

Side effects of non-steroidal anti-inflammatory drugs: The experience of patients with musculoskeletal disorders

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) are of choice for acute pain management in musculoskeletal disorders (MSDs) but they are not without side effects. The primary aim of this study was to investigate user’s experience of side effects of oral NSAIDs among patients with MSDs. Multi-stage sampling technique was used to select 296 patients with MSDs from physiotherapy out-patient clinics of five selected hospitals. A structured and close ended questionnaire was administered to investigate the side effects experienced by respondents. Descriptive statistics (mean, standard deviation, frequency and percentages) and Chi-square were used to compare the mean percentage difference in the knowledge of NSAIDs and their side effects. Only 15% of the respondents were able to recognize the listed side effects. A significant number of the respondents (58.7%) were not informed of the side effects of the NSAIDs at the time of prescription ($\chi^2 = 8.82, p = 0.003$). About 33.4% and 31% of respondents identified dizziness and abdominal pain respectively as side effects. Sixty two (22.3%) respondents had experienced dizziness while 15.9% experienced abdominal pains. Diclofenac was the most frequently prescribed NSAID (153 [51.7%]). Only 2.0% and 2.7% of respondents were aware of phonophoresis and iontophoresis respectively as alternative means of administering NSAIDs where applicable. The Chi-square test revealed that the number of respondents that preferred alternative means of administration (where applicable) was significantly higher than those who preferred the oral routes ($\chi^2 = 74.5, p = 0.001$). We concluded that this sample of Nigerian patients was not informed of the side effects of NSAIDs by the prescribers. Dizziness and abdominal pains were the most experienced side effects. The role of alternative methods to administer NSAIDs need to be made available to patients where applicable to increase their health care choices.

Keywords: Side Effects, Non-Steroidal Anti-Inflammatory Drugs, Patient’s Experience, Musculoskeletal Disorders

1. Introduction

Musculoskeletal Disorders (MSDs) are injuries and disorders that affect the human body’s movement or musculoskeletal system such as muscles, tendons, ligaments, nerves, discs and blood vessels [1]. Chronic pain as a result of MSD is a common reason for consultation in general practices [2]. Ekpenyong et al reported an

incidence rate of 20.1% for MSDs among adult population of South-South Nigeria while, Adegbehingbe, et al reported a prevalence of 3.0% among 4,441 Nigerian students [3, 4].

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs of choice for acute pain management that may characterize musculoskeletal disorders including low back pain [5, 6]. They are also commonly used in chronic musculoskeletal pain, although, the rationale remains

controversial. There is evidence to support the use of NSAIDs in chronic spinal pain but this is based on evidence from trials lasting only few days [7 - 9]. Some researchers, however, questioned the effectiveness of NSAIDs in spinal disorders over other agents like acetaminophen, narcotic analgesics, and muscle relaxants [10 - 11]. The anti-inflammatory effect of NSAIDs are exerted through inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes [12].

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients who have established sensitivity to aspirin and should also be used with caution in hypertensive patients [13]. In a Chocrane report, the prevalence of aspirin-exacerbated respiratory tract disease was about 10% in the general population and about 21% in adults when determined by oral provocation testing [14]. In North Sydney, NSAIDs was reported to be associated with rhino-sinusitis and nasal polyps when prescribed for asthma patients [15].

Upper GI tract injury is a major side effect of NSAIDs and includes abdominal pain, gastroduodenal ulcers, mild to severe dyspeptic symptoms, haemorrhage or perforation, non-specific colitis; and other events which may lead to hospitalization or death [16]. Also, non-selective NSAID users are four to eight times more likely to develop gastroduodenal ulcers during therapy [17], [18]. There is also an increase in renal toxicity when these agents are combined with antihypertensive agents and other potentially nephrotoxic drugs [18]. Few studies have also reported hepatic reactions, hepatotoxicity and liver damage [19 - 21]. Other reported risks are cardiovascular disorders, peripheral edema, hyperkalemia, particularly in patients who have diabetes, elderly patients, and patients on other hyperkalemia-inducing agents [22,23]. Patients may abstain or choose not to comply from taking oral drugs for fear of dependency and concern about these side effects.

The health care system is shifting towards shared decision making (SDM) and patients are becoming more involved in the prescription of drugs so as to enhance concordance [24 - 26]. This is an attitudinal shift in society towards greater individual autonomy and choice particularly in the United Kingdom [27, 28]. Powerful, complex and intrusive therapies demand greater understanding and active participation by the patient in decisions about therapy in order to promote greater efficacy and patient safety [29].

It is well known that the success of pharmacotherapy is highly dependent on patient's compliance and a rational choice of drug therapy regimen. A readable and correct prescription does not guarantee appropriate use by the patient [30]. Among the major principles of rational use of drugs is the need to inform the patient about pharmacological effects, side effects, potential interactions, instructions for use and warnings regarding the drug, and the diagnosis [30]. Lack of information on medication had

been reported to be one of the reasons why many patients fail to take their medications as prescribed and participate more meaningfully in health care decisions that affect them [31].

Despite the side effects, physicians and orthopaedic experts still prescribe oral NSAIDs. It is not known whether the patients are aware of the hazardous effects. It is also not known if they would continue to use the medication if they experience side effects. The primary aim of this study was to investigate user's experience of side effects of oral NSAIDs among patients with MSDs. Other objectives are to investigate awareness of side effects; and to identify NSAIDs most commonly prescribed to this group of patients.

2. Methodology

2.1. Study Settings

The study settings comprised physiotherapy departments of 5 hospitals (3 University Teaching and 2 State). These were selected because of the presence of specialist physiotherapists in the orthopaedic unit of each physiotherapy departments in South-west, Nigeria.

2.2. Research Design

This study was a cross-sectional survey. The study was carried out at a particular point in time at the selected hospitals and data were collected only on the orthopaedic days at the selected settings. In a cross-sectional survey study, respondents are expected to provide a snapshot of information being inquired at that particular time [32].

2.3. Sample

Two hundred and ninety-six (296) patients with musculoskeletal disorder were participants in this study. The major inclusive criteria are that the patient must have at least one musculoskeletal disorder, and had been prescribed at least an oral NSAID at the time of this study. Patients who were not willing to participate in the study and or could not name the NSAID being taken were excluded from the study.

2.4. Sample Size Determination

According to Mathers et al, we determined a sample size of 300 patients for this study with a 5% margin error based on assumption that the response rate would be 70% but only 296 patients met the inclusion criteria at the time of the study [32]. The hospitals were selected using sample of convenience. Multi-stage sampling technique was used to select the patients from the hospitals. The first stage involved identification of all patients with MSDs at the out-patient clinics of the selected hospitals. The second stage involved interviewing and recruiting those that were currently on NSAIDs and who could remember the name of the NSAIDs being used.

2.5. Instrumentation

The instrument used in obtaining information for this study was a structured and close ended questionnaire. Prior to the study, a draft of the questionnaire was piloted among three experienced orthopaedic physiotherapists. They examined the questionnaire for simplicity, viability and precision. They also ensured that the questionnaire reflected the underlying concept and objectives of the study [33]). Changes were made based on their responses and the revised questionnaire was used for the main study. The questionnaire had four sections namely:

Section A: contained general demographic questions such as age and gender.

Section B: contained questions on their medical status (diagnosis).

Section C: assessed the awareness and side effects of oral NSAIDs experienced by respondents. The checklist of drugs in the questionnaire includes:

Piroxicam (Feldene), Diclofenac sodium (Voltaren retard), Methyl Salicylate, Menthol, Ketoprofen, Felbinac, Fluribiprofen, Ibuprofen (Ibrucap), Ketoprofen, Lidocaine, Naproxen, Ketolovac, Glucosamine sulphate (Urah) and Flotac.

Section D: sought to inquire the attitude and preference for other complementary techniques and routes of administration.

2.6. Procedure

Ethical approval was obtained from the ethical research committee of the Institute of Public Health, Obafemi Awolowo University, (IPH/OAU/12/196) Ile-Ife, Osun State, Nigeria. Permission was sought and obtained from the heads of the physiotherapy departments and heads of orthopaedic units at each hospital. The aims of the study were explained to respondents, and they were assured of confidentiality of information. The participants consented to participate through a written informed consent. In order to maintain anonymity, participants' names were not required in the questionnaire. The patients provided information on their medical statuses, awareness, and experiences on noticeable side effects of oral NSAIDs; knowledge and preference on other routes of administration. There was no time limit for completion of the questionnaire.

2.7. Data Management

The questionnaire were collated and entered into SPSS, version 17 in a private and password protected computer which only members of the research team had access to. The sample's demographic characteristics were analyzed descriptively. Chi-square was used to compare the mean percentage difference in the frequency of choice for the side effects. The cumulative percentage of respondents who could identify the side effects was computed by summation of percentages of respondents for each drug, divided by the total number of drugs. Five physiotherapists with at least 15 years experience were asked to grade proportions ranging

from zero (0%) to one hundred (100%). The proportion refers to the sample of participants (296). The consensus proportional grading was used. The percentages were classified as:

0 – 20 (%) – *Very low proportion (of sample)*

21- 40(%) – *Low proportion*

41 – 60 (%) – *moderate proportion*

61- 80(%) – *Good proportion*

81- 100 (%) – *significant proportion*

3. Results

3.1. Demographic Characteristics of Respondents

Of the 296 participants, 141 were males (47.9%) and 155 were females (52.3%) participants who completed the survey. The mean age was 37.3 ± 15.3 years. Eighty six (29.1%) respondents had postgraduate degrees, and fifty seven (19.3%) had graduate degrees or diploma (Table 1).

3.2. Diagnoses, Prescribers and Sources of Information

Participant's diagnoses are presented in table 2. One hundred and twenty five (42.2%) were diagnosed at state hospitals. Two hundred and sixteen patients reported that doctors (73%) prescribed the NSAIDs while forty one (13.8%) nurses were reported to have prescribed the drug. The frequency distribution of other health professionals who prescribed the drugs is also presented in table 2. One hundred and twenty-six (42.6%) had been using the NSAIDs for more than a month; sixteen of them (5.4%) had used it for just one week. One hundred and four (35.1%) participants got information on side effects of NSAIDs from their doctors while 137 (46.3%) read the drug pamphlets in drug pack. Other sources of information of side effects are presented in table 3.

Table 1. Qualifications and work settings of respondents

Demography	Frequency	%
Qualifications		
Postgraduate	86	29.1
Tertiary	57	19.3
Secondary school	14	4.7
Primary school	36	45.9
< Primary school	3	1.0
Work settings		
Private hospital	67	22.6
General hospital	125	42.2
Primary health centre	30	10.1
Self employed	70	23.6
Others	4	1.4

One hundred and eighty seven (63.2%) respondents read the pamphlet literature in the drug pack before usage. The Chi-square test showed that the number of participants that read information contained in the pamphlets in the drug pack was significantly higher than those that did not 109 (36.8%), ($\chi^2=20.1$, $p=0.001$). Similarly, the number of participants that understood the content of the pamphlets (188 [63.5%]) was significantly higher than those that did

not (73 [24.7]), ($\chi^2=203.73$, $p=0.001$).

3.3. Awareness and Side Effects

The frequencies of specific NSAIDs prescribed to the respondents are presented in table 4. Ninety nine (33.4%) respondents were able to identify dizziness as a side effect of NSAIDs while ninety-two (31.1%) could identify abdominal pain as a side effect. The distribution for other side effects is presented in table 5. The cumulative proportion (%) of respondents who were able to identify the listed side effects of NSAIDs was 15%. In response to what side effects they had experienced, sixty two (22.3%) had experienced dizziness while forty seven (15.9%) experienced abdominal pains. Other experiences are also presented in table 5.

One hundred and ninety six (66.2%) of the respondents had experienced at least one side effect of NSAIDs (Figure 1). The result of the Chi-square test showed that the number of patients who had experienced the listed side effects was significantly higher than those who had not ($\chi^2=30.59$, $p=0.001$).

3.4. Preference for other Routes of Administration

Only 2.0% and 2.7% respondents were aware of phonophoresis and iontophoresis respectively as alternative means of administering NSAIDs (Table 6).

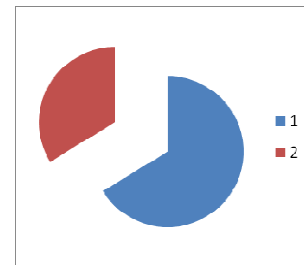
Table 2. Diagnoses, prescribers and duration of use

Variables	Frequency	%
Diagnoses: Osteoarthritis	31	10.5
Rheumatoid arthritis	56	18.9
Low back pain	56	18.9
Fracture	46	15.5
Surgical intervention	10	3.4
Dislocation	19	6.4
Soft Tissue Injuries	28	9.5
Others	50	16.9
Professionals: Physicians	216	73.0
Pharmacists	26	8.8
Nurses	41	13.9
Others	13	4.4
Duration: < 1week	25	8.4
1 week	16	5.4
2 weeks	49	16.6
3 weeks	37	12.5
4 weeks	43	14.5
> 4 weeks	126	42.6

One hundred and seventy nine (60.5%) respondents reported that they are aware of other means of administering NSAIDs. The chi-square test showed that the number of participants who knew about other means of administration was significantly higher than the number of those who did not ($\chi^2=12.24$, $p=0.001$). One hundred and fifty-five (52.4%) would not like to continue with the medication, this number was significantly higher than those who wished to continue ($\chi^2=141.7$, $p=0.001$), (Table 7).

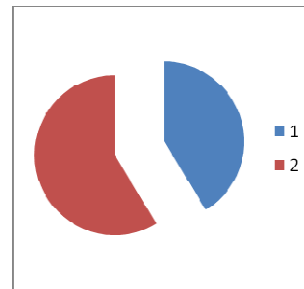
Table 3. Sources of information on side effects

Media	Frequency	Percentages
Doctor	104	35.1
Nurse	44	14.9
Literature	41	13.9
Radio	22	7.4
TV	45	15.2
Internet	35	11.8
Friend	48	16.2
Pamphlet in drug box	137	46.3



1. Experienced 2. None experienced

Figure 1. Experienced side effects



1. Informed 2. Not informed

Figure 2. Information on side effects

Two hundred and twenty three (75.3%) would prefer alternative means of administering NSAIDs considering the benefits. The Chi-square test result revealed that the number of participants that preferred alternative means of administration (where applicable) was significantly higher than those who preferred the oral route ($\chi^2=74.5$, $p=0.001$), (Table 7).

Table 4. Distribution of NSAIDs prescribed

NSAIDs	Frequency	%
Piroxicam	100	33.8
Diclofenac Sodium	153	51.7
Methyl Salicylate	114	38.5
Menthol	72	24.3
Ketoprofen	24	8.1
Felbinac	31	10.5
Fluribiproen	15	5.1
Ibuprofen	120	40.5
Ketoprofen	6	2.0
Lidocaine gel	3	1.0
Naproxen	18	6.1
Ketolovac	1	0.3
Glucosamine sulphate	46	15.5
Flotac	21	7.1

4. Discussion

Most respondents had been using the medication for more than three weeks; we assumed that this period would have given them the opportunity to notice side effects. A significant proportion was able to read and understand the literature pamphlets in the drugs pack. This might be attributed to the tertiary educational and post graduate qualifications of most respondents. Wahinuddin et al reported that factors such as knowledge, attitudes and motivation are important for patient compliance; and the effectiveness of therapy and that these factors might be influenced by the patient's education level, gender, the type of the disease and medication, as well as doctor-patient relationship, and culture [34]. The majority of participants (73%) were placed on NSAIDs by medical practitioners. It is only in the UK that specially trained non-medics were licensed as supplementary prescribers but we observed that other health professionals who were none prescribers also prescribed for patients [35]. The finding of inadequate information on side effects of NSAIDs by prescribers was a similar trend observed by Wynne and Long who also reported that 67% of participants were not informed of the side effects of NSAIDs [36]. Also, McMahon et al reported that doctors did not provide sufficient information on adverse effects of drugs and no reason was adduced for this [37]. Yilmaz et al reported that only half of the patients with osteoarthritis in Turkey were informed of the side effects of NSAIDs by their doctors [38]. However, current findings contradicted those of Cottrell et al who reported that participants in their study were informed of the side effects of NSAIDs prior to prescription [39].

Furthermore, almost half of respondents got information on side effects by reading drug literature inserted in the packs while few got it from TV (15.2%) and radio broadcast (7.4%). This is similar to the findings of Wahinuddin et al who also reported that 15% obtained information by surfing the internet and 9.2% from printed media in rheumatology clinic at Northern Malaysia [34].

Table 5. Side effects recognized and experienced

Side effects	Awareness		Experienced	
	Frequency	%	Frequency	%
High blood pressure	56	18.9	26	8.8
Low blood pressure	59	19.9	12	4.1
Indigestion	75	25.3	38	12.8
Gastro-intestinal bleeding	18	6.1	2	0.7
Ulcer	69	23.3	30	10.1
Vomiting	52	17.6	32	10.8
Diarrhea	26	8.8	15	5.1
Abdominal pain	92	31.1	47	15.9
Heart attack	14	4.7	20	0.7
Kidney disorders	20	6.8	3	1.0
Dizziness	99	33.4	62	22.3
Coma/unconsciousness	14	4.7	2	0.7
Nausea	65	22.0	37	12.5
Constipation	38	12.8	22	7.4
Gastric pain	25	8.4	14	4.7
Liver problems	11	3.7	3	1.0
Others	6	5.4	7	2.4

Table 6. Awareness on routes/techniques

Demography	Frequency	%
Transcutaneous	53	17.9
Injection	73	58.4
Transdermal massage	115	38.9
Lingual	13	4.4
Iontophoresis	8	2.7
Phonophoresis	6	2.0

Table 7. Attitude and preference for routes

		Freq	%	X2	P
Read drug pamphlet	YES	187	63.2	20.1	0.001
	NO	109	36.8		
Understood pamphlet info	YES	188	63.5	203.7	0.001
	NO	73	24.7		
Continuation of NSAID	YES	120	40.5	141.7	0.001
	NO	155	52.4		
Knowledge of other means	YES	179	60.5	12.2	0.001
	NO	117	39.5		
Preference for other means	YES	223	75.3	74.5	0.001
	NO	73	24.7		

*Based on valid % of those who responded to the questions

Diclofenac (voltaren retard) was the most frequently prescribed NSAID followed by ibuprofen (ibrucap) and this is consistent with the findings of Albsoul-Younes et al in a Jordanian population [40]. Diclofenac has been noted to be the most widely used NSAID in the world and this is despite hepatic reactions, hepatotoxicity and liver damage reported in several studies [19 - 21]. The usage might be attributed to its efficacy in pain management. It is also the most widely studied in reference to musculoskeletal disorders [41].

Dizziness, abdominal pain, indigestion and gastric ulcers characterized the most frequently experienced and recognized side effects of NSAIDs, although, very few were aware of the listed side effects. The study by Yilmaz et al, reported that most of the participants (84.5%) knew about dyspeptic disorders (characterized by stomach pains, indigestion, nausea) as side effects of NSAID [38]. We found that the number of patients who had experienced the listed side effects was significantly higher than those who had not. This is similar to results from a study by Cottrell et al and Albsoul-Younes et al, who reported that more than half of participants (67%) in their studies had experienced at least one side effect [39, 40].

The role of alternative methods aside oral and injections need to be available to patients where applicable to increase their health care choices as most respondents would prefer to discontinue with NSAIDs if other effective options with minimal or no side effect are available. Although, most respondents were unaware of alternative means of administering NSAIDs apart from oral and injections. However, Carnes et al reported that most patients on medication would be willing to continue with the drugs despite the side effects [42].

We felt the preference of most respondents for administration through injection might be a difficult task considering the daily use of the drug as this might necessitate daily hospital visits. Contrarily, Albsoul-Younes

et al found that 74% of participants in their study preferred the oral route while only 9% preferred injections [40]. The majority of patients (75.3%) would prefer other alternative of administering NSAIDs using procedures of iontophoresis and phonophoresis where applicable if they would reduce adverse reactions, although, very few knew about these procedures.

Gastro-intestinal disorders are the commonest adverse effects of NSAIDs, hence, there is need to know the medical and social profile of patients and also identify risk factors. Rusell observed that patients over 70 years, underlying respiratory dysfunction, cardio-vascular disorder, history of peptic ulceration and smoking are risk factors for developing gastro-intestinal disorders following NSAIDs prescription [16, 43]. These will guide dose adjustment, choice of alternative drugs (effective but with minimal side effects), dietary advice and co-prescription of suppressants which may reduce the adverse reaction of NSAIDs. This study did not take cognizance of the total population of patients with musculoskeletal disorders at the selected hospital settings and the findings can't also be generalized; this might be a limitation of this study. Similarly, the sources or manufacturers of the drugs were not considered. This is also another limitation because drugs adulteration can also increase side effects.

5. Conclusion

Diclofenac was the most prescribed NSAID. A significant number of the patients with MSDs reportedly experienced side effects which were mostly dizziness, abdominal pain, indigestion and gastric ulcers from NSAIDs. Most of them were not informed and were unaware of the side effects. Only 2.7% and 2.0% of respondents were aware of iontophoresis and phonophoresis respectively as alternative means of NSAIDs administration. The cost of the availability of alternative means should be a focus for future studies.

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