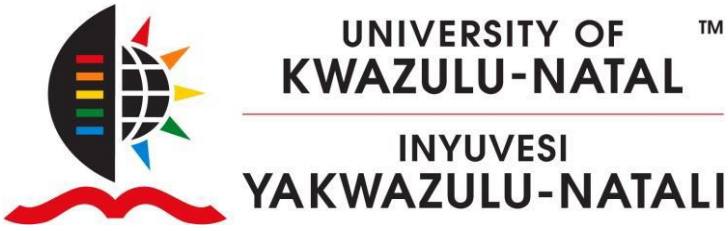

PHARMACOECONOMIC IMPLICATIONS OF INTERCHANGEABLE USE OF ORAL NSAIDS FOR PAIN MANAGEMENT AT A DISTRICT HOSPITAL

by

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Submitted as the dissertation component in partial fulfilment (50%) for the degree of

MASTER OF PHARMACY

In the

Discipline of Pharmaceutical Sciences

School of Health Sciences

University of KwaZulu-Natal

Supervisor: Lehlohonolo J. Mathibe (Revd.)

December 2015

MPharm Candidate's Declaration

I, **Mr Makhipha Johannes Nkosi**, declare that,

i. The research reported in this thesis, except where otherwise indicated, is my own original work.

ii. The work described in this thesis has not been submitted to the University of KwaZulu-Natal (UKZN) or other tertiary institutions for the purpose of obtaining an academic qualification, whether by myself or any other party.

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Supervisor's Declaration

As the MPharm candidateôs supervisor I, **Revd. Lehlohonolo J. Mathibe**, agree to the submission of this dissertation.

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ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to my supervisor, Reverend Lehlohonolo J Mathibe, for being so supportive and giving me the best advice and guidance throughout this research project.

I would also like to thank the Mpumalanga Department of Health for affording me an opportunity to conduct this study in one of their district hospitals, namely Tonga Hospital.

My gratitude also extends to the Tonga Hospital management, particularly the hospital CEO, Mr. J.S Aphane, for allowing me to conduct this study in his facility.

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ACRONYMS

COX	: Cyclooxygenase
DCI	: Data collection instrument
DDD	: Daily-defined dose
HPTC	: Hospital Pharmacy and Therapeutics Committee
NEML	: National Essential Medicines List
NSAIDs	: Non-steroidal anti-inflammatory drugs
PDSX	: Pharmaceutical Distribution System
PHREC	: Provincial Health Research and Ethics Committee
PTC	: Pharmacy and Therapeutics Committee
WHO	: World Health Organization

ABSTRACT

Background: Ibuprofen, diclofenac and aspirin belong to the same class of drugs called NSAIDs, but are used interchangeably at Tonga Hospital. The problem with this approach is that it may lead to preventable misguided and increased spending on pharmaceuticals.

Aim: To investigate the pharmacoeconomic implications of interchangeable use of oral NSAIDs for pain management at a district hospital.

Setting: This study was conducted at a district hospital in the Tonga village in the Nkomazi municipality, Mpumalanga Province, South Africa.

Methods: A quantitative retrospective descriptive study, using existing patient records as well as medicine stock control records, was conducted to investigate the cost-effectiveness of oral NSAIDs when used interchangeably in the management of pain in adult patients at a district hospital.

Results: The total number of patients included in this study was 211 in a split of 104 in 2013 and 107 in 2014. The mean ages of all the patients who participated in our study in 2013 and 2014 were 36 and 35 years respectively and there were more females than males. Most patients who presented at Tonga Hospital for pain management were suffering from minor bodily/joint pains (36.0%, n=76), whereas the least number of patients were suffering from bone fractures (10.9%, n=23). Our study found that most patients (31.3%; n=66) treated with ibuprofen were suffering from minor bodily/joint pains, whereas the least number of patients (1.4%; n=3) treated with diclofenac were suffering from inflammatory conditions. Females were the largest users of NSAIDs (both ibuprofen and diclofenac) in Tonga Hospital when compared with males. Patients between the ages of 19-35 years were the most prevalent (28.4%, n=60) who were treated with ibuprofen when compared with patients 18 years and below (9.5%, n=20). Also, patients who were 18 years and younger and treated with diclofenac were the least number of patients (1.4%, n=3). The highest total NSAID stock volumes issued from July to December of 2013 and 2014 combined was ibuprofen (36978 packs) when compared with diclofenac (11127 packs). The stock volumes for both ibuprofen and diclofenac were higher in July, with 8170 for Ibuprofen and 2099 for diclofenac. Diclofenac stock volumes fell to their lowest (1583) in September, whereas Ibuprofen stock volumes fell to their lowest (4478) in December. The fall in

stock volumes issued might be attributable to many factors including but not limited to non-delivery by the supplier or non-ordering by the pharmacy staff. In all instances ibuprofen stock volumes issued were higher than that of diclofenac. The acquisition cost of ibuprofen when calculated as mean price per tablet during 2013 to 2014 was consistently lower, with an average price of (0.285 ZAR) when compared with diclofenac (0.995 ZAR). 0.3% of the population of Nkomazi east, on average, gets treatment of ibuprofen daily whereas 0.01% of the population gets treatment of diclofenac daily. The mean cost per defined daily dose was consistently lower for ibuprofen in both 2013 (0.84 ZAR) and 2014 (0.87 ZAR) when compared with diclofenac in 2013 (2.94 ZAR) and 2014 (3.03 ZAR). The sensitivity analysis points in favour of ibuprofen over diclofenac as indicated when increasing or decreasing the mean price per tablet by 50% of either ibuprofen or diclofenac.

Conclusion: This study found that the acquisition costs of NSAIDs in relation to the mean price per pack of oral tablets had been consistently higher for diclofenac than they were for ibuprofen in Tonga Hospital. Therefore, the use of ibuprofen oral tablets in the management of pain at a district hospital is cost-effective when compared with diclofenac oral tablets.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION AND LITERATURE REVIEW

1.1 Background

The Tonga Hospital was opened in 1999. It is situated in the Tonga village in the Nkomazi municipality, Mpumalanga Province, South Africa. It has fourteen feeder primary health care centres, many of which are rural farming communities that are isolated and sparsely populated. Most health-care services are provided through mobile services. The hospital has a catchment population of about 393 030 (Census, 2011:42) and is a 143-bed district hospital (Chu *et al*., 2011:154) with a capacity for around 250 beds (Government gazette 35101, 2012:22). On average the Tonga Hospital treats about 5936 patients per month of combined in-patients and out-patients (DHIS, 2015). The cost per head of patients is about R1481.50 per day as at year 2010 (Chu *et al*., 2011:155). A considerable number of patients who visit the Tonga Hospital come from two neighbouring countries, Mozambique and Swaziland in search of better economic opportunities and health care. Only a small number of patients come from Zimbabwe and other Provinces or municipalities.

When the hospital management makes budget forecasts, the budget inputs do not take into account the extra number of patients who flock from outside the Tonga Hospital catchment area as numbers cannot be accurately quantified. These foreign patients have to be given treatment once they present to the facility. ñA countryôs difficult financial situation does not absolve it from having to take action to realize the right to healthò (World Health Organization, 2008:5). Tonga Hospital offers the following services among others: family medicine and primary health care, dental, pharmacy, trauma, rehabilitation, medicine, surgery, obstetrics, paediatrics, psychiatry, eye care, geriatrics, abuse victim empowerment, voluntary counselling and testing, male medical-circumcision.

Unemployment rate stands at about 34.3% at Nkomazi (Census, 2011:68). This means that the local community depends almost entirely on the state health care centres for its health care needs. This community has a low socio-economic status, thus Tonga Hospital forms the back-bone of its health care needs. This emphasizes the importance of the hospital being able to cater for a large number of

patients. This means that this hospital must be financially sound and be able to properly manage the appropriation of funds for health programs. In order to meet the health care needs of the community, Tonga Hospital management is always faced with the decision to allocate funds to health programs of which amongst others is medicines availability. Medicines are expensive and their prices continue to increase on a yearly basis. ñSouth Africa has implemented a number of important medicine pricing interventions in the post-apartheid era, informed by the 1996 National Drug Policyò (Gray *et al.,* 2015). The South African government controls medicine prices through the Medicines and Related Substances Act (101/1965) by way of the single exit price at the National Department of Health (National Department of Health, 2015).

In the Mpumalanga Province in particular, the health budget had risen from R8.084 billion in the 2013/2014 fiscal year to R8.9 billion in 2014/2015 fiscal year (Mpumalanga Department of Finance, 2015). Unfortunately, the budget allocation was reduced in 2015/16 to R7.317 billion due to National Treasury budget allocation cuts (Mpumalanga Department of Finance, 2015), partly due to South Africaôs shrinking fiscal budget and because of the ñcontinued weakness in the global economy and domestic structural constraintsò (African Economic Outlook, 2015). Medicines form part of the category ógoods and servicesô when the Mpumalanga Provincial Health budget is distributed among different health programs. A large portion of the budget is mostly directed to medicines procurement. To make things worse the reduced budget in the 2015/2016 financial year meant that medicine procurement budget allocation would also reduce. At this, the MEC for Mpumalanga Provincial Health issued the following stern advice: ñthe tight fiscal environment demands prudency in allocations, efficiencies in the utilisation of resources and slowing down of spending on non-critical activitiesò (Mpumalanga Department of Finance, 2015). Weinstein *et al.* reiterated this by saying ñlimits on health-care resources mandate that resource-allocation decisions be guided by considerations of cost in relation to expected benefitsò (Weinstein *et al*., 1977).

One of the objectives of the SAôs National Drug Policy, is ñto promote the cost-effective and rational use of drugs, as well as to optimize the use of scarce resources. The health objective of the NDP is to

ensure the availability and accessibility of essential drugs to all citizens. The NDP emphasizes the fact that drug procurement and distribution should be limited to drugs on the list of Essential drugsò (National Drug Policy, 1996:11). Therefore, it is imperative that all health care professionals put in place measures to cut costs while delivering quality healthcare service for all.

The availability of oral non-steroidal anti-inflammatory drugs (NSAIDs) for adult patients at Tonga Hospital is limited to Diclofenac, Ibuprofen, and Aspirin. These NSAIDs are only available in the following strengths and pack sizes: Diclofenac 50mg with a pack size of 21 tablets, Ibuprofen 200mg with a pack size of 15 tablets and Ibuprofen 400mg with a pack size of 28 tablets, and Aspirin 300mg with a pack size of 14 tablets. These NSAIDs are also listed in the National Essential Medicines List (NEML) (Standard Treatment Guidelines and Essential Drugs List, 2012: Chapter 13-14). The NEML is a national medicine formulary that can be used by Pharmacy and Therapeutics Committees (PTCs) in the public sector as a guide in crafting local medicines formularies. ôUsing an essential medicines list (EML) makes medicine management easier in all respects; procurement, storage and distribution are easier with fewer items, and prescribing and dispensing are easier for professionals if they have to know about fewer itemsò (World Health Organization 2002 :3).

The afore-mentioned NSAIDs have all been listed in the Tonga Hospital formulary for the management of adult patients with minor to moderate pain. The inclusion of all these NSAIDs in the local formulary means that they had been rated as essential for Tonga Hospital. ôThe World Health Organization (WHO) describes essential medicines as those that satisfy the priority health care needs of the population. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate quantities, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can affordò (Standard Treatment Guidelines and Essential Drugs List, 2012: XV).

As per the South African NDP (1996)

> *When two or more drugs are equivalent, preference would be given to those which have: the best cost advantage; best pharmacokinetic properties; has been the best researched; the best patient compliance; and the most reliable local manufacturer. If two or more medicine items belong to the same class and produce similar outcomes as would be demonstrated in chapter 2 with ibuprofen and diclofenac oral tablets, it may not be appropriate to list all of them in a formulary especially in the face of budgetary constraints. Despite the many other cost-containment measures which are implemented every financial year, medicine expenditure at Tonga Hospital remains high and continues to grow.* (National Drug Policy for South Africa, 1996:11).

The Tonga Hospital PTC is expected to play an essential role in addressing rational use of medicines in the hospital to ascertain that medicine expenditure is always kept under control. It is also is well-placed as a structure in the hospital to implement systems that promote rational use of medicines.

Health programs should be funded equitably through prioritization. Medicines are one of the priorities amongst health programs that require funding. This is affirmed by the National Health Ministerôs six priorities. ñThe economic impact of pharmaceuticals is substantial. Spending on pharmaceuticals represents 15 to 30% of health spending in transitional economies and 25 to 66% in developing countries. In most low income countries pharmaceuticals are the largest public expenditure on health after personnel costs and the largest household health expenditureò (Agrawal *et al.,* 2013). If medicines would always be allowed to take a huge portion of the budget, it would mean that other programs would have their progress stifled due to lack of funds. Also, if one medicine item would be allowed to take a large portion of the budget allocation, it would mean that other life-saving medicines would not be procured due to budget deficit. Therefore, any act of funds misappropriation has a negative impact on the number of patients needing to access a particular health program.

If targeted strategies of controlling medicine expenditure can be properly applied through the concept of cost-containment, it would help Tonga Hospital to treat more patients with the same budget allocation. According to section 38 of Public Finance Management Act it is considered fruitless or wasteful expenditure when resources are not used efficiently, this includes medicines budget (1999). This means that cost-effectiveness should be incorporated into the design of any health care strategy for Tonga Hospital, which includes medicines procurement, storage, and supply.

1.1.1 Significance

This study sought to encourage review of the existing medicine formulary at Tonga Hospital whereby the NSAID that would be lowest in cost or deemed cost-effective would be preferred for inclusion in the reviewed hospital formulary. The NSAID with higher costs, and or fewer benefits, would be omitted in the new formulary. Emphasis was placed on the value for money in the face of limited financial resource. The ultimate goal would be to reduce costs associated with medicine expenditure.

1.1.2 The research problem

Ibuprofen, diclofenac, and aspirin belong to the same class of drugs called NSAIDs, but are used interchangeably at Tonga Hospital. This hospital does not have unlimited resources, which include medicine storage space, finance, and human resource capacity. If medicine storage space is not managed properly due to the stock volumes of one medicine item being excessively higher than necessary, that would lead to unavailability of other essential medicine items. If the limited hospital budget is used to finance similar medicine items that have same clinical outcomes, this would mean that there would be less funding available for other essential medicines. It would also require more staff members to manage the cumulative stock volumes of each of the NSAIDs, in this way it would mean more costs in the form of salaries. It is therefore of paramount importance that the contributing factors to high medicine expenditure in the hospital be kept in check, including avoiding duplication of medicine items in the hospital formulary. This study investigated the cost-effectiveness when Ibuprofen, Diclofenac, and Aspirin are used interchangeably by the same health care facility.

1.2 Literature Review

1.2.1 Economic burden of pain management and the benefit of budget rationalization

ñPain represents a major clinical, social and economic problem, with estimates of its prevalence ranging from 8 to over 60%. The impact of pain on economies is enormous, with the cost of back pain alone equivalent to more than a fifth of one country's total health expenditure and 1.5% of its annual gross domestic product, while in another, it represents three-times the total cost of all types of cancer. The burden that pain imposes on individuals and the enormous costs that society has to bear as a result clearly demonstrate the need for collective thinking in the decision-making process. A broad, strategic perspective ï based on evidence relating to effectiveness (including tolerability), efficiency and equity ï is required in determining issues relating to the provision of services and resource allocationò (Phillips, 2006).

In most settings, the model of acute pain treatment, with its emphasis on pharmacological therapy, is used for acute and chronic pain alike. Persistent chronic pain, however, often leads to complex social and psychological maladaptations, as well as substantial direct and indirect costs. Thus, the proper treatment of chronic pain usually involves pharmacological, behavioural and psychological interventions. Pain is a subjective sensation, but persistent chronic pain often results in long term neurophysiological and psychological changes that might be more appropriately considered disease manifestations. The costs and outcomes of various treatment strategies vary considerably and there is a need for comparative studies (Zagari *et al.,* 1996).

However, it should be noted that more does not necessarily mean better health care, and diverting additional resources into health care facilities and services will not automatically generate improvement in the health of the population. Up to 25% of all health care services provided may be unnecessary (Phillips 2008, Chapter1: 2-3).

In assessing the direct costs of pain management, it is conventional to categorize the components. For example, a German study estimated that the cost of back pain accounted to US$5 billion each year,

with 22 percent of costs accounted for by medication. It is essential that policy makers are fully aware of all aspects associated with the costs of pain and its management. One such example of this limited economic perspective in pain management is the iatrogenic costs associated with NSAIDs, which often result in costly side effects. These iatrogenic costs have been estimated at between US$58 and US$127 for each patient prescribed an NSAID in the UK. Estimates of the economic burden associated with pain fail to do justice to the extent of suffering and reduced quality of life experienced by patients and warrants pain relief being regarded as a universal human right (Phillips 2008, Chapter 6:77).

Pharmaceutical prescribing currently represents around 10 percent of total National Health Service in South Africa expenditure, and is one of the most inflationary elements of spending. Pharmaceuticals are one of the most commonly used and important interventions available to doctors in clinical practice, and their appropriate use can reduce mortality, morbidity and costs falling on other parts of the health care system. In other countries, particularly Australia and Canada, policies have been introduced to limit the introduction of new drugs to those which demonstrate cost-effectiveness. Evidence of effectiveness and cost-effectiveness, when it exists, is not always used. In the hospital sector, formularies and treatment protocols may encourage cost-effective prescribing, by limiting the use of certain medicines or outlining their appropriate use, although cost-effectiveness is not normally a major criterion in formulary or protocol development. Economic evaluation assesses the costs and consequences of alternative health care treatments and programmes; a drug therapy may be compared with an alternative, which may be another drug, surgery, or doing nothing (Maynard, *et al*. n.d).

Prioritisation and streamlining of strategic health programmes at facility level can have cumulative effect on cost-minimisation in the health system. For example, if a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain (National Collaborating Centre for Primary Care, 2009). Indeed, the facilities at district hospital levels must promote cheaper generic drugs to patients ï and help contain medical inflation (Bateman & Chris, 2014).

According to Bloor, *et al.* (1996) the assessments of ócost-effectivenessô consider more than just comparative costs. Therefore the most cost-effective therapy is not necessarily the cheapest; it depends on whether the additional health status gained from a more expensive therapy justifies the extra cost (cost-benefit analysis). Assessments of comparative costs are not restricted to the costs of the medicines themselves; they may also include the costs of drug administration and the costs of treating side-effects (Bloor, *et al.,* 1996).

1.2.2 Chemical classification of Ibuprofen, Diclofenac, and Aspirin

Ibuprofen, Diclofenac, and Aspirin belong to the same class of NSADs but each has a different chemical structure. That may account for their differences in NSAIDs safety and perhaps acquisition costs.

1.2.3 Pharmacokinetic properties

The following aspects will be analysed for superior pharmacokinetic properties of the NSAIDs under study: absorption, plasma proteins binding, half-life, and elimination.

1.2.3.1 Diclofenac

Oral absorption is rapid and near-complete when administered in the form of sugar-coated tablets, and slower when administered as enteric-coated tablets, particularly when taken together with food. At therapeutic concentrations, diclofenac is more than 99% bound to plasma proteins. Its terminal half-life in plasma is approximately 1-2 hours (Geller *et al.,* 2010). Diclofenac is predominantly eliminated via hepatic biotransformation with less than 1% of the dose being excreted unchanged via the kidneys (Kirchheiner *et al.,* 2003). And Bort *et al*. (1999) suggest that this reaction may be implicated in the hepatotoxicity of diclofenac.

1.2.3.2 Ibuprofen

The absorption of ibuprofen is rapid and complete when given orally (Davies & Neal, 1998). Ibuprofen is more strongly bound to normal plasma proteins (Davies & Neal, 1998). Like other

NSAIDs, ibuprofen is extensively metabolised in the liver (Pozzi *et al*., 2011). Ibuprofen is eliminated following biotransformation to glucuronide conjugate metabolites that are excreted in urine, with little of the drug being eliminated unchanged (Davies & Neal, 1998). Ibuprofen has a serum half-life of 1.8 to 2 hours (Bushra *et al*., 2010). Ibuprofen blocks both the COX-1 and the COX-2 enzymes, but has been shown to be safe and cost-effective with a highly effective analgesic and anti-inflammatory action in post-endodontic pain (Pozzi *et al*., 2011).

1.2.3.3 Aspirin

After oral administration as an aqueous solution aspirin is rapidly absorbed at the low pH of the stomach millieu. Less rapid absorption is observed with other formulations due to the rate limiting step of tablet disintegration - this latter factor being maximal in alkaline pH. The rate of aspirin absorption is dependent not only on the formulation but also on the rate of gastric emptying. Both aspirin and salicylic acid are bound to serum albumin (aspirin being capable of irreversibly acetylating many proteins), and both are distributed in the synovial cavity, central nervous system, and saliva. The serum half-life of aspirin is approximately 20 minutes. Salicylic acid is renally excreted in part unchanged and the rate of elimination is influenced by urinary pH, the presence of organic acids, and the urinary flow rate (Needs *et al*., 1985).

1.2.4 Pharmacodynamic properties of NSAIDs

The cyclo-oxygenase-1 (COX-1) and COX-2 enzymes produce prostaglandins following the metabolism of omega-6 polyunsaturated fatty acid (arachidonic acid). Prostaglandins are chemical messengers that mediate inflammation, fever and the sensation of pain (Day *et al*., 2013). NSAIDs exert their therapeutic characteristics by inhibiting the production of prostaglandins by means of cyclooxygenase inhibition, particularly isoenzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which have been shown to catalyse the formation of prostaglandins in the arachidonic acid pathway1, 2. COX-1 is normally found in platelets, vascular endothelial cells, the stomach and kidneys, where it is involved in the production of prostaglandins that are responsible for the protection of the stomach wall (PGE2), platelet aggregation (TXA2) and kidney function (Geller *et al*., 2010).

The ratio of inhibition of COX-1 to COX-2 by NSAIDs determines the likelihood of adverse effects (Cashman, 1996). The beneficial actions of nonsteroidal anti-inflammatory drugs (NSAIDs) have been linked to their ability to inhibit inducible COX-2 at sites of inflammation, and their side effects (e.g., gastric damage) to inhibition of constitutive COX-1 (Warner *et al.* 2004). Ibuprofen inhibits almost completely COX-1 activity after single and repeated intake whereas COX-2 inhibition average 80% at corresponding times. Diclofenac reduced COX-1 activity by about 70% and COX-2 by about 96% whatever treatment duration (Blain *et al*., 2002).

Low-dose aspirin (Ò100 mg daily) irreversibly inhibits platelet COX-1 activity by acetylating the serine-529 residue, resulting in > 95% inhibition of thromboxane A_2 (TXA_2) production and thus inhibition of TXA_2-mediated platelet aggregation throughout the 24-hour dosing interval. Once COX-1 has been acetylated by aspirin, the substrate cannot gain access to the catalytic site of the enzyme for the lifetime of the platelet, so that upon aspirin withdrawal, restoration of TXA_2 biosynthesis is a linear function of platelet turnover (Baigent *et al*., 2003). This unique action probably explains why aspirin is so efficient in preventing arterial thrombotic events; randomized trials indicate that low-dose aspirin reduces the risk of vascular events (myocardial infarction, stroke, or vascular death) by approximately one-fourth in a wide range of high-risk patients (Baigent *et al*.). Aspirin also inhibits COX-1 in the gastric and duodenal mucosa, as a function of the dose level and dosing interval, resulting in a reduction in PGE_2-mediated cytoprotection against the acid milieu (Baigent *et al*., 2003).

Non-selective NSAIDs were associated with similar increased risks of serious gastrointestinal events, and all but naproxen were associated with similar increased risk of serious cardiovascular events, but the partially selective NSAID, nabumetone was gastroprotective compared with nonselective NSAIDs (Peterson *et al*., 2006). COX-2 selective NSAIDs significantly reduced symptomatic ulcers compared with placebo (RR 0.41, 95% CI: 0.3, 0.7). COX-2 specific NSAIDs appeared to significantly reduce serious gastrointestinal complications (RR 0.55, 95% CI: 0.4, 0.8) and symptomatic ulcers (RR 0.49, 95% CI: 0.4, 0.6) (Hooper *et al*., 2004).

1.2.4.1 Cardiovascular Risk

Short-term and long-term use of NSAIDs is associated with increased cardiovascular risk (Olsen *et al.*, 2011). Listing of NSAIDs on national EMLs should take account of cardiovascular risk, with preference given to low risk drugs (McGettigan *et al*., 2013). NSAIDs rated by relative risk for cardiovascular events (in ascending order): Naproxen < Celecoxib < Piroxicam < Ibuprofen < Meloxicam < Indomethacin < Diclofenac < Rofecoxib (at doses more than 25 mg). Diclofenac has a risk very similar to rofecoxib, which was withdrawn from worldwide markets owing to cardiovascular toxicity. Diclofenac should be removed from EMLs (ibid). Extensive use of diclofenac, similarly to rofecoxib and celecoxib, substantially increases the risk of acute myocardial infarction. There is little suggestion of such an effect in users of ibuprofen (Jick *et al.,* 2007). Aspirin reduces the risk of first Myocardial Infarction. The benefits of long-term aspirin therapy are likely to outweigh any risks (Eidelman *et al.,* 2003). Cardiovascular risk needs to be taken into consideration when prescribing any non-steroidal anti-inflammatory drug (Trelle *et al*., 2011).

1.2.4.2 Gastrointestinal risks

Although effective in the treatment of pain associated with rheumatic conditions such as osteoarthritis and rheumatoid arthritis, long-term use of NSAIDs is primarily limited by their association with upper gastrointestinal (GI) toxicity. Adverse effects range from dyspepsia and abdominal pain to ulceration and bleeding. GI damage elicited by NSAIDs arises as the result of biochemically induced topical irritant effects and by topical and systemic pharmacological suppression of gastroprotective prostaglandins. Variation in the physicochemical properties and pharmacological profiles among the individual NSAIDs translate into inter-agent differences regarding propensity to cause adverse GI effects (Bannwarth *et al*., 2008). A study conducted by Castellsague *et al*. (2013) found that the relative risk with regards to gastrointestinal risk of ibuprofen and diclofenac was 2 to <5. Levy *et al*. (1974) also alluded to the fact that Ibuprofen has the lowest gastrointestinal risk among NSAIDs, while diclofenac has intermediate risks.

In a systemic review Henry *et al.* (1996) found that the use of low risk drugs such as ibuprofen in low dosage as first line treatment would substantially reduce the morbidity and mortality due to serious gastrointestinal toxicity from these drugs. According to Lugardon *et al.* (2004) the reported risk of gastrointestinal events was low among patients treated with ibuprofen, compared with diclofenac and other NSAIDs. Lower rates of occurrence of GI complications in patients treated with ibuprofen could be attributed to its short half-life, about 2 hours (Pozzi *et al.*, 2011).

According to Day *et al.* (2013) the risk factors for gastrointestinal adverse effects associated with NSAID use include:

- Age over 65 years
- Previous adverse reaction to NSAIDs
- The use of other medicines that may exacerbate any gastrointestinal adverse effects, e.g. anticoagulants, selective serotonin reuptake inhibitors (SSRIs) and corticosteroids
- Liver disease
- Chronic kidney disease (CKD)
- Smoking

1.2.4.3 Hepatotoxicity during NSAID treatment

NSAIDs have been associated with idiosyncratic hepatotoxicity in susceptible patients (Boelsterli *et al.*, 2002). The percentage of patients with liver toxicity during NSAID treatment is very low during treatment with ibuprofen versus diclofenac (Pozzi *et al.*, 2011).

1.2.4.4 Nephrotoxicity during NSAID treatment

The use of NSAIDs is associated with risk of acute kidney injury (AKI). In a study conducted by Lafrance *et al.* (2009), it was demonstrated that the risk of AKI may vary among different NSAIDs with risk generally increasing with decrease in selectivity, for example it was found that diclofenac is more selective than ibuprofen. In this way, diclofenac may be a little safer to the kidney when compared with Ibuprofen.

1.2.4.5 NSAIDs use and hypersensitivity

NSAIDs hypersensitivity is characterised by symptoms ranging in speed of onset from anaphylaxis and bronchospasm to delayed skin and systemic reactions occurring over weeks (Kowalski *et al*., 2011). The reaction is due to COX-1 inhibition and is not mediated by IgE, therefore it is not a true allergy (Kowalski *et al*.). Aspirin may trigger respiratory reactions known as Aspirin-Exacerbated Respiratory Disease (Lee *et al.*, 2011). People with asthma are at a higher risk for experiencing serious allergic reaction (Lee *et al*).

1.2.4.6 NSAIDs and Pregnancy

The significant association between diclofenac and ibuprofen use late in pregnancy, and maternal bleeding and asthma in the child, respectively, is consistent with their pharmacological effects (Nezvalová *et al.*, 2013). Ibuprofen does not seem to increase global malformation risk but NSAID use in late pregnancy remains a concern (Damase-Michel *et al.*, 2014). The current literature suggests that the use of low-dose aspirin during pregnancy is safe with regard to congenital anomalies and fetal, neonatal, and maternal cardiovascular physiologic state and haemostasis (Dekker *et al.*, 1993).

1.2.4.7 Common non-communicable Conditions that can be managed with NSAIDs

There is no cure for inflammatory arthritis at present, so the treatments aim to relieve pain and stiffness and improve your ability to move. NSAIDs such as aspirin, ibuprofen, diclofenac and cyclo-oxygenase-2 inhibitors or COX-2s (for example celecoxib), are used to decrease pain and swelling (Colebatch *et al*., 2011).

NSAIDs are indicated for the symptomatic treatment of the following conditions (Standard Treatment Guidelines and Essential Drugs List, 2012):

- Rheumatoid arthritis. NSAIDs are particularly useful in the inflammatory forms of arthritis (such as rheumatoid arthritis) and, sometimes, in the more severe forms of osteoarthritis.
- Osteoarthritis

- Acute gout
- Inflammatory arthropathies: ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome
- Dysmenorrhoea (painful menstruation), menstrual cramps
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Back pain and sciatica
- Sports injuries, sprains, and strains
- Dental pain
- Pain from kidney stones (renal colic)
- Reduction of fever
- Prevention of blood clotting (Aspirin only)

1.3 The purpose of the study

The purpose of the study was to determine whether the use of oral NSAIDs interchangeably in the management of pain in adult patients at Tonga Hospital is cost-effective. The results of the study would be used by the Hospital Pharmacy and Therapeutics Committee (HPTC) and Hospital Management to inform their decision-making when designing hospital medicines formulary.

1.4 The objectives of the study

This retrospective study investigated the cost-effectiveness of oral NSAIDs when used in the management of pain in adult patients at Tonga Hospital.

The study was designed:

- To determine whether interchangeable use of each of the oral NSAIDs under study in the management of pain in adult patients at Tonga Hospital is cost-effective.
- To identify prescriber patterns or preferences between each of the oral NSAIDs under study in the management of pain in adult patients at Tonga Hospital

1.5 The research questions

- What is the average acquisition cost of each of the oral NSAIDs under study at Tonga Hospital?
- What is the average stock volume of each of the oral NSAIDs under study in regards to storage space requirements at Tonga Hospital?
- What are patterns of prescribing each of the oral NSAIDs under study when used in the management of pain in adult patients at Tonga Hospital?

CHAPTER 2: A SUBMITTED MANUSCRIPT – "At Small District Hospitals it is Cheaper to Use Ibuprofen Instead of Diclofenac for Oral Management of Inflammatory Conditions in Adults"

At Small District Hospitals it is Cheaper to Use Ibuprofen Instead of Diclofenac for Oral Management of Inflammatory Conditions in Adults

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Declaration: This manuscript has not been published and is not under consideration in the same or in substantially similar form in any other journal. All those listed as authors are qualified for authorship, and all who qualify to be authors are listed as authors. All listed authors have read and approved the final manuscript. To the best of the authorsô knowledge there is no conflict of interest, whether financial or others, exists. Funds to conduct the study were received from the University of KwaZulu-Natal.

ABSTRACT

Background: Ibuprofen, diclofenac and aspirin belong to the same class of drugs called NSAIDs, but are used interchangeably at Tonga Hospital. The problem with this approach of NSAIDs use is that it may present with preventable misguided and increased spending on pharmaceuticals.

Aim: To investigate the pharmacoeconomic implications of interchangeable use of oral NSAIDs for pain management at a district hospital.

Methods: This descriptive retrospective study used existing patient records as well as medicine stock control records to investigate the cost-effectiveness of oral NSAIDs when used interchangeably in the management of pain and inflammatory conditions in adult patients at a district hospital.

Results: A total of 211 (104 in 2013 and 107 in 2014) patients were included in this study. The mean age of participants in 2013 and 2014 was (36 ± 1,48) and (35 ± 1,49) years respectively and there were more females than males. Most patients who presented at Tonga Hospital for pain management were suffering from minor bodily/joint pains (36.0%, n=76), whereas the least patients were suffering from bone fractures (10.9%, n=23). Our study found that most patients (31.3%; n=66) who were treated with ibuprofen were suffering from minor bodily/joint pains. The acquisition cost of ibuprofen when calculated as mean-price-per-tablet during 2013 to 2014 was consistently lower, with an average price of (0.285 ZAR) when compared with diclofenac (0.995 ZAR). The mean cost per defined daily dose (DDD) was consistently lower for ibuprofen in both 2013 (0.84 ZAR) and 2014 (0.87 ZAR) when compared with diclofenac in 2013 (2.94 ZAR) and 2014 (3.03 ZAR).

Conclusion: The sensitivity analysis points in favour of ibuprofen over diclofenac as indicated when increasing or decreasing the mean price per tablet by 50% of either ibuprofen or diclofenac. Therefore, the use of ibuprofen oral tablets in the management of pain at a district hospital is cost-effective when compared with diclofenac oral tablets.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) play a vital role in the management of acute and chronic pain. The NSAIDs such as ibuprofen, diclofenac, and aspirin exert their therapeutic actions by inhibiting cyclooxygenase-1 and cyclooxygenase-2 (Geller *et al.,* 2010). These drugs are used interchangeably at the Tonga Hospital because they belong to the same class of drugs used for the management of pain. However, the differences in terms of the costs of each of these medications often present many pharmacoeconomic implications for the health care professional and for the government.

It cannot be disputed, however, that management of pain and inflammation represents a major clinical, social and economic burden globally (Phillips, 2006). The costs and outcomes of various treatment strategies vary considerably and there is always a need for comparative studies (Zagari *et al.* 1996). Also, frequent use of NSAIDs is associated with ñiatrogenic costsò, which often result from costly side effects (Phillips, 2008). Also, the chronic use of NSAIDs is associated with serious risks that may at times warrant hospitalization, for example, Rainsford & Velo indicated that hospitalizations as a result of renal impairment occur more frequently among NSAID users than would be expected among non-users in the same age-sex group (Rainsford & Velo 2012:373). However, not all NSAIDs are the same, as reported by Levy & Micha that ñibuprofen has the lowest gastrointestinal risk among NSAIDs, while diclofenac has intermediate risksò (Levy & Micha, 1974). Therefore, many patients who present with pain at a hospital may also be having other chronic conditions such as hypertension, retroviral disease, diabetes mellitus, etc. For example, some patients who are on anti-retro viral (ARVs) drugs may not benefit from NSAIDs use due to drug-drug interaction. For example, Morelle and colleagues found that diclofenac interfered with tenofovir clearance, thereby favouring its nephrotoxicity. It is therefore suggested that NSAIDs should be avoided in patients receiving tenofovir (Morelle *et al.,* 2009). In the public hospital settings, regular drug-utilisation reviews and consistent use of formularies and treatment protocols may enhance rational prescribing, and may decrease cost and prevalence of adverse reactions caused by chronic

plus inappropriate use of NSAIDs (Holloway & Green, 2003:2). Therefore, in this short communication, we report on cost-effectiveness of interchangeable use of oral NSAIDs in the management of pain, in adult patients, at the Tonga Hospital, Mpumalanga Province, South Africa.

RESEARCH METHODS AND STUDY DESIGN

This was a quantitative retrospective study using patient records as well as medicine stock control cards at a district hospital. Patientsô records were searched for past information with regards to the patterns of oral NSAIDs use in the management of pain in adult patients at Tonga Hospital. Medicine stock-control records were also searched for past information in regards to oral NSAIDs procurement practices and storage requirements in the hospital. Patients medical records included in this study were for patients who were 15 years and older, and who were treated with any oral NSAIDs for acute or chronic inflammatory conditions such as musculoskeletal pain, osteoarthritis, dental pain, low back pain and soft tissue injuries among others. Stock control and procurement records were included if they indicated 6 month old data of stock volumes and prices of each of the oral NSAIDS under study. Stock control and procurement records of other medicine items other than oral NSAIDs did not form part of this study. A pilot study was conducted whereby data were collected from 6 patient files that had any of the oral NSAIDs under study been prescribed within the last six months of 2013 and 2014. The purpose of the pilot study was to gain some background information on the patterns of each of the oral NSAIDs usage at Tonga Hospital, and to test the appropriateness of the proposed Data Collecting Instrument (DCI). The DCI for procurement and stock volumes was also tested for appropriateness by collecting a one month data.

Ibuprofen and diclofenac use and the costs thereof in the hospital was assessed by making use of the ñDefined Daily Doseò (DDD) as defined by WHO collaborating centre for drug statistics. The DDDôs of 1200mg and 150mg were used for ibuprofen and diclofenac respectively. A conversion of DDD for diclofenac was applied in cases whose DDD for diclofenac was 100mg, to align it to a diclofenacôs DDD of 150mg. A sensitivity analysis was performed on the cost of each of the oral NSAIDs in order

to determine what would happen if the stock volumes (quantities or stock levels) of each drug under study would be increased or decreased. The impact of increased or decreased cost on the quantities of each drug under study was also assessed. Where applicable, SPSS statistical package was used to assess statistical significance and unless indicated the results are presented as means with standard error of the mean (SEM).

The study received full ethical clearance from the UKZN Research Ethics Committee (BREC REF: BE444/14) and from the Mpumalanga Provincial Department of Health Research and Ethics Committee (PHREC REF: MP_2014RP10_721).

RESULTS AND DISCUSSION

NSAIDs usage by conditions

The records of two hundred and eleven (104 in 2013 and 107 in 2014) patients were included in this study. The mean ages of all the patients who participated in our study in 2013 and 2014 was (36 ± 1,48) and (35 ± 1,49) years respectively and there were more females than males. When the ages in 2013 and 2014 were combined, the mean ages of males versus females were similar at 35.9 and 35.8 years respectively and were representative of the general patient population at the Tonga Hospital. Most patients who presented at Tonga Hospital for pain management were suffering from minor bodily/joint pains (36.0%, n=76), whereas the least patients were suffering from bone fractures (10.9%, n=23). Our results, with regards to the prevalence of minor bodily/joint pains are in line with Edward and colleaguesô findings, who reported that joint pain is a common reason for consultation in a general practice (Edward *et al*., 2012).

Most patients (31.3%; n=66) who were treated with ibuprofen were suffering from minor bodily/joint pains, whereas the least patients (1.4%; n=3) who were treated with diclofenac were suffering from inflammatory conditions (Figure 1). These results support population studies and World Health Organisation (WHO) statistics which indicate that 10ï 50% of individuals suffer from musculoskeletal disorders (Kean *et al.* 2005). And there were significantly ($p < 0.05$) more females were using NSAIDs (both ibuprofen and diclofenac) than males at in Tonga Hospital. And patients who were 19-35 years were the most patients (28.4%, n=60) who were treated with ibuprofen when compared with patients 18 years and below (9.5%, n=20).

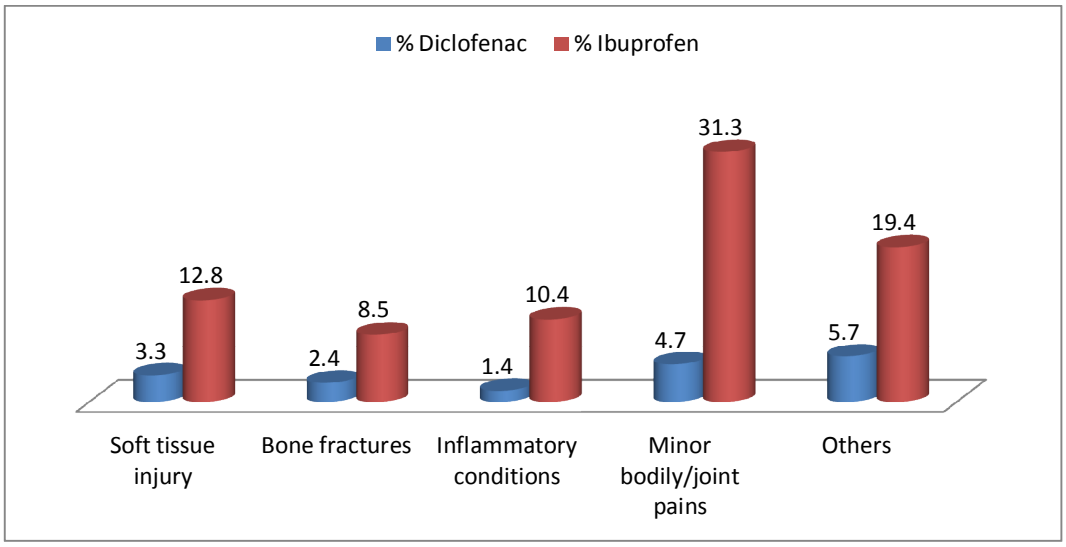

Figure 1: Various inflammatory conditions treated with NSAIDs in 2013 and 2014.

NSAID stock volumes issued

The highest total NSAID stock volumes issued from July to December of 2013 and 2014 combined was ibuprofen (36978) when compared with diclofenac (11127). The stock volumes for both ibuprofen and diclofenac were higher in July, with 8170 for Ibuprofen and 2099 for diclofenac. Diclofenac stock volumes fell to their lowest (1583) in September, whereas Ibuprofen stock volumes fell to their lowest (4478) in December. The fall in stock volumes issued might be attributable to many factors including but not limited to non-delivery by the supplier, non-ordering by the pharmacy staff. In all instances ibuprofen stock volumes issued were higher than that of diclofenac. The demand for both ibuprofen and diclofenac might have been driven more by prescriber preferences and to a lesser extent by the patients themselves when interacting with medical officers in the consulting rooms. However, these results show that the demand for ibuprofen had been consistently higher than that of diclofenac. These findings support the study by Skúladóttir *et al*. (2010), who reported that in countries like Iceland, Denmark, Norway, and Sweden the sales volumes of ibuprofen were higher than that of diclofenac when the sales were measured as defined daily doses/1000 inhabitants/day. It means that the results of this study are in keeping with the results of studies from other countries.

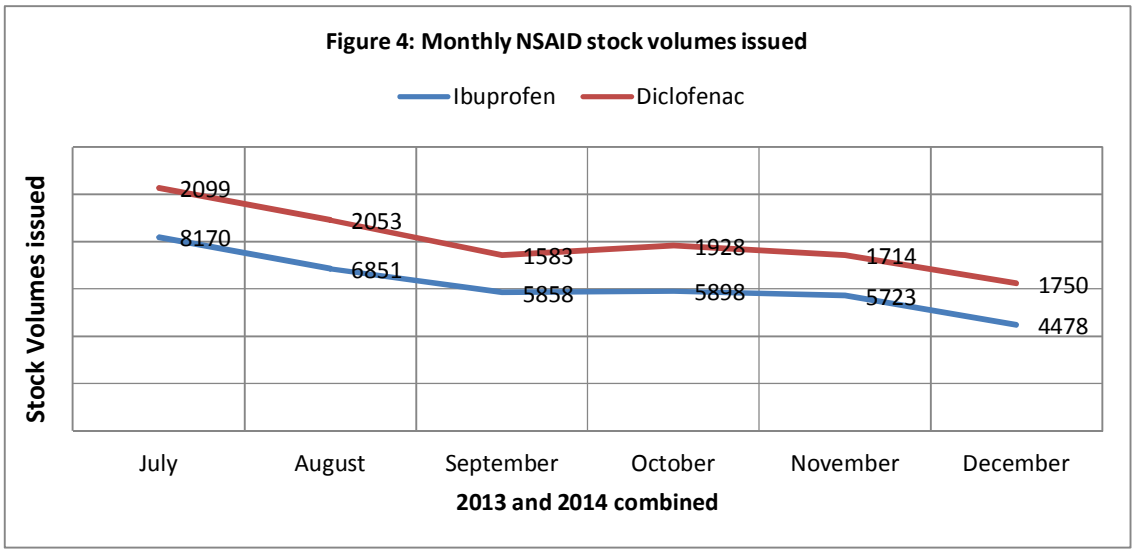

Figure 2: The patterns of stock volumes ibuprofen and diclofenac dispensed during 2013 and 2014 at the Tonga Hospital.

Acquisition costs of NSAIDs (in ZAR) and Utilisation Patterns

The acquisition cost of ibuprofen when calculated as mean price per tablet during 2013 to 2014 was consistently lower, with an average price of (0.285 ZAR) when compared with diclofenac (0.995 ZAR). The difference in the price structure of these NSAIDs is about 27.6%, making diclofenac the most expensive NSAID at Tonga Hospital. The average price increase of ibuprofen year on year is about 5.25% whereas that of diclofenac is about 8.96%. According to Smith (2000), ibuprofen is cheaper than diclofenac, in the same way the results of our study are in keeping with findings of other studies.

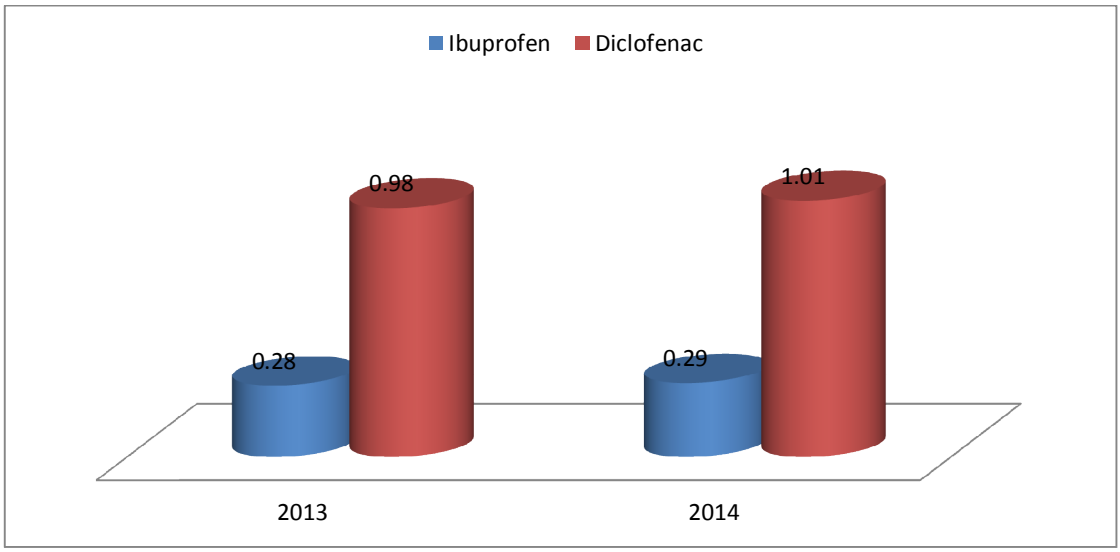

Figure 3: The difference in the acquisition costs between ibuprofen and diclofenac in 2013 and 2014

Only 0.3% of the population of Nkomazi east on average received ibuprofen treatment daily, whereas 0.01% of the population diclofenac daily. Therefore, the population of Nkomazi east utilises more ibuprofen tablets than it does to diclofenac tablets. In contrast to the findings of this study with regards to NSAIDs utilization, Marius *et al.* (2007) found that despite its cardiovascular toxicity diclofenac (19.26 DDDs/1000 inhabitants/day) was the most commonly used NSAID when compared with ibuprofen (4.421 DDDs/1000 inhabitants/day) . It is apparent that the reason for the high usage of diclofenac (2.42/DDD, ZAR) was that it was the cheapest when compared with ibuprofen (5.06/DDD, ZAR), (Marius *et al.,* 2007).

The mean cost per defined daily dose was consistently lower for ibuprofen in both 2013 (0.84 ZAR) and 2014 (0.87 ZAR) when compared with diclofenac in 2013 (2.94 ZAR) and 2014 (3.03 ZAR). The frequency of prescriptions was higher for ibuprofen in 2013 (85.6%) and 2014 (79.4%) when compared with diclofenac in 2013 (14.4%) and 2014 (20.6%). Prescribers were consistently engaging in rational prescribing and were probably conscious of cost-effectiveness when prescribing more ibuprofen over diclofenac. The issue of acquisition costs, as shown in Table 1, has influence in the usage of NSAIDs in other countries as demonstrated by Vukuğić *et al.* (2005) that diclofenac (2.40/DDD, ZAR) is cheaper than ibuprofen (3.31/DDD, ZAR).

Type of NSAID	**2013**			**2014**		
	Defined Daily Dose (DDD)	Mean Price in Rands (R)	Frequency of Prescription	Defined Daily Dose (DDD)	Mean Price in Rands (R)	Frequency of Prescription
Ibuprofen	400mg T.D.S	0,28 x 3 = **0,84**	85,6% (89)	400mg T.D.S	0,29 x 3 = **0,87**	79,4% (85)
Diclofenac	50mg T.D.	0,98 x 3 = **2,94**	14,4% (15)	50mg T.D.S	1,01 x 3 = **3,03**	20,6% (22)

Table 1: The sensitivity analysis of mean cost/DDD showing the mean cost per DDD of ibuprofen and diclofenac.

The sensitivity analysis, as shown in Table 2, points in favour of ibuprofen over diclofenac as indicated when increasing or decreasing the mean price per tablet by 50% of either ibuprofen or diclofenac. Ibuprofen was less expensive when compared with diclofenac.

	2013		**2014**	
	Variable(S)	**Mean Cost/ DDD (R)**	**Variable(S)**	**Mean Cost/ DDD (R)**
Increasing the mean cost/DDD of Ibuprofen	50% (R0,42)	1,26	50% (R0,44)	1,31
Decreasing the mean cost/DDD of Ibuprofen	50% (R0,42)	0,42	50% (R0,44)	0,44
Increasing the mean cost/DDD of Diclofenac	50% (R1,47)	4,41	50% (R1,52)	4,55
Decreasing the mean cost/DDD of Diclofenac	50% (R1,47)	1,47	50% (R1,52)	1,52

Table 2: The sensitivity analysis showing the impact on the price change when sensitivity analysis is used.

CONCLUSION

This study found that the use of ibuprofen oral tablets in the management of pain at a district hospital is cost-effective when compared with diclofenac oral tablets. Interchangeable use of oral NSAIDs for pain management at a district hospital may result in pharmacoeconomic implications. The acquisition costs of NSAIDs in relation to the mean price per pack of oral tablets had been consistently higher for diclofenac than they were for ibuprofen in Tonga Hospital. There is a need to exclude diclofenac from the current medicine formulary in order to realise some return on the investment to pain management in the hospital.

LIMITATIONS OF THE STUDY

The study had a few limitations; firstly it was conducted in one district hospital which may limit the generalizability of the findings to other hospital settings. Secondly, this study did not look at the cost of hospitalization due to NSAIDs side effects which could have given it a comprehensive picture of the impact associated with regular use of NSAIDs.

AUTHORS' CONTRIBUTION

MJN conceived and participated in the design of the study. He also carried out collection, performed the statistical analysis, interpretation of the results and drafted the manuscript. LJM helped with the study design, analysis and interpretation of the results and also performed substantial corrections of the draft manuscripts.

ACKNOWLEDGEMENTS

Authors would like to thank the Mpumalanga Department of Health for affording me permission to conduct this study in one of their district hospitals called Tonga Hospital. My gratitude also extends to the Tonga Hospital management particularly the hospital CEO Mr. J.S Aphane for allowing me to conduct this study in his facility.

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CHAPTER 3: SYNTHESIS & GENERAL DISCUSSION

Introduction

The objectives of the study were to determine whether the use of ibuprofen instead of diclofenac for oral management of pain in adults at small district hospitals is cost-effective. I also identified prescriber patterns or preferences between ibuprofen and diclofenac oral tablets using existing records. Injudicious use of oral NSAIDs for pain management may result in both health risk and pharmacoeconomic implications. Risks associated with NSAIDs use range from gastrointestinal, cardiovascular, nephrotoxicity, hepatotoxicity, to drug-drug interactions, and so on. The negative pharmacoeconomic implications may arise in the form of costs as a result of hospitalisation due to NSAIDs associated risk, as well as NSAIDs escalating market price and poor NSAID procurement practices.

The Central Theme of this Dissertation

The central theme, and a message running through the entire dissertation, is the cost-effectiveness of NSAIDs use in the management of pain at a small district hospital. We investigated retrospectively the comparison of cost-effective use of ibuprofen and diclofenac oral tablets by going through patientsô records to determine the most prescribed NSAID, as well as NSAIDs acquisition cost. Main attention was paid to the question of whether the use of ibuprofen instead of diclofenac for oral management of inflammatory conditions in adults at small district hospitals is cost-effective, since these two NSAIDs are used interchangeably in this hospital. Some prescribers would prefer to use ibuprofen instead of diclofenac and vice versa without the consideration of cost-effectiveness aspect of these NSAIDs. In our dissertation we proved that the use of ibuprofen oral tablets in the management of pain at a district hospital is cost-effective when compared with diclofenac oral tablets. Ibuprofen was found to be cost-effective in many respects, including its acquisition costs, mean price per defined daily dose, cardiovascular risk, gastrointestinal risk, and hepatotoxicity. This study, therefore, helped to identify and highlight what needed to be done to attain good clinical cost-effective practice at the Tonga Hospital, and similar district hospitals.

Limitations of this Study

- Our study was limited to a small sample size because a convenience sampling technique was used to collect data; therefore if patientsô files were not forthcoming it meant that the sample size could not be increased.
- Our findings may not be applicable to private health care settings or to large hospitals.
- Since pharmacoeconomics is a young science, there are not many published studies that could have been used to support or dispute aurguments in this study. This view is shared by other pharmacoeconomic studies such as the ones conducted by Wynne *et al.* (1993) which pointed out that ó*there are only limited available data on the cost-effectiveness of NSAIDs, despite their wide use*ôô as well as Ahmad *et al*. (2013) which emphasized that ó*the development of pharmacoeconomics is at an infancy stage at the moment*ôô.

Recommendations

Based on our findings, it is recommended that:

1. The PTC at Tonga Hospital should remove diclofenac from the Essential Medicines List, because it is expensive and also not the safest when compared with ibuprofen. Pharmacy must assess the eligibility of patients for NSAIDs especially those who have other comorbidities and are taking other drugs.

This is necessary in order to avoid harmful drug-drug interactions such as enhanced nephrotoxicity which is experienced by those who are on ARVôs who are also taking NSAIDs for pain management. Under the current economic outlook in the country, savings that would result from implementing the recommendation of this study could be most welcome as part of cost-minimization strategies.

2. This study attempted to address the many aspects of whether ibuprofen is cost-effective when compared with diclofenac oral tablets. However, further research would be required to

determine the extent of economic impact by which NSAIDs risks cause as a result of their acute or chronic use.

Conclusion

Many studies have demonstrated that ibuprofen and diclofenac oral tablets have comparable efficacy, but differ in their safety and cost profiles. For example, ibuprofen had been found to be relatively cardiac safe with significant lower acquisition costs. Hawkey *et al*. (2000) confirms that switching patients to ibuprofen may be a realistic way of reducing financial and medical costs associated with NSAIDs. Therefore, Ibuprofen may be considered a favourable NSAID for inclusion in a district hospital formulary.

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APPENDICES

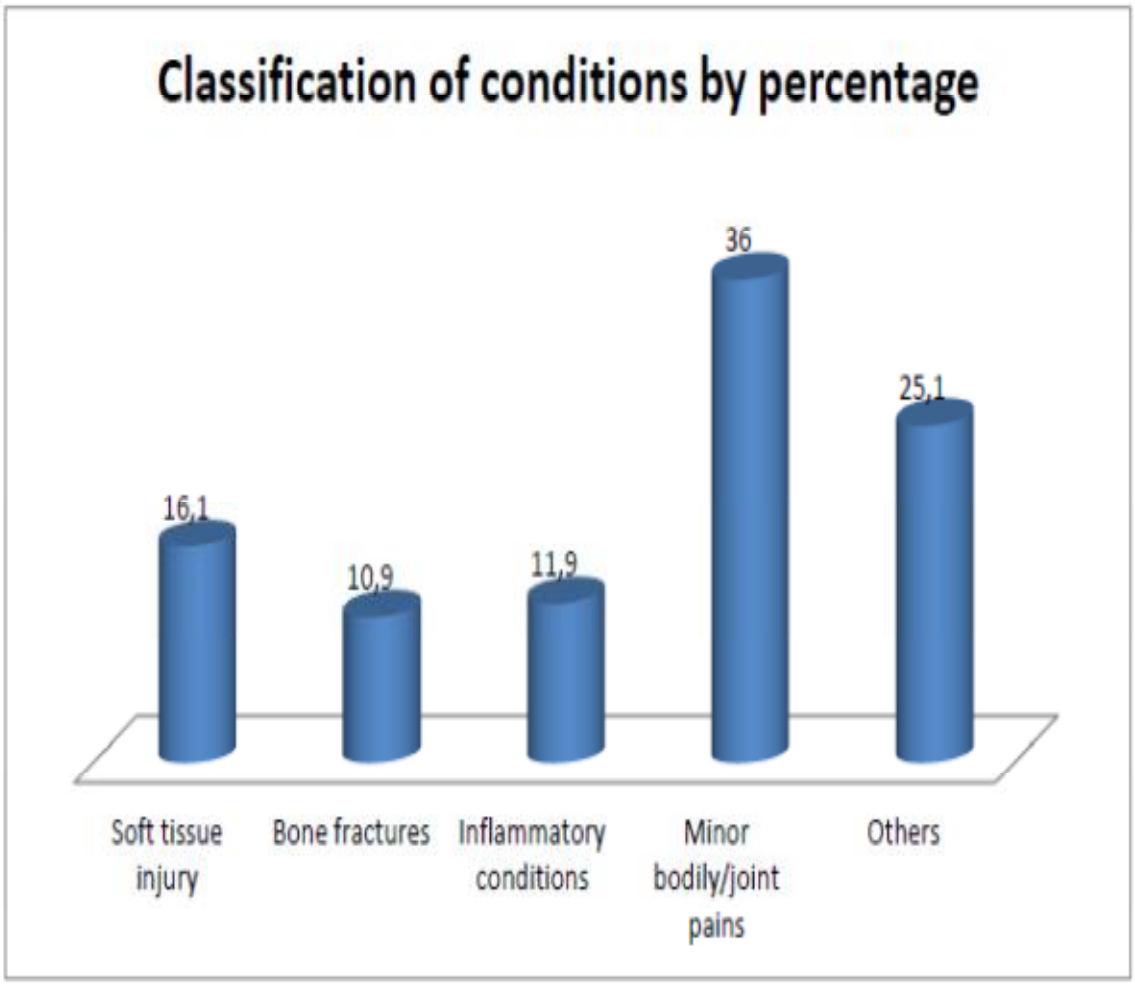
APPENDIX A – DATA COLLECTION INSTRUMENT (Patient records)

Entry number	Ref. Number	Age	Gender [M/F]	Ibuprofen / Diclofenac	Number of Scripts	Indication

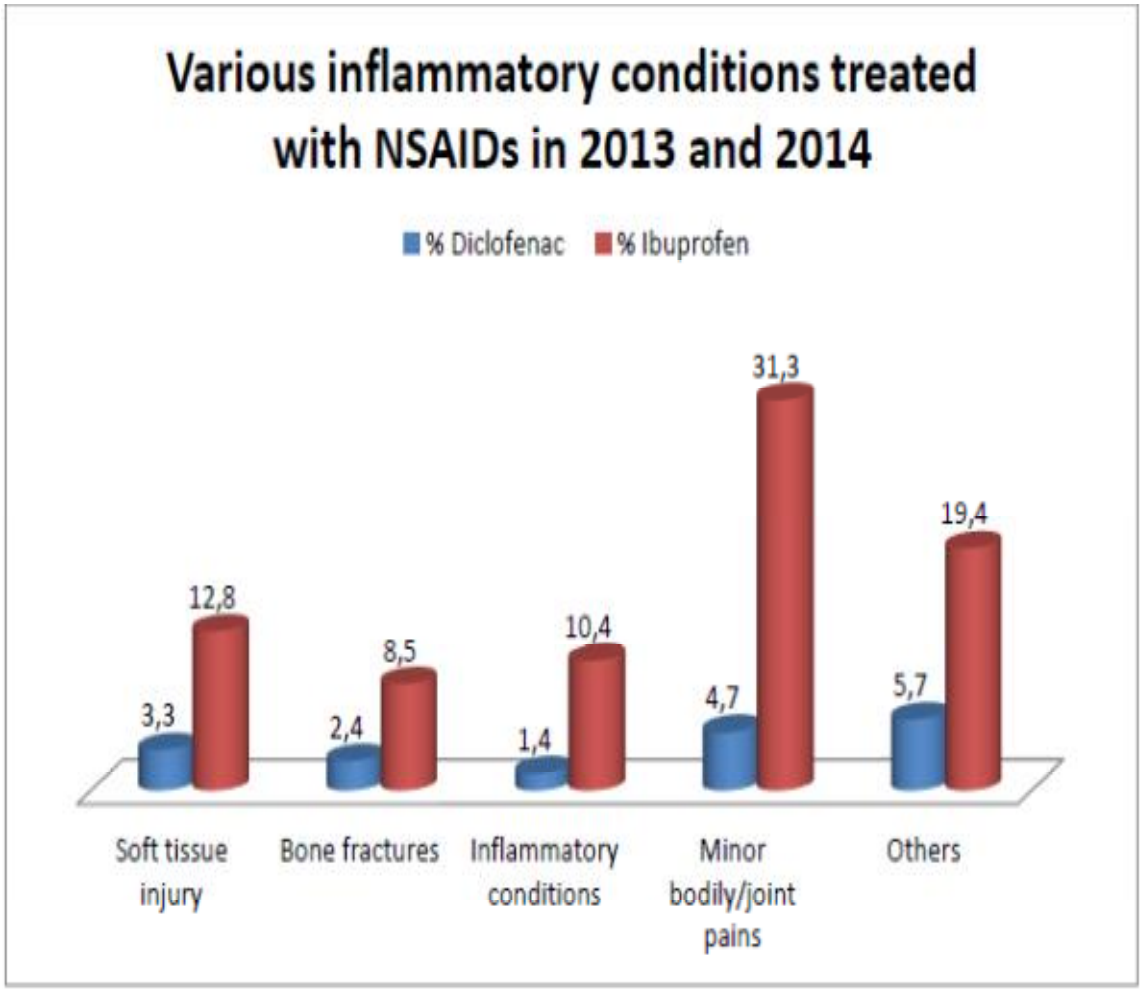
APPENDIX B – DATA COLLECTION INSTRUMENT (Procurement & Stock volumes)

MONTH NUMBER	AQUISITION COST (IN RANDS)		STOCK VOLUMES	
	Ibuprofen 400mg 28ôs	Diclofenac 50mg 21ôs	Ibuprofen 400mg 28ôs	Diclofenac 50mg 21ôs
1				
2				
3				
4				
5				
6				
MEAN				

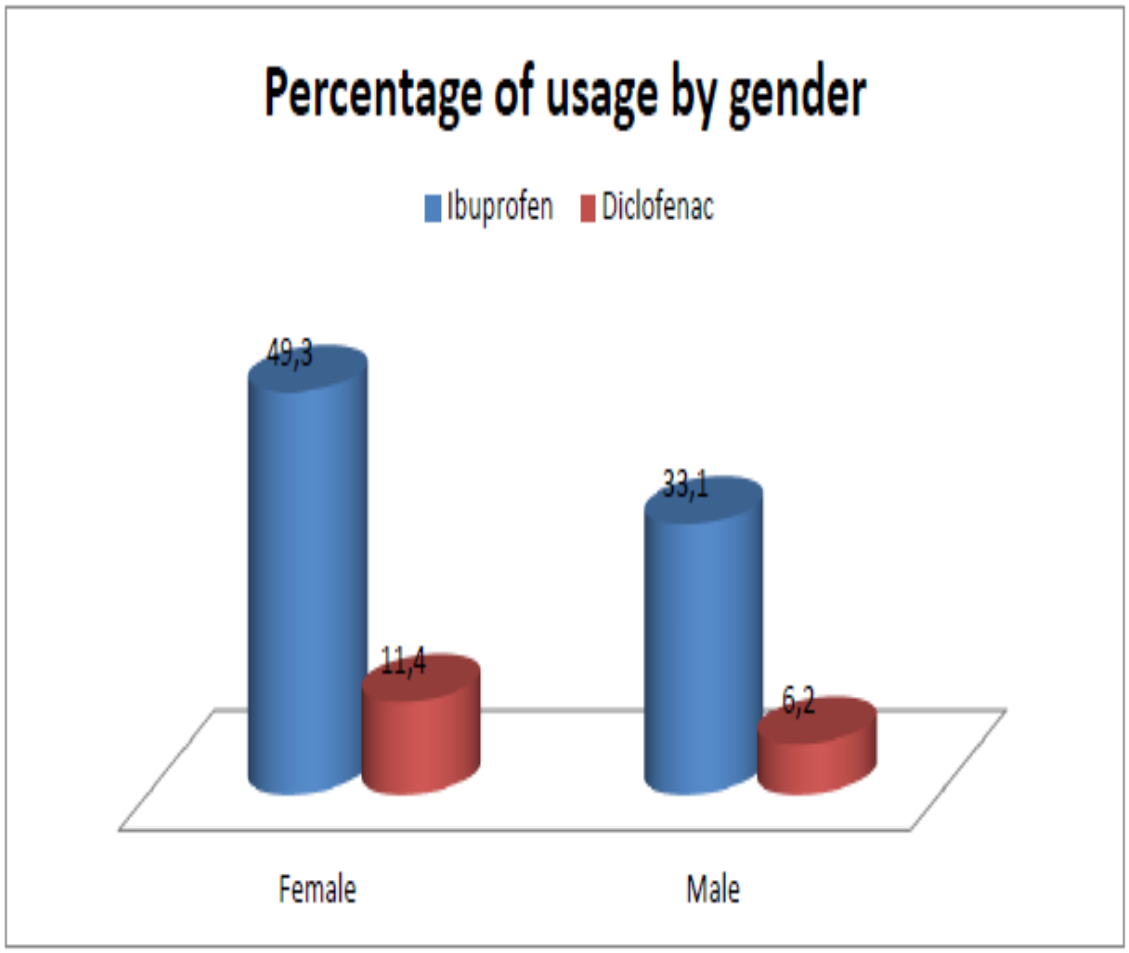
APPENDIX C


Classification of conditions by percentage
16,1
10,9
11,9
36
25,1
Soft tissue injury
Bone fractures
Inflammatory conditions
Minor bodily/joint pains
Others

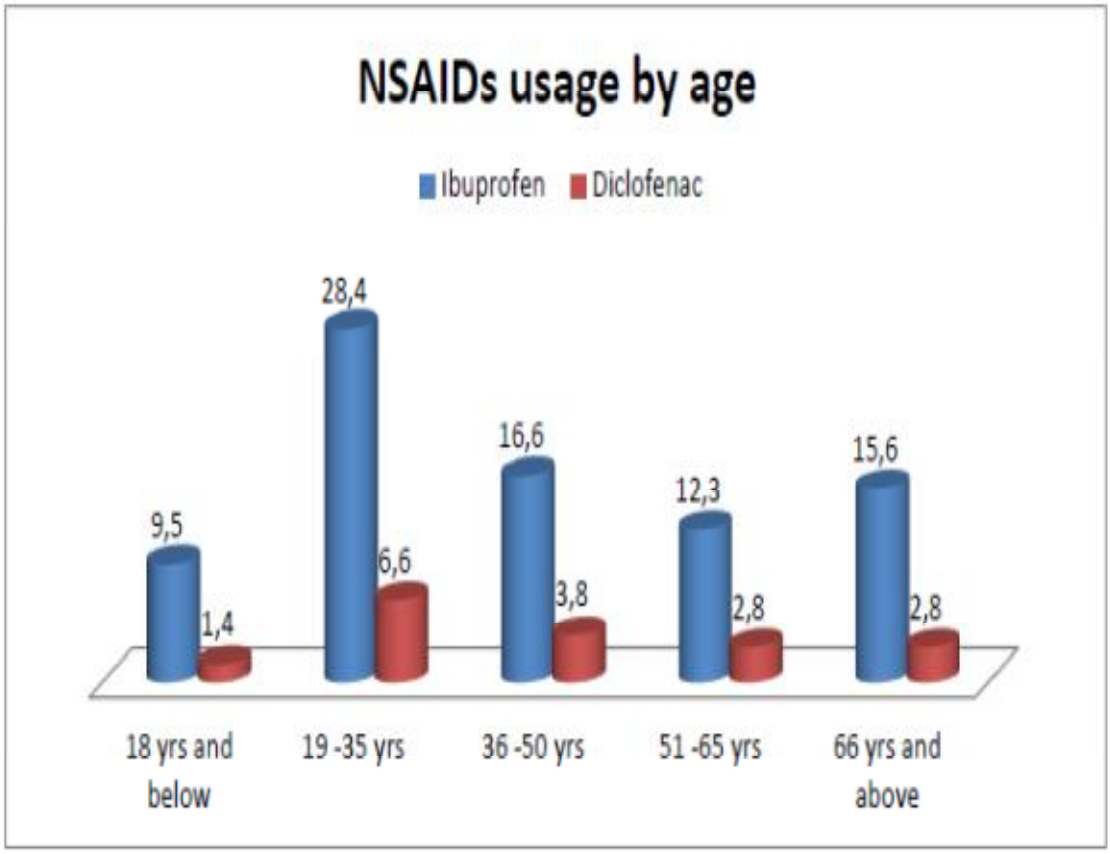
APPENDIX D


Various inflammatory conditions treated with NSAIDs in 2013 and 2014
% Diclofenac
% Ibuprofen
3,3
12,8
2,4
8,5
1,4
10,4
4,7
31,3
5,7
19,4
Soft tissue injury
Bone fractures
Inflammatory conditions
Minor bodily/joint pains
Others

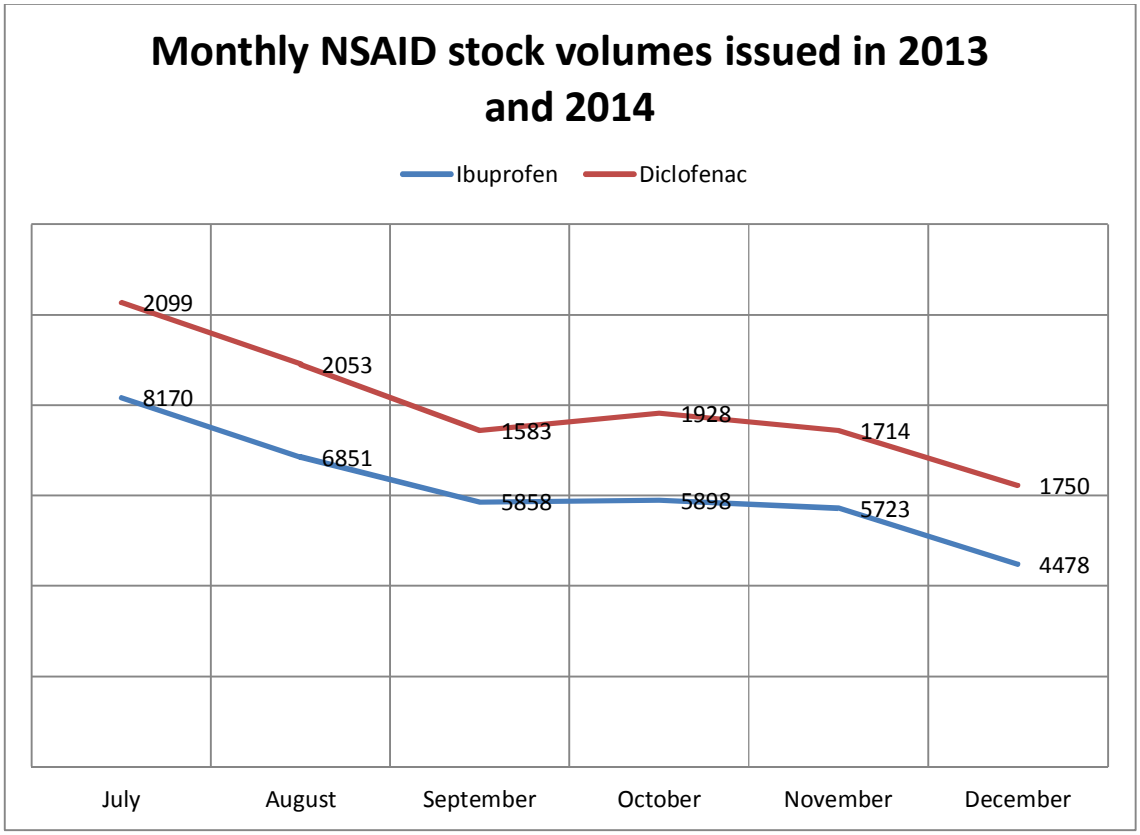
APPENDIX E


Percentage of usage by gender
Ibuprofen
Diclofenac
49,3
11,4
33,1
6,2
Female
Male

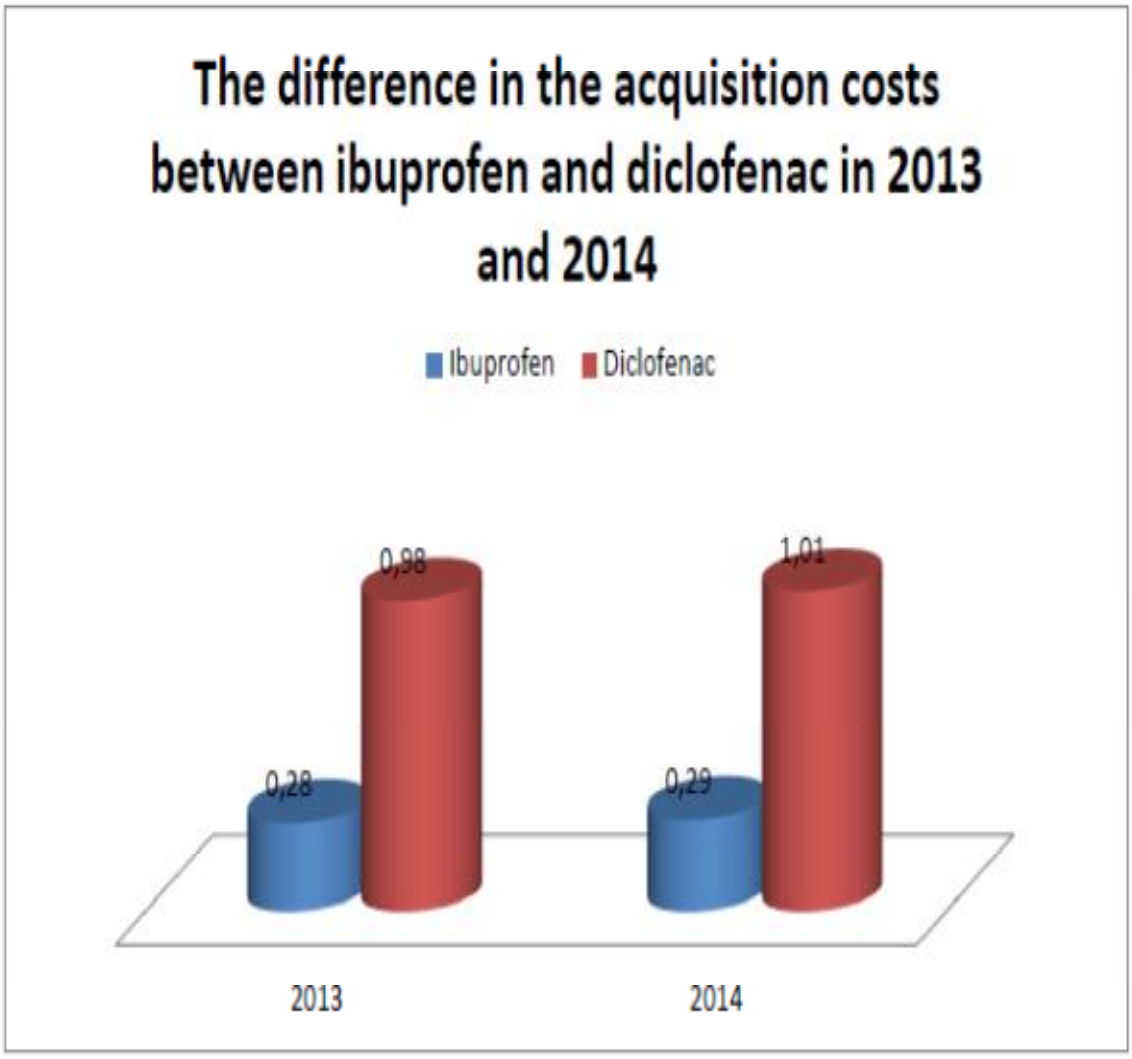
APPENDIX F


NSAIDs usage by age
Ibuprofen
Diclofenac
9,5
1,4
28,4
6,6
16,6
3,8
12,3
2,8
15,6
2,8
18 yrs and below
19 -35 yrs
36 -50 yrs
51 -65 yrs
66 yrs and above

APPENDIX G


Monthly NSAID stock volumes issued in 2013 and 2014
Ibuprofen
Diclofenac
2099
2053
1583
1928
1714
1750
8170
6851
5858
5898
5723
4478
July
August
September
October
November
December

APPENDIX H


The difference in the acquisition costs between ibuprofen and diclofenac in 2013 and 2014
Ibuprofen
Diclofenac
0,98
1,01
0,28
0,29
2013
2014

APPENDIX I: Cost/DDD of Ibuprofen versus Diclofenac Oral Tablets

Type of NSAID	**2013**			**2014**		
	Defined Daily Dose (DDD)	Mean Price in Rands (R)	Frequency of Prescription	Defined Daily Dose (DDD)	Mean Price in Rands (R)	Frequency of Prescription
Ibuprofen	400mg T.D.S	0,28 x 3 = **0,84**	85,6% (89)	400mg T.D.S	0,29 x 3 = **0,87**	79,4% (85)
Diclofenac	50mg T.D.	0,98 x 3 = **2,94**	14,4% (15)	50mg T.D.S	1,01 x 3 = **3,03**	20,6% (22)

APPENDIX J: Sensitivity Analysis

	2013		2014	
	Variable(S)	**Mean Cost/ DDD (R)**	**Variable(S)**	**Mean Cost/ DDD (R)**
Increasing the mean cost/DDD of Ibuprofen	50% (R0,42)	1,26	50% (R0,44)	1,31
Decreasing the mean cost/DDD of Ibuprofen	50% (R0,42)	0,42	50% (R0,44)	0,44
Increasing the mean cost/DDD of Diclofenac	50% (R1,47)	4,41	50% (R1,52)	4,55
Decreasing the mean cost/DDD of Diclofenac	50% (R1,47)	1,47	50% (R1,52)	1,52

APPENDIX K

MPUMALANGA PROVINCIAL GOVERNMENT

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Department of Health

Litiko Letemphilo | Umnyango WezaMaphilo | Departement van Gesondheid

Enquiries: Themba Mulungo (013) 766 3511

03 December 2014

Mr. Makhipha Nkosi
P.O. Box 2216
Shongwe Mission
1331

Dear Mr. Makhipha Nkosi

APPLICATION FOR RESEARCH & ETHICS APPROVAL: COST-EFFECTIVENESS ANALYSIS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) USED IN THE MANAGEMENT OF PAIN IN ADULT PATIENTS AT THE TONGA HOSPITAL, MPUMALANGA PROVINCE, SOUTH AFRICA.

The Provincial Research and Ethics Committee has approved your research proposal in the latest format that you sent.

PHREC REF: MP_2014RP10_721

Kindly ensure that you provide us with the soft and hard copies of the report once your research project has been completed.

Kind regards

MR. MOLEFE MACHABA
RESEARCH AND EPIDEMIOLOGY

MPUMALANGA PROVINCE
DEPARTMENT OF HEALTH
PLANNING & INFORMATION
2014 -12- 03
PRIVATE BAG X 11285
NELSPRUIT 1200

03/12/2014
DATE

APPENDIX L

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

27 November 2014

Mr Makhipha Nkosi
P.O. Box 2216
Shongwe Mission
1331
mathibel@ukzn.ac.za - (supervisor)

Dear Mr Nkosi

PROTOCOL: Cost-effective analysis of non-steroidal anti-inflammatory drugs (NSAIDs) used in the management of pain in adult patients at the Tonga Hospital, Mpumalanga Province, South Africa: Degree Purposes (MMedSc) - School of Health Sciences (Pharmaceutical Sciences). BREC REF: BE444/14.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 02 October 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 26 November 2014 to queries raised on 31 October 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from **28 November 2014.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **09 December 2014.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Professor D R Wassenaar (Chair)
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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx