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EVALUATION OF TREATMENT RESPONSE TO PAINS OF RHEUMATIC DISEASES' ORIGIN AND CLINICAL OUTCOME OF DRUG COMBINATIONS USED FOR PAIN MANAGEMENT IN A TEACHING HOSPITAL IN NIGERIA

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ABSTRACT

Background: Musculoskeletal diseases causing pain are common and increasing in frequency as well as causing a considerable burden to the individual and society. It is desirable to evaluate the various treatment options to identify optimal therapy that improve pain alleviation in order to guide their clinical and rational uses in the region. **Aim and Objectives:** The objectives of this study are to assess the status of arthritis pains in patients receiving drug therapy between clinic visits and to determine the optimal therapy or therapies for pain management with various drug combinations. **Methods:** The retrospective study reviewed 121 patients with various types of arthritis on regular clinic attendance. Pain status of patients on various drug combinations were assessed in-between clinic visits which cumulatively sum up to 372 visits and covering a period of 5 years. **Results:** The proportion of the male subjects was 36.4% compared to 63.6% of the female subjects. Osteoarthritis was the highest form of arthritis (being 65.3%) while rheumatoid arthritis was observed in 22.3% cases. Other forms are gouty arthritis (9.1%), juvenile arthritis (0.8%), and septic arthritis (0.8%). Pain regression occurred in 64.5% cases but was exacerbated in 5.1% cases. No changes in pain status were observed in 6.5% patients while in 22.6% of patients, there were complete alleviations with various drug combinations. However, in 1.1% proportion, resurged pain episode was observed. About 73 (62.9%) of patients placed on NSAIDs as lone agent had pain regression with 21 (18.1%) having complete pain resolution between clinic visits and while 3(2.6%) experienced resurged pain, 8 (6.9%) had pain exacerbation and

11(9.5%) had no change in pain status. There were marginal increases in patients who experienced pain regression and resolution when NSAID was combined with chondroitin/glucosamine (being 65.3% and 21.4% respectively), and with steroids (being 68.0% and 24.0% respectively), but DMARD and steroid combinations gave a very high proportion of patients with pain regression (92.3%). **Conclusion:** The treatment outcomes resulting from various drug combinations used in the management of arthritis pains varies with high proportion of patients experiencing pain regression but while a few others experienced no change in pain status, pain exacerbation occurred in minority. Complete pain remission also occurred in minority of patients. The combination of NSAIDS with other agents gave rise to various changes in pain status.

KEYWORD: Pain regression, Arthritis, NSAIDs, Rheumatoid arthritis, Osteoarthritis.

INTRODUCTION

Arthritis is a common ailment which affects a considerable number of people in any given society. In the United State of America alone, nearly 46 million people are affected and the prevalence is expected to rise by approximately 40% by 2030, impacting 67 million people. Arthritis causes wear-and-tear damage to joints' cartilages which results to damage arising from bone grinding directly on bone, and causing pain and restricted movement (Charles *et al*., 2005)**.**

There are many forms of arthritis but osteoarthritis is usually found in one weight bearing joint. In rheumatoid arthritis, the joint lining becomes inflamed. Some people have witnessed seronegative, spondylo-arthropathy, crystalline deposition and septic arthritis forms of the disease.

Arthritis is a major cause of lost work time and serious disability for many people (Charles *et al*., 2005)**.** Osteoarthritis is characterized by focal areas of loss of articular cartilage within synovial joints, which are associated with hypertrophy of bone (osteophytes and subchondral bone sclerosis) and thickening of the capsule. Joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation are often the presenting signs. They majorly affect the joints of the hips; knees; and the joints of the hand, foot, and spine although other joints can be affected (World Health Organization, 2003).

The worldwide estimates of 9.6% of men and 18.0% of women aged ≥60 years have symptomatic osteoarthritis. In US and European populations of people aged ≥45 years, osteoarthritis of the knee occurred in 14.1% of men and 22.8% of women (Charles *et al*., 2005)**.**

In terms of geographical or regional distribution, osteoarthritis is more prevalent in Europe and the USA than in other parts of the world but the African-American women are more prone than white women to osteoarthritis of the knee but not of the hip. Osteoarthritis of the hip occurs more often in European whites than in Jamaican blacks, African blacks, or Chinese (Gregory, *2014)*. According to the American Society of Arthritis, (2011), osteoarthritis is the most prevalent kind of arthritis, affecting more than three million Canadians.

Some arthritis forms especially in rheumatoid arthritis, the immune system cannot differentiate self from non-self-tissues leading to the attacks of the synovial tissue and other connective tissues. Antibodies in form of rheumatoid factors are formed though not an identified pathogenic factor nor does the quantity of these circulating antibodies always correlate with disease activity. However, seropositive patients can have more aggressive course of illness than seronegative patients (Arthur, 2003).

Many immunologic cells are involved in the disease process of some arthritis forms. For instance, the pro-inflammatory cytokines tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6 are key substances in the initiation and continuance of rheumatoid inflammation. But cartilage destruction is caused by a subset of T-cell (TH_{17}) which produces IL-17 that induces proinflammatory cytokines in fibroblasts and synoviocytes; and stimulates the release of matrix metalloproteinase and other cytotoxic substances leading to cartilage destruction(Arthur, 2003). Cytotoxins are produced when T cells are activated causing direct toxicity to tissues but it is the cytokines, which stimulate further activation of inflammatory processes thereby attracting cells to areas of inflammation. Macrophages may contribute to the process since they are stimulated to release prostaglandins and cytotoxins. Pro-inflammatory cytokines stimulates T- cell alone side with interaction between cell surface receptors, as co-stimulator. The co-stimulation interactions between CD28 and CD80/86 are interrupted by some agents binding to the CD80/86 receptor and thereby becoming an effective agent for the treatment through prevention of co-stimulation interactions between T cells (Arthur, 2003).

Osteoarthritis can be idiopathic (primary) but some are secondary to other diseases such as: trauma, bone and joint deformity, obesity, bone and joint infection, bone infarction, and haemophilia (Falase and Akinkugbe, 2007).

The heritability of RA to be approximately 60% but the association between RA and the HLA SE alleles (shared epitope) of the human leukocyte antigen (HLA-DRB1 gene) has been reported(Newton *et al.,* 2004). The HLA-DRB1 gene has been clearly demonstrated to be involved in RA with respect to disease-modifying elements (Newton *et al.,* 2004). Some individuals with poorly treated joint infection may be at risk of osteoarthritis in future but weight increment has been identified as a risk factor (Catherine and Gerald, 2008).

Many risk factors can influence the disease but obesity often precedes osteoarthritis and contributes to its development. The risk of developing osteoarthritis increases by approximately 10% with each additional kilogram of weight. In obese persons without osteoarthritis, weight loss of 5 kg (11 lbs.) decreases the risk of future knee osteoarthritis by half. Occupation, sports, and trauma are similarly risk factors of osteoarthritis. Occupations requiring prolonged standing, kneeling, squatting, lifting or moving of heavy objects, such as shipbuilding, mining, carpentry, farming, and some types of factory work are mostly affected (Lane, 2007).

Genetic links have been shown with osteoarthritis of the first metatarsophalangeal joint and with generalized osteoarthritis (Sun *et al*., 2007). The genetic associations to osteoarthritis include genes related to inflammation (IL1, IL-10), Wnt signalling (FRZB, LRP5), bone morphogenetic proteins (*BMP2*, *BMP5*, and *GDF5*), and proteases or their inhibitors (ADAM12, TNA, AACT) (Valdes *et al*., 2008).

Several risk factors are similarly identified in RA, in particularly family history of rheumatoid arthritis, immunogenetic susceptibility, female sex and environmental factors are documented (Scott *et al*., 2011). Rheumatoid arthritis is more common among females than males due to the role of female sex hormones, particularly in the peri-menopausal period (Kuiper *et al*., 2001). Androgen deficiency and prolactin excess also, explain the higher incidence of rheumatoid arthritis in females (Brennan & Silman, 1995). Pregnancy also influences the timing of the disease, with the postpartum period being a high risk time for developing first symptoms (Silman *et al*., 1992).

The survival rate for persons with rheumatoid arthritis is estimated to be lower than for those without the disease. Woolf and Pfleger (2003) estimated the death rate ratio for rheumatoid arthritis to be between 1.98 and 3.08. The disease is not commonly the underlying cause of death. Most of the increased mortality is through its contribution to other causes of death. Woolf and Pfleger (2003) also noted a specifically greater mortality due to infection, lymph proliferative malignancy and digestive disorders. In 2003, rheumatoid arthritis was listed as the underlying cause in 184 deaths. It was listed as an associated cause of death in 632 cases (CDC, 2010).

AIM AND OBJECTIVES

The objectives of this study are to assess the status of arthritis pains in patients between clinic visits and to determine the optimal therapy or therapies for pain management with various drug combinations

MATERIALS AND METHOD

The retrospective study was conducted at the Rheumatology and Orthopaedic Clinic of the University of Maiduguri Teaching Hospital (UMTH) Maiduguri, Borno State in the north-East Nigeria. The city lies between latitude 11.5^{o} North and 13.5^{o} East in the Sudan Savannah. A total of 121 patients managed for arthritis ailments with various drug combinations were assessed. Patients who are diagnosed of arthritis and placed on regular range of medications like Non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatoid drugs (DMARDs), steroids, chondroitin/glucosamine, and alpha-2-adrenergic agonist used alone or in combination with one another were investigated. The patients' folder review covers a period of 5 years (between 2010 and 2014). All newly diagnosed patients who are newly started on medication or yet to start commence drug therapy were excluded. Descriptive statistical was used to analyse variables and inferential statistics were performed to find level of significance existing between two or more variables using statistical package for social sciences (SPSS) version 19 and Excel spread sheets. Levels of significance and confidence intervals were determined at $P<0.05$. Variables were cross tabulated to find the relationship existing between them.

RESULTS

The frequency distribution of age of patients (Table 1) is skewed toward low frequency of lower age range with a mean and standard deviation of 50.2 ± 12.8 years when both genders are combined. The distribution for the female patients is similar to the pattern observed when

both genders are combined but has a mean age and standard deviation of 50.3 ± 12.5 years. The mean age and standard deviation for the male patients was 50.0 ± 19.9 years. The peak ages of the illness for both genders are those in their sixth decades of life (being 29.5% for male and 31.2% for female) but the incidence decrease in the male above 70 years. When the various age strata were evaluated for gender variation, there were no significant differences ($P>0.05$) between the proportions of male and female for each age stratum. Arthritis was observed present in about 4.6% of male subjects and 5.2% of the female subjects who are below 30 years.

The proportion of male subjects in the study was 36.4% (95% CI) compared to 63.6% (95% CI) of female subjects (Table 2). Patients who are married accounted for 79.3% compared to 20.7% of the unmarried subjects. Osteoarthritis was the highest form of arthritis (being 65.3%) while rheumatoid arthritis was observed in 22.3%. Other forms of arthritis are gouty arthritis (9.1%), juvenile arthritis (0.8%) and septic arthritis (1.6%). The duration of diagnosis indicated that about 8.3% of patients have been diagnosed with the illness for the last one year while 57.1% were diagnosed 1-4 years (Table 2). Those who are diagnosed within 4-6 years are about 13.2% while in 10.8% patients have been with the illness between 6-10 years. Those who have been diagnosed with arthritis for more than 10 years accounted for 11.7%.

When the intermediate evaluation of clinical outcome based on symptomatic alleviation and treatment response was evaluated in-between clinic visits of patients (Table 3), the results showed that pain regression occurred in 64.5% cases while it increased in 5.1% cases. No changes in pain status were observed in 6.5% patients while in 22.6% of patients, there were complete remissions. However in 1.1% proportion, resurged pain episode was observed.

About 73 (62.9%) of patients placed on NSAIDs as lone agent had pain regression with 21 (18.1%) having complete pain remission between clinic visits and while 3(2.6%) experienced resurged pain, 8 (6.9%) had pain exacerbation and 11(9.5%) had no change in pain status. There were marginal increases in patients who experienced pain regression and complete remission when NSAID was combined with chondroitin/glucosamine (being 65.3% and 21.4% respectively), and with steroids (being 68.0% and 24.0% respectively). A much higher results were obtained with DMARD and steroid combinations (The high proportion of patients with pain regression was 92.3%). Other agents when used alone gave a varying proportion of patients with pain regression. For instance, steroid when used alone led to 53.8% patients having pain regression and alpha-2 adrenergic agonist had 84.6%. Pain

resolutions (complete remissions) were observed in high proportion with triple combination of NSAID/DMARD/Steroid (66.7%) and NSAID/chondroitin/glucosamine (65.3%), NSAID/Analgesic/Opioid (74.4%) and NSAID/steroid/xanthine oxidase inhibitor (81.8%).
The duration of drug use leading to various outcomes in pain status is shown in Table 4. Pain regression occurred in 84.6%, 61.4%, 66.3%, 68.1%, 62.8%, 66.7% and 56.3% of patients as one moved from shorter duration to longer duration of clinic visits which corresponded with the duration of drug use between clinic visits. Pain resurgence occurred in 2.6% of NSAIDs lone agent users and 1.0% when NSAIDs are combined with glucosamine/chondroitin.

There were no changes in pain status in 11 (9.5%) of NSAIDs lone agent users, but this outcome decreased when NSAIDs was combined with other agents such as glucosamine/chondroitin (n=7, 7.1%), analgesic/opioid (n=1, 3.7%), steroid (n=2, 8.0%), and alpha-2-adrenergic agonist (n=1, 6.2%). These results however indicated no significance difference ($P>0.05$) compared with NSAIDs lone agents (X^2 being 0.39, 1.15, 0.09 and 0.047 respectively).

DISCUSSION

The age distribution of both genders when combined is skewed toward low frequency of lower age strata with a mean and standard deviation of 50.2 ± 12.76 years. This distribution pattern is similarly observed with the male and female subjects when analysed separately. The wide deviation in the male, female and combined gender population indicated that the ailment cut across a wide age strata and juvenile form of the disease is common. The highest cases in both genders were observed in those who are above their second decades of life while low cases were recorded in those in their sixth decades of life (Table 1). Before age 60 years, the proportion of patients with arthritis increases progressively and decreases afterward. According to Deepa *et al* (2007), nearly two-thirds of patients with arthritis are aged below 65 years. The proportion of male subjects with arthritis was observed lower than obtained in the female. In general, arthritis cases were Higher in Female than male in nearly all age strata with the overall women to men ratio of 1.8:1. This finding is not surprising since the preponderance for the disease is higher in women than men owing to hormonal influence (Kuiper *et al*., 2001). Furthermore, women are 2 to 3 times more likely to be diagnosed than men (O'Dell, 2011; Arthur, 2003). This pattern of results is in agreement with the work of Charles *et al* (2005). Gender has also been identified as one of the factors influencing the course of the disease and being a female is considered as potential risk factor

for the disease. However, there were no significance differences (P>0.05) when the proportions of the patients with the illness among various age strata were compared between male and female genders. In our study, we find the least onset and case of the disease to exist in patients in their third decades of life, which is in agreement with the literature (Firestone, 2008; O'Dell, 2011).

The distribution of forms of arthritis in the study (Table 2) indicated that osteoarthritis (AO) occurred in nearly two-third of the patients while rheumatoid arthritis was the second leading cases in the region with septic arthritis occurring as the least. Other authors have reported similar pattern like this (O'Dell, 2011).

The clinical outcome evaluation indicated that high proportions have persistent but reduced rheumatic pains during varying time of drug therapy and drug combination. There were also persistent pains which tend to increase in minority of patients while there appeared to be no change in pain status in some few patients. Another outcome observed is the case of few resurged pain in previously remitted cases. The pains in more than one-fifth of the patients were observed to resolve, that is, complete remission. The assessment of the duration of pain alleviation among patients indicated that pain persistent varies with the duration of therapy. Although there were reductions in pains as symptoms, but shorter duration of therapy is associated with high proportion of patients with persistent pain though with reduced intensity and severity.

The NSAIDs were observed used in high proportions to alleviate most arthritis pains. Many factors may favour their high recommendation in this study. Their availabilities couple with relatively low cost compared to most other agents make them very attractive to patients. They have been used in this study as lone agents and as adjunct in rheumatoid arthritis but as first choices in OA. Although some studies have shown comparable efficacy for acetaminophen and NSAIDs, but the recommendations of NSAIDs were higher than analgesic acetaminophen in this study. Some researchers have reported that patients experienced better pain control with NSAIDs than with acetaminophen, and that OA patients preferred NSAIDs to acetaminophen (Eccles *et al*., 1998; Pincus *et al*., 2000; Towheed *et al*., 2003).

Low-dose narcotic analgesics may be very useful in patients who experienced no relief with analgesic (acetaminophen), NSAIDs, intra-articular injections, or topical therapy (Hansen and Elliott, 2003). Opioid analgesics have been combined with several agents for many patients

in this study. However, the recommendations for pharmacologic therapy in OA begins with non-opioid analgesics such as acetaminophen, followed by non-steroidal anti-inflammatory drugs (NSAIDs), inhibitors specific for the cyclooxygenase-2 (COX-2) enzyme when indicated, and topical analgesic creams containing capsaicin or methylsalicylate (ACR, 2000; Manek, 2001). The ACR recommends acetaminophen as first-line drug therapy for pain management in OA, due to its relative safety, efficacy, and lower cost compared to NSAIDs (ACR, 2000; Towheed, 2003). Pain relief with acetaminophen (analgesic) can be similar to that obtained with aspirin, naproxen, ibuprofen, and other NSAIDs, although some patients will respond better to NSAIDs (ACR, 2000; Towheed, 2003). The NSAIDs especially the non-acetylated groups may also be used in the treatment of acute gouty arthritis (Hawkins and Rahn,). These agents are particularly useful in patients who cannot take NSAIDs due to renal failure or for patients in whom all other treatment options have failed and who are at high surgical risk, precluding joint arthroplasty.

Disease-modifying drugs are targeted not at pain relief but at preventing, retarding, or reversing damage to articular cartilage in OA (Brandt, 2001). Glucosamine and chondroitin has been used in this study as a single agent and in combinations with NSAIDs, analgesic acetominophen, and with steroid with various degrees of outcomes since both agents have good efficacy in reducing pain and improving mobility and since glucosamine reduced joint space narrowing (Richy *et al*., 2003). Other authors have previously reported that the use of glucosamine or chondroitin is associated with slower loss of cartilage than placebo, in knees affected by OA (Reginster *et al*., 2001; Uebelhart *et al*., 1998). Despite these attractive therapeutic benefits, its recommendation for patients is low in the region owing to its high cost.

Corticosteroids are another useful agents recommended for many patients in this study as a single agent as well as combination therapy with NSAIDs, DMARD and glucosamine/chondroitin. They are reported to have shown good results particularly in the treatment of acute attacks of gouty arthritis and when used as adjuncts with other therapies. They may also be reserved primarily for resistant cases or for patients with a contraindication to colchicine and NSAID therapy (Rott and Agudelo, 2003). However, intra-articular glucocorticoid injections can provide excellent pain relief in OA, particularly when a joint effusion is present. Narcotic analgesics are a final medication to prescribe for OA if other therapies are unsuccessful.

The combination of various drug agents in the management of arthritis pains resulted in many outcomes (Table 6). With NSAID lone agent users, the pains in high proportions of patients though persisted but have reduced intensities and severity when compared to the pain status in their previous hospital visits. There were poor pain control in nearly one-tenth of patients and no change in pain status in minority of those placed on NSAIDs as lone agent. Resurged pains and persistent pains that increased occurred in nearly close to one-tenth of the NSAIDs users. However, close to one-fifth of the patients have good control of pain with NSAIDs use (Table 6). The combinations of NSAIDs with some medications have varying results in the outcome of pain managements. Pain symptoms resolution does not improve when NSAIDs was combined with steroid and xanthine oxidase inhibitors in gouty arthritis management than when NSAIDs was used alone in other arthritis pain, although NSAID lone agent was not paired in this study and compliance was not monitored. There were however higher proportion of patients with improved pain resolution with the combination of NSAID with steroid, DMARD, chondroitin/glucosamine and with DMARD/Steroid which may be attributed to their synergistic action as anti-inflammatory agents and/disease modifying effects.

The proportion of patients with symptom (pain) regression was high with NSAID sole agent use but higher when NSAID was combined with chondroitin/glucosamine, acetaminophen/narcotic analgesic, steroid/xanthine oxidase inhibitor, steroid, but lower with alpha adrenergic agonist. Similarly, only few users of NSAID with chondroitin/glucosamine experienced resurged pains in the study but high proportions of patients whose pain symptoms increased between clinic visits were high with NSAID use but higher when NSAID was combined with alpha-2 adrenergic agonist.

When the sole use of steroid was evaluated, pain regression occurred in proportion of patients slightly above average of the users but nearly all patients experienced pain regression in steroid combination with DMARDs and a higher proportion of patients experienced symptoms' resolution when NSAID was added to these two combinations. Steroid uses particularly the glucocorticoids are recommended when other therapy failed or are inadequate to control pain. In this study, the addictive anti-inflammatory properties of these agents may have improved symptoms' control; however, a negative outcome may arise when optimum safety levels are exceeded. The alpha-2-adrenergic agonist appeared to give a good result in symptom regression but not in symptom resolution when used alone but its combination with

NSAID or with NSAID and chondroitin/glucosamine appeared not to improve symptom regression and resolution greatly though compliances were not monitored in these patients.

The duration taken for changes in pain outcome (Table 7) among patients indicated that high proportions of patients experienced reduction in pains but pain resolutions were generally low. Surprisingly, the proportions of patients who experienced pain reduction and resolution were lower in patients who have been on medication for over one year compared with users with shorter duration of time. This may probably be due to the fact that patients tends to comply with medication use when pains are severe or early after clinic visits and are less compliant with decreasing severity of pain or symptoms regression. This may have similarly accounted for the higher proportion of resurged pain cases and persistent pain with increased intensity with those with who visits clinic less regularly. Furthermore, because of longer duration of time taken for clinic visits, this may make early monitoring and modification of their drug therapies difficult.

The proportion of patients with no changes in pain status is high among the NSAIDs lone agent users compared to when NSAID is combined with other agents, although the differences were not found to be significant ($P>0.05$). For instance, the increase in the proportion of patients with no change in pain status when NSAID was used alone compared with when combined with glucosamine/chondroitin, analgesic/opioid, steroid, and alpha-2-adrenergic agonist resulted in a chi square value of 0.39, 1.15, 0.09 and 0.047 respectively. The reasons for this pattern of result is unknown but it is possible that non-compliance may play a major role

LIMITATIONS

Drug adherences were not monitored in the study; therefore the study may not have accurately described the effectiveness of these agents as lone agents or in their various combinations since patients' compliances are major determinant factor in outcome evaluation. Similarly, only patients' pain symptoms of disease were assessed, other markers for arthritis regression or progression were not studied.

TABLES OF RESULT

Table 1: The age distribution by gender of patients with joint diseases rheumatism

Age Range (Yrs)	Male/female n (%)	Male only n (%)	Female only n (%)
<20.0	0 (0)	0 (0)	0 (0)
20.0-29.9	6 (5.0)	2 (4.6)	4 (5.2)
30.0-39.9	21 (17.4)	10 (22.7)	11 (14.3)
40.0-49.9	32 (26.4)	9 (20.9)	23 (29.9)
50.0-59.9	37 (30.6)	13 (29.5)	24 (31.2)
60.0-69.9	17 (14.0)	8 (18.2)	9 (11.7)
70.0-79.9	7 (5.8)	1 (2.3)	6 (7.8)
80.0-89.9	1 (0.8)	1 (2.3)	0 (0.0)
Total	**121(100)**	**44 (100)**	**77 (100)**

Z-test: Column proportions for male and female do not differ significantly from each other at the 0.05 level.

Table 2: Background information of patients

Data	Variables	Freq. (%)		Data	Variables	Freq(%)
Gender	Male	44 (36.4)		Arthritis Types	Osteoarthritis	79 (65.3)
	Female	77 (63.6)			Rheum. arthritis	27 (22.3)
	Total	**121 (100)**			Gouty arthritis	11 (9.1)
					Juvenile arthritis	1 (0.8
Marital Status	Single	25 (20.7)			Septic arthritis	2 (1.6)
	Married	96 (79.3)			RA/Osteoarthrit.	1 (0.8)
	Total	**121 (100)**			**Total**	**121(100)**
Duration of Therapy	<6month	20 (16.5)		Duration of Diagnosis	<6month	2 (1.7)
	6-12months	28 (23.1)			6-12months	8 (6.6)
	1-2years	29 (24.1)			1-2years	21 (17.4)
	2-4years	14 (11.6)			2-4years	48 (39.7)
	4-6years	10 (9.1)			4-6years	16 (13.2)
	6-8 years	7 (5.8)			6-8 years	6 (5.0)
	8-10 years	3 (2.5)			8-10 years	7 (5.8)
	10-12years	3 (2.5)			10-12years	5 (4.1)
	>12 years	7 (5.8)			>12 years	8 (6.6)
	Total	**121 (100)**			**TOTAL**	**121(100)**

Key: RA= Rheumatoid arthritis

Table 3: Clinical outcomes on pain status between clinic visits during drug therapy

Status of pain symptom	Frequency	Percentage (%)
Persistent but reduced	240	64.5
Persistent but increased	19	5.1
Resolved	84	22.9
No change in pain status	24	6.5
Resurged pain	4	1.1
Not applicable	1	0.3
Total	372	100

Table 4: Drug combination in the management of Arthritis

S/no.	Drug combinations	Frequency	(%)
1	NSAID	116	31.2
2	NSAID/DMARDS/Steroids	6	1.6
3	NSAID/Chondroitin/Glucosamine	98	26.0
4	NSAID/Analgesic/Opioids	27	7.3
5	Steroids/Chondroitin/Glucosamine/Alpha-2-Adr Agonist	3	0.8
6	NSAID/Steroids/Xanthene oxidase inhibitors	11	3.0
7	Chondroitin/Glucosamine/Analgesic/Opioids	3	0.8
8	Colchicine/Steroids	1	0.3
9	Steroids	13	3.5
10	Alpha-2 adrenergic agonist	13	3.5
11	Chondroitin/Glucosamine	18	4.8
12	NSAID/Steroids	25	6.7
13	NSAID/DMARDS	5	1.3
14	Steroids/DMARDS	13	3.5
15	NSAID/Alpha-2 adrenergic agonist	16	4.4
16	Analgesic/Opioids	4	1.1
Total		**372**	**100**

Table 5: Outcome of pain symptom during various drug combinations

Drug Combinations	Pain status of patients during drug therapy						Total N (%)
	PBR N (%)	PBI N (%)	Resolved N (%)	NC N (%)	Resurged N (%)	NA n (%)	
NSAIDs	773(62.9)	8(6.9)	21(18.1)	11(9.5)	3 (2.6)	0 (0)	116(100)
NSAID/DMARD/Steroid	11 (16.7)	1(16.7)	4 (66.7)	0 (0)	0 (0)	0 (0)	6 (100)
NSAID/Chond/Glucosamine	64 (65.3)	4(4.1)	21(21.4)	7(7.1)	1 (1.0)	1 (1.0)	98 (100)
NSAID/Analgesic/Opioid	20 (74.4)	2(7.4)	4 (14.8)	1 (3.7)	0 (0)	0 (0)	27 (100)
NSAID/Chon/Glocus/α-2AA	2 (66.7)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	3 (100)
NSAID/Steroid/XOI	9 (81.8)	0 (0)	2((18.2)	0 (0)	0 (0)	0 (0)	11 (100)
Chon/Glucos/analges/Opioid	2 (66.7)	0 (0)	1(33.3)	0 (0)	0 (0)	0 (0)	3 (100)
Colchicine/Steroid	1(100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Steroid	7(53.8)	1(7.7)	5(38.5)	0 (0)	0 (0)	0 (0)	13 (100)
Alpha-2-Adrenergic Agonist	11(84.6)	0 (0)	2(15.4)	0 (0)	0 (0)	0 (0)	13 (100)
Chondroitin/Glucosamine	9(50.0)	1(5.6)	7(38.9)	1 (5.6)	0 (0)	0 (0)	18 (100)
NSAID/Steroid	17(68.0)	0 (0)	6(24.0)	2 (8.0)	0 (0)	0 (0)	25 (100)
NSAID/DMARDs	3(60.0)	0 (0)	1(20.0)	1(20.0)	0 (0)	0 (0)	5 (100)
DMARDs/Steroid	12(92.3)	0 (0)	1(7.7)	0 (0)	0 (0)	0 (0)	13 (100)
NSAID/ α-2-AA	8(50.0)	2(12.5)	5(31.2)	1 (6.2)	0 (0)	0 (0)	16 (100)
Analgesic Opoid	1(25.0)	0(0)	3(75.0)	0 (0)	0 (0)	0 (0)	4 (100)
TOTAL	240(64.5)	19(5.1)	84(22.6)	24(6.5)	4 (1.1)	1 (0.3)	372 (100)

*Key: **NSAID** (Non-steroidal anti-inflammatory drugs), **DMARD** (disease modifying ant-rheumatoid drugs), **XOI** (xanthine oxidase inhibitor), **α-2-AA** (alpha-2 adrenergic agonist), **PBR** (persistent but reduced), **PBI** (persistent but increased), **NC** (No change), NA (Not applicable)*

Table 6: Duration of Drug Therapy and Outcome of Pain Symptoms

Duration of Drug Use	Pain status of patients during drug therapy						Total N (%)
	PBR N (%)	PBI N (%)	Resolved N (%)	NC N (%)	Resurged N (%)	NA N (%)	
<14 days	111 (84.6)	0 (0)	1 (7.7)	1(7.7)	0 (0)	0 (0)	13 (100)
15-30 days	27 (61.4)	2 (4.5)	13 (29.5)	2 (4.5)	0(0)	0 (0)	44 (100)
1-3 months	69 (66.3)	3 (2.9)	25 (24.0)	6 (5.8)	1 (1.0)	0 (0)	104 (100)
3-6 months	47 (68.1)	1 (1.4)	19 (27.5)	2 (2.9)	0 (0)	0 (0)	69 (100)
6-9 months	27 (62.8)	0 (0)	12 (27.9)	4 (9.3)	0 (0)	0 (0)	43 (100)
9-12 months	18 (66.7)	1 (3.7)	5 (18.5)	2 (7.4)	1 (3.7)	0 (0)	27 (100)
>12 months	40 (56.3)	12(16.9)	9 (12.7)	7 (9.9)	2 (2.8)	1 (1.4)	71 (100)
TOTAL	240(64.4)	19(5.1)	84(22.6)	24(6.5)	4 (1.1)	1 (0.3)	372 (100)

*Key: **PBR** (persistent but reduced), **PBI** (persistent but increased), **NC** (No change), NA (Not applicable)*

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