CHAPTER 1

INTRODUCTION

"Rheumatoid Arthritis (RA) is a chronic syndrome characterised by non-specific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures, with or without generalised manifestations" (Beers, *et al*., 1999).

Management of mild RA includes educating the patient, non-pharmacological intervention such as bed rest and a nutritious diet, and symptomatic relief of pain with an appropriate anti-inflammatory drug (Williams, *et al*., 2003).

Non-steroidal anti-inflammatory drugs (NSAIDs) are indicated for the treatment of pain and stiffness in RA and for the short –term management of pain in osteoarthritis (OA) (SAMF, 2000). NSAIDs usually rapidly relieve pain and inflammation and are therefore considered as first-line therapy for RA (Harris, 2003).

NSAIDs are often used for long period of time but they do not alter the course of the disease, therefore, they are frequently combined with disease modifying agents (DMARDs). DMARDs include methotrexate, leflunomide (Arava®), etanercept (Enbrel®), infliximab (Revellex®), antimalarials, gold salts, sulfasalazine, d-penicillamine, cyclosporin A, cyclophosphamide and azathioprine (Matsumoto, *et al*., 2004).

The NSAIDs are classified into two classes i.e. the non-selective NSAIDs and the selective COX II inhibitors. Non-selective NSAIDs identified and discussed in this report include diclofenac, naproxen, indomethacin, ibuprofen, piroxicam, ketoprofen, sulindac, lornoxicam, nabumetone, flurobiprofen, diclofenac plus mistoprostol. Selective COX II inhibitors identified in the study include celecoxib, rofecoxib and meloxicam. Meloxicam, has a high affinity for COX II, but also inhibits COX I at therapeutic doses and shows to have less GI adverse events than that of diclofenac or piroxicam as reported in the Meloxicam Large-scale International Study Safety Assessment (MELISSA) trial, and the Safety and Efficacy Large-Scale evaluation of

COX-inhibiting therapies (SELECT) trial (Staud, 2000). Therefore, for the purpose of this study meloxicam will be included as COX II inhibitor.

Rofecoxib (Vioxx®) and celecoxib (Celebrex®) have been approved for the treatment of OA (SAMF, 2000). Rofecoxib does not have Food and Drug Administration (FDA) approval for the treatment of RA (Package Insert, 2003b). Valdecoxib (Bextra®), a new COX II inhibitor was launched and registered in South Africa for the short-term treatment of mild to moderate post –operation pain and primary dysmenorrhoea (MIMS, 2004) but the Medicine Control Council (MCC) has suspended valdecoxib from the South African market due to reported incidence of increased cardiovascular side effects (Pharmafocus, 2005).

The first COX II inhibitor (celecoxib) was approved by the FDA in 1998, followed by rofecoxib and valdecoxib. The American College of Rheumatology details how the COX II selective inhibitors changed the NSAIDs prescribing patterns. The overall NSAIDs prescriptions increased by 67%, from 1998-2003 because of the availability of the COX II inhibitors. The percentage of NSAIDs prescriptions written for COX II inhibitors peaked in 2001 (Schnirring, 2004).

"The calamity which threatened the sustainability of the Pharmaceutical Benefits Scheme (PBS) in 2000 and 2001 was the volume of prescriptions for cyclo-oxygenase (COX) II inhibitors. Celecoxib was listed on the PBS on 1 August 2000, and by the end of December 2000 over 1.5 million prescriptions had been written, costing the government more than $76 million. By the end of June 2001, the cost had exceeded $160 million" (Report, 2001).

The above is an excerpt from a retrospective study conducted in Australia. A similar trend has been identified in the South African managed health care environment. The use of the COX II inhibitors increased in terms of prescribing frequency for the treatment of RA, over what is known as the "corner stone" of treatment, the non-selective non-steroidal anti-inflammatory drugs (NSAIDs).

This study will determine the total number of NSAIDs, selective and non-selective prescribed in the managed care environment. The focus of this study is on describing

the characteristics of patients who are receiving COX II selective inhibitors as compared with those receiving non-selective NSAIDs and thus identify the usage pattern of the COX II inhibitors and its impact on the managed care environment.

Rheumatoid arthritis (RA) is a chronic progressive autoimmune inflammatory condition characterized by symmetric, erosive synovitis associated with various systemic features which leads to disability. Early diagnosis and initiation of appropriate treatment can limit progression of joint destruction and deformity. The goal of treatment is to stop the progression of the disease which may result in remission (American College of Rheumatology, 2002).

Some of the qualifying criteria for the diagnosis of RA include morning stiffness, inflammation involving three or more joints, joint pain of the hand, wrist joints, positive serum rheumatoid factor (RF), and radiographic evidence of RA (Gotleib, 2003).

Internationally the prevalence of RA is reported to be approximately one percent (King, *et al.,* 2005).

Mortality from RA is related primarily to the patient's overall deterioration in health, well-being and functionality. Female-to-male ratio is approximately 3:1 and the age of onset is usually between 25 and 50 years. Patients with RA may also become susceptible to infection and secondary organ dysfunction such as lung disease, kidney disease and GI haemorrhage. Arthritis presenting in children younger than 16 years is known as Juvenile Arthritis .It is characterised by three categories of the disease such as multiple joints affected, fewer than four joints affected and systemic such as high fever, rash and even organ involvement (King, *et al*., 2005).

RA affects the socio-economic status of the patient .In 1983 it was reported to cost the United States (US) $777 million per year. After 10 years, an estimated 90% of patients have been reported to have significantly reduced function, 50% of patients are reported to have severe disability after 10 years, 80% of patients are reported to have moderate disability after 17yrs and 30 to 50% of patients are unable to work

after 15 years. Mortality from RA is related to the patient's overall deterioration in health, well-being, and functionality (Gotlieb, 2000).

The prevalence rates of RA in rural Africans are reported to be low. The prevalence of RA increases with urbanisation, with a prevalence of 0.9% reported in urban South Africans (Tikly, *et al.*, 2003).

Early and aggressive drug intervention such as disease modifying anti-rheumatic drugs (DMARDS) should be initiated as first line. These include ledertrexate, (methotrexate), leflunomide (Arava®), sulphasalazine (salazopyrine), mycorisin (gold), antimalarials (nivaquine), cyclosporine and azathioprine. The patient should be educated about the disease and the possibility that joint damage may occur as a result of the disease RA (American College of Rheumatology, 2002).

Treatment with NSAIDs should be considered for control of inflammation and pain. All NSAIDs act by inhibiting the enzyme cyclo-oxygenase (COX). COX converts arachidonic acid derived from cell membranes to prostaglandins which are responsible for mediation of inflammation and pain, and also plays a role in platelet function, gastrointestinal (GI), lung and kidney protection. NSAIDs have anti-inflammatory action due to their inhibition of prostaglandin production. These drugs do not modify the course of the disease; however, they do reduce the signs and symptoms of inflammation (American College of Rheumatology, 2002).

COX is found in two isoforms, namely the COX I and the COX II. COX I was found to be necessary for platelet function and maintaining intact gastric mucosa. COX II produces enzymes that mediate pain, fever, inflammation (Cronstein, 2002).

The NSAIDs are therefore classified into two classes i.e. the non-selective NSAIDs and the selective COX II inhibitors. All non-selective NSAIDs affect the action of both the COX I and the COX II but produce most of their therapeutic effects by blocking COX I and as a result are associated with adverse gastrointestinal (GI) and renal effects (Katzung, 1998).

A large percentage of patients takings NSAIDs chronically for the treatment of RA experience serious GI side effects e.g. peptic ulcer disease or haemorrhage (Scottish Intercollegiate Guidelines Network, 2000).

Non-selective NSAIDs identified and discussed in this report include diclofenac, naproxen, indomethacin, ibuprofen, piroxicam, ketoprofen, sulindac, lornoxicam, nabumetone, flurobiprofen, diclofenac plus mistoprostol. The non-selective NSAIDs are indicated for the treatment of inflammation in rheumatoid arthritis and painful inflammatory conditions of non-rheumatoid origins (MIMS, 2004).

Selective COX II inhibitors identified in the study include celecoxib, rofecoxib and meloxicam. The low incidence of gastrointestinal (GI) effects is the major advantage the COX II inhibitors such as, celecoxib and rofecoxib have over traditional NSAIDs and has been marketed as such (Barclay, 2004).

"There have been studies published documenting an increased incidence and prevalence of cardiovascular (CV) conditions in patients with rheumatoid arthritis compared with individuals without rheumatoid arthritis. There has also been interest in the occurrence of cardiovascular(CV) risk factors in rheumatoid arthritis and in the role of anti-rheumatic therapy, including COX II selective non-steroidal anti-inflammatory drugs, methotrexate, corticosteroids, and tumour necrosis factor inhibitors" (del Rincon *et al*., 2003).

An increased risk of CV events was found in patients taking rofecoxib, which resulted in the drug company voluntarily withdrawing rofecoxib from the market in September 2004, as requested by the FDA (Sibbald, 2004). The European Union regulatory body known as European Agency for the Evaluation of Medicinal Products (EMEA) and MCC followed with a similar ruling.

The other COX II inhibitor on the market, celecoxib was also placed under investigation. The FDA and EMEA recommended that the following boxed warning should be included in the COX II package insert namely; potential for increased risk of cardiovascular events, GI bleeding associated with their use and use the lowest dose, for the shortest duration of time. The package insert should include a medication

guide to make patients aware of the potential for cardiovascular and gastro-intestinal adverse events associated with the use of this class of drug. In the US and Europe this warning label applies to all NSAIDs, including prescription and OTC non selective NSAID medication (Package Insert, 2005).

In South Africa the MCC has recommended a revised package insert for celecoxib. This new package insert should include new important safety data by way of a boxed warning. The new package insert should highlight that celecoxib may predispose the patient to cardiovascular events, cerebrovascular events, gastro-intestinal events or cutaneous reactions which may be fatal. It is also contra-indicated in patients with established ischaemic heart disease, stroke and peripheral arterial disease. Celecoxib is contra-indicated for use in peri-operative analgesia in the setting of coronary artery bypass surgery (CABG). Celecoxib should be prescribed with caution in patients with cardiovascular risk factors such as hypertension, diabetes, smoking and hyperlipidaemia (Letter, 2005).

In comparing the COX II selective inhibitors and the non-selective NSAIDs it was found the COX II selective inhibitors provide similar analgesic activity to that of the non-steroidal NSAIDs. COX II inhibitors cause fewer GI side effects, have no antiplatelet function and should be given with caution to patients who have a risk of developing CV diseases and in patient's with renal complications (Smucny, 2004).

Increase in health care costs in the 1970's, led to the prominence of managed care in the US. The emergence of managed care into SA took place after the rise of the US health care models. Managed care companies introduced the "fee for service" model and restricted administrative costs in order to sustain the business (Gotlieb, 1999).

In South Africa two health care systems exists. The first is the private health care system, known as managed health care, where the individual shares the responsibility of health care costs with a medical scheme. The member contributes a monthly premium to belong to a medical insurance and thus receives financial assistance from that scheme for certain medical conditions as stipulated by legislation or scheme rules. The second is the state health care system whereby the state provides basic health care (Gotlieb, 1999).

Council for medical schemes (CMS) is a statutory body established by the parliament of South Africa to provide supervision over medical schemes. Act 131 of 1998 was passed by the council for medical schemes to regulate the medical aid environment. The CMS has introduced the prescribed minimum benefits (PMB), the accreditation of managed health care organisations and implementation of standard operation guidelines for managed health care as a tool to regulate the managed care environment (Report, 2003a).

The objective for the introduction of PMB's is to improve efficiency of public and private health care resources and to prevent incidence's where members lose medical scheme cover in the case of serious illness (Report, 2003a).

Managed Health Care according to the council for medical schemes is defined as "evidence-based medicine, a conscientious, explicit and judicious use of current best evidence in making decisions about the care of beneficiaries, whereby individual clinical experience is integrated with the best available external clinical evidence from systematic research"(Report, 2003a).

Prescribed Minimum Benefits (PMB) includes the cover of 271 diagnosis and treatment pairs and the compulsory cover of an emergency medical condition (Report, 2003a). The South African managed care environment has also been legislated by the Council of Medical Schemes to provide cover for 25 Prescribed Minimum Benefits (PMB) conditions. This new legislation requires the medical schemes to provide cover for diagnosis; medical management and chronic medication for the 25 PMB chronic disease list (CDL) conditions. The schemes may make use of formularies, treatment protocols and designated service providers (DSP). The treatment protocols may include clinical entry criteria and treatment algorithms. A medical scheme must pay in full, according to legislation, without co-payment or the use of deductibles, the diagnosis, treatment and care cost of the prescribed minimum benefit conditions (Report, 2003a).

According to regulations the medical aid must have a written protocol in place and must use documented clinical review criteria that are based upon evidence-based

medicine, taking into account considerations of cost-effectiveness and affordability (Report, 2003a).

RA is listed as one of the 25 prescribed minimum benefits (PMB), chronic disease list conditions (CDL) (Report, 2003a). The council for medical schemes has drawn up a guideline, known as the treatment algorithm for each of the 25 PMB CDL conditions. This has left managed care to develop guidelines and policies on the appropriate funding in terms of cost and clinical effectiveness, according to the treatment options recommended on the algorithm. This translates to medical treatment and care for all members belonging to medical schemes and registered for the condition RA. The treatment algorithm is illustrated below (Report, 2003a).

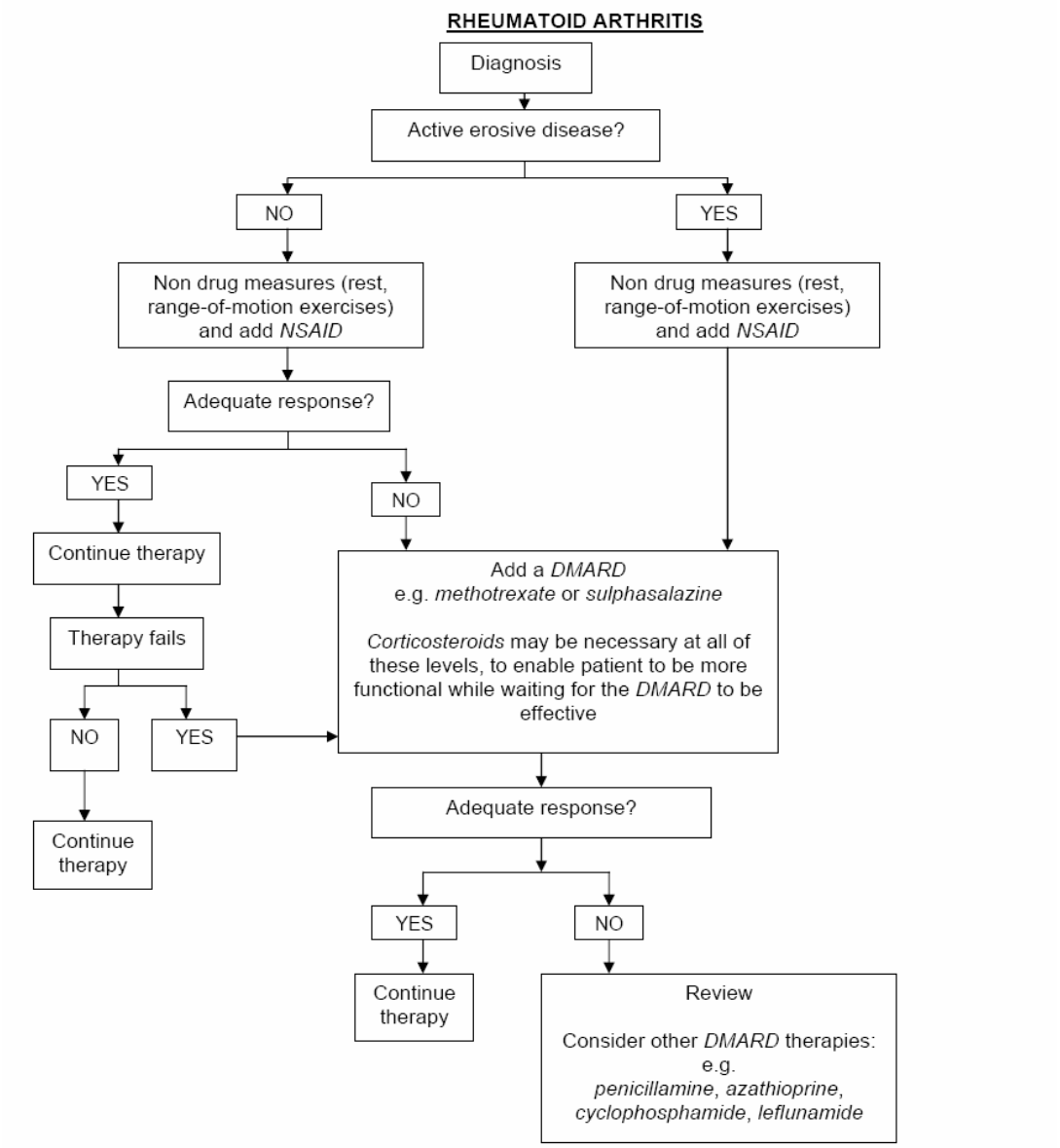


Figure 1.1 Council of Medical Schemes Algorithm for RA

The managed care company studied in this report, adopted the use of the national institute for clinical excellence (NICE) and South African Rheumatism and Arthritis Association guidelines (SARAA), as a clinical tool to manage RA. It states that COX II inhibitors are not recommended for routine use in patients with Osteoarthritis (OA) and RA. COX II should only be prescribed in preference to non-selective NSAIDs in the management of OA and RA patients at “high risk” of developing serious GI adverse events. Patient’s at high risk of developing serious GI adverse

events include patients with previous peptic ulcer disease, patients with previous GI bleed, patients with alcohol related diagnosis (e.g. gastritis, hepatitis, cirrhosis, pancreatitis, macrocytic anaemia, neuropathy or psychosis), patients receiving systemic steroids, patients receiving anti-coagulants, patients requiring very high doses of NSAIDs (greater than 120% average daily dose) and patients older than 65 years of age. COX II inhibitors should not be prescribed routinely in preference to standard NSAIDs, in patients with cardiovascular diseases (NICE, 2001).

The cardiovascular events or gastrointestinal related problems for which the members were registered for, in this research report, was analysed to determine if there is an association between the COX II inhibitors usage and NSAIDs usage and the prevalence of cardiovascular and gastrointestinal risk.

The National Institute for Clinical Excellence (NICE), in the UK, published a technology appraisal in July 2001 “guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolca for osteoarthritis and rheumatoid arthritis”. The appraisal is a guideline to assist the National Health System in the UK, with the appropriate prescribing of the COX II inhibitors. It documents that all NSAIDs including the COX II inhibitors may cause gastro-intestinal adverse events, such as gastro-intestinal perforations, ulcers and bleeds. These agents should not be used routinely and should be prescribed after careful consideration of the risk and benefits, especially in patients with risk factors of developing gastro-intestinal adverse events. Patients at high risk include those over the age of 65 years, those using concomitant medication that may predispose the patient to increased upper gastro-intestinal adverse events, such as warfarin and steroids.

The South African Rheumatism and Arthritis Association have also developed guidelines for the appropriate use of the COX II inhibitors. The SARAA guidelines recommend that since COX II has a superior safety profile these drugs should be reserved for patients with high risk who are identified as patients over the age to 60 years, with previous proven peptic ulceration and patients on chronic steroids and warfarin. These guidelines are very similar to the NICE guidelines. The SARAA guidelines were also used to compare if the prescribing patterns identified in the

managed care environment are similar to the recommended guidelines (NICE, 2001; Gotleib, 2003).

RA has significant impact on the economy for both the patient and society. A recent study showed that patients with RA have three times the direct medical costs, twice the hospitalization rate and 10 times the work disability rate. Low cost options were often offered for the treatment of RA. Recently, the introduction of COX II selective inhibitors and newer DMARDS and the more common use of combination therapy had contributed to the total cost for the treatment of RA (American College of Rheumatology, 2002).

The escalating health care costs and the perceived increased use of COX II led to the hypothesis of this study i.e. are the COX II inhibitors being prescribed more frequently than NSAIDs for the condition rheumatoid arthritis in the managed care company?

CHAPTER 2

MATERIALS AND METHODS

2.1 STUDY OBJECTIVES

The objective of the study was to assess the prescribing patterns of the NSAIDs and COX II selective inhibitors in RA patients in a Managed Health Care Environment.

2.2 HYPOTHESIS

The hypothesis of the study was that COX II inhibitors are being prescribed more frequently and routinely over the conventional NSAIDs for the management and treatment of RA in the managed health care environment.

2.3 METHODOLOGY

The frequency of NSAIDs and COX II inhibitors identified during the six month evaluation period was calculated.

A report was generated reflecting all members registered on the managed health care database for the chronic condition RA for the period 1 January 2003 to 30 June 2003. Each member was allocated a unique member number ensuring anonymity and confidentiality. Each member's profile was reviewed and identified as using either an NSAID or a COX II inhibitor. The NSAIDs and COX II inhibitors were identified by reference to the MIMS classification (MIMS, 2004). The members identified as using the COX II inhibitors were renamed Group A and all the members were logged onto a Microsoft Excel 2003 spreadsheet. The members identified as using the non-selective NSAIDs were renamed as Group B and all the members were logged onto a Microsoft office Excel 2003 spreadsheet.

The member's age and gender were also obtained from the database as this information had been captured by the managed health care administrators when the

member had initially enrolled. Since these members have already registered with the organisation the current drug therapy related to the treatment of RA was already available on the database. All claims related to co-morbid conditions and new diagnosis were submitted by doctors using the diagnostic coding system developed by the World Health Organisation (WHO), known as the International Classification of Diseases, tenth edition (ICD-10).

The data were then analysed to determine the total number of NSAIDs and COX II selective inhibitors prescribed over the evaluation period. The frequency of NSAIDs and COX II inhibitors prescriptions were determined by calculating it as a percentage of each identified NSAIDs or COX II inhibitor prescribed over the total number of NSAIDs and COX II inhibitors combined.

The data were further analysed to determine if there is a correlation between certain criteria e.g. age, gender, co- morbid conditions and the drug that has been prescribed.

The current medication use was analysed to determine if the COX II inhibitors were appropriately prescribed to members with presumably a high risk of gastrointestinal events as a result of using medication that may increase their risk of developing gastrointestinal events, such as warfarin and steroids.

All the anti-coagulants and steroids used by members registered for the chronic condition RA, either as acute or chronic medication, were identified as either being prescribed a COX II inhibitor or NSAIDs. This was obtained from the member database by identifying the unique NAPPI code classified as per MIMS grouping. A NAPPI code is a unique identifier for a given product which enables electronic transfers of information throughout the healthcare delivery chain. NAPPI file is governed by NAPPI Advisory Board (NAB) (Report, 2003b).The use of gastroprotective agents (GPA's) in combination with COX II inhibitors and NSAIDs was analysed to ascertain if the use of COX II inhibitors reduces the need for GPA's concomitant therapy.

The patient characteristics identified in the study, were analysed and the final findings were compared to the NICE and SARAA guidelines to illustrate the similarities or differences, in prescribing patterns compared to the recommended guidelines.

Descriptive statistics were used to draw conclusions and compare the two drug classes. A statistician was consulted regarding the statistical analysis of the research. The Paired Sample t-Test was employed to test the hypothesis that COX II inhibitors are being prescribed more frequently and routinely over the conventional NSAIDs for the management and treatment of RA in the managed health care environment. The t-test is a parametric test and the distribution assumed for the data is a normal distribution. The Mann-Whitney U test, tests for the equality of means in the two groups. This test is a non-parametric test and does not make any assumptions about the underlying distribution of the data. The Wilcoxon Matched-Pairs Signed-Ranks test was used to test if the results on gender and concomitant gastro-protective agent's use, analysed in the study were significant.

The research report protocol was approved by the Post-Graduate committee and the committee for Research on Human Subjects (Medical) of the University of Witwatersrand. The relevant approval documentation appears in Appendix A, Appendix B and Appendix C respectively.

CHAPTER 3

RESULTS

3.1 Total number of the COX II inhibitors and the NSAIDs prescribed.

The aim of the study was to determine the total number of the COX II inhibitors and the total number of NSAIDs prescribed in the Managed Care Environment, received over a six month evaluation period and this is reflected in Table 3.1.

Table 3.1 Total number of NSAIDs and COX II prescribed for RA

Total number of members registered for the chronic condition, Rheumatoid Arthritis, for the evaluation period 01 January 2003 to 30 June 2003	2818
Total number of members using COX II inhibitors during the evaluation period	1372(48.69%)
Total number of members using NSAIDs during the evaluation period	827(29.35%)
Number of members not using COX II or NSAIDs	619(21.97%)

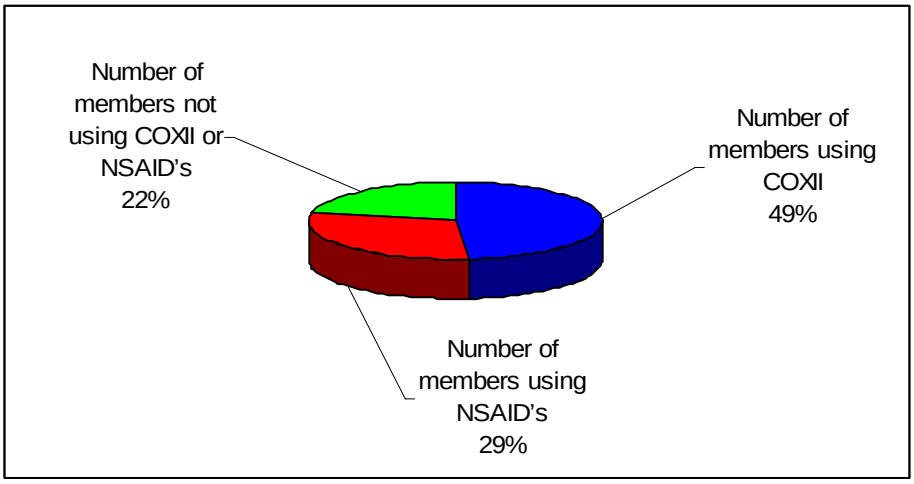


Figure 3.1 Percentage of the total number of NSAIDs and COX II inhibitors prescribed for RA

The prescribing frequency determined for the COX II inhibitors was 48.69% and that of the NSAIDs was 29.35 %, as illustrated in Figure 3.1.

The p-value reported from the Two-Sample t-test was 0.274224 which is greater than 0.05. Therefore, at a 10% level of significance conclude that the means are equal for the COX II and NSAIDs groups. The Mann-Whitney U test was also used to test for the equality of means in the two groups. The p-value for a two sided test was 0.1671464 which is greater than 0.05 which concludes that the means for the two groups are equal. The means between the groups were not statistically significant.

3.2 The COX II inhibitors and NSAIDs drug classes

The COX II inhibitors and NSAIDs were identified, as per their respective COX II or NSAID drug class, according to the MIMS Classification and were further analysed to determine which drug class was routinely prescribed. Table 3.2 and 3.3 lists the drug class of the COX II inhibitors and the NSAIDs identified during the study.

Table 3.2 COX II inhibitors drug class

COX II INHIBITORS IDENTIFIED IN THE STUDY	TOTAL NUMBER OF EACH COX II PRESCRIBED (n=1372), Number, %
Celecoxib	626 (46%)
Rofecoxib	415 (30%)
Meloxicam	331 (24%)

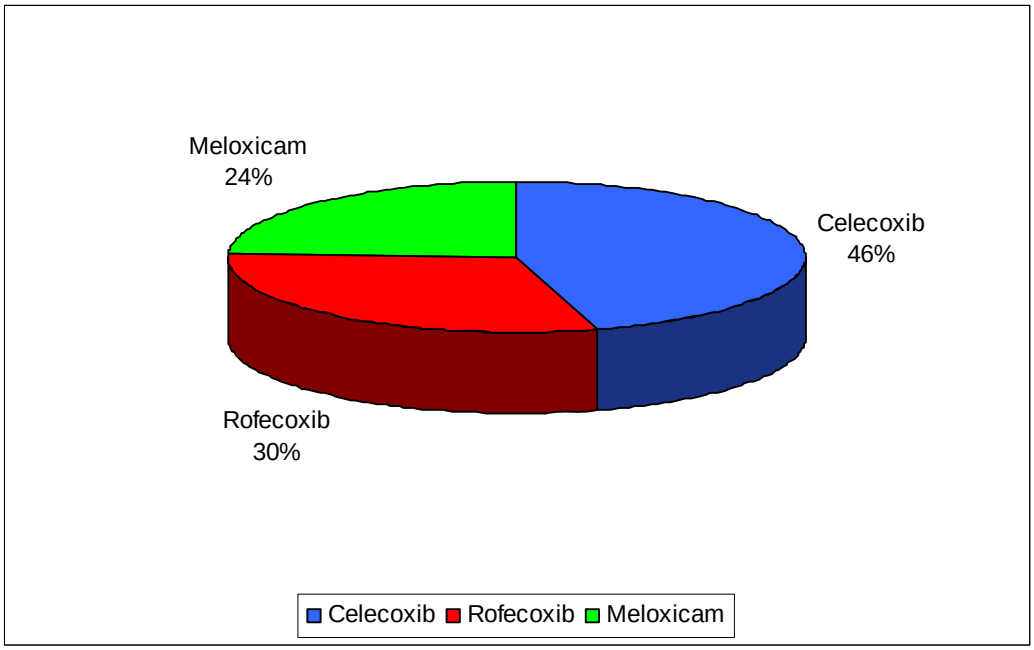


Figure 3.2 Percentage of the COX II inhibitors prescribed

Three COX II inhibitors, namely celecoxib, rofecoxib and meloxicam were identified as being prescribed for the chronic condition RA. The prescribing frequency of each of COX II inhibitors is represented in Figure 3.2 as a percentage of the total number COX II inhibitors in the study. Rofecoxib has been included in this study as this is a retrospective study observing the prescribing patterns of COX II inhibitors.

From the data above it is apparent that celecoxib was the more commonly prescribed COX II inhibitor for the treatment of RA in this managed care environment. The percentage frequency of celecoxib is 46%, compared to 30% for rofecoxib, and 24%

for meloxicam. Table 3.3 lists the total number of NSAIDs identified during the six month evaluation period 01 January to 30 June 2003.

Table 3.3 NSAIDs drug class

NSAIDs IDENTIFIED IN THE STUDY	**TOTAL NUMBER OF EACH NSAIDs PRESCRIBED (n=827), number , %**
Diclofenac	280 (34%)
Diclofenac plus Mistoprostol	133(16%)
Indomethacin	101 (12%)
Naproxen	89 (12%)
Ketoprofen	70 (8%)
Piroxicam	66(7.9%)
Ibuprofen	52(6.2%)
Nabumetone	11(1.3%)
Flurobiprofen	11(1.3%)
Sulindac	10(1.2%)
Lornoxicam	4(0.4%)

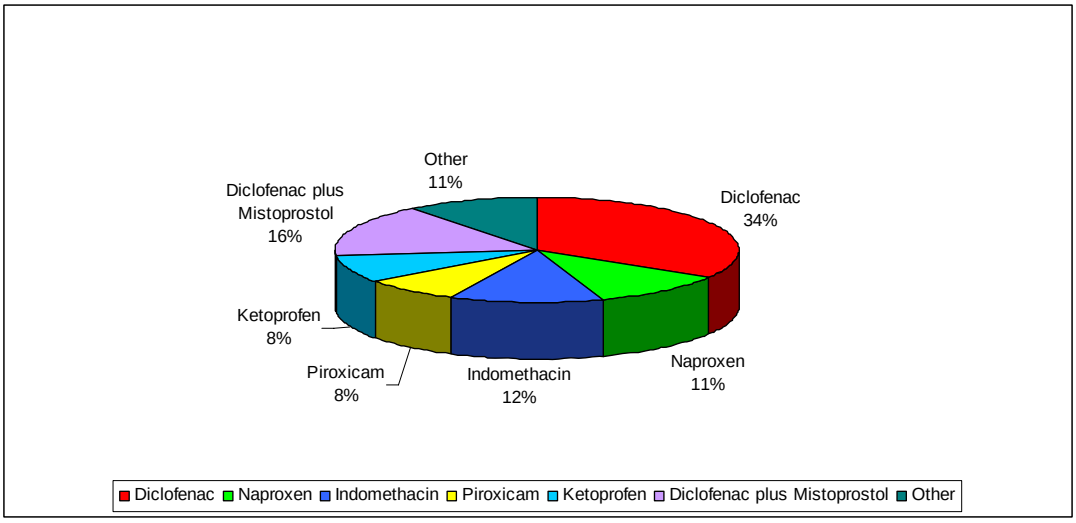


Figure 3.3 Percentage of the NSAIDs prescribed

During the six month evaluation period, NSAIDs were prescribed to 827 members**.** Eleven different NSAIDs class were prescribed for the condition RA. The top six NSAID's identified, in terms of frequency, accounted for 91% of the total number of NSAIDs prescribed, therefore, for the purpose of this study the top six most frequently prescribed NSAIDs will be further analysed, to establish prescribing patterns associated with significant NSAIDs usage. The most commonly prescribed NSAIDs that was identified during this evaluation period was diclofenac, with a reported frequency of 34% of the total number of NSAIDs prescribed in this study. The second most common NSAID identified was diclofenac with mistoprostol, with a reported frequency of 16%.This was followed by indomethacin, naproxen and ketoprofen and piroxicam. Figure 3.3 is a representation of the top six NSAIDs class as a percentage of the total number of NSAIDs prescribed.

3.3 The demographics of the patients identified as using COX II inhibitors and NSAIDs

The age and gender of each member who received either a COX II inhibitor or a non-selective NSAID during the six month evaluation period were obtained from the managed care database. The members were separated into their respective gender types and then grouped into different age categories. From the above data the mean age per gender was captured. Figure 3.4 and 3.5 are pie chart representations of the gender classification expressed as a percentage.

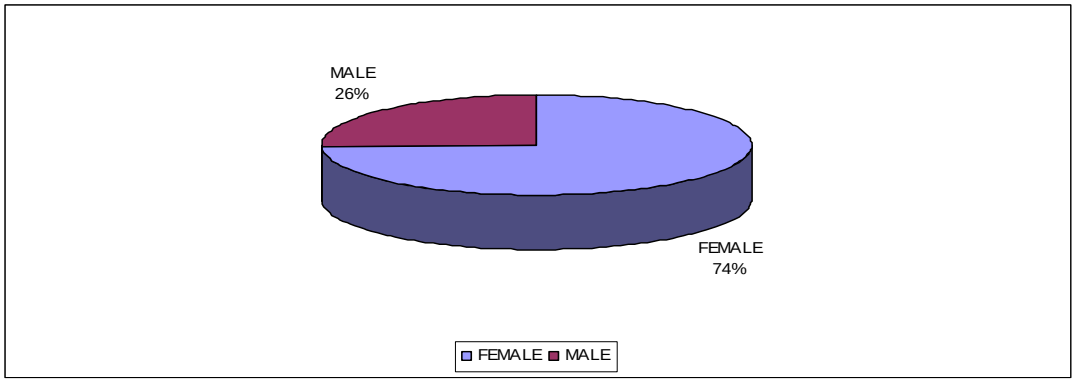


Figure 3.4 Gender classifications of members receiving COX II inhibitors

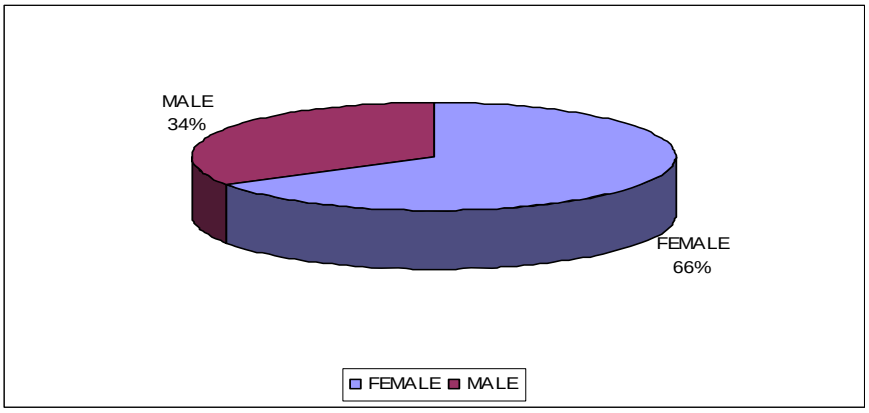


Figure 3.5 Gender classifications of members receiving NSAIDs

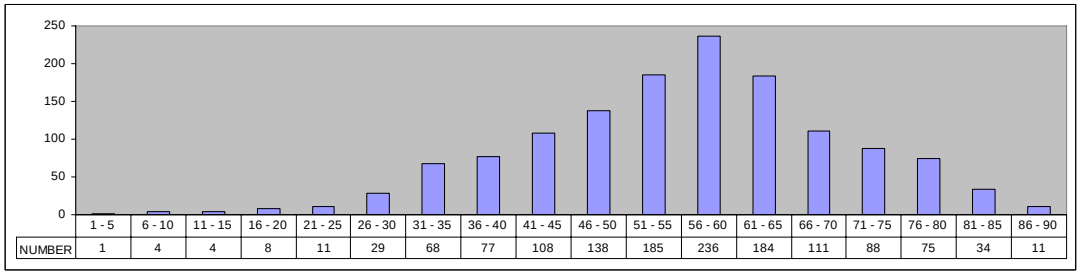


Figure 3.6 Age distribution of members prescribed with COX II inhibitors

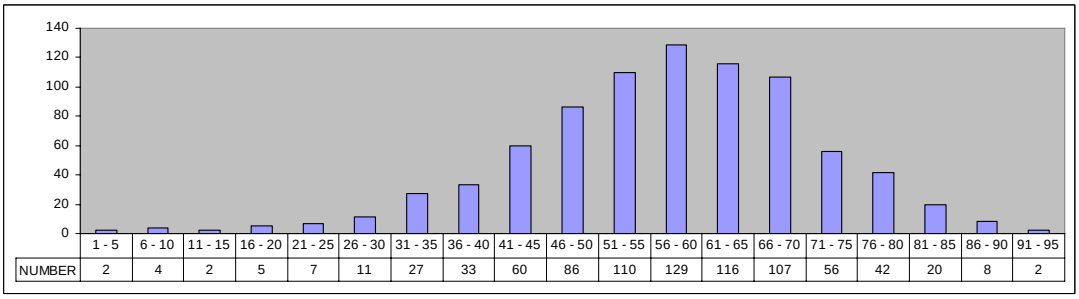


Figure 3.7 Age distribution of members prescribed with NSAIDs

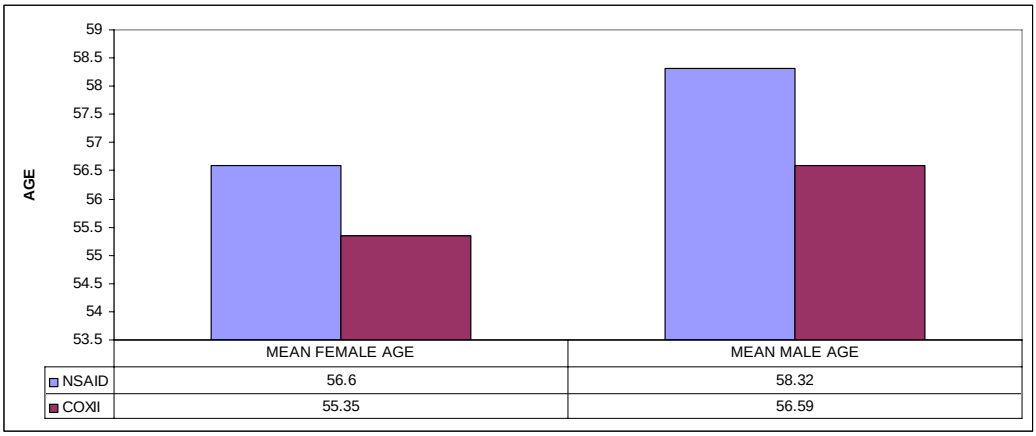


Figure 3.8 Mean ages and the gender classification of each member using either COX II inhibitors or NSAIDs

The figure above is a summary of the mean ages and gender distribution illustrating the prescribing pattern of the COX II inhibitors and NSAIDs in the managed care environment over the six month evaluation period.

The total number of members identified as using COX II inhibitors was 1372 and of that, approximately 74% of members identified were female. The mean age was 55 years. Twenty six percent of the members identified as using COX II inhibitors were male with a mean age reported as 56 years. The total number of members identified as using non- selective NSAIDs was 827 and approximately 66% of the members identified were female, with a mean age 56 years and males, with the mean age of 58 years accounted for 34% of the total number of NSAIDs prescribed.

3.4 Co-morbid medical conditions

There was a total of 78 co-morbid conditions identified for the COX II inhibitors users and a total of 64 conditions identified for the NSAID users (See Appendix D for the complete list of co-morbid conditions). Only the relevant ICD-10 codes were analysed such as cardiovascular, gastrointestinal, diabetes and renal ICD-10's.

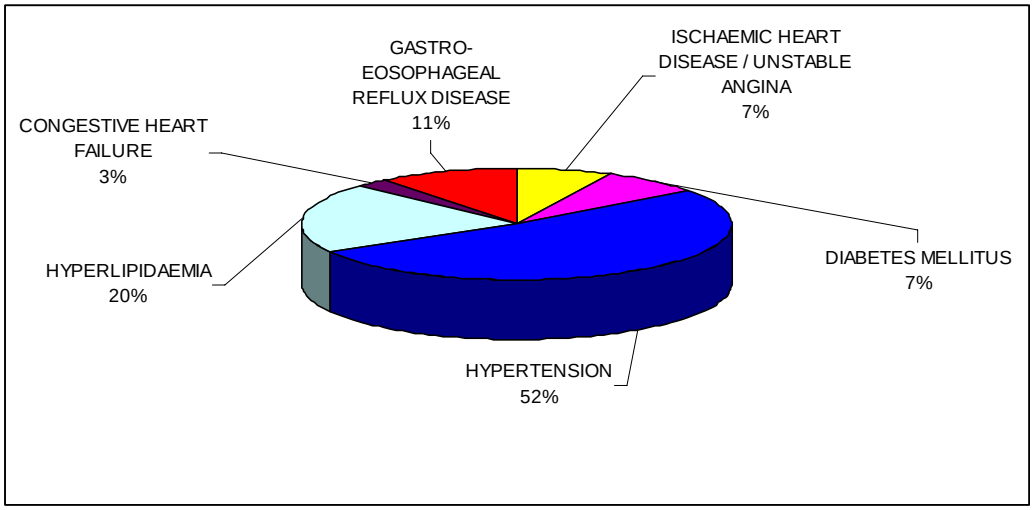


Figure 3.9 Co-morbid conditions identified for the COX II users

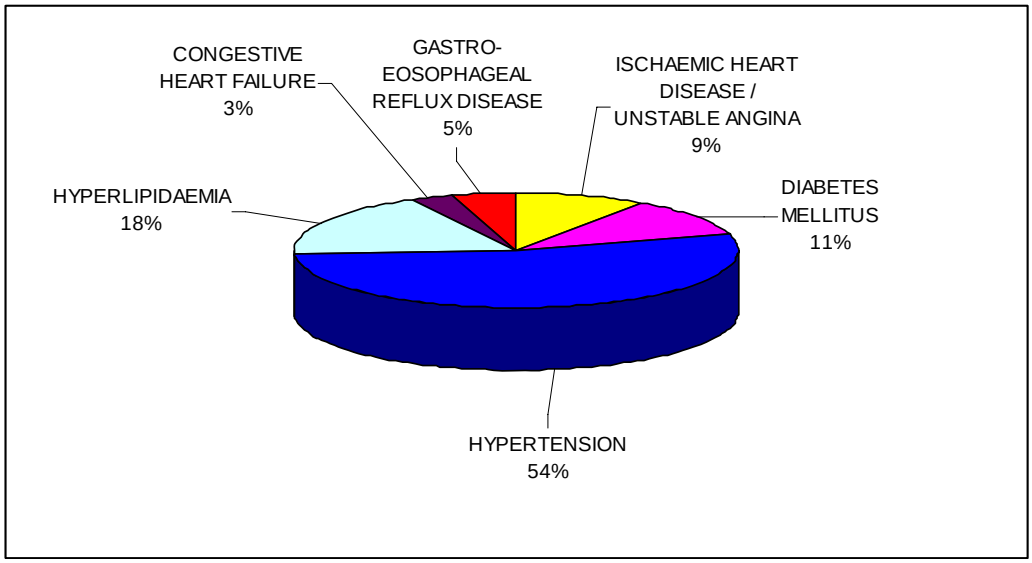


Figure 3.10 Co-morbid conditions identified for the NSAID users

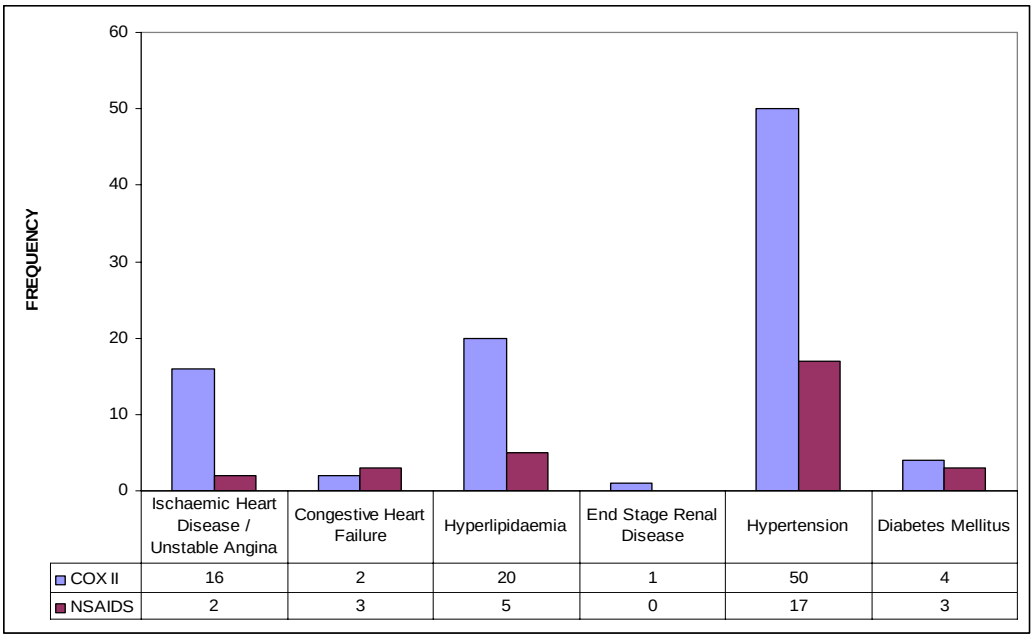


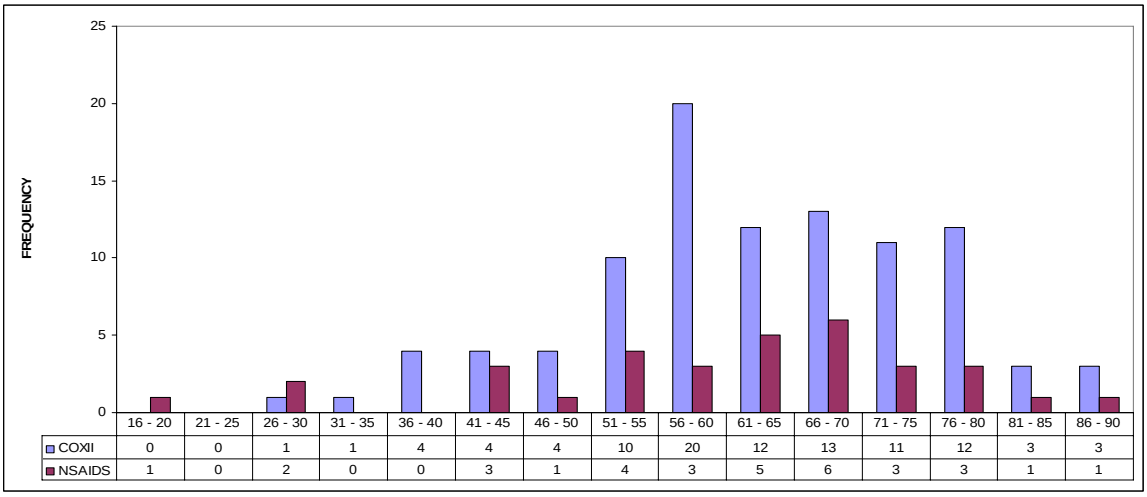
Figure 3.11 Comparison of the co-morbid conditions

Figure 3.9 and Figure 3.10 are pie chart representations of the co-morbid conditions that were most common amongst COX II and NSAID users. From the data above, the incidence of members registered for a concomitant cardiovascular condition and using either a COX II group or the NSAIDs did not show a significant difference. Seven percent of the members that were using COX II inhibitors also presented with a co-morbid ischaemic heart disease where as nine percent of members registered for NSAIDs were also registered for the condition ischaemic heart disease.

It was found that COX II was prescribed more commonly with concomitant GI events. Only five percent of the members using NSAIDs were concurrently registered on the managed care database for the chronic condition gastro-oesophageal reflux disease (GORD), during the six month evaluation period as compared to 11% of the members using COX II inhibitors. This report was unable to establish the cause or severity of the GI events as this information is not recorded by the managed health care database. These members were registered on the managed care database for GORD, identified by the ICD-10 coding system.

3.5 Current medication use that may increase the risk of GI side effects

The ICD-10 for concomitant GI conditions was further analysed to focus on the frequency of GI events per drug class since this was the market driver for the COX II inhibitors.



	16 - 20	21 - 25	26 - 30	31 - 35	36 - 40	41 - 45	46 - 50	51 - 55	56 - 60	61 - 65	66 - 70	71 - 75	76 - 80	81 - 85	86 - 90
COXII	0	0	1	1	4	4	4	10	20	12	13	11	12	3	3
NSAIDS	1	0	2	0	0	3	1	4	3	5	6	3	3	1	1

Figure 3.12 Age distribution of patients presenting with the co-morbid condition GORD

Figure 3.12 above appears to illustrate that the COX II inhibitors were prescribed commonly to patients in the age group over the age of 56 years with the condition GORD. From the managed health care database it was established that the COX II inhibitors were prescribed more frequently to members that were already registered for the condition GORD as these patients were regarded as patients with a higher risk of developing GI events.

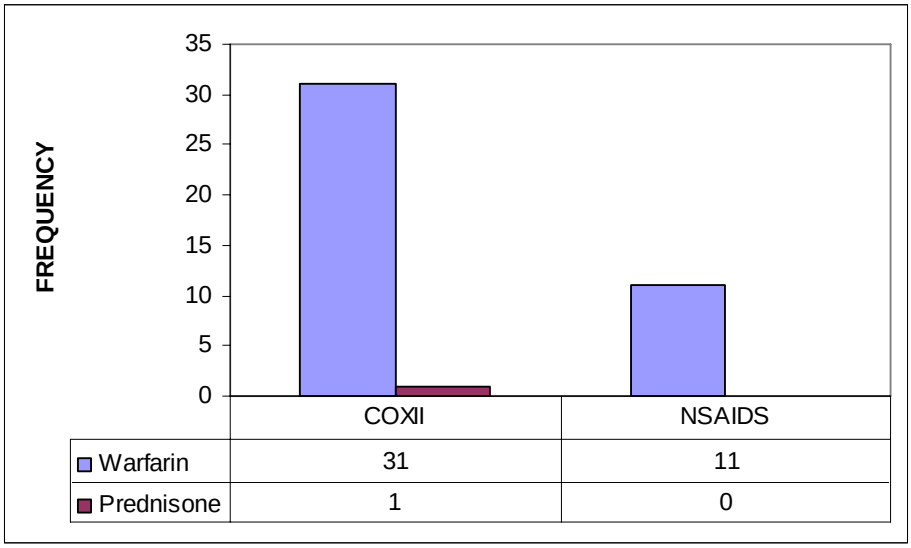
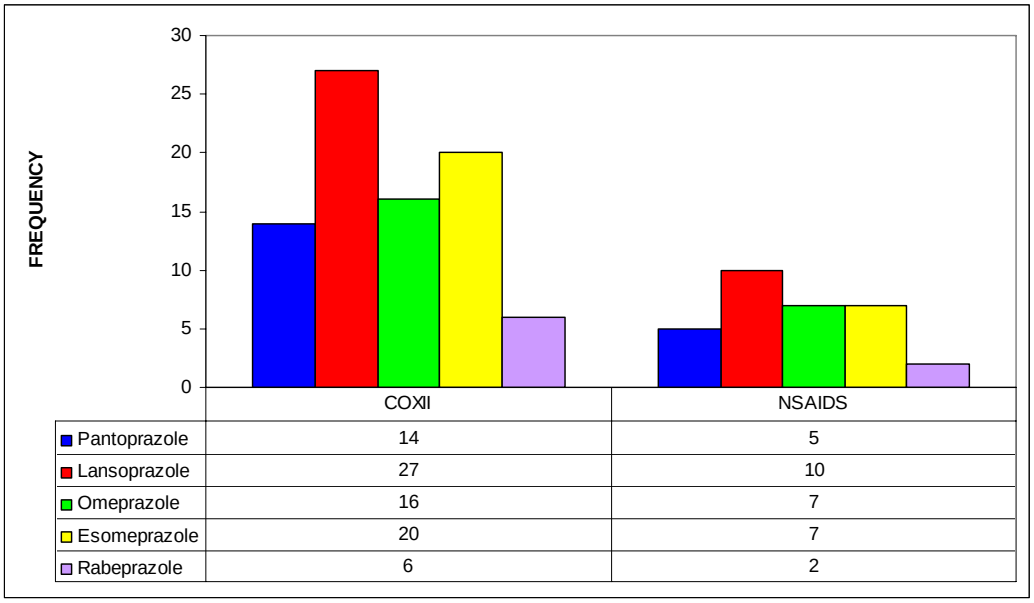


Figure 3.13 COX II inhibitor prescribed for patients on concomitant warfarin or steroid therapy

Figure 3.13 above illustrates that patients on warfarin or a steroid were prescribed the COX II inhibitors more frequently. These patients are reported to be at a higher risk of developing GI events.

3.6 Current use of gastro-protective agents

From the acute claims database, made available by the managed health care system the use of concurrent gastro-protective agents (GPA's) was obtained for each member receiving either a COX II inhibitor or non-selective NSAID over the six month evaluation period. These GPA's were identified according to the unique NAPPI code and were classified according to the MIMS classification.



	COXII	NSAIDS
Pantoprazole	14	5
Lansoprazole	27	10
Omeprazole	16	7
Esomeprazole	20	7
Rabeprazole	6	2

Figure 3.14 Gastro-protective agents identified

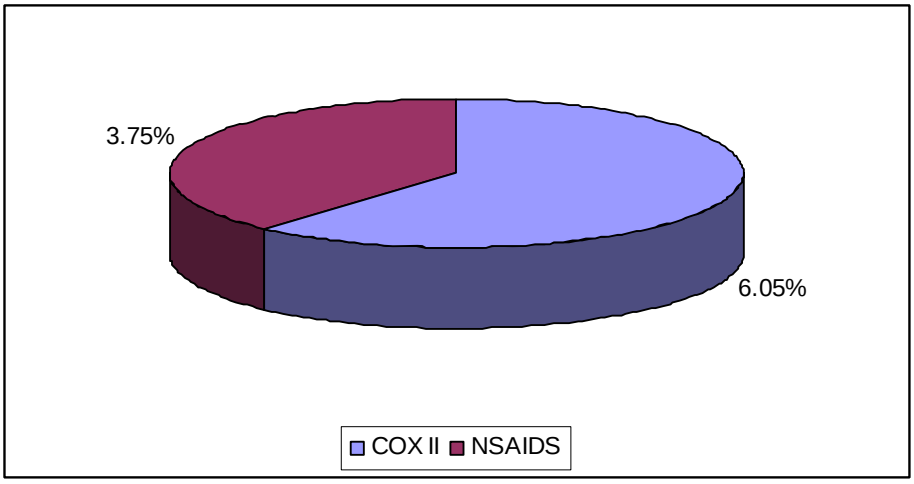


Figure 3.15 Distribution of gastro-protective agents between the COX II group and the NSAID group

The use of GPA's in combination with COX II inhibitors has been surprisingly higher than expected. It was reported that of the patients using a COX II inhibitor, 6.05 % used a GPA in combination with a COX II inhibitor, compared to 3.75% in the NSAIDs group. The most commonly prescribed GPA was lansoprazole (Lanzor®).

Lansoprazole was prescribed to 27 patients using COX II inhibitors and 7 patients using NSAIDs.

The Wilcoxon Matched-Pairs Signed Ranks test was used to test if there was a significant difference between GPA combinations for the CO X II and NSAIDs. The p-value here is 0.0625000. At a 5 % level of significance there is no statistical difference between the two groups since 0.0625 is less than 0.05.

CHAPTER 4

DISCUSSION

4.1 Total number of the COX II inhibitors and the NSAIDs prescribed

The prescribing frequency determined within the South African managed care environment, for the COX II inhibitors was 48.69% and that of the NSAIDs was 29.35%. Thus, the prescribing frequency of the COX II inhibitors determined in the South African managed care environment was higher than NSAIDs and this research report showed a similar trend with data available in Australia and the Canada. Celecoxib was listed on the Australian Phrameaceutical Benefit Scheme formulary in August 2000. This resulted in over 1.5 million celecoxib prescriptions being written by December 2000. The listing of celecoxib cost the Australian government $76 million (Report, 2001).

In another study conducted in Ontario, "initial patterns of use of COX II inhibitors by elderly patients in Ontario: Findings and implications" (Mamdani, *et al*., 2002) it was reported that COX II inhibitors were responsible for the increase in number of the combined prescriptions for COX II inhibitors and NSAIDs. This increase, of 68%, in the use of COX II inhibitors, was significant as the COX II inhibitors were first listed on the Ontario Drug Benefit (ODB) formulary in April 2000. COX II inhibitors accounted for 48% of the prescriptions in the post listing period (April to November 2000).

4.2 The COX II inhibitors and NSAIDs drug classes

The most commonly identified COX II in the South African managed care environment was celecoxib (46%) followed by rofecoxib (30%) and meloxicam (24%). In this report twelve different active ingredients from the NSAIDs class were identified. The most commonly prescribed NSAID in terms of frequency was diclofenac (34%) and the second most common NSAID was diclofenac with

mistoprostol (16%) followed by indomethacin and naproxen (12%), ketoprofen (8%) and piroxicam(7.9%).

Celecoxib and Rofecoxib have been documented to relieve the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) (Package Insert, 2003a; Package Insert, 2003b).

COX II inhibitors have become popular as they decreases the incidence of GI-bleeding and stomach ulcers in patients taking non-steroidal anti-inflammatory drugs and this has been market driven (LLévesque, *et al*., 2005). The theory that COX II inhibitors exhibits anti-inflammatory properties and have a reduced rate of ulcers and associated GI events has been tested by two large trials known as the: Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Celecoxib Long-term Arthritis Safety Study (CLASS) trial. Rofecoxib and celecoxib have been found to be associated with significantly reduced mild-to-moderate GI adverse events compared with non selective NSAIDs (Cox, *et al*., 2003a).

In a retrospective study conducted by a Quebec patient health management program, the most frequently prescribed NSAID's, for the treatment of osteoarthritis was reported to be either diclofenac sodium, a combination of diclofenac and mistoprostol, ibuprofen, or naproxen (Beaulieu, *et al*., 2004). The Prescribing Pricing Authority in the United Kingdom reported that the Committee on the Safety of Medicines (CSM) rated seven NSAIDs from highest to lowest risk for serious GI adverse effects. Ibuprofen was associated with lowest risk and naproxen, diclofenac, indomethacin, ketoprofen and piroxicam were associated with intermediate risks (Prescription Pricing Authority, 2000).

4.3 The demographics of the patients identified as using COX II inhibitors and NSAIDs

Seventy four percent of females were identified in this report as using COX II selective inhibitors compared to 26% male. The mean age of females was 55 years and the mean age of male was reported to be 56 years. The mean age of females using NSAIDs was identified to be 56 years with a prescribing frequency of 66% and that of males to be 58 years with a prescribing frequency of 34%.

According to literature published in the United States of America, the female to male prevalence of RA is 3:1 and the average age of onset is 50 years of age (King, *et al*., 2005).

Previous studies have concluded that there are significant gender differences in medication use, reporting that in general women are more likely to use a variety of medication including pain medication, than men. The chronic use of medication increases with age for both genders for chronic conditions (Roe, *et al*., 2002). Another study conducted in the United States, to examine gender differences in NSAID use, concluded that a greater number of women (37.4%) were prescribed an NSAID compared with men (29.6%). The study also reported that women were more likely to be prescribed the newer COX II inhibitors however; these differences did not take into account the risk of adverse GI events. Therefore, the reasons for the variation in patterns of NSAIDs use between genders needs to be studied further (Dominick, *et al*., 2003).

Reasons for these differences are still unknown and further investigations need to be conducted to clarify this.

4.4 Co-morbid medical conditions, and the use of gastro-protective agents, identified

4.4.1 Co-morbid medical conditions

The National Institute for clinical excellence published guidelines on the use of COX II inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. In summary, the guidelines suggested that COX II inhibitors are not recommended for routine use over the non-selective NSAIDs. The COX II inhibitors are indicated in patients with one or all of the following criteria: over the age of 65yrs, previous history of gastrointestinal bleeding, ulcer, or perforation, concomitant use of medication such as steroids or warfarin as these are known to increase the risk of GI adverse effects, the presence of co-morbid conditions such as cardiovascular disease, renal disease, diabetes or hypertension (NICE, 2001).

The VIGOR trial reported an increase in the number of myocardial infarctions in the rofecoxib group compared to the naproxen group. In the past year, the potential cardiovascular complications associated with selective COX II inhibitors have become an important concern (Solomon, *et al*., 2003).

In September of 2004, rofecoxib (Vioxx®) was found to be associated with an increased number of heart attacks and as a result was withdrawn from the from the market. Celecoxib (Celebrex®) and all other prescription NSAIDs will include a new warning label highlighting the potential for increased risk of cardiovascular (CV) events and gastrointestinal (GI) bleeding associated with their use (FDA, 2005).

In the COX II group, 52% of patients were reported to have co-morbid hypertension, 11% gastro-oesophageal reflux disease, and seven percent reported to have diabetes and ischaemic heart disease. In the NSAID group only five percent of patients were reported to have gastro-oesophageal reflux disease. Fifty-four percent of patients had co-morbid hypertension, 11% diabetes and nine percent had ischaemic heart disease. Non-selective NSAIDs and COX II inhibitors may result in the development of hypertension, oedema and congestive heart failure and should be prescribed with

caution in patients presenting with this condition (Nurmohamed, *et al*., 2002). In the elderly population with RA, hypertension is a common co-morbidity (Izhar, *et al*., 2004).

COX II inhibitors do not prevent gastrointestinal side effects but they are associated with fewer peptic ulcers and slightly fewer upper GI symptoms than reported with NSAIDs (The Australian Cox-2 Specific Inhibitor (CSI) Prescribing Group, 2002). The marketing of COX II inhibitors as being a superior product in terms of GI safety has recently been challenged by the council of medical schemes. This resulted in a change in the celecoxib package insert to include that celecoxib may predispose the patient to gastrointestinal changes and cardiovascular disease (Letter, 2005).

In this study it was found that the COX II were prescribed to patients with pre-existing GI events which illustrates that the prescribers are complying to the stated SARAA guidelines and NICE guidelines. The managed care has applied a selection tool to assist in pre-authorisation and this has proven successful.

4.4.2 Clinically significant GI events and current medication use that may increase the risk of GI side effects particularly with warfarin and prednisone

COX II inhibitors are reserved for patients with complicated life threatening GI adverse events such a perforation, obstruction, ulceration and bleeding. The reported increase in the use of COX II inhibitors for patients with mild symptoms of GI events such as dyspepsia, nausea, heartburn lead to the development of formal guidelines. The guidelines recommend to prescribers that COX II inhibitors are reserved for patients with high risk for GI adverse events. (Cox, *et al*., 2003a).

Over 15% of patients with RA will be prescribed a steroid for adequate management of the disease. Hypertension and hyperlipidaemia are associated with long term steroid use (Nurmohamed, *et al*., 2002). Patients using steroids are at a higher risk of developing gastrointestinal complications (NICE, 2001). Therefore, the COX II inhibitors have been reported to be the drug of choice in these patients.

Non-selective NSAIDs may enhance the anti-coagulation effect of warfarin by displacing warfarin from its protein site. The concomitant use of NSAIDs and warfarin should be avoided (Anonymous, 1996).

It is, therefore, recommended that COX II inhibitors are reserved for patients with concomitant warfarin therapy (NICE, 2001; Gotlieb, 2003).

From the above data it is clear that risk factors for upper gastro-intestinal adverse effects affected the prescribing pattern of COX II inhibitors over non-selective NSAIDs.

4.4.3 Current use of Gastro-protective agents

From the study it appears that GPA's are used routinely with COX II and non-selective NSAIDs. GPA's are often prescribed together with non-selective NSAIDs in order to reduce the potential GI adverse effect commonly associated with NSAIDs. It is estimated that co-prescribing rates ranges from 17% to 34 % (Cox, *et al*., 2003a). Lanzoprazole appears to be the most commonly prescribed GPA, in both patients groups. The rationale for this is unknown. The data revealed that GPA's were more commonly prescribed in the COX II selective group (6%) than the NSAID group (3.75%). A COX II cost-effectiveness model showed that the use of GPA's amongst the COX II group was higher than the non-selective NSAID group. The reported rate ranges from 20% to 22% (Cox, *et al*., 2003b). There is no evidence to justify the simultaneous use of GPA's with COX II selective inhibitors as a means to further reduce GI adverse events. These agents only partially prevent a GI adverse event. These agents also have side effects and ultimately add to the total cost of treating RA (NICE, 2001).

The findings' regarding the use of GPA's in COX II users is contrary to what is expected. Most literature review articles hypothesised that the COX II inhibitors displayed superior gastro protective safety (Warner, *et al*., 1999).

The reason for this is not clear. One would assume that the NSAID patient group would utilise GPA more frequently as this class of medication does not offer gastro-protective efficacy as does the COX II. An assumption could be that the patients that qualified for the use of a COX II selective inhibitor in the managed care environment as per the NICE and SARAA guidelines were patients that were identified as having a high risk of developing GI events, hence the high GPA utilisation. There is no scientific clinical data to accurately base the explanation of this utilisation pattern.

CHAPTER 5

5.1 LIMITATIONS

1. The datum in this report represents a single data set from one managed care's system. The datum is retrospective and therefore full patient medical history and patient profiles were not attainable. The datum covered all plan types within the managed care environment including the top end plans and lower end plans. The prescribing patterns could vary depending on numerous factors including plan design and doctors practice style.

2. The sample was from a managed care environment only and therefore could not be extrapolated to the entire population that utilises COX II inhibitors and NSAIDs.

3. The hospital events were logged onto the system by case managers. At the time the data was sourced, ICD-10 coding was not compulsory. As a result some of the diagnosis codes for the hospital events could have been missed. This could be due to a lack of documentation or the fact that these diagnoses were secondary to other conditions for which the patient was being seen and not captured in the ICD-10 coding.

4. The chronological order of whether the hospital event occurred prior to COX II inhibitor or NSAID initiation is unknown i.e. did the GI adverse event occur before the use of COX II and therefore patients were placed on the COX II inhibitor or where the patients on COX II inhibitors and then developed GI adverse events.

5. This report was unable to establish the cause or severity of the GI events as this information is not recorded by the managed health care database. These members were registered on the managed care database for GORD, identified by the ICD-10 coding system. The severity such as gastrointestinal bleeding,

history of upper gastrointestinal procedures, prior gastro-protective agents, and prior referral to gastroenterologist is not known.

6. GPA agent estimates in this study did not include use of over-the-counter (OTC) GPA agents, including OTC, H_2 receptor antagonists or antacids. Failure to capture OTC GPA usage may underestimate the true GPA rate amongst NSAID users.

5.2 RECOMMENDATIONS

1. Combination GPA's and COX II inhibitors in the managed care environment should be further investigated to evaluate the cost-effectiveness of the COX II inhibitors.

2. An in-depth analysis of the overall benefit of COX II selective inhibitors in reducing the risk of serious GI adverse events should also be undertaken.

3. The study was designed to compare the NSAIDs and COX II inhibitor usage pattern during a specified time period. This study could have been designed to compare the difference in prescribing patterns prior to the listing of the COX II onto the managed care formularies to the prescribing patterns after being listed on the formularies.

4. In light of recent publications this study needs to be further investigated to discuss the associated risk of cardiovascular events with patients using COX II inhibitors.

5.3 CONCLUSION

The aim of the study was to assess the prescribing patterns of the COX II inhibitors and the NSAIDs in the managed care environment. The hypothesis was that the COX II inhibitors were prescribed more frequently than the NSAIDs.

However, this study indicated that the COX II inhibitors were not over prescribed. The prescribing patterns identified in this study confirmed that the managed care environment have adopted clinical guidelines and protocols that were adhered to.

This study provides evidence that guidelines, protocols and formularies are efficient tools in managing drug utilisation and prescribing patterns.

REFERENCES

1. American College of Rheumatology. 2002. Guidelines for the management of Rheumatoid Arthritis. *Arthritis and Rheumatism*, vol. 46, no. 2, pp 326-346.

2. Anonymous. 1996. An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. *Canadian Medical Association Journal*, vol. 155, pp. 77-88.

3. The Australian cox-2 specific inhibitor (CSI) prescribing group. Considerations for the safe prescribing and use of COX-2 specific inhibitors. *The Medical Journal of Australia*,1 April 2002 vol. 176, no. 7, pp. 328-331.

4. Barclay, L. 2004. "Vioxx Withdrawal Prompts Re-evaluation of COX-2 Inhibitor Safety." *Medscape.* <http://www.medscape.com/viewarticle/490979> (Accessed on 31 March 2005).

5. Beaulieu, M., Choquette, D., Rahme, E., *et al*. 2004. CURATA: A Patient Health Management Program for the Treatment of Osteoarthritis in Québec: An Integrated Approach to Improving the Appropriate Utilization of Anti-Inflammatory/Analgesic Medications. *The American Journal of Managed Care*, vol. 10, pp. 569-575.

6. Beers, M.H., Berkow, R. 1999. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, N.J.: Merck Research Lab. pp. 418.

7. Cox, E.R., Motheral, B.R., Frisse, M., *et al*. 2003a. Vioxx Gastrointestinal Outcomes Research (VIGOR) Trial. Prescribing cox-2's for patients new to cyclo-oxygenase inhibition therapy. *American Journal of Managed Care*, vol. 9, pp. 735-742.

8. Cox, E.R., Motheral B.R., Mager D. 2003b. Verification of a decision analytic model assumption using real-world practice data: Implications for the cost effectiveness of cyclo-oxygenase 2 inhibitors COX-2's. *American Journal of Managed Care*, vol. 9, pp. 785-794.

9. Cronstein, B.N. 2002. Cyclooxygenase-2-selective inhibitors: translating pharmacology into clinical utility. *Cleveland Clinic Journal of Medicine*, vol. 69, Suppl 1, SI13-19.

10. del Rincon, I., Escalante, A. 2003. Atherosclerotic cardiovascular disease in Rheumatoid Arthritis. *Current Rheumatology Reports*, vol. 5, no. 4, pp. 278-286.

11. Dominick, K.L., Ahern, F.M., Gold, C.H., *et al*. 2003. Gender differences in NSAID use among older adults with Osteoarthritis. *The Annals of Pharmacotherapy*, vol. 37, no. 11, pp. 1566-1571.

12. FDA (U.S. Food and Drug Administration). 2005. "FDA Announces Series of Changes to the Class of Marketed Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)." <http://www.fda.gov/bbs/topics/news/2005/NEW01171.html> (Accessed on 10 April 2005).

13. Gotlieb, D. 1999. "Managed Health Care in South Africa, where to from here?" *South African Rheumatism and Arthritis Association*. <http://www.arthritis.co.za/managed%20care.htm> (Accessed on 31 March 2005).

14. Gotlieb, D. 2000. "Rheumatoid Arthritis." *South African Rheumatism and Arthritis Association*. <http://www.arthritis.co.za/ra.html> (Accessed on 31 March 2005).

15. Gotlieb, D. 2003. "Therapeutic Guidelines." *South African Rheumatism and Arthritis Association*. <http://www.arthritis.co.za/saraa/saraa%20guidelines.html> (Accessed on 31 March 2005).

16. Harris, E.D., Jr. 2003. "Rheumatoid Arthritis." *Best Practice of Medicine*. <http://merck.micromedex.com/index.asp?page=bpm_brief&article_id=BPM01RH15> (Accessed on 31 March 2005).

17. Izhar, M., Alausa, T., Folker, A., *et al*. 2004. Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated Blacks and Hispanics. *Hypertension*, vol. 43, no. 3, pp. 573-577.

18. Katzung, B.G. 1998. *Basic and Clinical Pharmacology*. 7th ed. Stamford : Appleton and Lange. pp. 304-318.

19. King, R.W., Worthington, R. 2005. "Rheumatoid Arthritis." <http://www.emedicine.com/emerg/topic48.htm> (Accessed on 2 April 2005).

20. Letter, 2005, Celebrex (celecoxib) Capsules: Health Care Professionals Notification: Important medicine safety information, Pfizer Laboratories, South Africa.

21. Lévesque, L.E., Brophy, J.M., Zhang, B. 2005. The Risk for Myocardial Infarction with Cyclooxygenase-2 Inhibitors: A population study of Elderly Adults. *Annals of Internal Medicine*, vol. 142, pp. 481-489.

22. Mamdani, M., Laupacis, A., Rochon, P., *et al*. 2002. Initial patterns of use of COX-2 inhibitors by elderly patients in Ontario: findings and implications. *Canadian Medical Association Journal*, vol. 167, no. 10, pp. 1125-1126.

23. Matsumoto, A.K., Bathon, J. 2004. "Rheumatoid Arthritis Treatments." *Johns Hopkins Arthritis.* <http://www.hopkins-arthritis.som.jhmi.edu/rheumatoid/rheum_treat.html> (Accessed on 31 March 2005).

24. MIMS (Monthly Index of Medical Specialities). 2004. vol. 44, no. 11, pp. 66-78.

25. NICE (National Institute of Clinical Excellence). 2001. "Guidance on the use of cyclo-oxygenase (COX II) selective inhibitors, celecoxib, refecoxib, meloxicam and etodalac and osteoarthritis and rheumatoid arthritis." *Technology Appraisal Guidance*. <http://www.nice.org.uk/pdf/coxiisummary.pdf > (Accessed on 31 March 2005).

26. Nurmohamed, M.T., van Halm, V.P., Dijkmans, B.A.C. 2002. Cardiovascular risk profile of antirheumatic agents in patients with osteroarthritis and rheumatoid arthritis. *Drugs*, vol. 62, no. 11, pp. 1599-1609.

27. Package Insert. 2003a, Celebrex, Pfizer Laboratories, South Africa.

28. Package Insert. 2003b, Vioxx, Merc & Co., Inc, United States of America.

29. Package Insert. 2005, Celebrex, Pfizer Laboratories, United States of America.

30. Pharmafocus. 2005. "Bextra withdrawal dents Pfizer's sales juggernaut." <http://www.pharmafocus.com/cda/focusH/1,2109,21-0-0-APR_2005-focus_news_detail-0-341418,00.html> (Accessed on 30 April 2005).

31. Prescription Pricing Authority (NHS). 2000. "Analgesics and Nsaids Prescribing." <http://www.ppa.org.uk/news/pact-042000.htm> (Accessed on 31 March 2005).

32. Report, 2001, Annual Report for the year ended 30 June 2001, Pharmaceutical Benefits Pricing Authority. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pricing-pbparpt01.htm> (Accessed on 31 March 2005).

33. Report, 2003a, Medical Schemes Act 131 of 1998, Council for Medical Schemes. <http://www.medicalschemes.com/publications/ZipPublications/Acts%20and%20Regulations/MSREGS19July2004.pdf> (Accessed on 31 April 2005).

34. Report, 2003b, Nappi product file layout, Medikredit Integrated Health Care Solutions (Pty) Ltd in association with Afrox Management services (Pty) Ltd, 9th ed, ver. 5.01.

35. Roe, C.M., McNamara, A.M., Motheral, B.R. 2002. Gender and age-related prescription drug use patterns. *The Annals of Pharmacotherapy*, vol. 36, no. 1, pp. 30-39.

36. Schnirring, L. 2004. Maker withdraws Vioxx. *The Physician and Sportsmedicine*, vol. 32, no. 11, pp. 9-12.

37. Scottish Intercollegiate Guidelines Network. 2000. "Management of early Rheumatoid Arthritis: A National Clinical Guideline." <http://www.sign.ac.uk/guidelines/fulltext/48/index.html> (Accessed on 31 March 2005).

38. Sibbald, B. 2004. Rofecoxib (Vioxx) voluntarily withdrawn from market. *Canadian Medical Association Journal*, vol. 171, no. 9, pp. 1027-1028.

39. Smucny, J. 2004. Are Selective COX-2 Inhibitors as Effective as NSAIDs in Patients with Rheumatoid Arthritis? *American Family Physician*, vol. 69, no. 3, pp. 595-598.

40. Solomon, D.H., Avorn, J. 2003. Pharmacoepidemiology and rheumatic diseases: 2001-2002. *Current Opinion in Rheumatology*, vol. 15, no. 2, pp. 122-126.

41. SAMF (South African Medicines Formulary). 2000. 5th ed. Department of Pharmacology, Medical School, University of Cape Town. Medical Association of South Africa. pp.323-328.

42. Staud, R. 2000. "Comparing the COX-2 Inhibitors with Traditional NSAIDs." <http://www.emedmag.com/html/pre/fea/features/111500.asp> (Accessed on 31 March 2005).

43. Tikly, M., Zannettou, N., Hopley, M. 2003. "Longitudinal study of Rheumatoid Arthritis in South Africans." <http://www.medscape.com/viewarticle/448141> (Accessed on 31 March 2005).

44. Warner T.D.,Giuliano F., Vojnovic I., *et al*. 1999. Nonsteroidal drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 13, pp. 7563-7568.

45. Williams, B., Panayi, G., Bosworth, A. 2003. "Rheumatoid Arthritis. The Painful Truth." <http://www.rheumatoid.org/pdf/ra_painful_truth.pdf> (Accessed on 31 March 2005).

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2005-06-09

MS M BEEKA
PO BOX 784179
SANDTON
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Dear Ms Beeka

Approval of protocol entitled the prescribing trends of the non-steroidal anti-inflammatory drugs (NSAID'S) and cyclo-oxygenase (OX) II selective inhibitors in the treatment of patients with a chronic condition, rheumatoid arthritis (RA), in the managed health care environment.

I should like to advise you that the protocol and title that you have submitted for the degree of Master of Science in Medicine (Part-time)(Coursework) have been approved by the Postgraduate Committee at its recent meeting. Please remember that any amendment to this title has to be endorsed by your Head of Department and formally approved by the Postgraduate Committee.

Professor AGS Gous has been appointed as your supervisor. Please maintain regular contact with your supervisor who must be kept advised of your progress.

Please note that approval by the Postgraduate Committee is always given subject to permission from the relevant Ethics Committee, and a copy of your clearance certificate should be lodged with the Faculty Office as soon as possible, if this has not already been done.

Yours sincerely

TD Boogerd (Ms) for
Assistant Postgraduate officer

S Benn (Mrs)
Faculty Registrar
Faculty of Health Sciences

Telephone: 717-2075/2076

Copies: Head of Department
Supervisor

APPENDIX A: Post-Graduate Committee Research Protocol approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Beeka

CLEARANCE CERTIFICATE **PROTOCOL NUMBER M040508**

PROJECT Prescribing trends of non-sterodial anti-inflammatory drugs (NSAIDS) and cycl-oxygenase (COS) II selective inhibitors in treatment of patients with chronic condition, theumatoid arthritis (RA) in the managed Health Care Environment.

INVESTIGATORS Miss M Beeka

DEPARTMENT Pharmacy, 5 Parklane,Princess PlaceParktown

DATE CONSIDERED 04.05.28

DECISION OF THE COMMITTEE*

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.07.09 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof A Gous

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B: Committee for Research on Human Subjects approval

Discovery Health

12 February 2004

Committee for Research on Human Subjects (medical)
University of the Witwatersrand
Johannesburg

Dear Sir/Madam

CONFIRMATION OF AUTHORISATION

We hereby confirm that **Menicksha Beeka** has been authorised by Discovery Health to use the clinical data required for her research protocol document titled "**The Prescribing Trends of the non-selective Non-steroidal Anti-inflammatory Drug's (NSAIDs) and Cyclo-Oxygenase (COX) II selective Inhibitors in the treatment of patients with a chronic condition, Rheumatoid Arthritis (RA) in the Managed Health Care Environment**" to complete her Masters of Science in Medicine (MSC. Med)

The study will analyze retrospective claims data to assess the **current use** of the NSAID's and COX II selective inhibitors in RA patients in a Managed Health Care Environment.

Please rest assured that the information contained in the data provided by Discovery Health will not include patient names and/or addresses in the interest of patient confidentiality.

Should you have any ethical concerns regarding patient confidentiality in the Medical Records provided by Discovery Health, please do not hesitate to contact me.

Yours faithfully,

Dr. Silvia Cornejo
Divisional Manager
Clinical Risk Management

155 West Street, Sandton, P. O. Box 786722, Sandton 2146, Tel 0860 99 88 77 (Client Services), (011) 529 2888 (Switchboard), Fax (011) 529 2958, www.discovery.co.za

APPENDIX C: Discovery Health authorisation confirmation

APPENDIX D: List of co-morbid conditions found for RA patients

Co-morbid conditions found for COX II prescribed patients

Acute Haemorrhagic Gastritis
Acute with Haemorrhage
Anaemia
Ankylosing Spondylitis
Aortic (valve) Stenosis
Asthma
Atherosclerosis of Aorta
Bipolar Affective Disorder
Bronchiectasis
Budd-chiari Syndrome
Cardiomyopathy
Chronic Obstructive Pulmonary Disease
Circumscribed Brain Atrophy
Congestive Heart Failure
Crohns Disease of Small Intestine
Diabetes Mellitus
Emphysema
End-stage Renal Disease
Epilepsy
Gastroesophageal Reflux Disease
Glaucoma
Gout
Hallucinosis
HIV
Hyperlipidaemia
Hypermetropia
Hyperplasia of Prostate
Hypertension
Hypopituitarism
Hypothyroidism
Interstitial Pulmonary Disease
Ischaemic Heart Disease
Isolation
Malignant Neoplasm
Menopausal and Female Climacteric States
Migraine
Mild Depressive Episode
Mitral Valve Insufficiency
Menjres Disease
Multiple Sclerosis
Multiple Sites
Multiple Sites in Spine
Myasthenia Gravis

Co-morbid conditions found for COX II prescribed patients

Obstetric Air Embolism
Osteoporosis
Other Adrenocortical Overactivity
Other Chronic Pancreatitis
Panic Disorder
Parkinsons Disease
Pemphigus Vulgaris
Peptic Ulcer
Person consulting on behalf of another person
Phlebitis/Thrombophlebitis Superfic Vessels Low Extremties
Polyarthritis
Polyneuropathy
Predominantly Obsessional Thoughts or Ruminations
Presence of Cardiac Pacemaker
Primary Arthrosis of Other Joints
Primary Generalized (osteo)arthrosis
Primary Hyperaldosteronism
Primary Pulmonary Hypertension
Progressive Systemic Sclerosis
Psoriasis Vulgaris
Pulmonary Emboli
Raynauds syndrome
Rheumatism
Sarcoidosis
Schizophrenia
Sicca Syndrome [sjogren]
Stroke
Systemic Lupus Erythematosus
Thyrotoxicosis
Ulcerative (chronic) Enterocolitis
Unspecified
Unstable Angina
Vasomotor Rhinitis
Ventricular Fibrillation and Flutter
Vertebro-basilar Artery Syndrome

Co-morbid conditions found for NSAID prescribed patients

Anaemia
Ankylosing Spondylitis
Aortic (valve) Stenosis
Asthma
Atherosclerosis of Aorta
Atrial Fibrillation and Flutter
Bipolar Affective Disorder
Budd-chiari Syndrome
Cardiomyopathy
Chronic Obstructive Pulmonary Disease
Congestive Heart Failure
Crohns Disease of Small Intestine
Diabetes Mellitus
Emphysema
Epilepsy
Gastroesophageal Reflux Disease
Glaucoma
Gout
Hyperkinetic Disorder
Hyperlipidaemia
Hyperplasia of Prostate
Hypertension
Hypopituitarism
Hypothyroidism
Interstitial Pulmonary Disease
Ischaemic Heart Disease
Kidney Transplant Status
Malignant Neoplasm
Menopausal and Female Climacteric States
Migraine
Mild Depressive Episode
Menjres Disease
Multiple Sites
Multiple Sites in Spine
Myasthenia Gravis
Not Elsewhere Classified
Nummular Dermatitis
Obstetric Air Embolism
Osteoporosis
Other Adrenocortical Overactivity
Other Chronic Pancreatitis
Panic Disorder
Parkinsons Disease
Person consulting on behalf of another person
Phlebitis/Thrombophlebitis Superfic Vessels Low Extremties
Polyarthritis

Co-morbid conditions found for NSAID prescribed patients

Post-traumatic Stress Disorder
Primary Arthrosis of Other Joints
Primary Generalized (osteo)arthrosis
Psoriasis Vulgaris
Raynauds Syndrome
Reflex Neuropathic Bladder
Schizoaffective Disorder
Sicca Syndrome [sjogren]
Stroke
Systemic Lupus Erythematosus
Ulcerative (chronic) Enterocolitis
Unspecified
Unspecified Chronic Bronchitis
Unstable Angina
Vasomotor rhinitis
Ventricular Fibrillation and Flutter
Vertebro-basilar Artery Syndrome
Vomiting following Gastrointestinal Surgery