Research Square

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Non-Steroidal Anti-Inflammatory Drugs: Usage and Co-prescription with Other Potentially Interacting Drugs in Elderly: a Cross-sectional Study

Nuru Abdu (pharmacistnuru@gmail.com)
Asmara College of Health Sciences https://orcid.org/0000-0003-2426-4337
Samuel Teweldemedhin
Asmara College of Health Sciences
Asmerom Mosazghi
Asmara College of Health Sciences
Luwam Asfaha
Asmara College of Health Sciences
Makda Teshale
Asmara College of Health Sciences
Mikal Kibreab
Asmara College of Health Sciences
Eyasu Habte
Asmara College of Health Sciences
Indermeet Singh Anand
Asmara College of Health Sciences
Mulugeta Russom
Eritrean Pharmacovigilance Centre

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Abstract

Introduction: Globally, non-steroidal anti-inflammatory drugs (NSAIDs) usage in the elderly with chronic pain has been reported as frequent. Though it is fundamental in maintaining their quality of life, the risk of polypharmacy, drug interactions and adverse effects is of paramount importance as the elderly usually require multiple medications for their co-morbidities. If prescriptions are not appropriately monitored and managed, they are likely to expose patients to serious drug interactions and potentially fatal adverse effects. Thus, the objective of the study was to assess the appropriateness of NSAIDs use and incidence of NSAIDs related potential interactions in elderly.

Methods: A descriptive cross-sectional study was conducted among elderly out-patients (aged 60 and above) who visited three hospitals in Asmara between August 22 and September 29, 2018. The sampling design was two-stage random sampling and data was collected using a questionnaire, exit interview and by abstracting information from patients' clinical cards. Descriptive and analytical statistics including chi-square test and logistic regression were employed using SPSS.

Results: A total of 285 elderly respondents were enrolled in the study with similar male to female ratio. One in four of all respondents were chronic NSAIDs users, of which 74.6% were not prescribed prophylactic gastro-protective agents (GPAs). About 20% of the elderly were involved in polypharmacy and nearly all of the encountered potential NSAIDs related interactions (n=322) with prescribed drugs were moderate. Diabetes and hypertension were significantly associated with chronic NSAIDs use (OR=3, 95% CI: 1.54, 5.84; OR=9.99, 95% CI: 4.46, 22.38) and incidence of drug interactions (OR=3.95, 95%CI: 1.92, 8.13; OR=3.12, 95%CI: 1.81, 5.33) while diabetes and cardiac problem were significantly associated with incidence of polypharmacy (OR=4.33, 95% CI: 2.36, 7.96; OR=3.56, 95% CI: 1.05, 12.11).

Conclusion: Though the overall reflection of prescription pattern of NSAIDs during the study period was almost satisfactory, gastro-protective agents were poorly prescribed as a prophylaxis.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used all over the world for their analgesic, anti-inflammatory, and antipyretic effects [1]. NSAIDs are one of the most commonly prescribed class of medications for pain and inflammation management and are also available as over the counter in Eritrea. They account for approximately 5–10% of all medications prescribed each year [2]. Numerous studies reported that elderly were among the frequent users of NSAIDs [3–5]. The elderly consume a disproportionate amount of prescription and nonprescription medications [6]. Thus, they are highly susceptible to polypharmacy, drug-drug interactions (DDIs) and ultimately to adverse drug reaction related complications, hospitalizations and death [7].

In clinical practice, there is an important gap between what is theoretically known about drug-drug interactions (DDIs) and appropriate monitoring and management of patients [7]. NSAIDs are administered frequently in the elderly with chronic pain who do usually require multiple medications for their co-morbidities.

The number of prescribed drugs (polypharmacy) is recognized as independent risk factor for serious adverse drug reactions (ADRs) in the elderly [8, 9]. On the other hand, the clinician's perception of the clinical relevance of DDIs is not fully appreciated [10, 11]; thus, underestimating the relevant risk when multiple drugs are co-administered.

In the elderly, it is estimated that 29% of fatal peptic ulcer complications are possibly due to NSAIDs [12]. Despite this fact, gastro-protective agents (GPAs) were poorly co-prescribed along with NSAIDs [13]. All the aforementioned factors contributed to the requirement of further research and stricter control on the use of NSAIDs in elderly.

The aim of this study was therefore to assess the appropriateness of NSAIDs usage and incidence of NSAIDs involving interactions in elderly in selected hospitals in Asmara, Eritrea.

Methods

Study design and setting

A descriptive cross-sectional study with a quantitative approach was conducted in three selected hospitals in Asmara (namely: Halibet, Sembel and Bet Mekae which are national referral, private and community hospitals respectively). Data was collected between August 22 and September 29, 2018 for a period of 30 working days.

Source and study population

The study has no specific source population as one of the selected hospitals was a national referral hospital. Elderly patients (aged 60 years and above) taking one or more NSAIDs attended the study sites during the study period formed the study population. Subjects who came up with prescriptions containing no NSAIDs or that were not legibly written, those unwilling to participate or with obvious debilitating conditions and who couldn't pass on reliable information were excluded.

Sampling design

In order to get representative samples from each hospital, two stage random sampling was utilized. The three hospitals were considered as strata, constituting the first stage of the stratified sampling technique. Systematic random sampling was used in the second stage rather than the simple random because of unavailability of prior information on patient visits.

Sample size determination

Sample size was computed by considering the finite population correction factor: $n = NZ^2pq/ [pqZ^2 + (N-1)d]$. The total sample size (n) was calculated using the following assumptions: expected proportion of elderly patients with drug interaction (p) and those without drug interaction (q) were taken as 0.5, Z statistic for 95% level of confidence (Z = 1.96), estimated population size (N) of 900, margin of error (d) of 0.05 and 5% non-response rate. Considering the above assumptions, the final sample size was found to be 285.

Data collection tools and approach

Patients' prescriptions, clinical cards, exit interview-based questionnaire and US-FDA drug interaction checker (www.drugs.com) were used to collect information. WebMD drug interaction checker was also used if information on potential interaction is unavailable in US-FDA drug interaction checker. Prescriptions were used to get information of the prescribed NSAIDs, while medical cards were used to assess disease and medication status of the patients. The questionnaire was aimed at exploring information on patients' socio-demographic characteristics, co-prescription of gastro-protective agents with chronic NSAIDs use, adverse effects encountered, medical and drug history. The study population consisted of randomly selected elderly patients (≥ 60 years) receiving prescriptions containing NSAIDs from the respective out-patient departments (OPDs) of the selected hospitals. The investigators explained purposes of the study to the participants and those who gave consent were enrolled.

Exit interview was conducted for each patient based on a self-designed questionnaire. Then, information contained in their prescriptions were recorded and their clinical cards were assessed to document their medical history including co-morbid conditions, diagnosis of the last visit and drug history. Finally, the potential drug-drug interactions were screened using US-FDA drug interaction checker. All the obtained data were documented and no follow ups were made.

Validity

Face and content validity of the questionnaire was determined through the review of experts in fields of pharmacy, pharmacoepidemiology and medicine.

Pre-test

A pre-test was conducted on 31 participants on August 17–21, 2018, to ensure comprehensibility and compatibility of the questionnaire at two randomly selected hospitals. Accordingly, some modifications were made in the final version of the questionnaire.

Statistical analysis

The collected data were double entered on CSPro (version 7.0) to minimize keying errors and was exported to SPSS (version 22) for statistical analysis. Descriptive summaries of the socio-demographic variables were computed using mean (SD) or median (IQR) as appropriate. Associates of polypharmacy were explored using logistic regression. Furthermore, factors that were related to

chronic NSAIDs use were identified using bivariate logistic regression. Chi-square test and logistic regression were used to explore existence of trend and magnitude of possible associations. Odds ratio with 95% confidence interval was reported in all logistic regression analyses. All analyses were considered significant when $p < 0.05$.

Ethical consideration

Ethical approval was obtained from the Ministry of Health (MOH) research ethics and protocol review committee and Asmara College of Health Sciences (ACHS) ethical clearance committee. Besides, permission was obtained beforehand from the medical directors and head of pharmacies of the respective hospitals. Study participants were informed about the objective of the study and written informed consent was obtained from each respondent. All the information gathered will be held confidential and used only for this study's purpose.

Operational Definitions

Mild-Interaction

An interaction is considered 'mild' if the interaction has minimal clinical significance. Manifestations may include an increase in frequency or severity of the side effects but generally would not require a major alteration in therapy [14, 15].

Moderate-Interaction

An interaction is considered 'moderate' if the interaction has clinical significance of moderate importance. The interaction may result in exacerbations of the patient's condition and/or require an alteration in therapy [14, 15].

Severe-Interaction

An interaction is considered 'severe' if the interaction is highly clinically significant. The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects [14, 15].

Polypharmacy

is defined as the concomitant use of four or more drugs prescribed at the same time [16].

Prescription pattern

includes information regarding type of NSAIDs, dosage form, route of administration of NSAIDs and number of drugs ordered per prescription.

Risky practice

A respondent and/or prescriber was considered at risky practice if respondents self-medicated themselves along with potentially interacting prescribed drugs, or if prescribers fail to prescribe gastro-protective agents for those with previous history of gastro-intestinal upset and/or were chronic NSAIDs users. Prescribers ordering two or more NSAIDs at the same time were also considered at risky practice.

Results

Socio-demographic and background characteristics

A total of 285 elderly individuals with a median age of 69 years (IQR: 15) were enrolled in to the study and about 78.2% of the respondents had not completed high school [Table 1]. Detailed demographic characteristics of the study population are provided in table 1.

Table 1: Socio-demographic characteristics of the respondents (N = 285)			
Variable		Number	Percent
Age (Md; IQR = 69.00,15)			
	60 to 69	144	50.5
	70 to 79	91	32
	80 or above	50	17.5
Gender			
	Male	143	50.2
	Female	142	49.8
Marital Status			
	Married	171	60
	Single	9	3.2
	Divorced	6	2.1
	Widowed	99	34.7
Level of Education			
	Illiterate	97	34
	Primary	73	25.6
	Middle	53	18.6
	Secondary or higher	62	21.7
Occupation			
	Governmental	49	17.2
	Private	26	9.1
	Self-employed	40	14
	Unemployed	54	18.9
	House wife	116	40.7
Md: Median; IQR: Interquartile range			

Majority of the respondents (66.7%) had chronic illnesses and the most common chronic illnesses reported were hypertension (52.3%), followed by diabetes (29.5%). About 35% of them had history of gastro-intestinal (GI) upset [Table 2].

Table 2: Background information of the respondents (N = 285)		
Chronic illness[]	Number	Percent
Hypertension	149	52.3
Diabetes	84	29.5
Asthma	14	4.9
Renal Failure	2	0.7
Cardiac problem	11	3.9
Others*	4	1.4
No chronic illness	95	33.3
History of GI upset		
Yes	101	35.4
No	184	64.6

[]Total percent might exceed 100 due to multiple answers. *Others include cancer and rheumatoid arthritis.

The most common reasons for prescription of NSAIDs were: anti-platelet effect (36.2%) with low dose aspirin, arthritis (5.35%), backache (4.95%), knee pain (3%), and leg pain (2.3%). The mean number of drugs per prescription was 2.61. The most prescribed NSAIDs were aspirin and diclofenac [Figure 1]. Most of the prescriptions had only one NSAID per prescription (76.1%) [Table 3].

Of those with previous history of GI upset (101/285), concomitant use with gastro-protective agents (GPA) were documented in only 9.9% and omeprazole was the most commonly prescribed drug as GPA (8.9%).

Table 3. Pattern of NSAIDs prescription among the elderly (N = 285)		
Variable	Number	Percent
Number of NSAIDs per prescription		
1	217	76.1
2	60	21.1
3	8	2.8
Total number of drugs per prescription (Md; IQR = 2,1)		
1	31	10.9
2	122	42.8
3	75	26.3
≥ 4	57	20
Md: Median; IQR: Interquartile range		

Incidence of polypharmacy among elderly NSAIDs users and associated risk factors

Out of the 285 elderly respondents, 20% were exposed to polypharmacy. Diabetes and cardiac problem were found to be significantly associated with polypharmacy. Patients with diabetes were four times more prone to polypharmacy compared to non-diabetic patients (COR = 4.33, 95% CI: 2.36, 7.96). Similarly, patients with cardiac problems were approximately four times more susceptible to poly-pharmacy compared to those without cardiac problems (COR = 3.56, 95% CI: 1.05, 12.11).

Usage of gastro-protective agents (GPAs) among chronic NSAIDs users

Majority (59.3%) of the elderly had history of NSAIDs use and 42% (71/169) of whom were chronic NSAIDs users. GPAs were co-prescribed in 25.4% (18/71) of those with chronic use of NSAIDs [Figure 2]. The most commonly prescribed GPAs were omeprazole (n = 11), antacid (n = 6) and famotidine (n = 1). Self-reported adverse drug reactions (ADRs) were documented in 12 (16.9%) of the chronic NSAID users and the most frequently reported ADR was GI upset (11.2%).

Respondents who had either diabetes or hypertension were found to be significantly associated with chronic NSAIDs usage. Respondents with hypertension were ten times more prone to chronic NSAIDs use compared to those who did not have hypertension (COR = 9.99, 95% CI: 4.46, 22.38). Similarly, respondents with diabetes were three times more prone to chronic NSAID use than those who did not have diabetes (COR = 3, 95% CI: 1.54, 5.84).

Analysis of NSAIDs related drug interactions and its associated risk factors

The number of respondents who reportedly self-medicated themselves was 26.7%. Potential NSAIDs related interactions with self-medication were observed in 37 respondents, giving a total of 41 potential drug interactions varying in severity [Figure 3]. Of all who were self-medicated themselves, 48.7% were at risky practice as they self-medicated with other drugs that have potential interactions with NSAIDs.

On the other hand, self-medicated NSAIDs with potentially interacting prescribed drugs were observed in 19 respondents, giving a total of 24 potential drug interactions. All were classified as moderate.

Potential NSAID drug interactions with other prescribed drugs were observed in 205 respondents (71.9%), giving a total of 322 potential drug interactions, of which 0.6% were classified as severe, 97.2% moderate and 2.2% mild.

The NSAIDs with the greatest risk of drug interactions were aspirin (n = 168), indomethacin (n = 52), ibuprofen (n = 46) and diclofenac tablet (n = 41). Table 4 displays the most common potential drug interactions with their severity and clinical implications.

Table 4: Most common potential drug interactions with their severity and clinical implications

Drug interactions		Severity	Clinical implication	Frequency (n)
Drug 1 (NSAID)	Drug 2			
Aspirin	Ibuprofen	Severe	Antagonization of anti-platelet and cardio-protective effect	2
Aspirin	Enalapril	Moderate	Attenuation of hypotensive and vasodilator effect	66
Aspirin	Glimepiride	Moderate	Increased risk of hypoglycemia	24
Aspirin	HCT	Moderate	Increased anti-platelet effect	23
Aspirin	Insulin	Moderate	Increased risk of hypoglycemia	15
Indomethacin	Depomedrol	Moderate	Risk of GI toxicity	15

HCT: Hydrochlorothiazide; n: number

NSAID therapeutic duplication due to prescribed and self-medicated drugs was also detected in 28.8% of the respondents.

Chi-square for trend analysis indicates that there is significant increase in interaction with increase the number of drugs prescribed ($\chi 2 = 67.45$, $p < 0.001$). As the number of drugs prescribed increases by one unit, the odds of interactions increase by 6.51 unit (COR: 6.51; 95%CI: 3.82, 11.10) [Table 5].

Table 5: Association between number of drugs prescribed and potential drug interactions									
		Total number of drugs in prescription						Linear-by-Linear Association	
		1	2	3	4	5	7	χ2-value	p-value
Interaction	Yes	0	82	69	40	13	1	67.45	< 0.001
	No	29	40	8	3	0	0		
	Total	29	122	77	43	13	1		

Respondents which had either diabetes or hypertension were found to be significantly associated with NSAIDs potential drug interactions. Diabetic patients were approximately four times more at risk of drug interactions than those without diabetes (COR = 3.95, 95%CI: 1.92, 8.13). While hypertensive patients were three times more at risk of drug interactions compared to those without hypertension (COR = 3.12, 95%CI: 1.81, 5.33).

After fitting to the multivariate logistic regression model both being hypertensive and diabetic were still significantly associated with occurrence of drug interactions among the respondents (AOR = 2.81, 95% CI: 1.61, 4.9 and AOR = 3.5, 95% CI: 1.68, 4.3 respectively).

Discussion

In this study, one in four of the respondents had two or more NSAIDs per prescription. Even though this is much lower than that reported by Jayakumari et al. (77.3%) [17], its implication on the consumers could be devastating as there is potentially serious risk of drug-drug interactions and adverse drug reaction with no additional therapeutic value.

Despite a substantial number of respondents had history of GI upset and were on chronic use of NSAIDs, the concurrent use of GPAs was not commonly practiced. This phenomenon does not comply with the guidelines as they recommend gastroprotection for elderly taking NSAIDs to prevent peptic ulcers [18–20].

GPAs were prescribed in only a quarter of the chronic NSAID users. This finding was higher than the finding of a similar study in UK (10%) [13]. Contrary to that, in a study conducted in US, standard or high-dose GPAs were prescribed in 99.8% of the respondents [21]. The possible explanation for the variation in results maybe the various prescription habits among countries and the level of knowledge about the concurrent use and importance of GPAs in preventing or minimizing NSAIDs induced gastro-intestinal complications.

One in five of our respondents were involved in polypharmacy. This was similar with findings of a Nigerian study on Geriatrics (23.4%) [22] but much lower than that reported by an Indian study which showed 57.8% of the respondents were using five to nine medicines per day [23]. Polypharmacy was however predominant in majority of our study participants who had comorbidities like diabetes and cardiac problems. In the Indian study, clinical conditions including hypertension, gastritis, osteoarthritis, and diabetes mellitus were identified as the main reasons for the practice of polypharmacy [23]. Taking the age of the study population into consideration, polypharmacy might be inevitable in many of the patients.

The variability in incidence of polypharmacy among the different studies could be due to variations in clinical practices, patient behaviors in different countries, definition of polypharmacy, study design, data sources used and/or the slight age difference. Despite the difference, it is clear that polypharmacy is a significant problem in the elderly that warrants immediate attention from healthcare professionals, program managers and policy makers. When at times polypharmacy becomes inevitable, a close and intensive monitoring of elderly using multidisciplinary approach is required to prevent serious drug interactions.

About half the respondents of in this study who self-medicated themselves were at risk of moderately significant potential drug interactions with prescribed NSAIDs. On the other hand, in all respondents who reported to have self-medicated themselves with

NSAIDs, potential DDIs with prescribed drugs were observed. This is consistent with the study conducted by Nunes and colleagues in Portugal [24].

This tendency normally put the elderly in a dangerous situation and aggravates the risk of potential drug interactions. These finding mandates prescribers to responsibly take medication history into account and pharmacists to strictly advise them not to self-medicate any medical products without the knowledge of healthcare professionals.

Compared to a similar Brazilian study, the practice of healthcare professionals in avoiding interacting drugs was found to be commendable as the severe DDIs documented in this study were relatively low [6]. Although, severe interactions were low, it should be noted that these interactions occurred of only four types of NSAIDs studied in Eritrea as compared to ten types of NSAIDs in Brazil [6]. Whereas, moderate interactions constituted nearly all interactions which made up a percentage more than double that of the Brazilian study. This is an alarming figure requiring close and regular monitoring by the prescribers and pharmacists as they may result serious health conditions. Emphasis should be given to diabetic, hypertensive and cardiac patients as they are more likely to encounter drug-drug interactions.

Due to the cross-sectional nature of the study design that lacks follow up of patients, this investigation did not confirm the occurrence of possible problems related to adverse drug reactions and drug-drug interactions, through prolonged systematic monitoring. Besides, incompleteness in medical cards, potential recall bias and NSAIDs supply inconsistencies due to stock outs were some of the limitations of the study.

Conclusion

Though, the overall reflection of prescription pattern of NSAIDs during the study period was almost satisfactory, GPAs were poorly prescribed as prophylaxis neither for those who have had previous history of GI upset nor for those who were on chronic use of NSAIDs. Besides, moderate drug-drug interactions and prescribing more than one NSAID were common that warrant attention of prescribers and pharmacists.

To minimize NSAID-related problems in elderly, regular updating of national standard treatment guidelines and formularies as well as introducing electronic medical records that trace drug interaction are highly recommended. Besides, educational programs targeting healthcare professionals and elderly patients on potential drug interactions, rational prescribing and dispensing at all levels should be promoted.

Abbreviations

ACHS:Asmara College of Health Sciences; ADR:Adverse Drug Reaction; AOR:Adjusted Odds Ratio; CI:Confidence Interval; COR:Crude Odds Ratio; CSPro:Census and Survey Processing System; DDI:Drug-Drug Interaction; GI:Gastrointestinal; GPA:Gastro-protective agent; IQR:Interquartile range; MOH:Ministry of Health; NSAID:Non-Steroidal Anti-Inflammatory Drugs; SM:Self-medicated; SPSS:Statistical Package for Social Sciences; US-FDA:United States Food and Drug Administration; WHO:World Health Organization

Declarations

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

All the authors designed the study and NA, ST, AM, LA, MT and MK collected and entered the data. Data was analyzed by EH. NA, ST, AM, LA, MT and MK drafted the manuscript with the guidance and supervision of ISA and MR and further edited by rest of the

authors.

Consent to publish

Not applicable.

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Figures

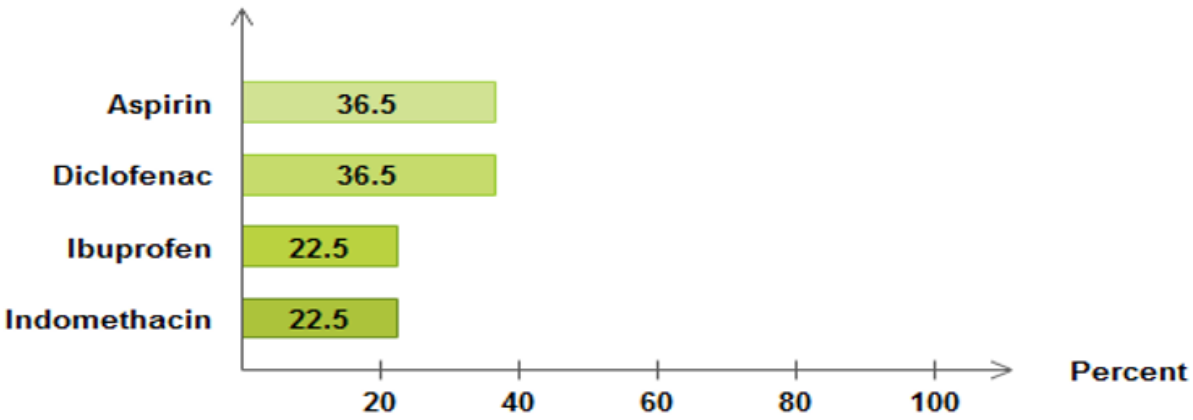


Figure 1

Prevalence of NSAIDs prescribed during the study

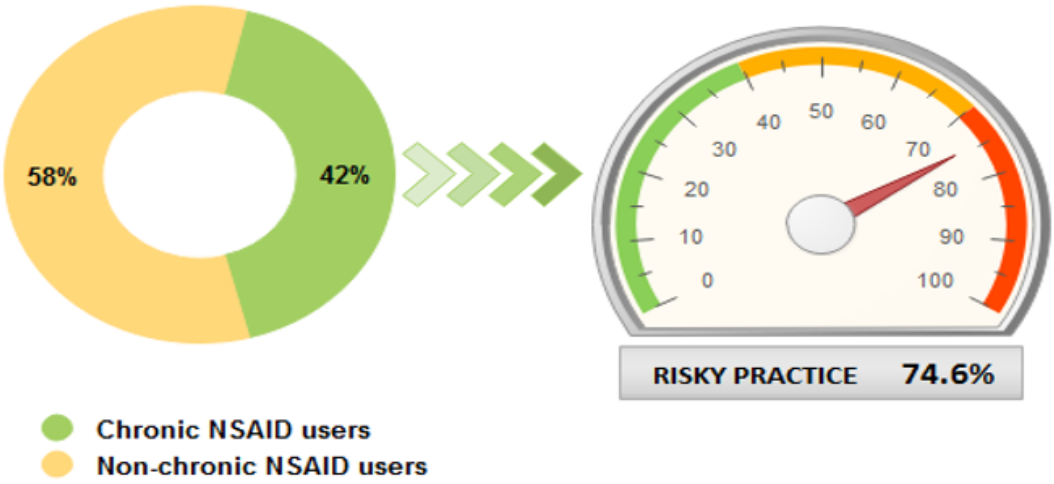


Figure 2

Prevalence of chronic NSAID users and risky practice

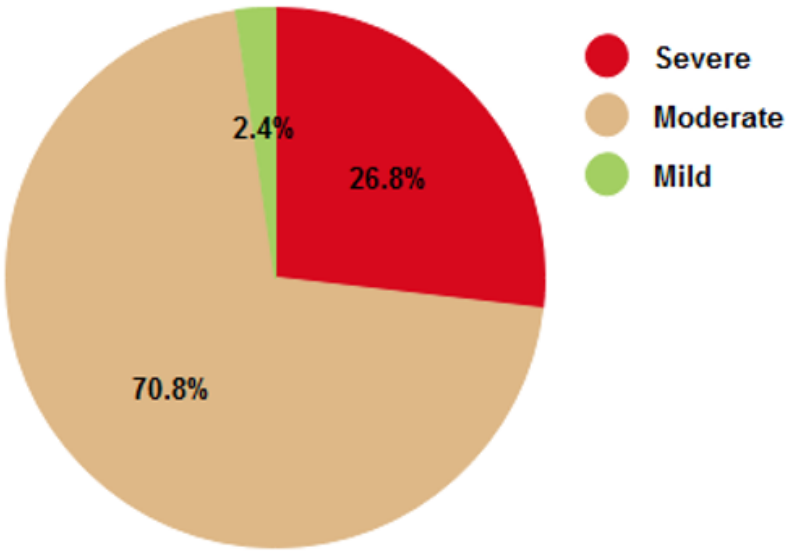


Figure 3

Severity of NSAID potential interactions with SM drugs