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AN INVESTIGATION OF OSTEOARTHRITIS MANAGEMENT AT THE UNIVERSITY OF BENIN TEACHING HOSPITAL, BENIN CITY, NIGERIA

Joshua Ogiangbe Idiake[1]*, Anthony Waka Udezi[2] and Stella Folajole Usifoh[3]

[1]BPharm, PharmD, MPharm Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria.

[2,3]BPharm, MPharm, PhD Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Benin, Benin City, Edo StaAte, Nigeria.

***Corresponding Author: Dr. Joshua Ogiangbe Idiake**
BPharm, PharmD, MPharm Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria.

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ABSTRACT

Introduction: Osteoarthritis (OA) is a degenerative disease that affects the joints of the body. There are different measures through which OA can be managed one of which is pharmacotherapy. Early detection and management is very crucial to the prognosis of the disease. Different patient factors especially co-morbid conditions influence the selection of these agents acclaimed for its management. **Methodology:** This retrospective study was conducted at the University of Benin Teaching Hospital. Information pertaining to OA management was obtained from the case notes at the records Department by the use of a data collection sheet. Data was analysed using SPSS version 24.0 and expressed in frequencies and percentages. With the use of graph-pad instat inferential statistics was done and a P-Value ≤0.05 was interpreted to be statistically significant. **Results:** Diclofenac (64.9%) was the most prescribed medication followed by paracetamol (22.1%), pregabalin (21.1%) and celecoxib (19.3%). Some patients with co-morbid hypertension (89.50%) were treated with NSAIDs while 87.18% of patients with co-morbid ulcer disease were treated with non-selective NSAIDs co-administered with gastro-protective agents. Omeprazole (81.62%) was the most commonly used gastro-protective agent. Patients' co-morbid conditions were the only socio-demographic factor that influenced the choice of medication for the treatment of osteoarthritis. (P = O.O311). **Conclusion:** Diclofenac was the most commonly used medication in the treatment of OA and co-morbid condition was considered by physicians when recommending medications for OA treatment.

KEYWORDS: Osteoarthritis, Treatment, Hospital, Side-effects, NSAIDs.

INTRODUCTION

Osteoarthritis (OA) is defined as a common degenerative disorder of the articular cartilage associated with hypertrophic changes in the bone.[1] It is one of the most prevalent disease conditions in the elderly population. Risk factors include genetics, female sex, past trauma, advancing age, and obesity. OA has a number of treatment measures and should be applied once disease is diagnosed. It is usually advisable to seek medical attention once detected as a delay may contribute to the advanced stage of the disease at the time medical attention is sought.[2,3] OA treatment choices can be classified into four main categories: non-pharmacologic, pharmacologic, surgical, complementary and alternative. Drug therapy (pharmacotherapy) is aimed at relieving symptoms, pains and improving joint functions capacity.[4]

Pharmacotherapy can be classified as either symptoms modifying osteoarthritis drugs or disease modifying osteoarthritis drugs.[5] Among the treatment options for OA, surgical procedure e.g. arthroplasty is the most expensive[6] and it's usually reserved as a last resort for those that do not respond to pharmacologic and behavioral approach. However it is not recommended for young individuals because of its short lifespan.[7] The Nigeria standard treatment guideline has recommended the use of acetaminophen, non-steroidal anti-inflammatory drug (NSAIDs), opioid analgesic, hyaluronic acid, glucosamine and chondroitin sulfate.[8] This is corroborated by Zhang et. Al[9] and Hochberg et al.[10] NSAIDs are the family of drugs commonly used for the management of osteoarthritis. They suppress the cyclooxygenase enzymes activity (especially COX-1 and COX-2) thereby resulting in the inhibition of prostaglandins (PGs). They also have analgesic, antipyretic and anti-inflammatory effects. More so, they are associated with several side effects such as gastrointestinal complications, bleeding disorder, cardiovascular toxicity, renal disease etc.[11,12]

Opioid analgesics are also considered in the treatment of osteoarthritis especially those unresponsive to NSAIDs or those in which NSAIDs are not appropriate. The major drawback in the use of opioid analgesic is high level of use dependence[13] and other side effects which may include nausea, vomiting, dizziness, constipation, drowsiness, fatigue, and headache.[14] For this reason long term use of opioid analgesic is not advisable.

Hyaluronic acid and glucocorticoids are used as intra-articular injectables. These agents are known to act by inhibiting the synthesis of inflammatory mediators. Glucosamine and chondrointin are natural dietary supplements which serve as substrates in the biosynthesis of proteoglycan in the joint. They act as chondroprotective agents and disease-modifying OA drugs (DMOADs)[15] thereby providing positive effect on pain relief and function improvement. They also provide cartilage with resistance and elasticity to resist tensile stresses during loading condition.[16]

There is need for early diagnosis of osteoarthritis and management with the right approach as the risk for disability associated with knee OA is as great as that associated with cardiovascular disease and greater than those associated with any other medical condition in elderly persons.[17] OA is ranked as second cause of disability by WHO[18] and has a worldwide prevalence of 9.6% among men and 18% among women.[19] Hence need for the assessment of different therapies (And their safety) used for its management.

MATERIALS AND METHODS

Setting

This retrospective study was conducted at the records sections of the Orthopedic and Rheumatology Departments of the University of Benin Teaching Hospital (UBTH), Benin City, Edo State. UBTH is a tertiary healthcare institution established on May 12th, 1973. It has a capacity of over 750 bed spaces.

Study Population

The study population consists of all the patients that visited the Orthopedic and Rheumatology Departments of the Hospital between January 2013 and December 2018 as obtained from the Medical Records Department of the Hospital. From this population, a study sample was systematically drawn using a sampling interval of 5 case notes.

Sample

The sample consists of all the patients diagnosed with OA within the stipulated period.

Sample Size Determination

Sample size was calculated to be 393 using the Yamane formula below.

$n = N/1+N(e)^2$

n=sample size

N=24,625

E=Precision (0.05)

Data collection

The case notes of the patients who were diagnosed with OA within the period of review were retrieved from the medical records department and with the aid of data collection sheet relevant information about the patients were obtained. The data collection sheet consists of two sections. Section A collected the socio-demographic data e.g. sex, age, occupation, marital status, educational level, family history of osteoarthritis, smoking and alcohol consumption. Section B obtained information pertaining to drug management of osteoarthritis.

Inclusion criteria

All patients diagnosed with OA during the period under review were included in the study.

Exclusion criteria

Patients who were not diagnosed with OA were excluded from the study.

Data analysis

Data collected were entered into Microsoft excel spread sheet and then transported to statistical package for social science (SPSS) version 24.0 for analysis. Results were expressed in frequencies and percentages. The management pattern of osteoarthritis was assessed with regards to the socio-demographic factors. Chi Square was used in inferential analysis with the aid of Graph pad instat. P-value ≤ 0.05 was interpreted as statistically significant

RESULTS

Females (316, 68.7%), patients aged 60-69years (149, 32.4%), self-employed (183, 39.8%) and patients with hypertension (181, 66.5%) were the most affected by osteoarthritis. See Table 1

Table 1: Socio-demographic data of patients.

Socio-demographic data	Variables	Frequency	Percentage (%)
Sex	Male	144	31.3
	Female	316	68.7
Age (Years)	<30	22	4.8
	30-39	27	5.9
	40-49	50	10.9
	50-59	98	21.3
	60-69	149	32.4
	70-79	90	19.6

	Above 80	24	5.2
Smoking Status	Yes	26	5.7
	No	434	94.3
Alcohol consumption	Yes	134	29.1
	No	326	70.9
Comorbidity	Hypertension	181	66.5
	Diabetes	42	15.4
	Peptic ulcer	39	14.3
	Asthma	4	1.5
	Glaucoma	1	0.4
Occupation	Students	24	5.2
	Government job	69	15.0
	Self-employed	183	39.8
	Unemployed	90	19.6
	Private Sector	4	0.9
	Retired	90	19.6

Table 2: Distribution of drugs used in the management of osteoarthritis.

Drugs	Frequency	Percentage use (%)
Acetaminophen	101	22.1
Aspirin	59	12.9
Celecoxib	88	19.3
Diclofenac	296	64.9
Aceclofenac	2	0.4
Meloxicam	2	0.4
Naproxen	19	4.2
Ibuprofen	11	2.4
Ketoprofen	5	1.1
Ketorolac	3	0.7
Tramadol	49	10.7
Codeine	49	10.7
Pentazocine	1	0.2
Pregabalin	96	21.1
Prednisolone	5	1.1
Prednisone	1	0.2
Hyaluronic acid	2	0.4
Glucosamine	46	10.1
Chondrointin Sulphate	46	10.1
Methylsalicylate	3	0.7
Hydrocortisone	1	0.2

Diclofenac (64.9%) was the most prescribed medication. This was followed by paracetamol (22.1%), pregabalin (21.1%) and celecoxib (19.3%). Whereas methylsalicylate (0.7%) and hydrocortisone (0.2%) were the least used as shown in table 2.

Table 3: Distribution of drug use in OA patients with different comorbid disease conditions.

Medications		Comorbid disease Conditions			
	Hypertension (n=181)	Diabetes (n=42)	Peptic ulcer (n=39)	Asthma (n=4)	Glaucoma (n=1)
Acetaminophen	45 (24.86)	11 (26.19)	15 (38.46)	1 (25)	0 (0.0)
Aspirin	28(15.47)	7 (16.67)	7 (17.95)	0 (0.0)	0 (0.0)
Celecoxib	29 (16.02)	10 (23.81)	12 (30.77)	0 (0.0)	1 (100)
Diclofenac	120 (66.30)	26 (61.90)	24 (61.54)	2 (50)	0 (0.0)
Aceclofenac	0 (0.0)	1 (2.38)	0 (0.0)	0 (0.0)	0 (0.0)
Meloxicam	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Naproxen	9 (4.97)	1 (2.38)	2 (5.13)	0 (0.0)	0 (0.0)
Ibuprofen	3 (1.66)	1 (2.38)	0 (0.0)	1 (25)	0 (0.0)
Ketoprofen	2 (1.10)	2 (4.76)	1 (2.56)	0 (0.0)	0 (0.0)
Ketorolac	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tramadol	21 (11.60)	7 (16.67)	2 (5.13)	1 (25)	0 (0.0)
Codeine	24 (13.26)	6 (14.29)	6 (15.38)	1 (25)	0 (0.0)
Pentazocin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregabalin	35 (19.34)	6 (14.29)	7 (17.95)	2 (50)	0 (0.0)
Prednisolone	2 (1.10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prednisone	1 (0.55)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

In table 3, some NSAIDs (diclofenac and ibuprofen) and tramadol were used in 4 patients with asthma. Of the 181 hypertensive patients, 162 (89.50%) were treated with NSAIDs other than celecoxib or naproxen. Thirty four (87.18%) patients with co-morbid peptic ulcer disease were treated with non-selective NSAIDs and were all co-administered with gastro-protective agents.

Table 4: Distribution of gastro-protective agents used as adjuncts in NSAID therapy.

NSAIDs	**Gastroprotective**	**Agents**			
	Misoprostol	**Omeprazole**	**Rabeprazole**	**Esomeprazole**	**Total**
Diclofenac(n=296)	14(7.65)	153(83.61)	14(7.65)	2(1.09)	183
Naproxen(n=19)	0(0)	6(37.5)	1(6.25)	9(56.25)	16
Ibuprofen(n=11)	0(0)	4(100)	0(0)	0(0)	4
Ketoprofen(n=3)	0(0)	3(100)	0(0)	0(0)	3
Aspirin(n=59)	2(7.41)	24(88.89)	0(0)	1(3.70)	27
Ketorolac(n=3)	0(0)	0(0)	0(0)	0(0)	0
Meloxicam(n=2)	0(0)	1(100)	0(0)	0(0)	1
Total	16(6.84)	191(81.62)	15(6.41)	12(5.13)	234

Omeprazole (191, 81.62%) followed by misoprostol (16, 6.84%) and rabeprazole (15, 6.41) were the most commonly used gastro-protective agents among ulcer patients taking non-selective NSAIDs while esomeprazole (12, 5.13%) was the least used.

Table 5: Determination of the influence of socio-demographic data on the choice of drugs prescribed in the management of osteoarthritis.

Socio-demographic data	**Medications**					
	Diclofenac	**Paracetamol**	**Celecoxib**	**Pregabalin**	**Frequency**	**P-value**
Age (years)						
<50	59 (52.68)	22 (19.64)	17(15.18)	14 (12.5)	112	
50-59	62 (46.62)	23 (17.29)	25(18.80)	23 (17.29)	133	0.4242
60-69	92 (48.42)	38 (20)	29(15.26)	31 (16.32)	190	
≥70	83 (56.85)	18 (12.33)	17 (11.64)	28 (19.18)	146	
Sex						
Male	88 (50)	26 (14.77)	28 (15.91)	34 (19.34)	176	0.5077
Female	208 (51.36)	75 (18.52)	60 (14.81)	62 (15.31)	405	
Occupation						
Students/Government workers	53 (50.48)	24 (22.86)	15 (14.29)	13 (12.38)	105	
Unemployed	66 (55.46)	21 (17.65)	13 (10.92)	19 (15.97)	119	0.6013
Private sector/self-employed	117 (48.55)	38 (15.77)	43 (17.84)	43 (17.84)	241	
Retired	60 (51.72)	18 (15.51)	17 (14.65)	21 (18.10)	116	
Co-morbid Condition						
Hypertension	120 (52.40)	45 (19.65)	29 (12.66)	35 (15.28)	229	
Diabetes	26 (49.06)	11 (20.75)	10 (18.87)	6 (11.32)	53	0.0311
Peptic Ulcer	12 (26.09)	15 (32.61)	12 (26.09)	7 (15.22)	46	

Table 5 shows that co-morbid condition was the only socio-demographic data that influenced the choice of medication for OA patients. (P = 0.0311).

DISCUSSION

OA management can be achieved either through drug or non-drug therapy. Often times both approaches are advocated for a better health outcome. The major aim of pharmacotherapy in osteoarthritis is pain alleviation and restoration/improvement of function as there is no apparent curative or preventive therapy. It is necessary to select and adapt medication therapy according to the patient specific socio-demographic data particularly in cognizance of co-morbid conditions.

NSAIDs are thought to be very potent in relieving pains associated with osteoarthritis but there are associated safety concerns due to their adverse effects mainly on the gastrointestinal tract, cardiovascular and renal system.[21,22] This makes it necessary to adopt suitable risk reduction measures when prescribing these medications. These measures may include administering the lowest possible doses for the shortest possible period, co-administering them with suitable medications that can protect against or ameliorate the deleterious effects or administering a suitable alternative medication.

The most frequently prescribed group of medications for the management of OA in this facility were the NSAIDs with diclofenac (296,64.9%) having the highest frequency.[22] Although diclofenac and other NSAIDs are highly reputable for the management of pains in OA, they are also known to heighten cardiovascular risk in individuals.[23,24,25] More so, International Nephrology Societies have warned against the use of NSAIDs in patients with hypertension, heart failure and chronic kidney disease.[26,27]

The mechanism behind this is through sodium retention and vasoconstriction. However, in this study it's not known if the high blood pressure is idiopathic or associated with the high rate of use of NSAIDs. Treating 84.53% of hypertensive patients with NSAIDs known to be unsafe in patients with cardiovascular diseases is a source of concern.[28] Studies have shown that NSAIDs such as celecoxib and naproxen have a more favorable safety profile in patients with comorbid cardiovascular disease condition hence should have been a better alternative for this group of patients.[29] However only 29 (16%) and 9 (4.97%) patients with hypertension were treated with celecoxib and naproxen respectively. It should be noted that most of the patients are low income earners and hence the prescribers are constrained in prescribing celecoxib and naproxen as they are relatively more expensive than the other NSAIDs. Despite the safety profile of celecoxib, optimum care should be taken during use as the use of higher than recommended doses have been reported to result in cardiovascular toxicity.[30]

Diclofenac and other non-selective NSAIDs were also used in Peptic Ulcer Disease (PUD) patients. However, gastro-protective agents such as misoprostol and proton pump inhibitors (omeprazole, rabeprazole or esomeprazole) were used concomitantly to prevent or protect against the gastrointestinal side effects[31] of non-selective NSAIDs. These side effects include bleeding gastric and/or duodenal ulcers, and to a lesser extent obstructions and/or perforations.[32,33] NSAIDs do this by interfering with the cyclooxygenase (COX) pathway thereby suppressing the production of prostanoids which play the role of gastric mucosa protection, inhibiting gastric mucosa blood flow and inhibiting the production of bicarbonate and mucus. These sequences of biological events expose the gastric mucosa to the toxic effect of gastric acid.

Proton pump inhibitors are potent inhibitors of gastric acid secretion and its co-administration with non-selective NSAIDs has been grossly associated with a reduction in upper GIT side effects. However there has been an increase in the frequency of lower GIT toxicity with significant clinical importance.[34] Misoprostol a prostaglandin analogue was also used concomitantly with non-selective NSAIDs. It protects the gastric mucosa by decreasing gastric acid secretion, increasing mucus and bicarbonate production and maintaining mucosal blood flow thereby protecting against the toxic effects of NSAIDs.[35,36] However, studies have shown that proton pump inhibitors are more effective in protecting the gastric mucosa than misoprostol.[37] This is evident in table 3 as the proton pump inhibitors were the most prescribed with omeprazole having the highest frequency of use (191, 81.62%).

It is seen in table 2 that celecoxib was the second most used NSAID (12, 30.77%) in patients with peptic ulcer disease. Celecoxib, a cyclooxygenase 2 (COX-2) selective NSAID spares the cyclooxygenase 1 (COX-1) enzyme which is responsible for the synthesis of gastro-protective substances such as mucus and bicarbonate. This unique property makes it a drug of choice in the management of osteoarthritis in peptic ulcer patients. It has been found to be safer in patients with PUD than the co-administration of a non-selective NSAID and a proton pump inhibitor.[38]

Paracetamol is the first choice of many treatment guidelines and it was used by many patients (22.1%). However its efficacy in the treatment of OA is considered limited[39,40] hence the need to frequently add or substitute with a better drug. Opioid analgesic is considered to be an option in the management of pains especially in patients that fail to respond to or do not tolerate the gastrointestinal and cardiovascular side effects of regular NSAIDs. However, only 21.4% of patients were treated with opioid analgesic such as tramadol (10.7%), codeine (10.7%) and pentazocine (0.2%)). This is because opioids are not considered as first choice in the early treatment of OA due to their low

clinical benefits.[41,42,43] and the associated potential for dependence and toxicity.[44] Those that received more of the opioids were those with comorbid hypertension, diabetes and PUD. Tramadol and codeine were the opioids used. This is in congruence with a study conducted by Cho et al.[45]

Although aspirin was completely avoided in asthmatic patients, a few of them received NSAIDs (ibuprofen and diclofenac) in the management of osteoarthritis. Aspirin and other non-selective NSAIDs are known to acutely exacerbate asthmatic attacks.[46] This effect is potentiated through their ability to inhibit cyclooxygenase (COX), prostaglandin synthesis and activation of the lipoxygenase pathway thereby culminating in increased leukotriene synthesis, release of mast cells, eosinophil and basophil and risk of bronchospasms or asthma exacerbation.[47,48] A COX-2 selective inhibitor such as celecoxib is largely preferable in the management of osteoarthritis in patients with respiratory diseases as the activities of COX-1 enzyme is spared.[49] However, none of the asthmatic patients received celecoxib for OA treatment. Although tramadol causes respiratory depression,[50] one of the asthmatic patients received it. However this effect is reportedly rare and commonly occurs when tramadol is co-administered with other Central Nervous System depressants such as anesthetics, alcohol etc.[51]

Although the management of OA in patients with peptic ulcer disease and hypertension did not fully comply with the recommended treatment guidelines, a reasonable consideration was given by physicians as depicted in table 5. This information helps to increase awareness of the limitations and difficulties encountered in translating these recommendations into clinical practice.

CONCLUSION

Non-steroidal anti-inflammatory drugs were most commonly used in the management of osteoarthritis even in high risk patients. Some high risk patients were either treated with appropriate drugs or co-administered appropriate agents to mitigate or prevent the deleterious effect(s) of the main drug for the management of osteoarthritis. Attention is also brought to the high rate of NSAID use that does not conform to recommendations given by appropriate regulatory agencies.

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