song et al., 2011).

Chronic medical conditions including hypertension and diabetes are very common among elderly. These medical conditions are attributable in general to increasing the prevalence of chronic kidney disease (CKD) (Ghaderian and Beladi-Mousavi, 2014). On the other hand, elderly patients are usually present with polypharmacy prescribing issues to control their multi-disease conditions (Maher et al., 2014). NSAIDs are among the highly prescribed medications in elderly and reports from various studies have shown that high cumulative utilization of NSAIDs could lead to rapid progression to CKD among elderly patients, which could raise the rate of morbidity and mortality among this population. The most updated Beers' Criteria developed by American Geriatric Society highlighted the caution use of NSAIDs in elderly and contraindicated their use in these patients with stage IV and V CKD (CRCL < 30 ml/min) according to beer's criteria (By the American Geriatrics Society Beers Criteria Update Expert, 2015, Al-Azayzih et al., 2019, By the American Geriatrics Society Beers Criteria Update Expert, 2019).

Concomitant use of NSAIDs with specific medications such as warfarin, heparin, corticosteroids, clopidogrel and other oral antiplatelet medications (e.g, dipyridamole and ticagrelor) could increase the risk of developing gastrointestinal bleeding or ulcer among elderly population (Comoretto et al., 2018). Therefore,

NSAIDs should be avoided when possible or at least used with more caution when used with these medications.

Methotrexate and digoxin are among the most common drugs used in elderly patients to control conditions of rheumatoid arthritis and symptomatic heart failure, respectively. Hence, their use with NSAIDs should be monitored carefully as their plasma concentration level might increase due to their low therapeutic index leading to toxicity as a result of the reduction in their renal clearance complicated by the use of some types of NSAIDs (Svanstrom et al., 2018, Wongrakpanich et al., 2018).

In Jordan, elderly represent almost 5% of the whole population according to the department of general statistics in Jordan 2018 (Department of Statistics, 2018). Several studies have reported before the high prevalence of various cardiovascular (CVS) diseases including hypertension and diabetes among the Jordanian population including elderly patients with higher prevalence of chronic diseases compared to other age groups (Khader et al., 2019, Ajlouni et al., 2019, Jarab et al., 2018). Irrational and inappropriate prescribing habits and high polypharmacy prevalence among Jordanian elderly patients were reported before in our previous reports (Al-Azayzih et al., 2017, Al-Azayzih et al., 2019).

Taking all together, elderly patients in Jordan are at high risk to develop other health conditions including CKD and GIT complications taking into account the high prevalence of leading risk factors that include the presence of other co-morbidities, polypharmacy and associated drug-drug interactions, beside administration of nephrotoxic drugs such as NSAIDs and other agents which contribute to NSAIDs toxicity.

### 1.1. Aims of the study

The aim of the current study is to evaluate the prescribing pattern of NSAIDs in elderly population and to evaluate the occurrence of co-prescribing these agents with other drugs, which can contribute significantly to NSAIDs-induce toxicity among these patients in Jordan.

### 1.2. Ethics Approval

The study has obtained the approval from the Institutional Review Board (IRB) of King Abdullah University Hospital (KAUH), Prince Hamza Hospital, and the Ministry of Health (MOH) Hospitals in Jordan.

## 2. Methods

### 2.1. Study settings, subjects, and data collection

A cross-sectional retrospective multicenter study was conducted in outpatient pharmacies of Four Hospitals in Jordan including, Al-Bashir Hospital, King Abdullah University Hospital (KAUH), Al-Karak Governmental Hospital and Prince Hamza Hospital (PHH). All prescriptions were collected over 3 months periods for all elderly patients of equal to or above 65 years of age) who attended the outpatient clinics in those hospitals and received one prescription at least during the entire study period. Further work was done to avoid any duplications in patients' encounters and to separate prescriptions containing NSAIDs from these containing no NSAIDs for further analysis.

A total number of (n = 5916) patient's prescription records were evaluated. Gathering of data was conducted through gathering information from patients' medication records including demographic data, clinical characteristics as well as the prescribed medications for all patients aged 65 years or more.

## 2.2. Statistical analysis

Statistics including averages, percentages, frequencies, and standard deviation (SD) were used to represent patients' characteristics and demographics, estimate the frequency of NSAIDs prescribing among elderly, and co-prescribing prevalence with other specific medications. Multivariable logistic regression analysis was used to investigate potential predictor factors linked to NSAIDs use. P value of <0.05 was considered statistically significant. All analyses were performed using SPSS-16.0 software and Microsoft Excel 2016 (Version 12.0).

## 3. Results

Elderly patients (n = 5916) were incorporated in this study. Mean age  $\pm$  SD was  $72.2 \pm 5.8$  years. Total number of male patients was 3174 (53.6%). Of total 20,450 prescribed drugs, NSAIDs number was 2115 (10.3% of total medications). Average number of drugs for each encounter (prescription) was  $3.5 \pm 2.35$ . Overall, 29.7% of total patients were prescribed at least five medications ( $\geq 5$  drugs) or more (polypharmacy) and excessive polypharmacy ( $\geq 10$  drugs) was found to be 2.1% of total subjects (Table 1). Aspirin was found to be the most prescribed NSAIDs among elderly patients (70.4%) followed by Diclofenac sodium in all dosage forms (25.1%) and oral ibuprofen (3.1%). Indomethacin, celecoxib, and meloxicam represent the remaining of the NSAIDs prescribed with total percentage of 1.4% of total NSAIDs utilized (Table 2). NSAIDs were prescribed with either ACEI /ARBs (N = 884 (47.4%)) or diuretics (N = 629 (33.7%)), or therapy of at least one NSAIDs with ACEI/ARBs and diuretics (N = 412 (22.1%)). Aspirin was found to be to most commonly co-prescribed NSAIDs with ACEI (e.g., enalapril), ARBs (e.g. candesartan and losartan), and diuretics (furosemide, indapamide, hydrochlorothiazide, amiloride, and spironolactone) followed by diclofenac sodium, ibuprofen, meloxicam, celecoxib, and indomethacin (Table 3). Evaluating the co-prescribing of NSAIDs with drug that could rise the risk of GIT bleeding or ulcer if administered with NSAIDs such as warfarin, corticosteroids, or oral antiplatelets (e.g. clopidogrel, dipyridamole, ticagrelor). Aspirin was found to be the most co-prescribed NSAIDs with those agents followed by diclofenac and ibuprofen. Meloxicam was only prescribed with other antiplatelet and was not co-prescribed with either warfarin or corticosteroids. Indomethacin and celecoxib were not co-prescribed with any of those drugs (Table 4). Then, we evaluated the co-prescribing prevalence of NSAIDs with drugs (e.g., digoxin and methotrexate). A total number of (n = 55) and (n = 12) patients were prescribed digoxin and methotrexate with

**Table 2**

Non-steroidal Anti-inflammatory Drug (NSAIDs) Prescribing Frequency.

Non-steroidal Anti-inflammatory Drug (NSAIDs)	Frequency N=(% of total)
Aspirin	
Tablets (100 mg and 325 mg)	N = 1488 (70.4%)
Diclofenac Sodium	
Tablets (50 mg and 100 mg)	N = 256 (12.1%)
Suppositories (100 mg)	N = 18 (0.9%)
Injections (25 mg/ml)	N = 7 (0.3%)
Topical 1% gel	N = 250 (11.8%)
TOTAL	N = 531 (25.1%)
Ibuprofen	
Tablet (400 mg)	N = 66 (3.1%)
Indomethacin Capsule (25 mg)	N = 11 (0.5%)
Celecoxib	
Capsule (200 mg)	N = 10 (0.5%)
Meloxicam	
Capsule (15 mg)	N = 9 (0.4%)
<b>Total</b>	<b>N = 2115 (100%)</b>

**Table 3**

NSAIDs co-prescribing frequency with ACEI/ARBs and diuretics, which could increase NSAIDs- induced nephrotoxicity and cause hyperkalemia.

Non-steroidal Anti-inflammatory Drug (NSAIDs)	NSAIDs + ACEI or ARBs N=	NSAIDs + Diuretics N=	NSAIDs + ACEI or ARBs + Diuretic N=
Aspirin	854	606	401
Diclofenac Sodium (without Diclofenac gel)	8	9	3
Ibuprofen	7	6	4
Meloxicam	7	5	3
Celecoxib	5	2	0
Indomethacin	3	1	1
<b>*Total</b>	<b>N = 884 (47.4%)</b>	<b>N = 629 (33.7%)</b>	<b>N = 412 (22.1%)</b>

ACEI: Angiotensin converting enzyme inhibitors, ARBs: Angiotensin II Receptor Blockers.

\* Total percentages were calculated based on total number of NSAIDs equal of 1865 drugs (without Diclofenac Topical)

at least one NSAIDs out of 192 and 34 patients, respectively (Table 5). We finally sought to determine the predictors of NSAIDs prescribing among elderly patients. We found that NSAIDs prescribing and utilization was significantly associated female gender. Age was not associated with more use of NSAIDs (Table 6).

**Table 1**  
Patients Characteristics and Demographics.

Variable	Category	N $\pm$ SD	Percentage (%)
Gender	Female	2742	46.3%
	Male	3174	53.6%
	Total	5916	100%
Total Number of Patients' Encounters (Prescriptions) included of Medications	1	1455	24.6%
	2	1107	18.7%
	3	917	15.5%
	4	678	11.5%
	$\geq 5$	1759	29.7%
Total Number of Drugs Prescribed for Patients		20,450	
Average Number of Drugs per Encounter (Prescription)		$3.5 \pm 2.35$	
Frequency of NSAIDs prescribing among patients		2115	(10.3%) of total Drug Prescribed
Polypharmacy index ( $\geq 5$ drugs)		1759	29.7%
Excessive Polypharmacy Prevalence ( $\geq 10$ drugs)		124	2.1%

**Table 4**

NSAIDs co-prescribing with other interacting drugs, which could increase NSAIDs- induced Gastrointestinal (GIT) bleeding and ulcer.

Non-steroidal Anti-inflammatory Drug (NSAIDs)	NSAIDs + Warfarin and other Anticoagulants N=	*NSAIDs + Corticosteroids N=	**NSAIDs + other NSAIDs or Antiplatelets N=
Aspirin	113	50	135
Diclofenac Sodium (without Diclofenac gel)	4	5	6
Ibuprofen	1	0	7
Meloxicam	0	0	1
Celecoxib	0	0	0
Indomethacin	0	0	0
<b>#Total</b>	<b>N = 118 (6.3%)</b>	<b>N = 55 (3.0%)</b>	<b>N = 149 (8.0%)</b>

# Total percentages were calculated based on total number of NSAIDs equal of 1865 drugs (without Diclofenac Topical).

\* Only oral and injectable Corticosteroids were included such as, Prednisone and Methylprednisolone.

\*\* Antiplatelet include Clopidogrel, Dipyridamole, and Ticagrelor.

**Table 5**

NSAIDs Co-prescribing frequency with either Digoxin or Methotrexate.

Non-steroidal Anti-inflammatory Drug (NSAIDs)	*NSAIDs + Digoxin N=	**NSAIDs + Methotrexate N=
Aspirin	55	4
Diclofenac Sodium (without Diclofenac gel)	0	5
Ibuprofen	0	0
Meloxicam	0	1
Celecoxib	0	2
Indomethacin	0	0
<b>Total</b>	<b>55</b>	<b>12</b>

\* Total Number of Prescriptions including Digoxin was 192.

\*\* Total Number of Prescriptions Including Methotrexate was 34.

**Table 6**

Predictors of NSAIDs prescribing among elderly patients.

Variable	AOR (95% CI)	*P value
Gender (Female)	1.344 (1.211–1.493)	<0.001
Age	0.992 (0.983–1.001)	0.075

AOR: Adjusted Odds Ratio.

CI: Confidence Interval.

\* P value was considered statistically significant at &lt;0.05.

#### 4. Discussion

The current study and to the best of our knowledge, is the first to evaluate the NSAIDs prescribing prevalence among elderly out-patients in Jordan. Moreover, it does evaluate the co-prescribing pattern of NSAIDs and other medications that interact with them leading to severe adverse effects among elderly population. Hence, evaluating the prescribing and co-prescribing of NSAIDs with other drugs is of high importance, as it will lead to better understanding of how to prohibit and discourage irrational drug prescribing and utilization and how we can improve the treatment outcomes with lessen possible harm to elderly population.

Our results showed that almost one third of elderly patients were subjected to polypharmacy prescribing with high prevalence of NSAIDs prescribing among patients with at least one of every three prescriptions include a NSAID. As expected, Aspirin was the most frequently prescribed NSAIDs due to its antiplatelet properties and indication as either primary or secondary prophylaxis therapy against major cardiovascular events and stroke among elderly. A recent report has shown that NSAIDs was prescribed for around 60% of elderly patients attending the primary care units at the Kingdom of Bahrain (Al Khaja et al., 2017). A study was conducted in Kingdom of Saudi Arabia found that NSAIDs were pre-

scribed in 38.5% of diabetic patients attending the primary care facilities there (Mazhar et al., 2018). Other studies from Netherlands and Italy reported a NSAIDs prescription rate of 73% and 20% among elderly patients (Visser et al., 2002, Motola et al., 2004) respectively.

Administration of triple nephrotoxic therapy including NSAIDs, ACEI/ARBs, and diuretics could lead elevated creatinine level and progress of acute kidney injury (Thomas, 2000, Loboz and Shenfield, 2005), especially in elderly patients with a number of comorbidities, polypharmacy problems, and the aging process itself that is characterized by general decline in various organ functions including kidney and liver. A cohort study from Canada has shown that triple therapy of NSAIDs plus ACEI/ARBs and diuretics was accompanying with higher risk of developing acute kidney injury (AKI) among patients, and the greatest risk of AKI and renal function was noticed at the beginning of treatment and also, was correlated positively with the frequency of NSAIDs prescription within short period of time (Lapi et al., 2013, Bouvy et al., 2003).

The co-prescribing pattern of NSAIDs with other drugs responsible for more frequent GIT bleeding or ulcer cases when used with NSAIDs was evaluated in this study and results showed a co-prescribing prevalence of 6.3% with warfarin and other anticoagulants, 3.0% with corticosteroids, and 8.0% with other NSAIDs and/or antiplatelets. A recent cohort study has conducted in United States has shown that bleeding risk could be different among individual NSAID, when co-utilized with clopidogrel. Suggesting the need for furthered assessment of which NSAID could be associated with less bleeding risk when co-prescribed with clopidogrel (Nam et al., 2018).

Previous studies have reported that Co-utilization of two or more NSAIDs at the same time could be associated with folded increase in liver toxicity among those utilizing more than one NSAIDs simultaneously or use of NSAIDs with other hepatotoxic medications including antimicrobial agents (Garcia Rodriguez et al., 1994).

Elderly population is generally present with various conditions and a large number of diseases are generally connected to aging process and changes in the physiological functions in this population. Arthritis and other autoimmune diseases, heart failure, and arrhythmia commonly seen among elderly patients. Thus, Methotrexate and digoxin are generally more prescribed for elderly. Additionally these drugs are known to interact with NSAIDs as there renal clearance could be affected and declined by co-utilization of NSAIDs (Colebatch et al., 2012, Crofford, 2013, Jorgensen et al., 1991). Therefore, it is very important to evaluate the co-prescribing pattern of these drugs with NSAIDs. Our results indicated that out of 192 and 34 prescriptions included digoxin and methotrexate, respectively; NSAIDs were co-prescribed with digoxin and methotrexate in 55 (28.6%) and 12 (35.3%) prescriptions respectively.

In our current study, female gender was found to be associated with more prescribing of NSAIDs among elderly. Females are generally more susceptible to develop chronic and autoimmune diseases and conditions such as arthritis, which could explain the more use of NSAIDs and pain killer among female compared to male patients (van Vollenhoven, 2009).

The strengths of our study are as follows: (i) the research evaluated a large sample size. Indeed patients records included were taken from different Jordanian hospitals covering different geographical areas in Jordan (North, Middle, and South regions). (ii), these hospitals are among the busiest hospitals in Jordan and serve a large portion of the Jordanian population. (iii), our study was the first report to evaluate the co-prescribing pattern of NSAIDs and other interacting medications among elderly Jordanian patients.

The retrospective nature of our study and the inclusion of only public governmental hospitals without including the private sector health facilities or hospitals are two limitations for our study.

## 5. Conclusion

This study demonstrates an elevated rate of NSAIDs prescribed among elderly patients in Jordan as well as a high prevalence of co-prescribing and dispensing of NSAIDs with other interacting drugs, which might potentiate the NSAIDs-induced nephrotoxicity or gastrointestinal bleeding and toxicity. A number of measurements and comprehensive health care plans for elderly should be adopted taking in consideration the risk of inappropriate prescribing for NSAIDs.

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## Declaration of Competing Interest

None.

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