

Prescription Pattern Analysis of Nonsteroidal Anti-inflammatory Drugs in the Northeastern Iranian Population

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ABSTRACT

Objective: Inappropriate nonsteroidal anti-inflammatory drugs (NSAIDs) therapy is a common cause of actual and potential adverse effects, such as bleeding and gastrointestinal ulceration, which exacerbates the patient's medical condition and might even be life threatening. We aimed to evaluate and analyze the prescription pattern of NSAIDs in Northeastern Iranian population and also provide suggestions for a more rational prescription behavior for such drugs. **Methods:** In this cross-sectional retrospective study, pattern of 1-year prescriptions was inspected based on 9.3 million prescriptions from two insurance companies. Type of NSAIDs, all dispensed doses and the number of NSAIDs ordered per prescription, and the route of administration for each patient were extracted from the databases. The prescription pattern of NSAIDs was analyzed seasonally. **Findings:** Out of 9,303,585 prescriptions, 19.3% contained at least one NSAID. Diclofenac was the most commonly prescribed NSAID (49.21%). At least two NSAIDs were simultaneously prescribed in 7% of prescriptions. General practitioners prescribed NSAIDs more frequently (67%) than specialists. Orthopedic surgeons and internists more frequently prescribed NSAIDs in comparison with other physicians (6% and 4%, respectively). Gastroprotective agents (GPAs) were coprescribed to only 7.62% of prescriptions. **Conclusion:** The frequency of NSAIDs prescription was relatively high in Northeast of Iran. A significant number of prescriptions were associated with irrational prescribing in both coadministration of NSAIDs and GPAs and NSAIDs combination. A strategy must be developed and implemented for prescribing and rational use of medications, e.g., continuing medical education regarding the potential risks of NSAIDs, importance of their appropriate and rational use, and necessity of appropriate prescription writing regarding both content and indication.

KEYWORDS: Iran, nonsteroidal anti-inflammatory drugs, prescribing behaviors, rational prescription pattern

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used groups of drugs^[1] since they

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are easily available and reachable. NSAIDs are used to alleviate pain, fever, and inflammation by decreasing prostaglandin synthesis through blockage of the cyclooxygenase (COX) enzymes. Physicians should take precautions based on the patient's risk, once they prescribe NSAIDs.^[2] NSAIDs have a wide range of adverse effects, such as upper and lower gastrointestinal disturbances, blood pressure elevation, and increased risk of cardiovascular disorders.^[3-8] It has been previously found that NSAIDs cause adverse effects in 25% of patients.^[7,9]

Important factors that can contribute to adverse effects include availability of NSAIDs as over-the-counter (OTC) medicines, duration of treatment, dose, coadministration with other drugs, especially in elderly, and exclusion of proton-pump inhibitors (PPIs) as gastroprotective agents (GPAs).^[8,10,11] NSAIDs account for approximately 10% of hospitalizations among elderly patients in the United States.^[7,12,13] Elderly are using NSAIDs more than other age groups. Age-related changes in NSAID pharmacodynamics predispose the elderly to NSAID-related adverse effects. Furthermore, the increasing risk of adverse drug reactions in the elderly may be due to pharmacological interactions among multiple drugs prescribed to deal with concomitant multiple diseases.^[8] The highest risk for children taking NSAIDs is dosage errors (especially overdose), which can cause significant morbidity and mortality.^[14] Appropriate use and safe prescription of these drugs can lead to maximum potential benefits and minimum adverse events.^[15]

Numerous studies have reported inappropriate prescription of NSAIDs.^[16-20] Irrational prescribing has furtherly exacerbated the adverse effects of NSAIDs.^[21] Hence, rational use and safe prescription of NSAIDs, in combination with other drugs, are crucial in preventing or minimizing the adverse effects.^[22]

To the best of our knowledge, the exact number of prescriptions of NSAIDs in Iran is unknown. However, their widespread use^[23-26] suggests that the adverse effects of these drugs are inevitable. Since there was no reliable report on the prescribing pattern of NSAIDs in Iran, a retrospective study was conducted to inspect the pattern of NSAIDs prescription and consecutively provide suggestions for a more rational prescription behavior in general practise.

METHODS

This cross-sectional descriptive study was carried out in Khorasan-Razavi province in Northeast of Iran. Prescriptions were collected from Social Security Organization (SSO) and Iranian Health

Insurance Organization (IHIO) databases which include prescription-related data on drugs that are (a) prescribed by general practitioners (GPs) and specialists; (b) dispensed by pharmacists and/or other outlets; and (c) being reimbursed under the insurance organization. About 99,303,585 prescriptions were collected from March 20, 2012 to March 19, 2013. Using the formulation in excel 2010, only the prescription containing at least one dispensed dose of NSAIDs were included. Entire records of all patients receiving NSAIDs were analyzed. Ophthalmic and topical dosage forms were not included in the analysis. Anatomical Therapeutic Chemical drug classification was used for identifying NSAID medications.

Unfortunately, not all demographic data (e.g., age and gender) of patients were recorded by SSO and IHIO. In addition to name and number of drug items, patient identity number and date of prescription are the only available variables in databases.

Type of NSAIDs, all dispensed doses of NSAIDs, number of NSAIDs ordered per prescription, and the route of administration for each patient were extracted from the database. There were no restrictions on the physician specialty. The prescription pattern of NSAIDs was analyzed seasonally. Since the daily aspirin 80 mg use is a preventive therapy, we did not consider it in the analysis. Categorical variables were expressed as frequencies (percentage). Chi-square test was used to compare NSAIDs prescriptions in different seasons and months. $P < 0.05$ (two sided) was considered as statistically significant. Statistical analyses were performed using SPSS 16 (SPSS, Chicago, IL, USA).

This study has been approved by the Ethics Committee of the Mashhad University of Medical Sciences, Mashhad, Iran.

RESULTS

Out of 9,303,585 prescriptions reviewed, 1,795,591 (19.3%) contained at least one NSAID. The average number of medications per prescription was 2.94. In prescriptions with at least one NSAID, the mean number of drugs found to be 3.59.

The most prescribed NSAIDs was diclofenac (49.21%), followed by ibuprofen (28.6%) and naproxen (8%) [Figure 1]. Considering each dosage form, ibuprofen syrup (25%) and diclofenac suppository 100 mg (21%) were the most frequently prescribed NSAIDs. Our data showed that oral (77%) and rectal (16%) administrations were the most frequent routes for prescribed NSAIDs.

NSAIDs combinations (two, three, or four) were observed

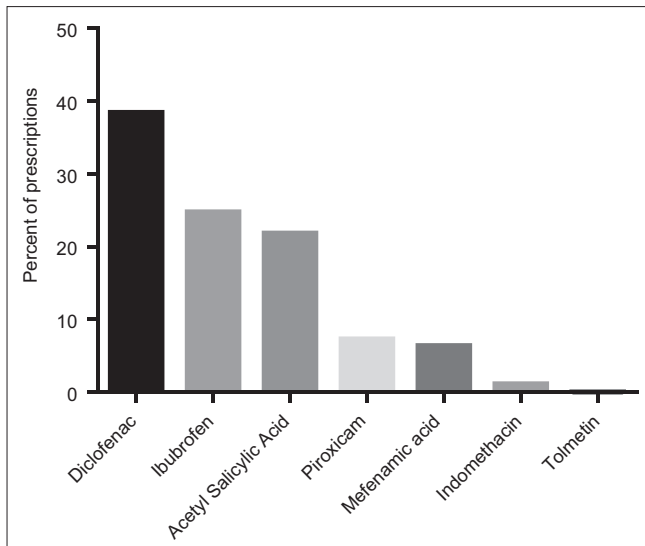


Figure 1: Prevalence of nonsteroidal anti-inflammatory drugs prescription; March 20, 2012 to March 19, 2013, in Northeast of Iran

in 7%, 0.6%, and 0.01% of prescriptions, respectively. Coadministration of rectal and oral NSAIDs was present in 4% of prescription.

GPs and specialists prescribed 67% and 33% of NSAID prescriptions, respectively. Orthopedic surgeons and internists more frequently prescribed NSAIDs (6% and 4%, respectively).

There was no significant seasonal variation in the prescription pattern. However, diclofenac suppository 100 mg was more prescribed in spring and summer (29% and 25%) and ibuprofen syrup was more prescribed in autumn and winter (25% and 35%). NSAIDs were less prescribed in August ($P < 0.001$).

GPs were coprescribed to only 7.62% of prescriptions that contained at least one NSAIDs. H_2 -receptor blockers (H_2 Bs) and PPIs consisted 60% and 40% of agents, respectively. Ranitidine (43%) and omeprazole (40%) were the most prescribed H_2 Bs and PPIs, respectively.

DISCUSSION

A few studies have been conducted to determine the prescription pattern of drugs in Iran that indicated a high prevalence of inappropriate NSAIDs prescription.^[23-25] To the best of our knowledge, there is no reliable report on the prescription pattern of NSAIDs in Iran. This is the first prescription-based study that evaluates and analyzes the prescribing pattern of NSAIDs in Northeastern Iranian population. Thus, comparison to other patterns in Iran was not applicable.

Our findings revealed that 19.3% of the prescriptions included at least one NSAID. It is estimated that in the USA, NSAIDs accounted for approximately 12.1%

of prescriptions in 2010.^[27] The frequency of NSAIDs prescriptions in 2012 in Khorasan-Razavi province is thus higher in compared with the USA.^[28] On the other hand, the frequency of NSAIDs prescriptions in Northeast of Iran was found to be much less than what has been reported in Southwest of Saudi Arabia (19.3% vs. 29.4% [regardless of aspirin]).^[29] These could be explained by some factors which might influence prescribing habits. The different traditions of prescribing in these countries can have long-term consequences on the cultural behavior and the prescribing habits of GPs and specialists.

We assume that the frequency of NSAIDs prescriptions in our study has been underestimated because it was not possible to access the data of uninsured prescriptions, prescriptions belonging to other insurance companies, and OTC NSAIDs.^[30] A particular problem is that the most prominent members of NSAIDs, including ibuprofen, diclofenac, mefenamic acid, and naproxen are available as OTC medications in Iran.^[31]

A recent meta-analysis that included 31 trials and 116,429 patients showed an increased number of myocardial infarction, stroke, and cardiovascular mortality in patients consuming NSAIDs.^[32] Inappropriate NSAIDs prescription in Iran has been previously reported.^[24,25] As we reported here, the frequency of NSAIDs prescriptions in the top two largest Middle East countries is higher than the USA. Further steps are needed to be applied on the prevention of adverse effects. Policymakers are encouraged to establish strategies that lean too heavily on professional education.^[24]

Unfortunately, simultaneous prescription of two or more NSAIDs has also been frequently reported. However, despite the established efficacy of NSAIDs, their uncontrolled and irrational use significantly decreases their safety and also is a leading cause of drug-related morbidity.^[33] Concurrent usage of two or more systematic NSAIDs has no pharmacological rationalization; this may be associated with an excessive risk of adverse events such as hepatic injury, acute renal failure, and gastrointestinal hemorrhage. This may emerge as a crucial public health problem with the increasing use of OTC nonsteroidal anti-inflammatory agents.^[34] NSAIDs combinations should clearly be avoided. Physicians should inform patients about risks related to the use of NSAIDs combinations.

Traditional NSAIDs such as aspirin (1), ibuprofen (2), and diclofenac (3) that exhibit nonselective COX inhibition represent some of the most widely prescribed NSAIDs.^[35] In confirmation to our results, diclofenac has been reported as the most widely prescribed NSAIDs to relieve

short-term fever, pain, and inflammation.^[36,37] Furthermore, diclofenac 100 mg suppositories, ibuprofen syrup, and ibuprofen 400 mg tablets were the most prescribed drugs. Following reasons might explain this:

1. Relatively low price of the whole dosage forms of diclofenac
2. The rectal suppository could provide faster onset of relief and lower gastric irritation in patients with gastric sensitivity to NSAIDs.

In spite of the fact that the GPs ($n = 2916$) and specialists ($n = 2397$) were equal in number in 2012 in Khorasan Razavi, GPs more frequently prescribed NSAIDs. Due to socioeconomic factors, the most common clinical problem regularly was managed by GPs. There were differences among the specialist categories with regard to preferences for NSAIDs prescription, and orthopedic surgeons prescribed more NSAIDs [Figure 2].

We found that oral administration (77%) was the most common route of administration. This could be explained by the fact that oral administration route is convenient, easy to use, safe, acceptable, and the most cheapest available route.

A clear seasonality in spring and winter was seen which could be associated with the highest ibuprofen use. This would be probably related to prescription of ibuprofen to young children for fever and fever-like symptoms.

Although PPIs are more effective than H_2 Bs for treatment and prevention of GI toxicity associated with NSAIDs,^[38] H_2 blockers were more commonly coprescribed by GPs in our study. This could be explained by the fact that H_2 blockers are relatively safe, inexpensive, and more likely to be covered by insurance organizations, while PPIs have the higher co-pays or might not be covered.

However, some important limitations which might have led to an underestimation of the prescription

pattern of NSAIDs should also be noted. First, our analysis was based on insurance coverage component drugs. Thus, prescriptions which were not covered by insurance organizations (e.g., Gelofen[®] and Novafen[®]) were not included. Second, particular dosage forms of NSAIDs including celecoxib and naproxen (500 mg) are covered by insurance only when they are prescribed by specialists; therefore, prescriptions by GPs are not included. Third, not all demographic data (e.g., age and gender) of patients were available. Then, we could not analyse data in specific age group/gender.

NSAIDs were commonly prescribed in the Northeastern Iranian population. It should be noted that appropriate use of medications enhances the quality of life of patients and leads to community development. This should be carefully considered by GPs and specialists. Thus, a strategy must be developed and implemented for prescription, and rational use of medications which includes continuing medical education regarding the potential risks of NSAIDs, the importance of their appropriate and rational use, and the necessity of appropriate prescription writing regarding both content and indication is noticeable.

AUTHORS' CONTRIBUTION

Zhila Taherzadeh jointly conceived the study with Saeid Eslami, and participated in the design of the study and drafted the manuscript; Seyed Vahid Maziar and Majid Zeinali participated in the data collection. Jamshid Tabeshpour and Kamal Razavi Azarkhiavi drafted the manuscript; Mohammad Reza Zirak performed the statistical analysis and Saeid Eslami supervised its analysis and edited the manuscript. Zhila Taherzadeh, Danielle Sent, and Saeid Eslami revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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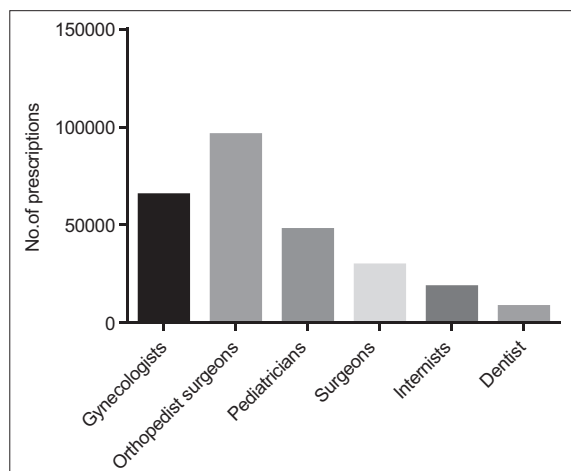


Figure 2: Number of prescriptions, prescribed by different specialists

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